

University of Southampton Research Repository ePrints Soton

Copyright © and Moral Rights for this thesis are retained by the author and/or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder/s. The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given e.g.

AUTHOR (year of submission) "Full thesis title", University of Southampton, name of the University School or Department, PhD Thesis, pagination

UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Primary Care and Population Sciences

Exploring the role of
Chinese herbal medicine in primary care
for oligomenorrhoea and amenorrhoea in
polycystic ovary syndrome

BY

Lily Yuen Wan Lai

Thesis for the degree of Doctor of Philosophy

October 2014

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE

Primary Care and Population Sciences

Doctor of Philosophy

**EXPLORING THE ROLE OF CHINESE HERBAL MEDICINE IN PRIMARY CARE
FOR OLIGOMENORRHOEA AND AMENORRHOEA IN POLYCYSTIC OVARY
SYNDROME**

by Lily Yuen Wan Lai

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age. Oligomenorrhoea and amenorrhoea are cardinal symptoms of PCOS but the effectiveness and acceptability of current conventional treatments for regulating menses remains questionable and other treatments need to be explored. Chinese herbal medicine (CHM) is widely used for PCOS in China and in the UK. This PhD aimed to explore the role of CHM for PCOS-related oligomenorrhoea and amenorrhoea in UK primary care.

I conducted a systematic review and meta-analysis which included 4 methodologically-poor quality randomised controlled trials (RCTs). Preliminary results appear to suggest CHM is likely to be safe, with few adverse effects, and have a potential benefit on testosterone and luteinising hormone. A Delphi study with CHM practitioners was conducted which resulted in 85 items being included within good clinical practice guidelines for CHM treatment of PCOS. These guidelines were used to inform the protocol for an RCT. My initial RCT protocol involved a feasibility study in primary care comparing three treatments: standardised CHM plus usual care, placebo plus usual care and usual care alone. Unfortunately the CHM manufacturer experienced difficulties obtaining documentation in a timely manner, necessitating a protocol revision. A feasibility study was finally conducted in private practices successfully recruiting 40 women who were randomised to either standardised CHM or individualised CHM. Study results suggest both standardised and individualised CHMs are safe and acceptable, and both have similar clinically important benefits on menstrual status in PCOS.

My findings suggest further research into CHM for PCOS-related oligo- and amenorrhoea is warranted. I have demonstrated that rigorous CHM RCT evidence can benefit by consulting CHM practitioners to maximise model validity. Clinical data from the feasibility study provides effect size estimates and pilot data that will facilitate planning for a larger-scale definitive study.

List of contents

ABSTRACT.....	I
LIST OF CONTENTS.....	III
LIST OF TABLES	XI
LIST OF FIGURES.....	XIII
AUTHOR'S DECLARATION	XV
ACKNOWLEDGEMENTS.....	XIX
DEFINITIONS AND ABBREVIATIONS.....	XXI
CHAPTER 1: POLYCYSTIC OVARY SYNDROME AND CONVENTIONAL MEDICAL TREATMENT	1
1.1. INTRODUCTION AND EPIDEMIOLOGY	1
1.2. CLINICAL PRESENTATION AND DIAGNOSIS.....	3
1.3. EVOLUTION OF THE DIAGNOSTIC CRITERIA	4
1.4. AETIOLOGY AND PATHOLOGICAL MECHANISMS	6
1.4.1. <i>Hyperandrogenism</i>	6
1.4.2. <i>Hyperinsulinaemia</i>	7
1.4.3. <i>The role of abdominal obesity</i>	8
1.4.4. <i>Developmental origins, genetics and socio-economic factors</i>	8
1.4.5. <i>Summary</i>	10
1.5. MANAGEMENT OF PCOS.....	10
1.5.1. <i>Oligomenorrhoea and amenorrhoea in PCOS</i>	11
1.5.2. <i>Management of oligomenorrhoea and amenorrhoea in PCOS</i>	13
1.6. CONCLUSION	19
CHAPTER 2: THE DEVELOPMENT OF CHINESE HERBAL MEDICINE AND MODERN DAY USE	21
2.1. INTRODUCTION.....	21
2.2. CHM APPROACH TO HEALTH	23
2.3. CHM TREATMENT AND BASIC CONCEPTS	24
2.4. CHM DIAGNOSIS, TREATMENT AND BASIC CONCEPTS.....	29
2.5. CHM AND PCOS	30

2.6. CHM IN PRIMARY CARE.....	31
2.7. CONCLUSION	34

CHAPTER 3: THE EFFECTIVENESS OF CHINESE HERBAL MEDICINE FOR OLIGOMENORRHOEA AND AMENORRHOEA IN POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS 35

3.1. BACKGROUND.....	35
3.2. METHODS	36
3.2.1. <i>Types of studies</i>	36
3.2.2. <i>Types of participants</i>	37
3.2.3. <i>Types of interventions</i>	37
3.2.4. <i>Types of outcome measures</i>	38
3.2.5. <i>Clinical data on CHM methods</i>	39
3.2.6. <i>Search methods for identification of studies</i>	39
3.2.7. <i>Management of study searches</i>	41
3.2.8. <i>Assessing eligibility</i>	41
3.2.9. <i>Data extraction and management</i>	41
3.2.10. <i>Risk of bias assessments</i>	42
3.2.11. <i>Measures of treatment effect</i>	43
3.2.12. <i>Dealing with missing data</i>	44
3.2.13. <i>Assessment of publication bias</i>	44
3.2.14. <i>Assessment of statistical heterogeneity</i>	44
3.2.15. <i>Subgroup analysis and investigation of heterogeneity</i>	45
3.2.16. <i>Data synthesis</i>	45
3.2.17. <i>Sensitivity Analyses</i>	46
3.3. RESULTS.....	47
3.3.1. <i>Results of the search</i>	47
3.3.2. <i>Description of studies</i>	49
3.3.3. <i>Effects of interventions</i>	56
3.3.4. <i>CHM plus Diane-35 versus Diane-35 alone</i>	59
3.3.5. <i>Other analyses</i>	62
3.4. DISCUSSION	62
3.4.1. <i>Summary of main results</i>	62
3.4.2. <i>Implications for practice</i>	63

3.4.3. <i>Implications for research</i>	65
3.4.4. <i>Strengths and limitations of this review</i>	71
3.5. CONCLUSION	72
CHAPTER 4: DEVELOPING CLINICAL PRACTICE GUIDELINES FOR THE TREATMENT OF POLYCYSTIC OVARY SYNDROME WITH CHINESE HERBAL MEDICINE: A MIXED-METHODS DELPHI STUDY	75
4.1. INTRODUCTION.....	75
4.2. BACKGROUND TO METHODS.....	76
4.3. METHODS.....	77
4.3.1. <i>Phase 1</i>	78
4.3.2. <i>Phase 2</i>	89
4.4. RESULTS	90
4.4.1. <i>Phase 1</i>	90
4.4.2. <i>Phase 2</i>	106
4.5. DISCUSSION	110
4.5.1. <i>Study strengths</i>	111
4.5.2. <i>Study Limitations</i>	113
4.5.3. <i>Reflections on the Delphi process</i>	117
4.6. CONCLUSION	121
CHAPTER 5: DEVELOPMENT OF A PROTOCOL FOR A PLACEBO- CONTROLLED RANDOMISED FEASIBILITY AND PILOT STUDY IN PRIMARY MEDICAL CARE	123
5.1. INTRODUCTION.....	123
5.1.1. <i>Designing the study protocol</i>	123
5.1.2. <i>The initial study design</i>	125
CHAPTER 6: PROTOCOL FOR A RANDOMISED FEASIBILITY AND PILOT STUDY IN PRIVATE HERBAL PRACTICES.....	135
6.1. INTRODUCTION.....	135
6.1.1. <i>Research questions</i>	135
6.2. STUDY OBJECTIVES AND ENDPOINTS.....	136
6.3. STUDY DESIGN AND RATIONALE	137
6.4. STUDY POPULATION.....	139
6.4.1. <i>Inclusion and exclusion criteria</i>	139

6.4.2. <i>Identifying participants</i>	140
6.4.3. <i>Recruitment plan</i>	141
6.4.4. <i>Screening</i>	142
6.4.5. <i>Consenting participants</i>	144
6.4.6. <i>Randomisation</i>	144
6.1. PATIENT AND PUBLIC INVOLVEMENT	146
6.2. STUDY INTERVENTIONS	146
6.2.1. <i>Study Practitioners and Study Sites</i>	149
6.2.2. <i>Study Medications</i>	149
6.2.3. <i>Summary of CHM Product Characteristics</i>	154
6.2.4. <i>CHM Side-effects</i>	154
6.2.5. <i>CHM Dispensary and Manufacturer</i>	154
6.2.6. <i>Stability data</i>	155
6.2.7. <i>Labelling and Packaging</i>	155
6.2.8. <i>Justification for expiry dates</i>	156
6.2.9. <i>Study Medication Distribution and Disposal</i>	156
6.2.10. <i>Dosing regimen and instructions</i>	156
6.2.11. <i>Participant Adherence</i>	157
6.2.12. <i>Changes to CHM prescription</i>	158
6.2.13. <i>Excessive dosing</i>	158
6.2.14. <i>Prior and concomitant medications and interventions</i>	159
6.2.15. <i>Concomitant advice</i>	160
6.2.16. <i>Study Restrictions</i>	160
6.3. OUTCOME MEASURES	161
6.3.1. <i>Safety Assessments</i>	161
6.3.2. <i>Chinese medicine clinical assessment</i>	161
6.3.3. <i>Study Assessments</i>	162
6.4. PROPOSED ANALYSES	165
6.4.1. <i>Statistical methods</i>	169

CHAPTER 7: RESULTS OF A RANDOMISED FEASIBILITY AND PILOT STUDY IN PRIVATE HERBAL PRACTICES..... 171

7.1. INTRODUCTION	171
7.2. RECRUITMENT.....	171
7.2.1. <i>Recruitment of practitioners</i>	171

7.2.2. Recruitment of participants	171
7.3. ELIGIBILITY	177
7.3.1. Further assessments required	180
7.3.2. Retention and withdrawal	180
7.4. SAFETY AND ADVERSE EVENTS.....	181
7.5. CLINICAL DATA.....	184
7.5.1. Baseline demographics and variables.....	185
7.5.2. Primary outcome measure: Menstrual cyclicity.....	189
7.5.3. Secondary outcome measures	193
7.5.4. MYMOP ranking.....	196
7.5.5. Practitioner-blinding assessment.....	198
7.5.6. Security of randomisation and allocation procedures	201
7.5.7. Adherence to CHM administration	201
7.5.8. Study assessments: Adherence.....	204
7.5.9. Study assessments: Resource usage and management.....	204
7.5.10. CHM intervention.....	205
7.5.11. Lifestyle and dietary advice.....	207
7.5.12. Piloting and feedback data	208
7.6. DISCUSSION	219
7.6.1. Is oligomenorrhoea and amenorrhoea appropriate as the primary outcome measure for the main study?.....	220
7.6.2. Are other measures more appropriate for investigation as the primary outcome measure for the main study?.....	221
7.6.3. What is the safety profile of CHM?.....	224
7.6.4. How should the CHM intervention in the main study be delivered?.....	225
7.6.5. Can a double-blind, randomised trial with CHM for PCOS be conducted?.....	226
7.6.6. Strengths and limitations of this study.....	229
7.6.7. Directions for further work	233
7.7. CONCLUSION	236
CHAPTER 8: DISCUSSION.....	239
8.1. INTRODUCTION.....	239
8.2. SUMMARY OF FINDINGS	239
8.3. REFLECTIONS AS A PRACTITIONER-RESEARCHER	241

8.4. RECOMMENDATIONS FOR FUTURE RESEARCH	242
APPENDICES	245
APPENDIX 1. PHENOTYPES ACCORDING TO EACH CRITERIA.....	245
APPENDIX 2: SEARCH STRATEGY	247
APPENDIX 3: SCRIPT FOR EMAIL CONTACTING.....	249
APPENDIX 4: SCRIPT FOR TELEPHONE CONTACTING.....	251
APPENDIX 5: REASONS FOR EXCLUSION FOR REMAINING STUDIES	253
APPENDIX 6: COMMONLY PRESCRIBED CHINESE HERBAL MEDICINES IN POLYCYSTIC OVARY SYNDROME RANDOMISED CONTROLLED TRIALS.....	261
APPENDIX 7: FOREST PLOTS FOR NON META-ANALYSES	263
APPENDIX 8: EMAIL SCRIPT TO POTENTIAL DELPHI STUDY PARTICIPANTS.....	267
APPENDIX 9: TELEPHONE CALL AND MESSAGE SCRIPT TO POTENTIAL DELPHI STUDY PARTICIPANTS	269
APPENDIX 10: DELPHI STUDY INVITATION LETTER.....	271
APPENDIX 11: PARTICIPANT INFORMATION SHEET FOR DELPHI STUDY.....	273
APPENDIX 12: CONSENT FORM FOR DELPHI STUDY.....	277
APPENDIX 13: DELPHI STUDY FOCUS GROUP TOPIC GUIDE.....	279
APPENDIX 14: DELPHI STUDY INTERVIEW TOPIC GUIDE.....	283
APPENDIX 15: INITIAL CODES GENERATED FROM LINE-BY-LINE CODING	285
APPENDIX 16: CODING MANUAL	287
APPENDIX 17: EXCERPT FROM A CODED TRANSCRIPT	293
APPENDIX 18: CHART FOR FRAMEWORK ANALYSIS.....	295
APPENDIX 19: QUESTIONNAIRE DISTRIBUTED IN DELPHI ROUND TWO	299
APPENDIX 20: EXAMPLE OF PERSONALISED QUESTIONNAIRE DISTRIBUTED TO ONE PARTICIPANT IN DELPHI ROUND THREE	307
APPENDIX 21: GOOD CLINICAL PRACTICE GUIDELINES FOR THE TREATMENT OF POLYCYSTIC OVARY SYNDROME WITH CHINESE HERBAL MEDICINE	311
APPENDIX 22: REVISED PROTOCOL FOR ORCHID STUDY.....	315
APPENDIX 23: LETTER OF CONFIRMATION FROM MEDICINES HEALTHCARE REGULATORY AGENCY	401
APPENDIX 24: TABLE TO SHOW FEASIBILITY AND STUDY OBJECTIVES WITH JUSTIFICATIONS	405
APPENDIX 25: ROTTERDAM DIAGNOSTIC CRITERIA FOR POLYCYSTIC OVARY SYNDROME.	409
APPENDIX 26: FAST ALCOHOL SCREENING TEST (FAST) QUESTIONNAIRE	411

APPENDIX 27: ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)	413
APPENDIX 28: EXAMPLE OF PARTICIPANT RECRUITMENT FLYER.....	415
APPENDIX 29: EXAMPLE OF REQUEST FOR PRACTITIONER REFERRALS	417
APPENDIX 30: ORCHID STUDY WEBSITE SCREENSHOTS.....	419
APPENDIX 31: PARTICIPANT INFORMATION SHEET FOR ORCHID STUDY.....	423
APPENDIX 32: WEB-BASED SCREENING QUESTIONNAIRE FOR ORCHID STUDY	427
APPENDIX 33: STUDY INVITATION LETTER FOR ORCHID STUDY.....	433
APPENDIX 34: CONSENT FORM FOR ORCHID STUDY	435
APPENDIX 35: NOTIFICATION OF STUDY PARTICIPATION LETTER TO GP	437
APPENDIX 36: SUMMARY REPORT OF COMMENTS BY PATIENT AND PUBLIC INVOLVEMENT REPRESENTATIVES	439
APPENDIX 37: REPORTING RANDOMIZED, CONTROLLED TRIALS OF HERBAL INTERVENTIONS: AN ELABORATED CONSORT STATEMENT	441
APPENDIX 38: GOOD CLINICAL PRACTICE TRAINING CERTIFICATE.....	443
APPENDIX 39: SUMMARY OF PHARMACOLOGICAL PRODUCT CHARACTERISTICS FOR CHINESE HERBAL MEDICINES COMMONLY USED IN POLYCYSTIC OVARY SYNDROME.....	445
APPENDIX 40: CERTIFICATE OF STUDY DISPENSARY AS A SUPPLIER APPROVED BY THE REGISTER OF CHINESE HERBAL MEDICINE	453
APPENDIX 41: CERTIFICATE OF DISPENSARY AND PHARMACOGNOSY TRAINING FOR A MEMBER OF THE DISPENSING TEAM	455
APPENDIX 42: CERTIFICATE OF GOOD MANUFACTURING PRACTICE BY THE STUDY MANUFACTURER	457
APPENDIX 43: CERTIFICATE OF ANALYSIS FOR A SINGLE CHINESE HERBAL MEDICINE	459
APPENDIX 44: LABEL FOR DISPENSED ORCHID STUDY CHINESE HERBAL MEDICINES.....	461
APPENDIX 45: LETTER TO CONFIRM MANUFACTURER RECOMMENDATIONS	463
APPENDIX 46: MORISKY MEDICATION ADHERENCE SCALE (MMAS8).....	465
APPENDIX 47: RECORD OF CHINESE HERBAL MEDICINE ASSESSMENT DATA	467
APPENDIX 48: DEMOGRAPHICS QUESTIONNAIRE	469
APPENDIX 49: DERMATOLOGY LIFE QUALITY INDEX (DLQI) QUESTIONNAIRE	471
APPENDIX 50: MEASURE YOURSELF MEDICAL OUTCOME PROFILE (MYMOP) QUESTIONNAIRE	473
APPENDIX 51: MODIFIED FERRIMAN-GALLWEY (MFG) QUESTIONNAIRE.....	475
APPENDIX 52: PRACTITIONER BLINDING QUESTIONNAIRE	477
APPENDIX 53: CREDIBILITY/EXPECTANCY QUESTIONNAIRE (CEQ)	479
APPENDIX 54: END-OF-STUDY QUESTIONNAIRE FOR STUDY PARTICIPANT	481

APPENDIX 55: END-OF-STUDY QUESTIONNAIRE FOR STUDY PERSONNEL	483
APPENDIX 56: ORCHID STUDY PROTOCOL PUBLICATION	485
REFERENCES	493

List of tables

TABLE 1: CLINICAL SIGNS AND SYMPTOMS OF PCOS.....	3
TABLE 2: COMPARISON BETWEEN THE THREE SETS OF PCOS DIAGNOSTIC CRITERIA: NIH 1990, ROTTERDAM 2003 AND AES 2006.....	4
TABLE 3: CHARACTERISTICS OF INCLUDED STUDIES	50
TABLE 4: DETAILS OF CHM INTERVENTIONS IN INCLUDED STUDIES.....	52
TABLE 5: CLINICAL GUIDELINE CRITERIA FOR CLASSIFICATION OF ITEM GRADING	89
TABLE 6: DEMOGRAPHICS AND CHARACTERISTICS OF RECRUITED PARTICIPANTS.....	94
TABLE 7: NUMBER OF STATEMENTS GENERATED BY THEME FOR INITIAL QUESTIONNAIRE.....	100
TABLE 8: CLARIFICATION OF ORIGINAL STATEMENT ITEM BY INCORPORATING FREE-TEXT RESPONSES.....	103
TABLE 9: RETENTION AND DISCARDING OF ASSOCIATED ITEMS IN GUIDELINE DEVELOPMENT	107
TABLE 10: COMBINING OF TWO STATEMENT ITEMS FOR GUIDELINE PRESENTATION	108
TABLE 11: FREQUENCY OF GUIDELINE ITEMS BY THEME AND BY CONSENSUS GRADING.....	109
TABLE 12: A TABLE TO SHOW ELIGIBILITY CRITERIA CHECKED AT EACH SCREENING PHASE....	143
TABLE 13: AMENDMENTS TO DOCUMENTS FROM PATIENT AND PUBLIC INVOLVEMENT FEEDBACK	146
TABLE 14: CONTENTS OF STANDARDISED CHINESE HERBAL MEDICINE	153
TABLE 15: SUMMARY OF STUDY ASSESSMENTS.....	165
TABLE 16: NUMBER AND PERCENTAGE RECRUITED BY RECRUITMENT METHOD	174
TABLE 17: RANKING OF RECRUITMENT METHOD BY TIME LAG BETWEEN INITIATION OF RECRUITMENT METHOD TO FIRST ENQUIRY	177
TABLE 18: FREQUENCY AND RANK ORDER OF REASONS FOR INELIGIBILITY	179
TABLE 19: NATURE AND FREQUENCY OF ADVERSE REACTIONS COMPARED BETWEEN GROUPS	184
TABLE 20: BASELINE DEMOGRAPHICS OF ORCHID STUDY PARTICIPANTS.....	186
TABLE 21: COMPARABILITY AT BASELINE BETWEEN TREATMENT GROUPS	188
TABLE 22: UNADJUSTED MENSTRUAL RATES AT 6 MONTHS, AT END OF STUDY, AND CHANGE FROM BASELINE FOR STANDARDISED AND INDIVIDUALISED CHM TREATMENT GROUPS ..	190
TABLE 23: ANCOVA OF MENSTRUAL RATE AT 6 MONTHS AND AT END OF STUDY	191
TABLE 24: RESPONDERS AND NON-RESPONDERS TO CHM TREATMENTS	193
TABLE 25: ANCOVA COMPARING SECONDARY OUTCOME MEASURES WITHIN AND BETWEEN GROUP	194
TABLE 26: FREQUENCY AND RANK ORDER OF MYMOP 1 AND 2 SYMPTOMS.....	197

TABLE 27: FREQUENCY AND RANK ORDER OF MYMOP 1 AND 2 SYMPTOMS COMBINED	197
TABLE 28: PRACTITIONER-BLINDING RESULTS USING BANG BLINDING INDEX.....	199
TABLE 29: FREQUENCY TABLE OF REASONS FOR PRACTITIONER-TREATMENT GUESS.....	200
TABLE 30: MMAS SCORES BY TREATMENT GROUP AND BY ASSESSMENT	202
TABLE 31: BETWEEN-GROUP CHANGES IN CATEGORIES OF ADHERENCE USING MMAS	203
TABLE 32: ATTENDANCE RATES BY STUDY ASSESSMENT	204
TABLE 33: FREQUENCY, RANK ORDER AND MEAN DAILY DOSE OF 20 MOST FREQUENTLY PRESCRIBED CHMs	206
TABLE 34: FREQUENCY AND RANK ORDER OF CM PATTERNS OF DISHARMONY DIAGNOSED AT BASELINE	207
TABLE 35: TYPES AND COUNT OF LIFESTYLE AND DIETARY ADVICE RECORDED ON-STUDY	208

List of figures

FIGURE 1: PATHOLOGICAL MECHANISMS IN PCOS	6
FIGURE 2: MANAGEMENT OF PCOS	11
FIGURE 3: XI YUAN CHINESE MEDICINE HOSPITAL IN HAI DIAN DISTRICT, BEIJING CHINA	22
FIGURE 4: BEIJING TONG REN TANG CHINESE MEDICINE CLINIC	23
FIGURE 5: CHINESE HERBS AVAILABLE TO THE GENERAL PUBLIC AT A MARKET STALL IN BEIJING	25
FIGURE 6: DRIED CHINESE HERBS - GOJI BERRY, CHINESE WILD YAM, TANGERINE PEEL, REHMANNIA ROOT AND GINSENG	27
FIGURE 7: CHINESE HERBAL TEA	28
FIGURE 8: CHINESE HERBAL EXTRACT IN POWDERED FORM	28
FIGURE 9: PRISMA (PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META- ANALYSES) FLOW-CHART OF STUDY SELECTION	47
FIGURE 10: RISK OF BIAS SUMMARY FOR INCLUDED STUDIES	54
FIGURE 11: FOREST PLOT OF COMPARISON CHM ALONE VERSUS PHARMACOLOGICAL TREATMENT ALONE FOR OUTCOME: TOTAL TESTOSTERONE.....	57
FIGURE 12: FOREST PLOT OF COMPARISON CHM ALONE VERSUS PHARMACOLOGICAL TREATMENT ALONE FOR OUTCOME: LUTEINISING HORMONE.....	58
FIGURE 13: FOREST PLOT OF COMPARISON CHM PLUS DIANE-35 VERSUS DIANE-35 ALONE FOR OUTCOME: TOTAL TESTOSTERONE.....	60
FIGURE 14: FOREST PLOT OF COMPARISON CHM PLUS DIANE-35 VERSUS DIANE-35 ALONE FOR OUTCOME: LUTEINISING HORMONE.....	61
FIGURE 15: FLOWCHART TO SHOW PROCESSES INVOLVED IN PHASES 1 AND 2.....	78
FIGURE 16: OVERVIEW OF DATA COLLECTION AND ANALYSIS IN PHASE 1	81
FIGURE 17: STAGES OF FRAMEWORK ANALYSIS.....	83
FIGURE 18: FLOWCHART OF RECRUITMENT PROCESS.....	92
FIGURE 19: FLOWCHART TO SHOW RESULTS OF PROCESSES INVOLVED IN PHASES 1 AND 2	95
FIGURE 20: GENERATION OF A STATEMENT FROM INTERVIEW DATA.....	99
FIGURE 21: DELPHI ROUND TWO DATA ANALYSIS AND ITEM PREPARATION FOR DELPHI ROUND THREE	104
FIGURE 22: SAMPLE OF THE CONCLUDING SET OF CLINICAL GUIDELINES FOR THE CHM TREATMENT OF PCOS	110
FIGURE 23: OVERVIEW OF FEASIBILITY STUDY PROCEDURES	148

FIGURE 24: DECISION-MAKING PROCESS FOR CONTENTS OF STANDARDISED CHM.....	152
FIGURE 25: TARGET AND ACTUAL CUMULATIVE RECRUITMENT NUMBERS	172
FIGURE 26: CUMULATIVE RECRUITED PARTICIPANTS BY STUDY SITE.....	173
FIGURE 27: PERCENTAGE OF ENQUIRIES GENERATED BY RECRUITMENT METHOD	175
FIGURE 28: PERCENTAGE RECRUITED BY RECRUITMENT METHOD	176
FIGURE 29: ELIGIBILITY FLOWCHART.....	178
FIGURE 30: CONSORT PARTICIPANT FLOW DIAGRAM	181
FIGURE 31 : FLOWCHART TO SHOW SAFETY ASSESSMENTS AND OUTCOMES BY TREATMENT GROUP.....	182

Author's declaration

I, Lily Yuen Wan Lai, declare that the thesis entitled 'Exploring the role of Chinese herbal medicine in primary care for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome' and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- part of this work has been published before as:

Lai, L. Flower, A. Moore, M., Lewith, G. (2015) 'Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: a mixed-method modified Delphi study' *Complementary Therapies In Medicine*, (In Press, Available online 14 March 2015).

Lai, L. Flower, A. Moore, M., Prescott, P. Lewith, G. (2014) 'Polycystic ovary syndrome: A Randomised feasibility and pilot study using Chinese Herbal medicine to explore Impact on Dysfunction (ORCHID) – Study Protocol', *European Journal of Integrative Medicine*, 6, 392-399.

- part of this work has been presented at peer-reviewed conferences before as:

Oral presentations:

- 2015 Society for Academic Primary Care South West meeting, Birmingham, UK. 'Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: A randomised feasibility study in the United Kingdom'.
- 2014 NIHR School for Primary Care Research Showcase, Oxford, UK. "Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: Initial findings from a randomised feasibility study in the United Kingdom".
- 2014 Society for Academic Primary Care South West meeting, Bristol, UK. 'Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: Initial findings from a randomised feasibility study in the United Kingdom'.
- 2013 International Congress for Complementary Medicine Research annual conference, London, UK. 'Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: Preliminary findings from a randomised feasibility study in the United Kingdom'.
- 2013 Society for Academic Primary Care South West meeting, Southampton, UK. 'Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: A mixed methods modified Delphi study'.
- 2012 European Congress for Integrative Medicine annual congress, Florence, Italy. 'Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: A mixed methods modified Delphi study'.
- 2012 Society for Academic Primary Care South West meeting, Torquay, UK. 'Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: A mixed methods modified Delphi study'.

Poster presentations:

- 2014 International Congress for Complementary Medicine Research annual conference, Miami, UK. 'Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: Preliminary findings from a randomised feasibility study in the United Kingdom'.

'Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: A systematic review and meta-analysis'.
- 2013 Society for Academic Primary Care annual meeting, Nottingham, UK. 'Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: A mixed methods modified Delphi study'.

‘Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: Preliminary findings from a randomised feasibility study in the United Kingdom’.

- 2013 International Congress for Complementary Medicine Research annual conference, London, UK. ‘Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: A mixed methods modified Delphi study’.
- 2013 Society for Academic Primary Care South West meeting, Southampton, UK. ‘Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: Preliminary findings from a randomised feasibility study in the United Kingdom’.
- 2012 International Congress for Complementary Medicine Research annual conference, London, UK. ‘Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: A mixed methods modified Delphi study’.
- 2012 NIHR School for Primary Care Research Showcase, London, UK. ‘Investigating the use of Chinese herbal medicine for polycystic ovary syndrome in the United Kingdom’

Signed:

Date:.....

Acknowledgements

I would like to thank my supervisors Professor George Lewith, Professor Michael Moore and Dr. Andrew Flower for being the incredible team that has been behind me throughout this PhD. Their guidance, enthusiasm and patience have been a constant source of inspiration to me, and I remain grateful that they have afforded time and space for both this PhD and myself as a practitioner-researcher to evolve.

My thanks also go to the School for Primary Care Research, the National Institute for Health Research and the University of Southampton's Primary Care and Population Sciences for providing financial support through this PhD. Without this financial backing, it would not have been possible for me to carry out this project.

I would like to acknowledge the help of all participants of the ORCHID study whose generosity and stories have inspired me to continue doing work in this poorly-understood area of research. I remain indebted to the Chinese herbal medicine practitioners who generously volunteered their time and insights during the Delphi study, and to the many practitioners – of both Chinese medicine and other complementary medicine backgrounds – for their support throughout this PhD; Trevor Wing and his team for their generosity and time during the study; Professor Jianping Liu and Tina Xun Li for their help with the systematic review and for welcoming me to Beijing during my trip; Professor Alan Bensoussan for his generosity in advice and time especially in the setup phase of the ORCHID study; Professor Philip Prescott for his statistical advice and wisdom throughout the ORCHID project; George He and the rest of the team at Phoenix Medical for CHM dispensing support; Mazin Al-Khafaji, Dr. Mingzhao Cheng, Mark Bovey and Peter Deadman for support during study recruitment. Emma Farrant and Nick Lampert along with others from the Register of Chinese Herbal Medicine have been instrumental in the completion of this PhD.

Thank you to the staff, GPs, postdocs and PhD students in Primary Medical Care and in Complementary Medicine each of whom have helped to shape this PhD in one way or another. A very special thanks to Sarah Tonkin-Crine, Jenny McSharry, Catherine Woods, Andy Penn for their ongoing peer support and for sharing laughter, tapas and tiny cups of tea. Thanks to Team 109 Katie Ekberg and Saima Ali for their postdoctoral wisdom and advice. Many thanks also go to Caroline Eyles, Flis Bishop, Judy Chatwin and Jane Cousins for their kind words of wisdom and support over these years – their contribution to this PhD cannot be underestimated.

Thank you to Martin Logue, Lou Hughes and Suzanne Waterworth for being there with cupcakes, cackling and xiao long bao; the Dannelly boys who helped to prepare me for this PhD all those many years ago.

I would like to thank my beautiful and raucous family: Mum, Dad, Jennifer, Mark, Jessica, Steve, Ella, Rosie and Steven. Dimsum, roast duck and trips down memory lane with you all have kept me going – thank you for being there throughout this journey.

Finally I would like to thank my husband Sean, who remains a constant source of incredible strength, lateral-thinking and amusement, and without whom this work would not have been possible.

Definitions and abbreviations

AR	Adverse Reaction
AE	Adverse Event
CRF	Case Report Form
CHM	Chinese Herbal Medicine
CM	Chinese Medicine
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
IR	Insulin resistance
ISA	Insulin-sensitising agent
LH	Luteinising hormone
OC	Oral contraceptive
PCOS	Polycystic Ovary Syndrome
REC	Research Ethics Committee
RCT	Randomised Clinical Trial
SOPs	Standard Operating Procedures
TCM	Traditional Chinese Medicine

Chapter 1: Polycystic ovary syndrome and conventional medical treatment

1.1. Introduction and epidemiology

Polycystic ovary syndrome (PCOS) is a heterogeneous female endocrinopathy characterised principally by menstrual irregularities, ovulation disturbances, elevated levels of androgens and metabolic disturbances (Stein and Leventhal, 1934, Michelmore et al., 1999, Franks, 1995). It may also be referred to as polycystic ovarian syndrome, polycystic ovarian disease (PCOD) or Stein-Leventhal syndrome after the American gynaecologists who first identified the condition in 1934 (Stein and Leventhal, 1934). Despite the name, polycystic ovaries (PCO) are not present in all women with PCOS and only forms part of the criteria for PCOS diagnosis when using the widely applied Rotterdam criteria (2004). This set of criteria states that after the exclusion of related hormonal disorders, a diagnosis of PCOS is reached when two of the three following criteria are met: Oligo- or anovulation, clinical/biochemical signs of hyperandrogenism and polycystic ovaries.

PCOS is recognised as being the most common female endocrine disorder, affecting an estimated 8% of women of reproductive age in the UK, though worldwide prevalence estimates range from 6% to 19.9% (March et al., 2010, Azziz et al., 2005, Asuncion et al., 2000, Yildiz et al., 2012, Mani et al., 2012, Michelmore et al., 1999). Obesity, hyperinsulinaemia and hyperandrogenaemia play a central role in the presentation and the variation in PCOS prevalence as well as heterogeneity in PCOS expression is likely to be due to associated genetic and environmental factors. It is also of concern that the prevalence of PCOS has risen dramatically in the last decades (Dunaif et al., 2008). This may be explained partly by earlier detection and diagnosis but given that obesity has been associated with the expression of PCOS in susceptible individuals, experts in the field agree that the increasing worldwide incidence of obesity is likely to correlate with subsequent increase in the prevalence of PCOS and its co-morbidities (Dunaif et al., 2008). This appears to be particularly relevant to more affluent societies such as in the UK and US where body weight has been

associated with increased prevalence of metabolic and ovulatory disturbances in PCOS (Dunaif et al., 2008, Di Fede et al., 2009).

The speculated increase in PCOS prevalence will likely increase the economic burden subsequently placed on the NHS. PCOS is strongly associated with co-morbidities as type II diabetes and metabolic syndrome which affects 10% and 15.8% of those diagnosed with PCOS respectively (Ehrmann et al., 1999, Panidis et al., 2013). In the US, the total cost of evaluating and treatment provision for women with PCOS during the reproductive life-span is estimated to be \$4.36 billion (Azziz et al., 2005). A significant proportion of these costs are in treating menstrual dysfunction (31.0%) and PCOS-associated diabetes (40.5%) that frequently involves the use of prescription drugs as oral contraceptives (OCs) and anti-diabetic drugs (Azziz et al., 2005). To compare these figures with UK-prescribing data, a recent publication by the Health and Social Care Information Centre reported an increase in the use of OCs in primary care between 2001 and 2011, resulting in an increased cost to the NHS of £4.4 million, a 4.8 per cent increase over this decade (HSCIC, 2011). For anti-diabetic drugs, the cost of prescribing was £281.0 million in 2011/12, representing an increase of 91.4 per cent since 2005/6 (HSCIC, 2012). Metformin, the most frequently prescribed anti-diabetic for PCOS, was reported as one of the top 20 drugs in 2011 with 15.6 million items during this year alone being dispensed (HSCIC, 2012). The cost of treatment provision of PCOS as it currently stands already poses a significant burden in UK primary care. This is likely to rise given the expected increase both in PCOS prevalence as well as in the subsequent costs of chronic disease burden in an ageing population. It is therefore important to prioritise further research that could reduce this economic and clinical burden through more effective management of PCOS and its long-term co-morbidities. This mirrors recent guidance published by the King's Fund on NHS healthcare delivery that highlighted the need to manage more effectively preventable disease burdens such as diabetes and obesity (Ham et al., 2012). In the next section, I will provide an overview of the clinical presentation and diagnosis of PCOS before presenting my arguments for focusing this thesis on menstrual disturbances in PCOS.

1.2. Clinical presentation and diagnosis

PCOS is a multisystem heterogeneous disorder and clinical presentation can vary from woman to woman. Signs and symptoms can be categorised as being reproductive such as oligomenorrhoea and amenorrhoea, anovulation, infertility, polycystic ovaries; metabolic for example abdominal obesity, impaired glucose tolerance, impaired insulin resistance; cutaneous such as hirsutism and acne; and psychological such as depression and anxiety (Ehrmann, 2005). Other signs and symptoms are described in Table 1 that provides a summary of the clinical presentation of PCOS.

Table 1: Clinical signs and symptoms of PCOS

Categories	Signs and Symptoms
Reproductive	Amenorrhoea and oligomenorrhoea Oligo- or anovulation Enlarged ovaries containing multiple small immature cysts Menometrorrhagia Infertility Raised levels of androgens Raised levels of luteinising hormone
Metabolic	Obesity, in particular abdominal obesity Impaired glucose tolerance Impaired insulin resistance Reduced levels of HDL Elevated levels of LDL, cholesterol and triglyceride
Cutaneous	Hirsutism Acne Androgenic alopecia Acanthosis nigricans
Psychological	Depression Anxiety

Abbreviations: HDL=high density lipoprotein; LDL=Low density lipoprotein.

PCOS is a diagnosis of exclusion that can be made only after ruling out other conditions associated with hyperandrogenism and menstrual irregularities such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome (Fauser et al., 2012). After these conditions have been excluded, one of three different sets of PCOS criteria may be consulted before reaching a diagnosis: the National Institutes of Health (NIH) 1990 criteria, the Rotterdam

European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) 2003 criteria and the Androgen Excess Society (AES) 2006 criteria. The details of each set of criteria are given in Table 2.

Table 2: Comparison between the three sets of PCOS diagnostic criteria: NIH 1990, Rotterdam 2003 and AES 2006

	NIH 1990	Rotterdam ESHRE/ASRM 2003	AES 2006
Fulfillment of criteria	Both	2 of 3	Both
Criteria	Oligo- or anovulation <i>and</i> Hyperandrogenism (clinical or biochemical)	Oligo- or anovulation <i>or</i> Hyperandrogenism (clinical or biochemical) <i>or</i> Polycystic ovaries	Oligo- or anovulation or polycystic ovaries <i>and</i> Hyperandrogenism (clinical or biochemical)
Plus	Exclusion of other disorders of androgen excess and menstrual disturbances		

Abbreviations: NIH=National Institutes of Health, ESHRE/ASRM= European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine, AES=Androgen Excess Society

1.3. Evolution of the diagnostic criteria

Since Stein and Leventhal's initial identification of amenorrhoeic women with polycystic ovarian morphology and clinical signs of androgen excess in 1934, PCOS has been traditionally defined alongside evidence of chronic anovulation with excess androgen levels (Stein and Leventhal, 1934). It was not until 1990 during an international PCOS conference held by the NIH when the first consensus on the diagnostic criteria for PCOS was determined and which required both criteria be met of 1) chronic anovulation and 2) clinical and/or biochemical signs of hyperandrogenism as well as exclusion of other causes of androgen excess (Kawadzki and Dunaif, 1992). Under the new NIH criteria, the observation of PCO as was first described by Stein and Leventhal was therefore not necessary for diagnosis. Other causes of androgen excess that could mimic symptoms of PCOS were also to be excluded such as late onset congenital adrenal hyperplasia, androgen-secreting tumours of the ovary or adrenal gland and Cushing's syndrome.

Thirteen years later in 2003, a consensus workshop in Rotterdam was held by the ESHRE and the ASRM during which a revised consensus on PCOS diagnostic criteria was established (2004). Experts in the field felt that in light of further evidence from clinical studies, polycystic ovary morphology should indeed be considered within the diagnosis of PCOS and the Rotterdam criteria were thus created. These criteria expanded on the original NIH definition, and which stated that after exclusion of other aetiologies of androgen excess or ovulatory disorders, any two of the following three criteria should be met: 1) oligo- and/or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism 3) polycystic ovaries (2004).

In 2006, yet a further revision of the criteria was offered by the Androgen Excess Society (AES) task force who reviewed the available published literature on PCOS and used an evidence-based approach to define its diagnostic criteria (Azziz et al., 2006). As a result of their findings, hyperandrogenism emerged as an essential criteria for PCOS and it was proposed that diagnostic criteria should include the satisfaction of 1) hyperandrogenism (hirsutism and/or hyperandrogenaemia) and 2) ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) as well as 3) the exclusion of other androgen excess or related disorders (Azziz et al., 2006).

The three sets of diagnostic criteria that are currently available have resulted in the presentation of different PCOS phenotypes that are illustrated in Appendix 1.

Understandably the confusion around the definition of PCOS in the last two decades has created problems with determining precise implications of being diagnosed with PCOS and which has made estimating its prevalence and interpreting findings from research studies difficult. The AES criteria have however been poorly adopted, perhaps because the authors anchored their definition of the syndrome with insulin resistance (IR), a well-recognised feature of PCOS but that is unreliably measured (Azziz et al., 2006).

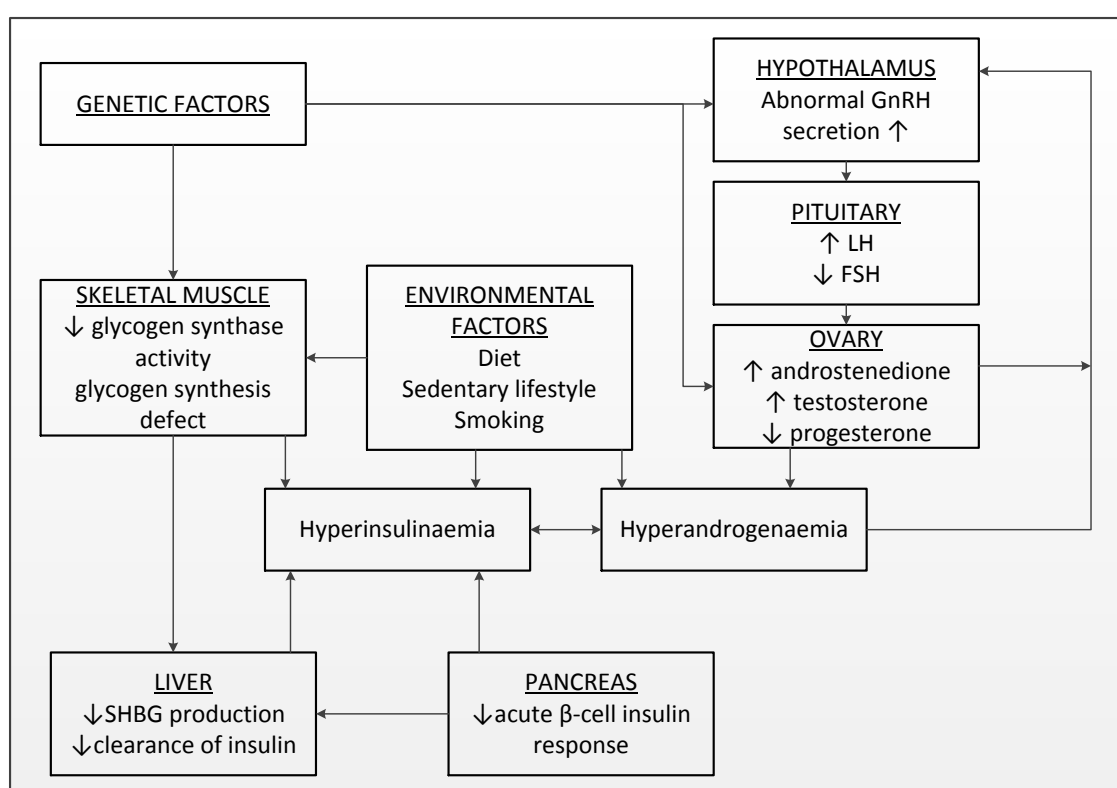
Considering their evidence-based approach, this may have raised concerns over the reliability of these latest criteria, and the Rotterdam criteria instead remain the predominant definition that is currently used. Clinical studies have therefore focused on researching the classic NIH and the new Rotterdam

phenotypes which have been regarded over the years as being universally accepted definitions (Moran and Teede, 2009).

1.4. Aetiology and pathological mechanisms

Though PCOS has been recognised since the 1930s, its aetiology still remains poorly understood. Numerous theories have been put forward surrounding the pathogenesis of PCOS and are summarised in Figure 1. Two pathophysiological processes emerge as playing a particularly central role to the development of PCOS; these are hyperandrogenism and hyperinsulinaemia (Barbieri et al., 1986, Dunaif, 1997).

Figure 1: Pathological mechanisms in PCOS



Abbreviations: SHBG=sex-hormone binding globulin; GnRH=gonadotropin releasing hormone; LH=luteinising hormone; FSH=follicle stimulating hormone

1.4.1. Hyperandrogenism

Hyperandrogenism forms part of the diagnostic criteria for PCOS and is therefore a common finding, occurring in 60-80% of PCOS patients (Azziz et al., 2006). Excess levels of androgens found in PCOS are the result of both increased production of ovarian androgen and of an increased expression of androgens overall (Ehrmann et al., 1992, Gervasio et al., 2014).

There are a number of mechanisms which may lead to an increase in both androgen production and expression. For example, a disturbance in the hypothalamic-pituitary-ovarian axis has been suggested. Chronically elevated luteinising hormone (LH) levels are found in 40-50% of PCOS patients and which may be due to excessive LH production relative to follicle stimulating hormone (FSH) by the anterior pituitary (Balen et al., 1995, van Santbrink et al., 1997). There are speculations that this is induced by an increased frequency of the hypothalamic gonadotropin releasing hormone (GnRH) pulse, commonly associated with PCOS (Waldstreicher et al., 1988). This may itself be an intrinsic defect within the hypothalamus, or as a result of infrequent menses that leads to a reduction in progesterone which would normally slow the pulse frequency (Garcia-Rudaz et al., 1998). The increased pulse rate causes a favourable production of LH compared with FSH and the resulting high concentration of LH to FSH stimulates the ovarian theca cells to convert 17-hydroxyprogesterone to the testosterone precursor androstenedione (Ehrmann, 2005). Furthermore, ovarian theca cells from PCOS patients have been found in laboratory studies to convert androstenedione to testosterone much more readily than do theca cells from patients without PCOS (Franks et al., 2008, Gilling-Smith et al., 1994). This results not only in an overall increase in the production of androgen precursors, but also in the increased conversion of such precursors into testosterone.

1.4.2. Hyperinsulinaemia

The excess androgen condition described in the previous section may be further aggravated by the hyperinsulinaemic state which has been found to exist amongst 50-70% of PCOS patients (Dunaif, 1997). The pathophysiological mechanisms that bring about IR within the PCOS patient remain unclear but there are speculations that abnormalities exist in the synthesis of glycogen, the pancreatic β -cell response to glucose stimulation, peripheral target tissue resistance as well as in the clearance of insulin from the liver (Dunaif, 1997).

Hyperinsulinaemia has been demonstrated to exacerbate hyperandrogenism, supported by evidence that excess insulin levels appear to increase ovarian activity of the cytochrome P450c17 which causes an increased output of androstenedione (Nestler and Jakubowicz, 1996). Additionally excess insulin

causes a decrease in the hepatic production of sex hormone binding globulin (SHBG), a glycoprotein that binds to testosterone (Ehrmann, 2005, Nestler and Jakubowicz, 1996). These situations lead to an increase in the production of testosterone as well as the expression of testosterone by making more testosterone bioavailable, contributing further to the androgen excess presentation.

The severity of PCOS appears to be more pronounced when both hyperinsulinaemia and hyperandrogenism are present. There is a growing body of evidence to now suggest that it is hyperinsulinaemia that precedes androgen excess rather than the converse to this and which appears to be closely correlated with abdominal obesity (Lord et al., 2003b, Dunaif and Graf, 1989, Moghetti et al., 2000, Diamanti-Kandarakis et al., 1995).

1.4.3. The role of abdominal obesity

Obesity itself has been strongly correlated with PCOS and which may be due to the association between obesity and IR. However, abdominal obesity has been shown to be strongly correlated with even lean women and which may be particularly deleterious in the PCOS state (Carmina et al., 2007). This can be explained by the association between abdominal adipose tissue and its secretion of various bioactive and inflammatory proteins such as adiponectin and chemokines, which have been correlated with PCOS patients and which may have varying roles in glucose metabolism, IR, ovarian steroidogenesis and ovulation (Glintborg and Andersen, 2010). In addition visceral tissue offers a site for the local metabolism of androgens since it produces a number of enzymes that are involved in the conversion and secretion of both androgens and oestrogens (Kershaw and Flier, 2004, Chen et al., 2014). It is therefore unsurprising that abdominal adiposity has not only been linked with impaired peripheral insulin sensitivity and decreased hepatic insulin clearance, but also with elevated androgen levels in PCOS studies (Evans et al., 1983, Peiris et al., 1987, Chen et al., 2014).

1.4.4. Developmental origins, genetics and socio-economic factors

Whilst it is clear by now that a number of highly complex pathological mechanisms are involved in PCOS, there is evidence to suggest that these may originate during embryonic development and that genetic predisposition may play at least a partial role. For example, when studying at the ovarian level, it

is apparent that follicular arrest at various stages is apparent in PCOS whilst oocytes and granulosa cells of the same follicle have also shown to be at different stages of development (Webber et al., 2003, Wei et al., 2014). It is this irregular asynchronous development of pre-antral follicles as well as an increased density of follicles that leads to the formation of multiple follicles on the ovaries characteristic of PCOS. This presentation may be influenced by elevated insulin and androgens within the intrafollicular environment, or possibly due to the presence of excess androgens in utero or prior to puberty that alter the ovarian morphology and function in the very early stages of ovarian development (Abbott et al., 2002, Abbott et al., 2005). It is worthwhile noting here that although this presentation is frequently referred to as being polycystic, the term multifollicular is considered more appropriate owing to the appearance of small immature follicles frequently 2-9mm in diameter, rather than cysts which are conventionally diagnosed when larger than 2cm in diameter (2004).

PCOS also has a strong familial link, demonstrated by the clustering of PCOS patients in families (Legro et al., 1998). In light of the pathophysiological processes discussed above, studies have since looked at genes that regulate the hypothalamic-pituitary-ovarian axis, hyperandrogenism, insulin levels and folliculogenesis (Franks et al., 1997, Torchen et al., 2014). Whilst the involvement of a single gene has been postulated, it is now much more likely owing to the syndrome's heterogeneity that the aetiology involves the combined influence of several genetic defects (Franks et al., 1997, Escobar-Morreale et al., 2005). Furthermore, differences in the prevalence of PCOS between populations suggest that the expression of PCOS is determined by the combination of a woman's genetic predisposition that allows environmental factors such as nutritional status and lifestyle to increase her susceptibility to insulin resistance and obesity, and that eventually leads to the clinical presentation of PCOS (Knochenhauer et al., 1998, Azziz and Kashar-Miller, 2000, Legro et al., 1998, Franks et al., 1997, Kauffman et al., 2002). Indeed there is some evidence to support that low childhood and family socioeconomic status (SES) is associated with an increased risk of developing PCOS and which appears to be consistent with the wider SES literature linking low SES with an increased risk of obesity and IR (Merkin et al., 2011, Di Fede et al., 2009). It is possible that low SES leads to a greater risk of engaging in

adverse health behaviours such as lack of physical activity and poor dietary habits and which appears to be evident even in upwardly mobile individuals stating low childhood but high current SES (Merkin et al., 2011, Di Fede et al., 2009). It is interesting to note however that low childhood SES may also be suggestive of poor maternal health status leading to inadequate intrauterine nutrition and prenatal hyperandrogenaemia and which may contribute to an adverse prepubertal metabolic state that facilitates in the expression of PCOS (Merkin et al., 2011).

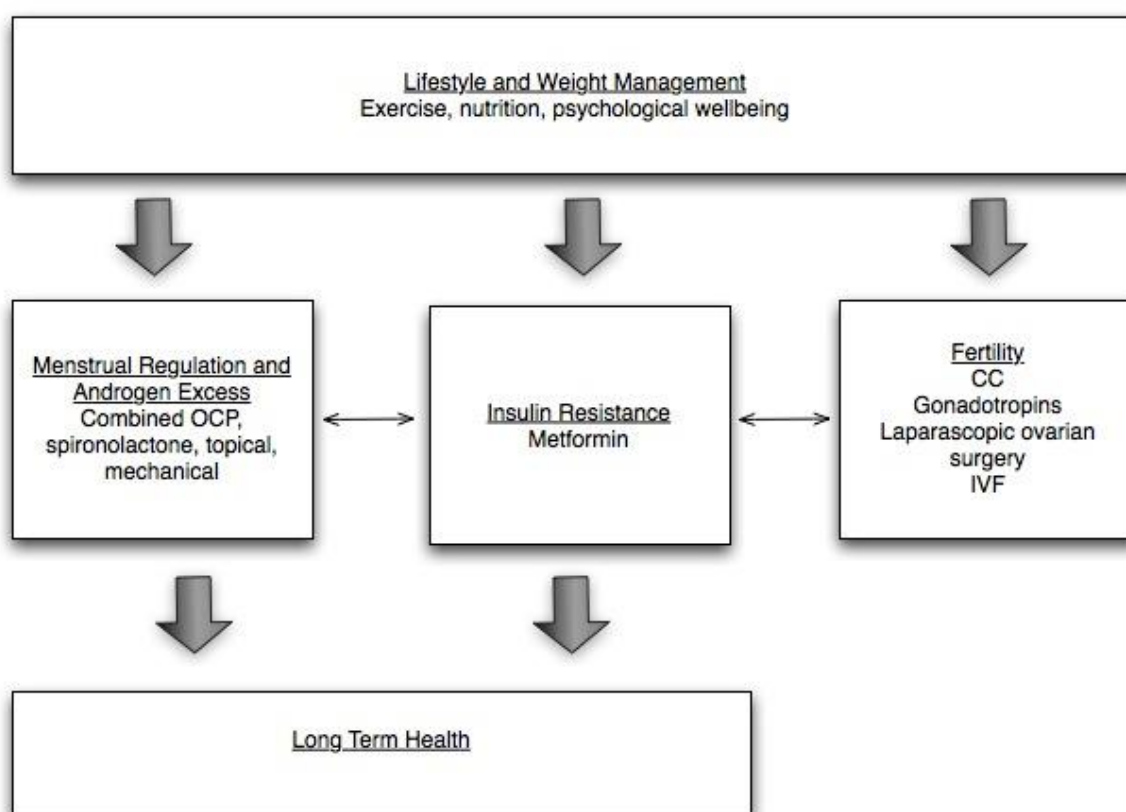
1.4.5. Summary

The pathological mechanisms behind PCOS are a complex interaction between the excessive androgen status that may be aggravated, and perhaps caused, by the insulin resistant state. This may be more apparent in genetically predisposed women and is likely to be mediated by a number of environmental factors such as diet and physical activity. In the next section, I will provide further elaboration into the management of PCOS and put forward the clinical arguments justifying my focus in this thesis on regulating menstruation as a particularly important management strategy in PCOS.

1.5. Management of PCOS

Because the clinical presentation of PCOS is so heterogeneous, conventional management of PCOS typically involves a multidisciplinary approach and which can change over the patient's lifespan owing to specific needs (Sheehan, 2004). It is quite typical that sequential management of PCOS follows that outlined in Figure 2.

Figure 2: Management of PCOS



Abbreviations: OCP=oral contraceptive pill, CC=clomiphene citrate, IVF=in vitro fertilisation

PCOS is commonly first expressed in the early teens with young adolescents presenting in primary care with cardinal symptoms of oligomenorrhoea or amenorrhoea and hyperandrogenaemia (Franks, 2002, West et al., 2014, Legro et al., 2013). Oligomenorrhoea and amenorrhoea is reported to affect about 43 per cent and 28 per cent respectively of adolescent girls (Bekx et al., 2010). In studies involving adults with PCOS, approximately 47 per cent may be oligomenorrhoeic and 19.2 per cent amenorrhoeic (Balen et al., 1995, Vutyavanich et al., 2007). As it is one of the diagnostic criteria in both the commonly used NIH 1990 and Rotterdam 2003 criteria, the high prevalence of menstrual irregularities in this population is unsurprising.

1.5.1. Oligomenorrhoea and amenorrhoea in PCOS

There are a number of reasons why the management of menstrual cycle irregularities is particularly important as part of the overall care plan for PCOS. Studies have shown that oligomenorrhoea and amenorrhoea appear to place women with PCOS at particular risk of profound endocrine and metabolic

disturbances (Panidis et al., 2012, Taponen et al., 2003, Strowitzki et al., 2010). These disturbances include parameters as body mass index (BMI), fasting insulin, free androgen index (FAI), LH and testosterone and have been demonstrated when comparing PCOS patients with oligomenorrhoea or amenorrhoea against PCOS patients with normal cycles (Taponen et al., 2003, Strowitzki et al., 2010). These disturbances appear to be particularly profound amongst those with amenorrhoea. Women with PCOS are also reported to have greater odds of developing endometrial carcinoma (OR 2.89, 95% confidence interval 1.52-5.48) and this increased risk has been associated with disturbances in menstrual regularity, supported by studies that suggest a correlation between menstrual cycle length and endometrial hyperplasia in women with PCOS (Chittenden et al., 2009, Soliman et al., 2005, Cheung, 2001, Haoula et al., 2012). There is therefore a clear correlation between menstrual irregularities and long-term health consequences as metabolic disease and diabetes as well as potentially increased risk of endometrial carcinoma.

Menstrual cyclicity has often been used as a simple and clinically accepted proxy measure for ovulation frequency. Oligo- and amenorrhoea has therefore been linked with increased time to conception and of decreased fecundability as a result of reduced ovulation frequency. When prescribing ovulation-induction treatment, the presence of oligo- and amenorrhoea has been shown to predict response to treatment with amenorrhoeic women having a significantly reduced chance of ovulating with clomiphene citrate administration compared to oligomenorrhoeic women (Koivunen et al., 2008, Imani et al., 1998). Besides these effects on fertility, studies have also suggested that PCOS-related oligomenorrhoea and amenorrhoea is associated with increased psychological morbidity and that women presenting with menstrual cyclicity issues are at increased risk of depression and anxiety, have lower self-esteem and greater fear of negative appearance and feel less feminine (de Niet et al., 2010, Himelein and Thatcher, 2006, Benson et al., 2009, Kitzinger and Willmott, 2002, Jones et al., 2011).

In summary, these points suggest that women with PCOS who are eumenorrhoeic or who have less severe menstrual disturbances have a more favourable clinical presentation, particularly in terms of reducing the risk of

associated clinical and psychological co-morbidities. It is clear that regulating menstrual disturbances at an early stage of diagnosis has beneficial effects to the patient, some of which are immediate and some which can have an important role in improving the patient's long term prognosis. In this next section I will now describe the most common conventional medical approaches used to regulate menstruation in primary care and aim to provide a critical evaluation to highlight advantages and potential disadvantages of each treatment.

1.5.2. Management of oligomenorrhoea and amenorrhoea in PCOS

The range of conventional treatments available to women with PCOS for the purpose of regulating menstruation include: lifestyle and weight management, oral contraceptives and insulin-sensitising agents.

1.5.2.1. Lifestyle and weight management: Exercise and nutrition

Given the role that the obesity status in a PCOS patient can play in the pathomechanism of the condition, it is unsurprising that weight management has been the main focus of lifestyle interventions such as exercise and nutrition. Obesity, defined as having a BMI of greater than 30, occurs in approximately 35% of PCOS patients, although more recent estimates have suggested a percentage as high as 42% (Kiddy et al., 1990, Azziz et al., 2004). Obesity exacerbates the condition of PCOS since these patients are more likely to experience menstrual dysfunction and anovulation and consequent infertility than do patients with BMI of less than 30.

Considering what is understood so far about abdominal adiposity and PCOS, it seems logical that weight loss particularly from the abdomen in PCOS patients has been correlated with substantial improvements in ovulatory cycles, conception rates, insulin response, hirsutism and psychological state (Hollmann et al., 1996, Kiddy et al., 1992, Galletly et al., 1996). It has also been encouraging that as little as 5-10% loss in body weight will allow the obese PCOS patient to enjoy these benefits, indicating that these relatively small reductions in weight can translate to better clinical outcomes (Kiddy et al., 1992).

Whilst weight reduction strategies are generally offered to those who are obese, there is still a proportion of women with PCOS who do not fall under the obese category. Nonetheless, the PCOS state and obesity independently place women at greater metabolic risk and it is therefore in the interest of both obese and lean patients to adopt lifestyle changes. These will help patients lose or maintain a healthy weight, improve nutritional status and increase time to onset of both obesity as well as other long-term health complications such as cardiovascular disease and diabetes (Teede et al., 2010, Dahlgren et al., 1992). Furthermore, benefits of exercise independent of weight loss such as on lipoprotein profiles have been demonstrated amongst PCOS patients, suggesting both lean and obese patients would indeed benefit from exercise and nutritional interventions without placing sole focus on achieving weight loss (Palomba et al., 2008, Brown et al., 2009).

Exercise interventions that have been studied amongst PCOS populations include aerobic exercise (walking, running and cycling), resistance training and brisk walking programmes (Randeve et al., 2002, Brown et al., 2009, Thomson et al., 2008, Orio et al., 2008, Palomba et al., 2008). Regarding optimal nutrition, the benefits of a well-balanced diet with plenty of fresh fruit and vegetables, reducing alcohol intake and stopping smoking are well recognised from a metabolic perspective. However, specific dietary approaches such as calorie restriction, high protein, low carbohydrate and low glycaemic index have also been tested in a number of studies (Moran et al., 2003, Stamets et al., 2004, Kasim-Karakas et al., 2009). Some studies have been promising, demonstrating that certain exercise or dietary regimens can lead to improvements in weight, fat mass, fasting insulin levels, ovulation rate and fertility and androgen levels (Kasim-Karakas et al., 2009, Palomba et al., 2008, Huber-Buchholz et al., 1999). However, most studies lacked a control group, used small sample sizes or were not randomised nor of adequate duration. Further research is still needed that should address these methodological issues before specific evidence-based exercise and dietary advice can be given.

Despite wide acceptance of the importance of weight loss in PCOS, formal recommendations for specific exercise and dietary programmes for PCOS have been difficult to make due to the heterogeneity of the interventions used. Current guidance on weight loss and lifestyle management for PCOS offered by

the Endocrine Society and the Androgen Excess and Polycystic Ovary Syndrome Society suggest a structured daily exercise routine lasting 30 minutes or more, and a nutritionally adequate hypocaloric diet of a 500-1000 kcal/day reduction (Moran et al., 2009, Legro et al., 2013). Amongst populations with metabolic syndrome and diabetes, combining diet and exercise together has been correlated with greater weight loss in the long term than dieting alone, suggesting that the benefits of adopting both strategies have a synergistic effect that may also be seen amongst PCOS patients (Wu et al., 2009a).

It is also interesting to note that in a study that compared four groups of patients for infertility, out of clomiphene citrate (CC), metformin, CC plus metformin and lifestyle only, the lifestyle group saw statistically significant improvements in waist circumference, insulin and low density lipoprotein levels when compared with the other treatment groups (Karimzadeh and Javedani, 2010). It also demonstrated equivalence in the rates of menstruation and pregnancy compared to other groups (Karimzadeh and Javedani, 2010). There are some flaws with this study however, for example, there was no placebo control group and neither miscarriage nor live birth rates were reported. Nonetheless, what this study does is highlight that benefits to be gained from lifestyle interventions should not be underestimated and may be comparable to those gained from pharmacological interventions, at least in the context of fertility treatment.

Another issue that often plagues exercise and dietary studies is the substantial dropout rates of between 15% and 39% (Palomba et al., 2008, Moran et al., 2003). This may also mirror with what is often found to be the case in community care amongst patients advised to lose weight who may subsequently follow an exercise or dietary programme for a shorter period of time than initially prescribed. It has been suggested that patients are often more motivated to make changes to their diet rather than increase activity levels. Benefits in metabolic and cardiovascular parameters appear to be lost after cessation of these interventions, highlighting the importance of long term adherence to these protocols (Moran et al., 2003, Stamets et al., 2004, Orio et al., 2008, Palomba et al., 2008). This could be improved by using a variety of strategies to overcome barriers to implementing lifestyle changes, such as improved education about the risk profile of PCOS, offering a structured

programme for exercise and diet, meal plans, regular follow-ups within groups or by dieticians and personal trainers, as well as addressing psychosocial issues such as depression, binge-eating and perceived self-worth (Teixeira et al., 2004, Lombard et al., 2009).

In conclusion, there is wide acceptance that PCOS patients would benefit from increased activity levels and following a nutritionally balanced diet regardless of obesity status. However, there is a paucity of studies from which adequate conclusions can be drawn from in order that clear and clinically useful advice can be given. This may be due to methodological as well as pragmatic issues relating to the research such as high dropout rates from RCTs, low uptake rate in the community and the requirement for education, counseling or guidance to be offered alongside advice to further facilitate behavioural change. These issues place under question the true effectiveness of lifestyle and weight management interventions that are currently available and therefore of its real impact in the management regulating menses in PCOS.

1.5.2.2. Oral contraceptives

For adolescents and women who do not wish to conceive, oral contraceptives (OCs) have traditionally been the first line treatment for PCOS patients for regulating menstruation. Of particular note is the combined OC that contains both ethinylestradiol and the antiandrogen progestin cyproterone acetate which favourably alters the androgen state in PCOS patients when compared with progestin-only OCs (Ehrmann, 2005). The combined OC is able to suppress the secretion of gonadotropins as well as increase the production of SHBG which in turn reduces both the production of androgen from ovarian theca cells and the amount of free androgens (Raudrant and Rabe, 2003, Rosen et al., 2003). This makes prescribing of the combined OC particularly relevant in the management of PCOS and studies have demonstrated that OCs can significantly improve menstrual cyclicity in PCOS patients as well as symptoms of androgen excess such as hirsutism and acne that are common amongst this population (Morin-Papunen et al., 2000, Harborne et al., 2003).

Concerns have however been raised regarding potential adverse effects of combined OCs. These may be related to effects on cardiometabolic measures such as IR, lipids, cholesterol, glucose tolerance and arterial stiffness which have been demonstrated in a number of studies (Vrbikova et al., 2004, Morin-

Papunen et al., 2000, Meyer et al., 2007, Costello et al., 2007a, Falsetti and Pasinetti, 1995). This is clearly of concern since women with PCOS are already at significantly greater risk of developing cardiovascular and metabolic complications in later life. As a result, guidelines have suggested prescribing low-dose OC for up to one year after which continued administration may have adverse effects on IR in patients (Fauser et al., 2012). Due to increased cardiovascular disease risk, low-dose OC is also contraindicated for use in age over 35, smoking and hypertension. Therefore, despite benefits in potential protection from endometrial carcinoma and reducing hyperandrogenism, these drawbacks limit the suitability of prescribing OC in the long term amongst those with PCOS and suggest a need for alternative methods of treatment that can be administered without increasing cardiometabolic risk.

The effectiveness of OCs is also compromised by low adherence with studies suggesting that up to 33% of OC users will discontinue use within the first year (Trussell, 2011). Adherence rates have been associated with side effects such as breakthrough bleeding, nausea, weight gain and mood changes (Rosenberg et al., 1995, Rosenberg and Waugh, 1998). Other factors affecting adherence are higher poverty levels, education levels less than a bachelor's degree and obesity (Westhoff et al., 2012). In an adolescent study, low compliance was also linked with psychosocial characteristics such as feelings of hopelessness and low evaluation of personal health (Durant et al., 1984). This suggests that although OC is frequently prescribed in primary care and can be highly efficacious, there are factors that clearly limit its clinical usefulness and which ultimately affect its overall effectiveness in regulating menstruation in PCOS.

1.5.2.3. Insulin sensitising agents

Owing to the central role that hyperinsulinaemia appears to play in the pathomechanism of PCOS, the use of insulin-sensitising agents (ISAs) has generated much interest. Early management of a patient's insulin state can lead to clinical improvements in various signs and symptoms such as in regulating menses but it can also prolong the time interval to developing diabetes which is clinically important. This is especially since PCOS is associated with an increased rate of conversion from impaired glucose tolerance (IGT) into diabetes, supported by estimates that 10% of women with PCOS develop diabetes by the time they are 40 years of age (Norman et al.,

2001, Ehrmann et al., 1999). Early detection of IGT and thus swift management of IR would therefore be ideal.

Of the ISAs, metformin and thiazolidinediones such as pioglitazone and rosiglitazone have been adopted in interventional studies with PCOS. However, metformin remains the most researched and most widely used. Metformin is a biguanide, an oral antihyperglycaemic that reduces hepatic production of glucose from glycogen and increases peripheral sensitivity to insulin. Laboratory studies have shown that it may also have a direct effect on reducing androgen production within ovarian thecal cells (Attia et al., 2001, Mansfield et al., 2003, Nestler and Jakubowicz, 1996).

Intervention studies have demonstrated a number of beneficial effects following metformin administration. Studies comparing metformin with placebo have shown that it can improve menstrual patterns, IR and testosterone levels within PCOS patients (Moggetti et al., 2000, Morin-Papunen et al., 2000, Nestler and Jakubowicz, 1996). Ovulation frequency may also be improved though it has been shown that it can take up to six months before reaching maximum effectiveness, suggesting that it may not be appropriate for patients who wish to fall pregnant quickly (Fleming et al., 2002, Essah et al., 2006). Metformin may also aid weight loss when compared with placebo, though a review of the evidence showed that metformin did not significantly affect weight, BMI or waist circumference (Fleming et al., 2002, Lord et al., 2003b). Other favourable metabolic effects include improvements in blood pressure, low density lipoprotein and high density lipoprotein (Lord et al., 2003a, Fleming et al., 2002).

Compared with the combined OCP, metformin appears to be more effective at reducing fasting insulin levels but less effective at regulating menstruation and reducing androgen levels (Costello et al., 2007b, Morin-Papunen et al., 2000, Rautio et al., 2005). Metformin does however have a similar effect to the combined OCP at improving hirsutism and acne, and furthermore does not appear to lead to the adverse effect that the combined OCP may have on triglyceride levels, suggesting that it may be more suitable for use in particular patients (Harborne et al., 2003, Costello et al., 2007a).

Although there is evidence to support the use of metformin for PCOS, there are certain factors that may reduce its effectiveness. For example, metformin has a high incidence of side effects, particularly gastrointestinal-related effects as nausea and diarrhoea. This caused dropout rates of up to 33% in several studies which questions the internal and external validity of these studies but side-effects are also one of the key reasons patients in the community describe as a barrier to adherence (Moll et al., 2006, Moll et al., 2008, Fleming et al., 2002). Adherence rates as low as 34% have been reported in prospective and retrospective studies (Donnan et al., 2002, Dailey et al., 2002), and persistence rates can be as low as 60% at 12 months with one study reporting a mean time to therapy discontinuation of 83 ± 71 days (Boccuzzi et al., 2001). Besides side effects, other reasons for patient nonadherence may relate to other factors as complexities in treatment regimen, inconvenience of treatment regimen as well as knowledge and beliefs regarding perceived risks and benefits of glycaemic control, all of which may require practitioner time or additional interventions for patient education and counseling to maximise treatment adherence (Hauber et al., 2009, McPherson et al., 2008, Colombo et al., 2012, Donnan et al., 2002, Chao et al., 2005). For these reasons, its clinical effectiveness is questionable despite demonstrating potential benefits in regulating menses and improving metabolic parameters in clinical studies.

1.6. Conclusion

Although there is some evidence to support use of current conventional options for regulating menstruation, methodological issues with these studies threaten their internal validity for reasons such as high level of heterogeneity within the studies, small sample sizes and high dropout rates. A range of barriers to use for all conventional treatments have also been identified from the literature which highlight some issues in terms of the practicalities of delivering such treatments and which have made it subsequently difficult for these treatments to be truly effective within the community. It is clear that gaps exist in the evidence for using these treatments and which has resulted in fragmented care when managing women with PCOS. This has led to an unmet medical need and dissatisfaction with current conventional management such as oral contraceptives and a high degree of receptivity to safe and effective alternative treatments (Sills et al., 2001). Further research is therefore required

in this area and other avenues of treatment should be explored that may be more acceptable and more effective for women with PCOS.

In the next chapter, I will offer Chinese herbal medicine as one of these possible avenues for treatment, provide a narrative review of the available evidence to date and give a brief outline into how the empirical work that will be undertaken as part of this PhD aims to answer the central research question within this thesis.

Chapter 2: The development of Chinese herbal medicine and modern day use

2.1. Introduction

CHM is an integral part of Chinese medicine (CM), an ancient healing system that encompasses a range of practitioner-led interventions and self-care activities including acupuncture, moxibustion, Tuina massage and manipulation, dietary therapies and physical exercises such as Tai Chi and Qi Gong. The theoretical origins of CM can be traced back to the folk traditions, customs and health beliefs of the indigenous Chinese between 300 and 100 BCE (Kaptchuk, 2000) and has continued to evolve over the last 2000 years as it has been increasingly practiced within China and neighbouring East Asian countries. Acupuncture and CHM first arrived in Europe in the 17th century and was mentioned in the first edition of the *Lancet* (Tweeddale, 1823), but substantial interest in CM did not gather until the 1970s when an American journalist wrote of his experience with post-operative acupuncture during a visit to China (Reston, 1971). The popularity of CM in the West has grown immensely since this time, and CM has since been endorsed by the World Health Organisation and National Institutes of Health. Acupuncture and herbal medicine are now named as two of the 'Big Five' in complementary and alternative medicine according to a UK House of Lords Science and Technology report (2000).

In 2011, the UK government announced proposals for the statutory regulation of herbal medicine practitioners. Presently, there are approximately 1200 CHM practitioners who are registered voluntarily with professional bodies such as the Register of Chinese Herbal Medicine (RCHM) or the Association of Traditional Chinese Medicine (ATCM). This is likely to be a conservative estimate given the voluntary nature of registration. CHM has been reportedly used by 5% of the UK population (2008) and annual out-of-pocket expenditure for herbal medicines has been estimated to be £31.03 million (Posadzki et al., 2013b, Eardley et al., 2012, Thomas et al., 2001). In China, CM plays a significant role in healthcare provision where there are almost 3000 hospitals

dedicated to CM and integrated CM and conventional medicine, which provides approximately 40% of all healthcare and treats 907 million out-patients per year (WHO, 2002, WHO, 2012, IBISWorld, 2013). Figure 3 shows a picture of such an integrated CM hospital named Xi Yuan hospital, located in the Hai Dian district in Beijing, China. Figure 4 shows the exterior of a Beijing Tong Ren Tang Chinese medicine clinic, one of the most well-known brands in the Chinese medicine field.

Figure 3: Xi Yuan Chinese medicine hospital in Hai Dian district, Beijing China



Figure 4: Beijing Tong Ren Tang Chinese medicine clinic



2.2. CHM approach to health

CHM as a medical system has developed a unique perception of health and disease and which has evolved with accumulative empirical observations and practice that have been recorded by scholar-physicians and philosophers over the last two millennia. One of the fundamental concepts underpinning CM is the Daoist belief that humans and their surrounding natural environment are interconnected and interdependent, and that health depends on a harmonious interplay between physical, emotional and spiritual factors. The role of a CHM practitioner is to diagnose imbalances within a patient and to provide corresponding CHMs and supplementary advice on diet and lifestyle with the

aim of restoring balance and therefore health in the individual. This creates a holistic, patient-centred and multifaceted approach to wellness, and one which can be appealingly tangible, relevant and empowering from the patient's perspective.

Despite the strengths of this approach, the subjective and pluralistic nature of CHM posed a significant problem for China in its quest for modernisation in the 1940s and 1950s. As a result, CM came to be integrated alongside Western Medicine (WM) within the national healthcare system under government initiatives and was introduced to modernised thinking by way of standardising education, introducing legislation and regulation and promoting scientific reasoning within the profession. This led to the development of a standardised and modernised 'version' of CM termed 'traditional Chinese medicine' (TCM) which, despite some attributing to its survival and continued use in modern society, has resulted in what others view as a substantially reduced and simplified form of practice that could facilitate further scientific research and dissemination of CM (Taylor, 2005, Scheid, 2002, Unschuld, 2010). The integration of Chinese and Western medicine clearly reflected a period during which there was increasing acceptance in China for WM and of objective and scientific thinking. Yet it also acted as a pragmatic response to the public health demands of a growing but largely rural population for whom CHM remained more acceptable, more readily available and considerably cheaper than its allopathic counterpart. CHM therefore became one of the tools used to address the challenge that faced the Chinese government at the time to meet rising healthcare needs in a manner that was as cost-effective as possible, a scenario which is not completely dissimilar to the purposes of evaluating CHM for use in primary care in this present thesis.

2.3. CHM treatment and basic concepts

There are approximately 5000 substances documented in the Chinese materia medica which consist predominantly of plant species as well as a smaller number of animal and mineral products. Although CHMs can be prescribed as a single herb, they are more frequently prescribed as a combination of 5 to 18 herbs designed to work synergistically. These combinations are frequently devised from 'base formulae', combinations of herbs which historically have a designated function for frequently seen CM presentations. These base

formulae have been documented in historical texts based on extensive clinical experience and can be used as a starting point from which a practitioner writes an individualised prescription for a patient.

CHM treatment is widely available in China in a variety of forms such as dried herbs, powders, granules, tablets and capsules. Standardised pre-packaged remedies and dried herbs can be purchased for health maintenance or for a range of common ailments from over-the-counter in pharmacies, in grocery stores or in herb markets in China such as that shown in Figure 5.

Figure 5: Chinese herbs available to the general public at a market stall in Beijing



Standardised CHMs are popular, convenient and more affordable and seen to be suitable for treating common ailments. Individualised treatments however are generally regarded as being more effective and for this reason is often seen to be best practice {Bensky, 1990 #5297}. Individualised treatments involve a consultation with a practitioner before being given a prescription of different herbs. This prescription may be guided by a base formula but which is frequently modified to the patient's presentation, taking into consideration the patient's signs and symptoms and their basic health status or 'constitution'.

Using this approach, it has been argued that individualised CHMs can target health imbalances more directly and which makes this form of treatment more effective over a standardised approach. It also allows the treatment to be adapted according to changing needs or clinical presentation of a patient and which enhances effectiveness but has the additional advantage of reducing side-effects of treatments. It is for these reasons that whilst standardised CHMs are generally seen to be appropriate for common and minor ailments, it is individualised CHMs that are considered to be better-placed to address the complexities of chronic conditions such as PCOS. Despite this, there is at present limited evidence from RCTs to suggest that clinically important differences exist between standardised and individualised CHMs. This lack of available evidence may be explained partly by the nature of research and medical settings which lends itself more to researching standardised CHMs. Standardised CHMs can be more readily implemented within an existing healthcare and research framework and funding restrictions usually require prioritization of comparison between CHM and current conventional care. It is possible however that these apparent disconnects will become less important as conventional medicine moves towards a more person-centred and individualised approach. This may subsequently lead to a changes in research and clinical settings that enable meaningful comparisons to be made between individualised and standardised CHM and which would help healthcare providers and patients make more informed decisions.

When individualised CHMs are prescribed by a practitioner, they are compiled at a CHM dispensary and can be provided as whole dried herbs, or as herbal extracts. Whole dried herbs would traditionally be prepared at home by decoction which involves boiling the dried herbs in water and straining it to take as a tea. Figure 6 shows a mixture of commonly used dried Chinese herbs, whilst Figure 7 shows Chinese herbal tea.

Figure 6: Dried Chinese herbs - goji berry, Chinese wild yam, tangerine peel, rehmannia root and ginseng



Figure 7: Chinese herbal tea



Figure 8: Chinese herbal extract in powdered form



Nowadays, dispensaries are increasingly equipped to boil prescriptions in-house and package the teas into liquid sachets which can be conveniently heated up at home. However, the increasingly popular alternative to dried herbs are herbal extracts which can be powdered (Figure 8) or granulated and taken as a tea by adding hot water, or further compressed into tablets or encapsulated. The production of herbal extracts typically involves a large scale decoction process using whole dried herbs cooked in water, sometimes with the addition of alcohol. The liquid is then drained and evaporated using low heat and vacuum to form a concentrated liquid which is spray-dried to produce a dry powdered extract. This process brings with it several advantages such as prolonged shelf-life, standardisation of manufacturing methods, increased quality control measures and increased convenience to the patient. However, it can also alter the chemical composition and concentration of the finished product. This is particularly important when single herbal extracts are produced since some argue that it is the chemical interaction between herbs during the traditional decoction process that plays a central role in the resulting composition and therefore effectiveness of the treatment (Williamson, 2001). When looking at the emerging evidence of comparative effectiveness however, the literature appears to suggest extracts and traditional decoctions are equivalent in effect (Luo et al., 2012). Nonetheless, the information to date is sparse and further investigation with comparative effectiveness studies would certainly be warranted.

2.4. CHM diagnosis, treatment and basic concepts

When providing CHM treatment, practitioners emphasise the whole-world view of the patient and during a consultation will gather information on symptoms, signs and behaviour, and make observations of the tongue and pulse in order to identify energetic imbalances within that patient. These imbalances are explained using concepts central to the philosophy of CM including Yin and Yang, Five Elements, Qi and Blood, each of which are ascribed particular functions in the body and which work closely together in order to maintain health. For example, Yin is important for nourishing, cooling, calming and moisturising functions in the body and is an energy that is predominant at night. The role of Yang is in energising, warming and activating functions in the body and is more abundant during the daytime. Both Yin and Yang functions are needed to be in balance in order for a patient to be well. A

patient who presents with symptoms such as poor circulation, cold limbs, lethargy and muscle pain for example could be diagnosed with a pattern of ‘Yang deficiency’, for which CHMs targeted at tonifying the Yang would then be prescribed. Furthermore, these imbalances can be linked to particular systems in the body according to CM such as the Zangfu organ system or the meridian system which represent traditional understanding of the internal organs. It is important to highlight here that some terms such as ‘Kidney’ and ‘Blood’ that are used within CM will be recognisable by the reader from a WM perspective. These terms however should not be taken literally as from a WM approach. When these terms are discussed in CM, their functions can differ greatly from that of the conventional understanding. Though these have been translated into anatomical organs within the traditional system, they represent more functional systems that integrate a number of different physiological and psychological processes. To clarify the reference point, the CM terms are typically written in title case and this notation will be maintained throughout this thesis.

Using the Zangfu organ system to continue illustrating the above example, the Yang energy of the Kidney organ in CM influences reproduction and fertility, and excretory functions such as urination and defecation. If the above patient presents with a declining Kidney Yang function, the presentation of the patient could include low libido, amenorrhoea, diarrhoea and night urination, and treatment would aim to address this accordingly. This is a simple example for illustrative purposes since in practice, it is commonplace for patients to present with a mixture of different symptoms that belong to a number of CM patterns. The skill of the practitioner lies in identifying the imbalances to focus on at this particular time, to provide and adjust the treatment as appropriate, and where relevant to provide the patient with self-care activities and advice that work in tandem with the current treatment as well as act as prophylactic care to prevent future relapses.

2.5. CHM and PCOS

PCOS is a conventional medical diagnostic term but symptoms and signs of PCOS such as amenorrhoea and infertility are well-recognised in CM literature and the treatment of such symptoms can be found in ancient CM and gynaecological texts dating back to the 2nd century CE. Contemporary CM

textbooks describe a range of imbalances that can lead onto a number of symptoms frequently seen in PCOS. For example, the Kidney in CM terms dominates reproduction and may be the focus for a patient presenting with infertility; the Liver regulates the flow of Blood and of Qi, and plays an important role in emotional wellbeing and resilience to stress and for these reasons would be an important area to investigate if a patient presents with irregular ovulation or depression; the Spleen oversees digestive functions and metabolic processes and could be imbalanced in a patient with obesity or difficulties controlling appetite (Flaws, 2005, Maciocia, 2011, Lyttleton, 2013). The various functions of the organs and energetics from a CM perspective are seen to interact and depend on each other to achieve wellbeing; thus in illness it is common for a number of dysfunctions to arise and which are addressed simultaneously in CM for optimal effectiveness.

2.6. CHM in Primary Care

Although CM and WM may appear to differ enormously in the way they are delivered, recent evaluations of acupuncture and other CAM services that are currently provided on the NHS suggest the services to be effective and highly valued by patients (Cheshire et al., 2013, Fixler et al., 2012, Weston and Grabowska, 2013). There are a number of reasons why CHM in particular can play an important role in primary care for PCOS. The evidence-base for CHM appears to be promising in addressing chronic and complex conditions such as PCOS for which effectiveness gaps in WM exist. Cochrane reviews of RCTs have suggested that CHM can be clinically beneficial such as for regulating ovulation in PCOS and improving obesity status, but the evidence appears to be especially convincing when CHM is combined with other commonly prescribed interventions such as clomiphene-citrate and lifestyle modification (Zhang et al., 2010b, Grant et al., 2009). This suggests exploration of CHM as a standalone treatment is warranted but that it could also potentially have a role as an adjunct to existing conventional treatments to bolster overall effectiveness. Furthermore, additional benefits may be gained from prescribing CHMs which include fewer and less serious adverse effects, a higher degree of acceptability amongst patients, and delays in requirement either to medicate or to conduct invasive and costly treatments such as surgery (Zhang et al., 2010b, Smallwood, 2005, Grant et al., 2009). These potential

benefits provide the opportunity for further cost-savings to the NHS and preservation of quality of life to the patient, but which need to be addressed systematically with methodologically rigorous studies that include long-term follow ups as well as cost-effectiveness analyses.

Safety remains an important issue in the examination of CHM, particularly given previous reports of adulteration of manufactured CHMs (Keane et al., 1999, Posadzki et al., 2013a) and isolated incidents of hepatotoxicity and nephrotoxicity (Cosyns et al., 1999). Although the MHRA's Yellow Card Scheme is designed to assist in the post-marketing surveillance of all medicines available to the public including CHMs, this has so far been largely unsuccessful at gathering complete safety data on CHMs. Published safety data is therefore limited to prospective trials and the sparse safety data that is currently available from CHM and PCOS studies at present appears to suggest adverse events are frequently minor and include events such as headache and tiredness (Zhou et al., 2010). Studies involving populations with impaired glucose tolerance and in PCOS populations which combine CHM with conventional treatments have reported no adverse renal or liver findings nor in ECG tests, and no difference in adverse event rates between groups, suggesting that combining CHM with conventional medicine at least in the context of these PCOS-relevant studies appears not to be associated with additional risk (Grant et al., 2009, Zhou et al., 2010). Although these findings in terms of safety profile are encouraging, it is imperative that further research remain a priority in order that a more complete safety picture can be obtained. Ideally, safety reporting in future work should involve biochemical testing by assessing liver and kidney function in addition to the usual requirements for adverse event (AE) reporting stipulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Department of Health's Research Governance Framework for Health and Social Care. Furthermore, public health measures designed to encourage more pro-active AE reporting by members of the public, or to promote the importance of healthcare providers in eliciting CHM and CAM use would be extremely helpful.

The majority of CHM research has been conducted in China and it could be argued that this could limit the generalisability of these findings to the UK. However, acupuncture and PCOS studies in Western countries have

demonstrated encouraging effects when compared with physical exercise, no intervention or an attention control, demonstrating that benefits of CM can indeed be potentially transferable (Jedel et al., 2011, Johansson et al., 2013, Stener-Victorin et al., 2008). Furthermore, mechanistic studies have demonstrated biological plausibility for frequently-prescribed CHMs for PCOS and which suggests an initial exploration of CHM in a Western setting is warranted. For example animal studies have shown potential anti-obesity effects with Dang Gui (*Radix Angelica Sinensis*) which may reduce triglyceride formation (Guo et al., 2009), whilst Dang Shen (*Codonopsis lanceolata*) can lower serum levels of triglycerides, total cholesterol and low density lipoprotein cholesterol (Choi et al., 2013). Gui Zhi (*Cinnamomum cassia* Blume), commonly used for metabolic disorders, has demonstrated potential in improving type 2 diabetes by influencing the insulin-dependent signalling pathway and activating insulin receptors (Han et al., 2013, Heibashy et al., 2013, Cao et al., 2007). These CHMs are commonly prescribed in PCOS and provide some insight in terms of the potential mechanisms of action they may have for PCOS.

In comparison to some CAM treatments, CHM as an intervention has greater potential in primary care, as it is arguably more readily subject to the scientific methods of investigation and exploration for biological plausibility. This is especially the case for standardised CHMs which are increasingly manufactured to GMP standards and thus increasingly subjected to the same safety, stability and batch consistency tests as in pharmaceuticals production. This increases its potential acceptability amongst the wider scientific community and subsequent readiness for implementation within primary care, an important factor to consider given its status as a CAM treatment. It would be possible, for example, for such standardised CHMs to be prescribed by nurses and dispensed by pharmacists following additional training, and the possibility of taking CHM in the form of tablets and capsules could mean greater acceptability and adherence amongst patients. It is important that this is examined in a systematic and rigorous manner and that model validity is considered throughout this process of exploring how and whether a traditional medicine as CHM can be transferred for provision in the context of the NHS. This will be discussed in more detail through the thesis as an ongoing theme. At this stage however, it is important to highlight that the manner in which

CHM lends itself to be offered within the NHS infrastructure increases its potential to be introduced without significant additional expense to the public purse. To my mind, this increases its worthiness of further exploration as an intervention to be offered in primary care.

2.7. Conclusion

In this chapter, I have provided an overview on CHM and have argued my position that CHM in the context of UK primary care is worthy of further exploration for the treatment of oligo- and amenorrhoea in PCOS.

Accordingly, the main research question I aim to answer by the end of this thesis is:

‘What is the role of CHM in the treatment of PCOS-related oligomenorrhoea and amenorrhoea in UK primary care?’

This research question can be divided further into sub-questions:

1. What is the evidence for CHM treatment of PCOS-related oligomenorrhoea and amenorrhoea?
2. What constitutes good clinical practice for CHM practitioners treating PCOS?
3. Is it feasible to conduct an RCT using CHM to treat PCOS-related oligomenorrhoea and amenorrhoea in UK primary care?

In the following chapters, I describe the methods that I used to answer the above sub-questions and how the findings I made from each phase of the project were drawn on to shape the remainder of this thesis.

Chapter 3: The effectiveness of Chinese herbal medicine for oligomenorrhoea and amenorrhoea in polycystic ovary syndrome: A systematic review and meta-analysis of randomised controlled trials

3.1. Background

A systematic review and meta-analysis was conducted in the first phase of this PhD to review the available evidence regarding the effectiveness and safety of CHM for oligomenorrhoea and amenorrhoea in PCOS. A Cochrane review on the effectiveness of CHM for PCOS-related subfertility had been conducted recently and which looked primarily at live birth rate and secondarily at pregnancy rate, ovulation rate and adverse events (Zhang et al., 2010a). This review concluded from four trials that the evidence for using CHM for PCOS-related infertility in terms of live birth rate is unclear as this was not reported in any of the included studies. There was some evidence however to suggest that combining CHM with clomiphene is associated with improved clinical pregnancy outcomes when compared with clomiphene alone (Zhang et al., 2010a). Furthermore, adverse events such as ovarian hyperstimulation syndrome (OHSS) were poorly reported and a lack of data was available in terms of allergy to CHMs and specifically on liver and kidney function.

Although this Cochrane review provided a comprehensive summary of the literature for PCOS-related subfertility, menstrual cyclicity was not systematically evaluated within this review. I therefore conducted a systematic review and meta-analysis between December 2010 and March 2012 to examine the evidence of effectiveness and safety for CHM in treating oligo- and amenorrhoea in PCOS. The purpose of this was to determine whether it was worthwhile pursuing subsequent exploratory work that was planned within the PhD and if so, to inform the design of these forthcoming studies.

The primary research question that this systematic review aims to answer is:

- What is the effectiveness of CHM for the treatment of oligomenorrhoea and amenorrhoea in PCOS?

Secondary research questions of this review are:

- What is the effectiveness of CHM on other PCOS-related endocrine, reproductive, metabolic and quality of life measures?
- What is the safety and adverse effects profile of CHM administration in PCOS populations?
- What clinical and CHM data is available regarding the CM diagnostic categories, forms and dosage of CHM administration, base formula and individual herbs?

3.2. Methods

It was anticipated that a significant majority of studies included in this review would be published in Chinese. This review therefore required collaboration with the Beijing Centre for Evidence-Based Chinese Medicine with whom my department had an existing relationship. This involved working closely with a native Chinese PhD student (XL) and which enabled me to gain access to relevant Chinese language literature databases in order to conduct an extensive literature search.

3.2.1. Types of studies

Only randomised controlled trials (RCTs) were accepted in this review as data from these are considered to be the most reliable in comparison to other study designs (Reeves et al., 2011). Study designs were excluded if they were identified as non-randomised or quasi-randomised, for example randomising by date of birth or date of visit. Non-randomised and quasi-randomised studies are systematically subject to bias (Reeves et al., 2011) and for this reason were excluded from this review.

Both open label and blinded RCTs were acceptable for this review. Crossover trials were also included where the data from the first period was available or obtainable directly from the author. No restrictions were imposed in terms of language, publication status or publication dates.

3.2.2. Types of participants

Since menstrual cyclicity was the primary focus of this review, studies were accepted if they recruited only women of reproductive age, defined a priori as being aged 18 to 44 years. It is widely acknowledged that outside of this age range, menstrual cyclicity issues are commonplace and cannot be reliability attributed to PCOS (Fauser et al., 2012). Studies on animals were excluded.

To be eligible for this review, participants entered into the trials needed to have received an internationally-accepted diagnosis of PCOS, determined a priori as being consistent with the Rotterdam 2003 criteria (2004). Given the difficulties in changing diagnostic criteria for PCOS previously discussed within this thesis, attention to these internationally-recognised criteria was important to ensure that results from this review would be generalisable to the wider PCOS population. Where a study did not explicitly state use of the Rotterdam 2003 criteria, the diagnostic criteria reported in the study were individually assessed.

3.2.3. Types of interventions

3.2.3.1. CHM interventions

CHM interventions were accepted that reported using Chinese herbs recognised by the Chinese materia medica (Luo, 2003). The CHM materia medica includes products that are of plant, animal and mineral origin. A number of products are restricted or illegal to dispense in UK clinical practice including mineral products and animal species. However, such products remain available for dispensing in other countries and this review therefore did not place restrictions in terms of the origin of the CHM.

The CHM interventions that were accepted for this review were oral administrations and could contain one or multiple herbs within the preparation. Acceptable oral administrative forms were decoction, tablet, granule, concentrated powder and tincture. Non-oral administration methods such as injections, enemas, pessaries and external applications such as dermatological plasters were excluded.

No restrictions were placed in terms of the length of the intervention.

3.2.3.2. Control and co-interventions

Control interventions that were accepted were placebo, no treatment, and treatments that could be used for regulating menses and other PCOS-related parameters such as pharmacological interventions e.g. combined oral contraceptive, metformin, as well as non-pharmacological interventions e.g. diet, exercise, laparoscopic ovarian surgery. Control and co-interventions that involved ovulation-inducing agents such as clomiphene citrate and letrozole, and assisted conception treatments such as in-vitro fertilization (IVF) were not accepted since these treatments are not routinely used for regulating menses. Otherwise, co-interventions were permitted if they were provided to all trial arms. Acupuncture was not accepted as a control or co-intervention owing to anticipated difficulties in separating out factors associated with CHM or acupuncture. A different type of CHM was not acceptable as a control intervention as it would not enable me to make a reasonable assessment of the effectiveness of CHM versus no CHM.

3.2.4. Types of outcome measures

To be eligible for this review, at least one of either the primary or secondary outcome measures of interest had to be reported. I required internationally-accepted and validated measures to be used where available for an outcome measure.

3.2.4.1. Primary outcome measure

Menstrual cyclicity was the primary outcome measure in this review.

3.2.4.2. Secondary outcome measures

Secondary outcome measures of interest to this review were:

- Biochemical hyperandrogenism (total and free testosterone);
- Clinical hyperandrogenism (hirsutism and acne, using internationally-accepted measures);
- Polycystic ovarian morphology;
- Luteinising hormone (LH);
- Obesity (body mass index, waist circumference, waist-hip-ratio);
- Glucose tolerance and insulin resistance (fasting glucose, fasting insulin);
- Lipid profile (cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides);

- Health-related quality of life (HRQoL) using internationally validated scales such as the 36-item Short Form Health Survey (SF-36) or Polycystic Ovary Syndrome Questionnaire (PCOSQ);
- Liver and kidney toxicity;
- Adverse events, defined using the International Conference on Harmonisation (ICH) Guidelines as ‘any unfavourable or unintended sign, symptom or disease temporarily associated with the use of a medicinal product, whether or not it is considered to be related to the medicinal product’ (ICH, 2004);
- Adverse drug reactions, considered to be ‘all noxious and unintended responses to a medicinal product related to any dose’ (ICH, 2004);
- Serious adverse events and adverse drug reactions defined as ‘any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or in a congenital anomaly/birth defect, or may jeopardise the patient or may require intervention to prevent one of the other outcomes listed previously’ (ICH, 2004);
- Chinese medicine outcome measures.

3.2.5. Clinical data on CHM methods

Descriptive information regarding the herbs, diagnoses and treatment approaches was also extracted from the studies included in this review. It is acknowledged that as the review focused on RCTs in order to evaluate the evidence of effectiveness, this clearly restricts the amount of information I could gather related to CHM treatment methods. However, the aim of assessing the descriptive information from these studies was to produce an initial framework of clinical treatment to guide the design of a forthcoming RCT and this approach was deemed adequate with this in mind.

3.2.6. Search methods for identification of studies

3.2.6.1. Electronic database search

A comprehensive search strategy was used to locate studies, details of which are provided in Appendix 2.

To identify RCTs relevant for this review, searches were made in December 2010 and repeated in July 2011 using the following databases from the date of inception:

International databases:

Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), EMBASE (Ovid), PUBMED, Allied and Complementary Medicine (AMED), Cochrane Complementary and Alternative (CAM) Field Specialized Register, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Manual Alternative and Natural Therapy Index System (MANTIS) and Centralised Information Service for Complementary Medicine (CISCOM).

Chinese databases:

Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Chinese Biomedical Literature Database (CBM), Wan Fang, Chinese Medical Citation Index (CMCI) using the Chinese terms for 'polycystic ovary syndrome' (duo nang luan chao zong he zheng), 'polycystic ovaries' (duo nang luan chao), 'PCOS', 'traditional Chinese medicine' (zhong yi), 'traditional Chinese herbs' (zhong yao), 'traditional Chinese herbal medicine' (zhong yi yao).

3.2.6.2. Searching other sources

A hand search was performed in December 2010 in Peking Union Medical College for missing full texts and for relevant studies not published or indexed in the aforementioned electronic databases. Owing to access and time constraints, a further hand search was not possible. Bibliographies of relevant studies and review articles were checked for further references. Authors of significant publications and experts in the fields of PCOS, acupuncture and CHM were also contacted by email to identify studies that may have been missed.

To identify recently completed trials that may not yet have published results, the following databases of ongoing trials were searched: Current Controlled Trials (www.controlled-trials.com), ClinicalTrials.gov, CenterWatch Clinical Trials Listing Service (www.CenterWatch.com), National Institutes of Health (clinicalstudies.info.nih.gov), International Federation of Pharmaceutical Manufacturers & Association Clinical Trial Portal

(http://clinicaltrials.ifpma.org/clinicaltrials/no_cache/en/myportal/index.htm), WHO International Clinical Trials Registry Platform (www.who.int/trialsearch), Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), Chinese Clinical Trial Register (www.chictr.org), European Medicines Agency (EMA) (www.emea.europa.eu), Hong Kong clinical trials register (www.hkclinicaltrials.com), UK Clinical Trials Gateway (www.controlled-trials.com/ukctr) and University Hospital Medical Information (UMIN) Clinical Trials Registry for Japan (www.umin.ac.jp/ctr).

3.2.7. Management of study searches

I conducted the searches in international databases and in databases of ongoing trials. XL conducted the searches of the Chinese language databases and performed hand searching in Peking. Both XL and I checked bibliographies of relevant studies and review articles and cross referenced these against studies identified from database searches.

3.2.8. Assessing eligibility

All potentially eligible studies that were identified were pooled together and initial screening for potential eligibility was performed independently by both myself and XL. Initial screening was performed by assessing the study title, the abstract and keywords. During the Initial screen, XL and I excluded abstracts clearly identified as animal studies, literature reviews, duplicate publications of the same study, studies that were not RCTs and studies not involving a PCOS population. Following screening and where studies appeared eligible or whose potential eligibility remained unclear, XL and I attempted to retrieve the full texts for further examination. Where duplicate publications of an eligible study were found, the earlier publication was accepted.

XL and I assessed full texts for eligibility independently and disagreements were resolved either by discussion or by consulting one other reviewer (GL).

3.2.9. Data extraction and management

Data extraction was performed independently by both reviewers using a spreadsheet created with Microsoft Excel 2010. This was piloted by independently extracting data from one study and then comparing the data collected in order to clarify ambiguities and check coding methods. Following this initial pilot, data for the remaining studies was then independently

extracted before convening again to check accuracy in data extraction and to resolve differences through discussion. Where agreement was not reached, GL was consulted.

For this review, XL and I extracted the following data:

- **Background details:** Article title in Chinese and in English, names of authors, year of publication, contact details, country, setting, funding source;
- **Study characteristics:** Study duration, study design, evidence of randomisation and details of randomisation method, evidence of allocation concealment and details of method used, evidence of blinding and details of methods used;
- **Participants:** Age, inclusion and exclusion criteria, time since diagnosis, diagnosis consistent with Rotterdam criteria, ethnicity, comparability of groups at baseline and based on which characteristics, number approached, consented and randomised, number in each treatment group, number withdrawn or lost to follow up, number analysed, reasons for withdrawals or lost to follow up;
- **Interventions:** Treatment and control interventions, CHM intervention details (CM aims of treatment, individualised or standardised, names and dosages of individual herbs, route of administration, form of administration, preparation method, timing and frequency of dose), control intervention details (manufacturer, dose prescribed, route of administration, timing and frequency of dose), duration of interventions;
- **Outcome measures:** Data on outcome measures specified in this review, study's primary outcome measures, assessment timepoints, statistical approach (e.g. intention-to-treat, per-protocol), assessment of suitability of statistical analysis used.

3.2.10. Risk of bias assessments

A risk of bias assessment was made independently by both reviewers using the Cochrane Collaboration risk of bias tool (Higgins et al., 2011a). This process involved assessing the adequacy of addressing bias relating to selection, performance, detection, attrition and reporting and which was performed by using the following seven quality criteria:

1. Sequence generation: Was allocation sequence adequately generated?
2. Allocation concealment: Was allocation of participants adequately concealed?
3. Blinding of participants and study personnel: Was the allocated treatment adequately blinded from the participant and study personnel?
4. Blinding of outcome assessors: Was the allocated treatment adequately blinded from outcome assessors?
5. Incomplete outcome data: Were incomplete outcome data adequately addressed?
6. Selective reporting: Did the study appear to be free of selective outcome reporting?
7. Other risks of bias: Did the study appear to be free of other risks of bias?

For each study, a response of 'Yes' to the quality criteria indicated a low risk of bias, 'No' indicated a high risk of bias and 'Unclear' to indicate unknown risk of bias as defined by the Cochrane Collaboration risk of bias tool (Higgins et al., 2011a). This rating was conducted independently by both reviewers who then convened to compare assessments. Any disagreements were resolved by GL.

3.2.11. Measures of treatment effect

I anticipated that the following pair-wise comparisons would be conducted:

- CHM alone versus no treatment;
- CHM alone versus placebo alone;
- CHM alone versus pharmacological intervention alone;
- CHM alone versus lifestyle intervention alone;
- CHM alone versus laparoscopic ovarian surgery;
- CHM + pharmacological intervention versus pharmacological intervention alone;
- CHM + lifestyle intervention versus lifestyle intervention alone;
- CHM + laparoscopic ovarian surgery versus laparoscopic ovarian surgery alone.

However, it was also possible that other comparisons would be conducted after the review literature was obtained in which case these would be clearly identified as being post-hoc.

Statistical analysis for this review was performed using ReviewManager (RevMan 2011) software.

Dichotomous data were expressed as relative risks (RR) with 95% confidence interval (CI). For continuous data and where outcomes were measured in the same manner, I used the mean difference with 95% CI. Where different continuous data was available using different scales, the standardised mean difference (SMD) and 95% CI were calculated.

3.2.12. Dealing with missing data

Where intention-to-treat (ITT) analyses had been conducted, I planned to use the available ITT data (Higgins et al., 2011b). For studies where participant data was missing, I did not plan to use imputation and included data only for participants with known outcomes. In cases of missing data, I addressed the potential impact of the missing data in the risk of bias assessment.

3.2.13. Assessment of publication bias

Where 10 or more studies were to be included in the meta-analysis, I planned to assess publication bias by testing for funnel plot asymmetry (Egger et al., 1997).

3.2.14. Assessment of statistical heterogeneity

Statistical heterogeneity was assessed by visual inspection of forest plots to check overlaps of CIs for the results of individual studies. Where poor overlap existed, this suggested statistical heterogeneity.

If more than 10 studies could be included, I planned to perform a formal evaluation for heterogeneity firstly using the Chi^2 statistic, and secondly the I^2 statistic (Deeks et al., 2011). However, the Chi^2 test has low power when few studies are included in a meta-analysis or where studies have small sample sizes (Higgins et al., 2003). Furthermore identifying the presence of statistical heterogeneity with the Chi^2 test may not be helpful since some degree statistical heterogeneity will always exist between studies (Higgins and

Thompson, 2002, Higgins et al., 2003). The I^2 statistic was additionally used to test for the existence of heterogeneity (Higgins and Thompson, 2002). As an approximate guide for interpretation, I^2 values of 0-40% are deemed possibly unimportant, whilst 30-60% may represent moderate heterogeneity, 50-90% substantial heterogeneity and 75-100% considerable heterogeneity (Deeks et al., 2011).

Where I did not have more than 10 studies or where sample sizes were considered to be small, the χ^2 test would not be used and I would instead look to the I^2 statistic.

3.2.15. Subgroup analysis and investigation of heterogeneity

Where more than 10 studies were available, it was planned that subgroup analyses would be performed to explore potential sources of heterogeneity in terms of:

- CHM administrative form
- Duration of the intervention
- Study setting
- Funding source

3.2.16. Data synthesis

To describe the observed intervention effect, summary statistics were calculated for each study. For dichotomous data, I used risk ratios (RR); for continuous data reporting the outcome using the same scale, difference in means was used; for continuous data reporting the outcome using different scales, the standardised mean difference (SMD) was used. Where both dichotomous and continuous data were available for the same outcome, I re-calculated odds ratios as standardised mean differences to allow this to be pooled with the continuous data (Deeks et al., 2011).

A summary (pooled) intervention effect estimate was then calculated as a weighted average of the intervention effects estimated in the individual studies. The standard error of the summary (pooled) intervention effect was then used to derive a CI to communicate the precision of the summary estimate and to derive a P value.

I used Mantel-Haenszel fixed-effect methods for meta-analysis of dichotomous outcomes, inverse-variance fixed-effect method for meta-analysis of continuous outcomes, and generic inverse-variance method for combined dichotomous and continuous outcomes (Deeks et al., 2011). I chose to use the fixed effects model of meta-analysis as the primary analysis since this has been deemed more suitable where fewer trials exist or where such trials are smaller in size (Deeks et al., 2011). However given that this approach is based on the assumption that the true intervention effect is the same, i.e. fixed, across each study and with no statistical heterogeneity, I planned to compare these findings against a random-effects meta-analytic model.

3.2.17. Sensitivity Analyses

I planned to conduct sensitivity analyses to evaluate the robustness of the findings in light of decisions that had been made during the review process.

To assess the effects of internal validity on the findings, I planned to observe whether any pooled results that were significant in the analysis of all trials remained significant when I restricted the analysis to trials judged to be adequate in terms of the following risks of bias:

- Sequence generation
- Allocation concealment
- Blinding of outcome assessors
- Incomplete outcome reporting
- Selective reporting

As stated in the previous section, I also planned to conduct sensitivity analyses to compare the findings against a random-effects meta-analytic model.

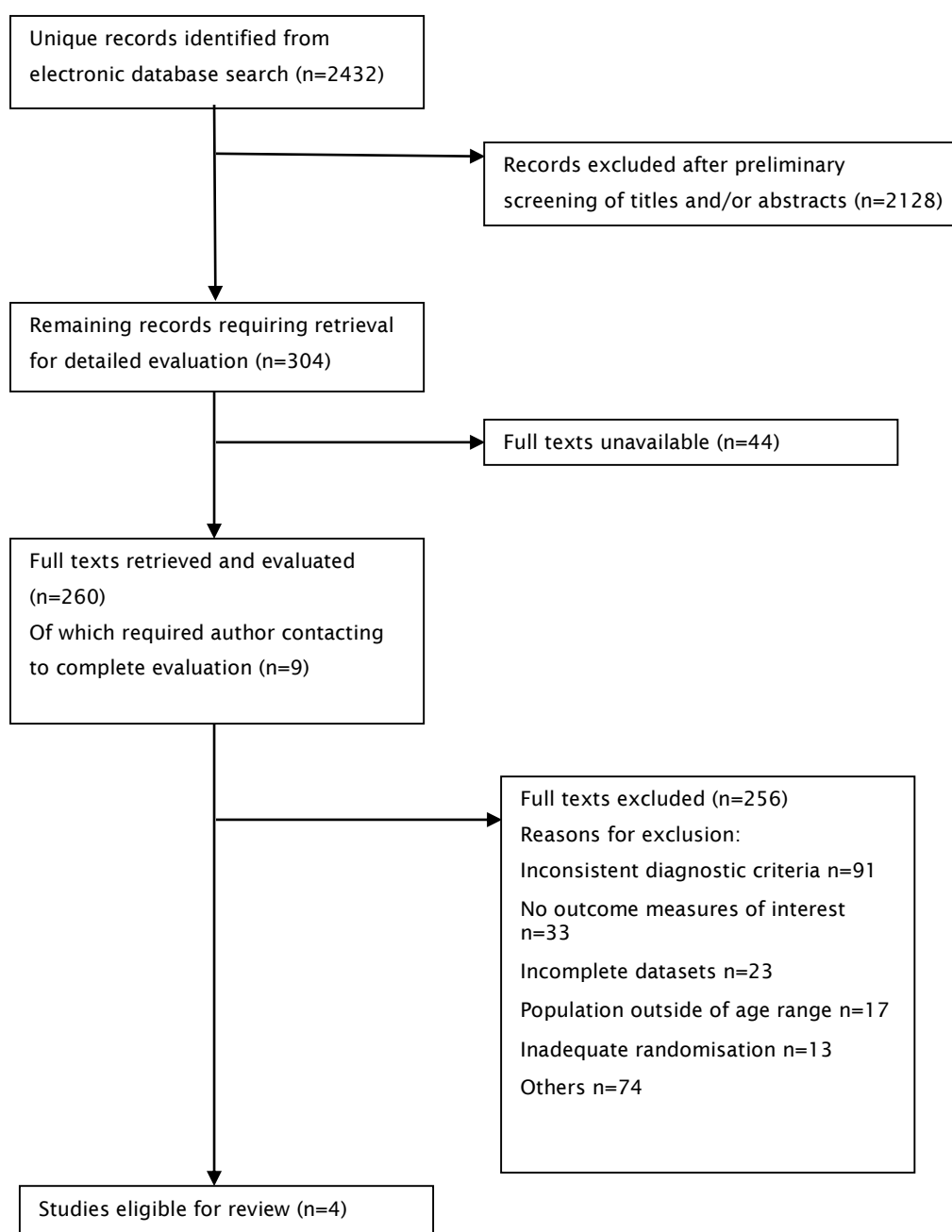
It was possible that other sensitivity analyses would be conducted as a result of decisions that would be made during the review process. Where this was the case, these analyses were clearly identified as post-hoc.

3.3. Results

3.3.1. Results of the search

A PRIMSA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow-chart of study selection and brief reasons for exclusion are provided in Figure 9.

Figure 9: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of study selection



From searching the literature in December 2010 and in July 2011, I and XL identified 2432 references in total. After reading titles and abstracts, 2128 (87.5%) of these articles were excluded due to being duplicates, animal studies, literature reviews or clearly non-randomised studies. A total number of 304 (12.5%) articles therefore remained potentially eligible.

XL and I attempted to obtain full texts of these 304 abstracts, and of these we were successful in retrieving 260 (85.5%) full texts, whilst 44 were unavailable. Out of the 260 full texts retrieved, 251 papers were not eligible for the review, and 9 required further information to complete the assessment for eligibility. As the study selection had progressed, it had become increasingly apparent that a large number of trials were not providing sufficient information regarding randomisation procedures. Additionally, the Rotterdam diagnostic criteria that were reportedly used were frequently misquoted in the publications. Since these were eligibility criteria for this review and in light of concerns that have been recently raised regarding the methodological quality of Chinese-language RCTs (Wu et al., 2009b, Zheng et al., 2009, Shang et al., 2007), it was agreed during the review process that XL would contact the authors of the remaining 9 papers to enable a more informed assessment of eligibility to be made.

Of the 9 studies, email addresses were available for 3 authors (Wu, 2008, Zheng et al., 2008, Li et al., 2011a). These authors were contacted firstly by email using a bilingual email presented in both traditional full Chinese characters and in English. One author failed to respond and 2 provided incomplete responses to our questions. Due to the poor and incomplete responses obtained by email, XL and I agreed that the best course of action was for XL to attempt contact with all 9 authors by telephone. Where it was not possible to reach the first author by telephone, telephone contacting of remaining authors in the publication in order of authorship was attempted. The phrasing and wording of all email and telephone communications were discussed and agreed in advance between us to maximise consistency in data collection and were based on the telephone script published in a systematic review conducted by Wu et al. (2009b). The email and telephone scripts that were used are presented in Appendix 3 and Appendix 4.

XL was successful in contacting all 9 authors by telephone. 4 authors reported randomisation processes that XL and I deemed inadequate (Bao, 2009, Dong and Tian, 2010, Wang and Xie, 2010, Wu, 2008) and 1 study author could not provide data for the outcome measures of interest to this review (Zheng et al., 2008). These 5 papers were subsequently excluded and which left 4 studies to be included in this review (Hao, 2010, Li et al., 2011a, Li et al., 2011b, Zhou et al., 2010).

3.3.2. Description of studies

The characteristics of the included studies can be seen in Table 3. Reasons for exclusion for remaining studies can be found in Appendix 5.

Chapter 3

Table 3: Characteristics of included studies

Study ID	Study design and setting	Number of participants	Inclusion/exclusion criteria	Interventions	Treatment length	Outcome measures
Hao HN 2010	Parallel RCT, outpatients clinic, China	Total: 60 T: 30 C: 30	Inc: Diagnosed with PCOS; Exc: Other causes of hyperandrogenism.	T: CHM + Diane-35 C: Diane-35	3 months	Menstrual frequency, LH, total testosterone
Li XB 2011	Parallel RCT, gynaecology outpatients clinic, China	Total: 62 T: 31 C: 31	Inc: Diagnosed according to Western medical PCOS criteria and TCM syndrome criteria, informed consent, aged 18-35, no hormonal medications in last 3m; Exc: Use of ovulation-inducing medications during trial, history of cardiovascular, liver, kidney, hematopoietic system and other serious conditions, history of mental illness, malignant tumours, adrenal conditions and other organ failure, failure to comply with treatment.	T: CHM C: Metformin	3 cycles	BMI, WHR, LH, testosterone, fasting blood glucose, fasting insulin, triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, Apolipoprotein A, Apolipoprotein B, TCM syndrome score
Li XP 2011	Parallel RCT, gynaecology outpatients clinic, China	Total: 66 T: 33 C: 33	Inc: Diagnosed according to Western medical PCOS criteria and TCM criteria; Exc: Does not meet diagnostic criteria for Liver and Kidney yin deficiency, other endocrine conditions, hormonal medication in last 3m, allergies or allergies to study medications, heart, liver, kidney and hematopoietic system conditions, other serious conditions, unable to comply with intervention e.g. mental or psychological conditions, or refuse consent.	T: CHM C: Diane-35	3 cycles	LH, total testosterone, hirsutism, acne, adverse events
Zhou YH 2010	Parallel RCT, gynaecology outpatients clinic, China	Total: 60 T: 30 C: 30	Inc: Diagnosed with PCOS acc. to Rotterdam 2003, diagnosed with Kidney deficiency and Phlegm stagnation TCM syndrome, informed consent; Exc: None reported.	T: CHM + Diane-35 C: Diane-35	6 cycles	Menstrual frequency, LH, total testosterone, liver function (AST), adverse events

Abbreviations: RCT=randomised controlled trial; CHM=Chinese herbal medicine; LH=luteinising hormone; BMI=body mass index; WHR=waist hip ratio; TCM=traditional Chinese medicine; AST=aspartate aminotransferase

3.3.2.1. Included studies

Design and setting

All 4 trials included in this review were RCTs conducted in China with 2 parallel groups (Hao, 2010, Li et al., 2011a, Li et al., 2011b, Zhou et al., 2010). All 4 trials were conducted in outpatient clinics with 3 trials conducted within TCM hospital gynaecology clinics (Li et al., 2011a, Li et al., 2011b, Zhou et al., 2010) and one trial conducted in a county hospital clinic (Hao, 2010).

Participants

In the 4 trials, a total of 246 participants were included in the review, with the trial sample size ranging from 60 to 66 women in each trial. The age of participants ranged from 19 to 39 years. All 4 trials reported using the Rotterdam diagnostic criteria. The ethnicity of patients was not explicitly reported in the trials.

Interventions

All studies used an active control with 3 studies using Diane-35 alone (Hao, 2010, Li et al., 2011b, Zhou et al., 2010) and 1 study using metformin alone (Li et al., 2011a). Of the 4 trials, 2 studies used CHM alone as the treatment (Li et al., 2011a, Li et al., 2011b) and the remaining 2 studies used CHM in combination with Diane-35 (Hao, 2010, Zhou et al., 2010).

A different set of standardised CHMs were used in each of the four studies that were not individualised at the patient level although one study permitted modifications based on the time of the menstrual cycle (Li et al., 2011b). 2 studies used decoction administration with 1 administering 100ml twice daily (Zhou YH, 2010) and 1 administering 200ml twice daily (Hao, 2010). The remaining 2 studies used granules and limited dosage information was available with one stating that one 'sachet' was to be administered three times daily (Li et al., 2007) and one stating that one 'sachet' was to be administered twice daily (Li et al., 2011b). Duration of treatment were reported as being 3 months (Hao, 2010), 3 menstrual cycles (Li et al., 2011a, Li et al., 2011b) and 6 menstrual cycles (Zhou et al., 2010). Details of the CHM interventions used across the 4 studies can be viewed in Table 4. A list of all CHMs used within these RCTs was collated and can be seen in Appendix 6.

Chapter 3

Table 4: Details of CHM interventions in included studies

Study ID	Standardise d/individua lised at patient level	Form	Pattern differenti ated prior to trial inclusion?	TCM pattern diagnosis/treatment principle	CHM prescription name, individual herbs and dosages per day	Dosage (BID=twice a day, TID=three times a day)	Duration of course
Hao HN 2010	Standardised	Decoction	No	Nourish Kidney and strengthen Spleen Expel Phlegm and release Damp	Name: Huatan Bushen Tang <i>Zi Shi Ying, Zi He Che, Yin Yang Huo, Shu Di Huang, Tu Si Zi, Bai Zhu, Fu Ling, Chen Pi, Jiang Ban Xia, Tian Zhu Huang, Bai Jie Zi, Dan Shen, Xiang Fu, Chuan Niu Xi</i>	200ml BID	3 months
Li XB 2011	Standardised	Granules	Yes	Nourish Kidney, regulate Spleen Resolve Phlegm Dampness Move Blood	Name: Ling Zhu Ke Li <i>Yin Yang Huo 9g, Xian Mao 9g, Bai Zhu 15g, Dang Gui 9g, Fa Ban Xia 9g, Dan Nan Xing 9g 'etc'</i>	One sachet TID	3 cycles
Li XP 2011	Standardised	Granules	Yes	Benefit Kidney Clear Liver Move Blood	Name: Jia Jian Zi Gui Tang <i>Base formula: Shan Zhu Yu 15g, Nu Zhen Zi 12g, Han Lian Cao 9g, Tu Si Zi 12g, Bai Shao 12g, Zi Shi Ying 30g, Yin Yang Huo 9g, 'etc'</i> <i>Modifications: Between menses add Dan Shen 15g, Bie Jia 15g, Lu Lu Tong 10g; During menses remove Nu Zhen Zi, Han Lian Cao, Bai Shao and add Chuan Xiong 9g, Dang Gui 6g, Chi Shao 15g, Dan Shen 15g</i>	One sachet BID	3 cycles
Zhou YH 2010	Standardised	Decoction	Yes	Nourish Kidney and reinforce Yang Strengthen Qi and nourish Spleen Dry Damp and dispel Phlegm Activate Blood circulation and unblock the meridian	Name: Zi Ni Tiao Jing Tang <i>Bu Gu Zhi 10g, Ba Ji Tian 10g, Dang Shen 10g, Bai Zhu 10g, Fu Ling 20g, Dan Shen 20g, Dang Gui 10g, Su Mu 10g, Xiang Fu 10g, Zhi Ban Xia 6g, Cang Zhu 10g, Da Zao 6g</i>	100ml BID	6 cycles

Outcomes

None of the four studies explicitly stated a primary outcome measure. Menstrual cyclicity, the main outcome measure of interest to this review, was reported in 2 studies (Hao, 2010, Zhou et al., 2010), though data from only one of these studies was usable in this review (Zhou et al., 2010). The secondary outcome measures of interest to this review were biochemical hyperandrogenism (Hao, 2010, Li et al., 2011a, Li et al., 2011b, Zhou et al., 2010), clinical hyperandrogenism (Li et al., 2011b), BMI and waist-hip ratio (WHR) (Li et al., 2011a), LH (Hao, 2010, Li et al., 2011a, Li et al., 2011b, Zhou et al., 2010), fasting blood glucose (FBG) and fasting insulin (FI) (Li et al., 2011a), triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoproteins A and B (ApoA, ApoB) (Li et al., 2011a), liver toxicity (Zhou et al., 2010), kidney toxicity (Zhou et al., 2010), adverse or serious adverse events (Li et al., 2011b, Zhou et al., 2010) and Chinese medicine outcome measure (Li et al., 2011a). One study reported measuring polycystic ovarian morphology as an outcome measure but data was not available in the report (Hao, 2010). Quality of life was not measured in any of the four studies.

No studies reported conducting intention-to-treat analysis. Two studies conducted per-protocol analysis (Li et al., 2011a, Li et al., 2011b), one study conducted available-case analysis (Zhou et al., 2010) and for the remaining study, it was unclear what analysis had been conducted (Hao, 2010).

Timepoints

Outcome measures were reported before and after treatment for two studies, one of which used a 3-month intervention (Hao, 2010) and one used a 3-cycle intervention (Li et al., 2011a). One study using a 3-cycle long intervention reported outcomes at baseline and at Cycle 4 and Cycle 9 i.e. 1 month and 6 months post-intervention respectively (Li et al., 2011b). The study by Zhou et al. (2010) involving treatment for 6 cycles reported outcomes at baseline, during the treatment at Cycle 3 and Cycle 6, and after the treatment at Cycle 9 and Cycle 12 i.e. at 3 cycles and 6 cycles after the treatment had ceased.

3.3.2.2. Excluded studies

For a list of the studies that were excluded and reasons for exclusion, the reader is referred to Appendix 5.

3.3.2.3. Risk of bias in included studies

A methodological summary and graph presenting the risk of bias assessments for the seven domains for the included trials can be seen in Figure 10.

Sequence generation was conducted by using random number table in all studies and therefore regarded as being at low risk of bias for this domain. Allocation concealment was regarded as adequate in one study (Zhou et al., 2010) and unclear in the three remaining studies (Hao, 2010, Li et al., 2011a, Li et al., 2011b).

Figure 10: Risk of bias summary for included studies

Study ID	1. Sequence generation (selection bias)	2. Allocation concealment (selection bias)	3. Blinding of participants and study personnel	4. Blinding of outcome assessors (detection bias)	5. Incomplete outcome data addressed (attrition bias)	6. Selective reporting (reporting bias)	7. Other bias	Overall risk of bias
Hao HN 2010	+	?	-	?	+	-	?	C
Li XB 2011	+	?	-	?	+	-	?	C
Li XP 2011	+	?	-	?	?	-	?	C
Zhou YH 2010	+	+	-	?	?	-	?	C

For individual risk of bias assessments 1-7, + indicates low risk of bias, - indicates high risk of bias, ? indicates unclear risk of bias; For overall risk of bias, A=All quality criteria met, low risk of bias; B=one or more quality criteria only partly met, moderate risk of bias; C=one or more criteria not met, high risk of bias

Blinding of participants, study personnel and outcome assessors

Blinding of neither participants nor study personnel was reported in any of the four studies and XL and I together rated this as being at high risk of bias owing to the performance bias that this could have introduced into this study. There

was no report of blinding of outcome assessors in any of the studies, but since some outcome measures in these studies were objective e.g. testosterone, LH, XL and I judged all four studies as being at unclear risk of bias for this domain.

Incomplete outcome data

2 studies reported no drop-outs and were subsequently scored at low risk of bias for this domain (Hao, 2010, Li et al., 2011a). The remaining two studies reported drop-outs but did not provide reasons for attrition (Li et al., 2011b, Zhou et al., 2010) and subsequently were given an unclear risk of bias as it was not possible to ascertain whether the reasons for the missing outcome data were likely to be related to the outcome.

Selective reporting

Trial protocols were not available for any of the included studies. XL and I judged all 4 studies as being at high risk of bias for this reason and because of failure to report complete data on menstrual cyclicity (Hao, 2010) and on safety outcome measures (Li et al., 2011a, Zhou et al., 2010) that had been specified as being outcome measures of interest within the publication. One study reported measuring acne status that had not been specified earlier in the publication as being an outcome measure (Li et al., 2011b).

Other potential sources of bias

There were a number of other sources of bias that were evident. For example, sample size calculations were not performed in 3 studies (Hao, 2010, Li et al., 2011b, Zhou et al., 2010). Whilst a sample size calculation was reportedly conducted in one study (Li et al., 2011a), it was unclear on what basis this calculation was made, and the author was unable to provide us with further information during telephone contact.

One study (Zhou et al., 2010) reported menstrual cyclicity as an outcome measure in terms of number of women with normal menses, although no definition of normal menses had been provided. Baseline comparison between groups was reported for three studies (Hao, 2010, Li et al., 2011a, Li et al., 2011b) but was not available for one study (Zhou et al., 2010). Inclusion criteria were not clearly reported in one study (Hao, 2010) and in one study, the CM diagnostic criteria were unclear and exclusion criteria were not provided (Zhou et al., 2010).

2 studies described provincial sources of funding (Li et al., 2011a, Li et al., 2011b) with no funding details provided in the remaining 2 studies (Hao, 2010, Zhou et al., 2010).

3.3.3. Effects of interventions

Owing to the small number of studies in this review, the following pairwise comparisons were possible:

- CHM alone versus pharmacological treatment alone;
- CHM plus pharmacological treatment versus pharmacological treatment alone.

Two meta-analyses were conducted for CHM alone versus pharmacological treatment alone and which explored effects on total testosterone and LH. Similarly, the two meta-analyses performed for CHM plus pharmacological treatment versus pharmacological treatment alone were also for the outcomes of total testosterone and LH. Data for remaining outcome measures of interest was synthesised qualitatively.

3.3.3.1. CHM alone versus pharmacological treatment alone

2 studies (Li et al., 2011a, Li et al., 2011b) involving data for a total 125 participants compared the effects of CHM alone versus conventional medical treatment alone. One study used Diane-35 as the control (Li et al., 2011b) and one study administered metformin (Li et al., 2011a). Forest plots are provided within text for meta-analyses and in Appendix 7 for all other instances.

Primary outcome measure: Menstrual cyclicity

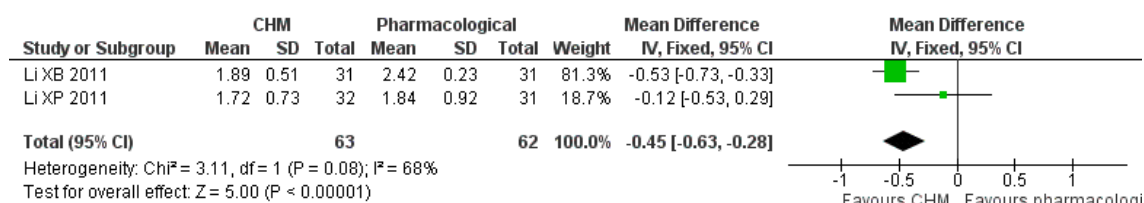
Menstrual cyclicity was not reported in either of the two studies and it was thus not possible to conduct a meta-analysis for this intervention comparison.

Secondary outcome measures

Biochemical hyperandrogenism (total and free testosterone)

A meta-analysis using a fixed effects model showed that CHM resulted in a significantly greater reduction in total testosterone levels when compared with pharmacological treatments (MD -0.45, 95% CI -0.63 to -0.28, $p < 0.0001$). The forest plot for this comparison can be viewed in Figure 11.

Figure 11: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Total testosterone



However, a moderate level of statistical heterogeneity was detected ($I^2=68\%$) and when using a random effects model, this difference was found to be insignificant (MD -0.37, 95% CI -0.76 to 0.03, $p=0.07$). The results of this analysis should therefore be interpreted with caution.

Free testosterone levels were not recorded as part of the outcome measures in these two studies.

Clinical hyperandrogenism (hirsutism and acne)

One study (Li et al., 2011b) involving data for 63 participants compared the effects of CHM alone versus Diane-35 alone on hirsutism and acne. There was no effects observed within-groups from baseline in Ferriman-Gallwey scores and no significant differences between groups (MD 0.05, 95% CI -0.42 to 0.52, $p=0.83$). However, a significant reduction in acne presentation as determined by Rosenfield score was observed from baseline in both groups that was evident 1 month post-treatment, but which only remained significant for the CHM group at 6 months post-treatment (MD -0.89, 95% CI -1.26 to -0.52, $p<0.00001$).

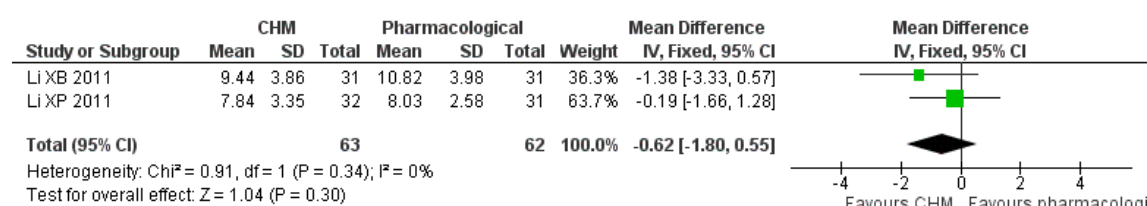
Polycystic ovarian morphology

This was not recorded as an outcome measure in either of these two studies.

Luteinising Hormone (LH)

Both studies (Li et al., 2011a, Li et al., 2011b) reported on LH levels. A meta-analysis using a fixed effects model showed there was no difference between interventions in reducing LH levels (MD -0.62, 95% CI -1.80 to -0.55, $p=0.30$). Figure 12 shows this comparison as a forest plot.

Figure 12: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Luteinising hormone



The same result was reached when analysis was substituted with using a random effects model.

Obesity (BMI, WC and WHR)

In one study (Li et al., 2011a) involving 62 participants and for which data for 40 participants was available for obesity outcomes, there were significant within-group reductions from baseline and no significant difference between-groups found for both BMI (MD -1.39, 95% CI -3.22 to 0.44, $p=0.14$) as well as for WHR (MD 0.00, 95% CI -0.03 to 0.03, $p=1.00$). Data for waist circumference (WC) was not available in this publication.

Glucose tolerance and insulin resistance

In one study (Li et al., 2011a) involving 62 participants, subgroup analysis involving data for 40 participants on glucose tolerance and insulin resistance showed that there were no changes within-group and between-group for either CHM alone or metformin alone in fasting blood glucose after 3 months (MD -0.02, 95% CI -0.19 to 0.15, $p=0.81$). Both groups demonstrated equivalence in terms of achieving significant within-group reductions from baseline in fasting insulin levels after 3 months of treatment (MD -0.05, 95% CI -1.95 to 1.85, $p=0.96$).

Lipid profile

In one study (Li et al., 2011a) involving 62 participants, subgroup analysis included data for 44 participants for lipid profiles. This study reported within-group reductions from baseline in triglycerides, total cholesterol and Apolipoprotein B. There were no between-group differences in these reductions for triglycerides (MD 0.14, 95% CI -0.08 to 0.36, $p=0.20$) and total cholesterol (MD -0.23, 95% CI -0.78 to 0.32, $p=0.41$). There was however a significant difference seen in the reduction of Apolipoprotein B in favour of

CHM (MD -0.32, 95% CI -0.44 to -0.20, $p < 0.00001$). There were neither within-group nor between-group differences found for the measures of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or Apolipoprotein A.

Quality of life

This was not measured in either of the two studies.

Liver and kidney toxicity

This was not measured in either of the two studies.

Adverse events

In one study (Li et al., 2011b), the Diane-35 only group experienced irregular vaginal bleeding ($n=4$), and nausea and vomiting ($n=2$). There were no adverse events reported for the CHM only group.

Chinese medicine outcome measures

One study (Li et al., 2011a) measured TCM syndrome scores and reported a significant reduction in scores from baseline within-group as well as at the end of the intervention between groups favouring the CHM group (MD -2.75, 95% CI -4.99 to -0.51, $p=0.02$). However, though the TCM scoring system used in this study has been published in clinical publications, it has not yet been validated and this result should be interpreted with caution.

3.3.4. CHM plus Diane-35 versus Diane-35 alone

2 studies (Hao, 2010, Zhou et al., 2010) involving a total of 120 participants compared the effects of CHM plus Diane-35 versus Diane-35 alone. Unless otherwise specified, the timepoints chosen for these analyses were at after treatment for Hao (2010) and at 6 months for Zhou 2010. Again, forest plots have been provided in text for meta-analyses that were conducted, and in Appendix 7 for all other outcomes.

3.3.4.1. Primary outcome: Menstrual cyclicity

Meta-analysis was not possible for the primary outcome measure of this review for this comparison.

One trial (Zhou et al., 2010) involving 60 women reported on the number of responders in terms of women with normal menses after stopping the

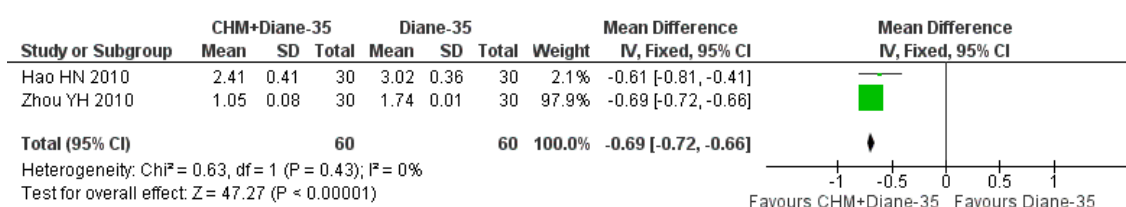
interventions. At 6-months post-treatment, a significantly greater number of responders (n=13) were found in the experimental group when compared with the control group (n=5) (RR 2.60, 95% CI 1.06 to 6.39, p=0.04).

3.3.4.2. Secondary outcomes

Biochemical hyperandrogenism (total and free testosterone)

The two studies (Hao, 2010, Zhou et al., 2010) reported on testosterone levels post-treatment. Pooled analysis using a fixed effects model showed a significant difference in reduction of total testosterone levels after treatment favouring the CHM plus Diane-35 group (MD -0.69, 95% CI -0.72 to -0.66). Figure 13 shows the forest plot for this comparison.

Figure 13: Forest plot of comparison CHM plus Diane-35 versus Diane-35 alone for outcome: Total testosterone



Analysis using random effects model resulted in no change to this outcome. Free testosterone was not measured in either of the two studies.

Clinical hyperandrogenism (hirsutism and acne)

This was not declared as an outcome measure in either of the two studies.

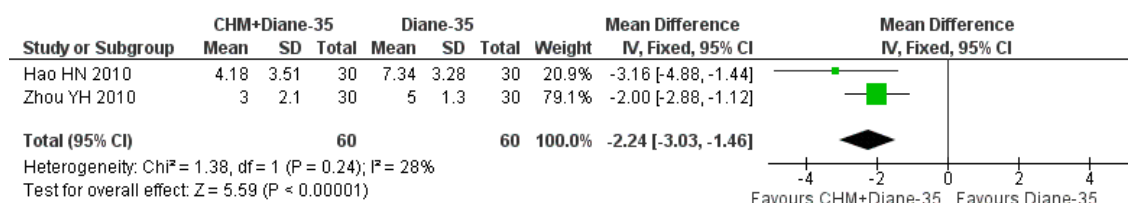
Polycystic ovarian morphology

This was stated as an outcome measure in one study (Hao, 2010) though results were not available. Polycystic ovarian morphology was not measured as part of the outcomes in the remaining study.

Luteinising Hormone (LH)

Both studies (Hao, 2010, Zhou et al., 2010) reported on LH levels post-treatment. A meta-analysis using a fixed effects model showed that CHM plus Diane-35 led to a significantly larger difference in a reduction in LH levels after the intervention (MD -2.24, 95% CI -3.03 to -1.46, p<0.00001). The forest plot for this analysis can be seen in Figure 14.

Figure 14: Forest plot of comparison CHM plus Diane-35 versus Diane-35 alone for outcome: Luteinising hormone



Using a random effects model resulted in a larger mean difference and wider confidence intervals of the pooled estimate that remained significant (MD - 2.34, 95% CI -3.37 to -1.30, $p < 0.00001$).

Obesity (BMI, WC, WHR)

This was not recorded as part of the outcome measures in the two studies.

Glucose tolerance and insulin resistance

This was not declared as an outcome measure in the two studies.

Lipid profile

This was not declared as an outcome measure in the two studies.

Quality of life

This was not recorded as part of the outcomes in the two studies.

Liver and kidney toxicity

One study (Zhou et al., 2010) reported monitoring liver function in both groups and found no change in aspartate aminotransferase (AST), although the raw data was not provided in the publication. Kidney toxicity (blood urea nitrogen) was monitored in this study but results were not provided. Hao (2010) did not address liver or kidney toxicity.

Adverse events

One study (Zhou et al., 2010) reported on adverse events. In this study, the Diane-35 only group there were reports of decreased libido ($n=2$) and breast tenderness ($n=5$) whilst in the CHM plus Diane-35 group, there were reports of mild headache ($n=1$) and lassitude ($n=2$). Hao (2010) did not address adverse events in the publication.

Chinese medicine outcome measures

This was recorded in neither of the two studies.

3.3.5. Other analyses

Owing to the small number of studies included in this review, it was not possible to conduct neither sensitivity analyses nor subgroup analyses for any of the meta-analyses using the parameters specified. For the same reason, it was not possible to assess publication bias by testing for funnel plot asymmetry.

3.4. Discussion**3.4.1. Summary of main results**

For this systematic review and meta-analysis, only 4 studies were considered to be of sufficient quality to be included. Meta-analysis was not possible for this review's primary outcome measure of menstrual cyclicity since only one study provided adequate data for this measure. This is similar to the findings of the Cochrane review by Zhang et al. (2010a) who could only include 4 of 123 potentially eligible studies.

Pooled comparisons suggest that CHM when used alone or when combined with Diane-35 leads to significantly greater reductions in total testosterone levels in a PCOS population. Pooled comparisons also suggest that when looking at reduction of LH levels, CHM demonstrates equivalence to other pharmacological treatments when prescribed alone, although when CHM is combined with Diane-35, this leads to significantly greater reductions in LH than does Diane-35 alone. The reduction in testosterone and LH levels achieved by CHM found in my systematic review is potentially one of the mechanisms by which CHM may improve the efficacy of clomiphene in pregnancy rate which was found in the Cochrane review on subfertility (Zhang et al., 2010a). The Cochrane review also found no added benefit of adding CHM to follicular aspiration or laparoscopic ovarian drilling (LOD) in women resistant to first-line ovulation-inducing agents which the authors suggest could indicate women resistant to WM ovulation-inducing agents may also be resistant to CHMs used for inducing ovulation. It is interesting to compare this against the results of my review which found CHM may have a potential role as an adjunct or alternative to Diane-35 or metformin. These medications are

typically used in the early stages of PCOS diagnosis. Although RCTs in both reviews only included women of reproductive age, this could point to a difference in response to CHM based on factors such as age and severity of reproductive presentation and which would be worthy of further exploration.

There is some limited evidence from this systematic review to suggest that CHM has no adverse effects on liver function, and that CHM is associated with fewer adverse events either when administered alone, or alongside Diane-35 when compared to controls. As in my review, the Cochrane review also found deficiencies in the reporting of adverse events. Within the Cochrane review, adverse events such as luteinised unruptured follicle syndrome, ovarian hyperstimulation syndrome and multiple pregnancy were reported only in one RCT and which showed no difference when CHM was used as an adjunct to follicular aspiration and ovulation induction when compared with follicular aspiration and ovulation induction alone (Zhang et al., 2010a). The findings from my systematic review should be interpreted with caution owing to the small number of studies included in each meta-analysis, the moderate to high levels of statistical heterogeneity and high risk of bias found. However, it does provide limited evidence to suggest that CHM may display effects on reducing testosterone and LH levels that are comparable to other pharmacological interventions, and which would be worthy of further investigation.

3.4.2. Implications for practice

There are a number of conventional treatment options available for regulating menses in PCOS, the most widely-prescribed being the OC and metformin. Although meta-analysis was not possible in this review for menstrual cyclicity, data from one study in this review suggested that CHM when combined with Diane-35 results in a significantly larger proportion of women reporting normal cycles at 6 months post-treatment compared with Diane-35 alone. This suggests that CHM could be used alongside Diane-35 for women who do not wish to use the OC continuously, such as those who wish to try to conceive or those who experience side-effects whilst being prescribed Diane-35. However, these are based on the results of one study only and with a small sample size and must therefore be seen as preliminary findings which warrant further investigation.

Aside from effectiveness, there are also implications for practice in terms of safety and adverse events. Although safety data is sparse in this review, there is some evidence to suggest that the OC alone is associated with a higher number of reports of side-effects compared with CHM alone. However, dropout rates between groups were balanced and suggest that the differences between groups in incidence of side-effects were not associated with differences in withdrawal rates. Whilst it would have been interesting to note whether there were any differences found in terms of treatment adherence, this was not measured.

Concerns relating to safety when administering CHM alongside conventional medicines are also frequently raised (Singh et al., 2012), and are particularly important given that up to 71.6% of patients from a number of disease populations report using CAM alongside prescribed treatments, and that up to 77% of CAM users report non-disclosure of use to their healthcare providers (Davis et al., 2012, Harrigan, 2011, Thomson et al., 2012, Lambert et al., 2010, Wallen and Brooks, 2012). In this review of two studies that combined CHM with the OC, no serious adverse events were reported as a result of combining such treatments for this population, at least for the duration of these trials and for the CHMs used within these trials, which is further supported by some limited evidence of no adverse effects on liver function. On the contrary, combining the OC with CHM appeared to lead to fewer side-effects when compared with the OC alone and which suggests that it is possible for CHM to play a role in moderating side-effects, at least when prescribing the OC for this population. Though these are interesting points and provide a preliminary basis of findings, this data is based on limited data that is by no means definitive and safety concerns regarding administering CHM alone and alongside conventional medicines need to be addressed further in larger and well-conducted studies.

A further important practice point of note relates to the CHM treatments that were used in the studies. CHM, at least as it is practiced in the UK, typically emphasises the importance of individualising treatments to each patient according to their corresponding Chinese medicine pattern. In this review, the 4 studies featured standardised CHM treatments, each of which aimed to treat a specific CM pattern. 3 of these 4 studies featured an inclusion criterion

requiring the patient be diagnosed and therefore matched with the pattern corresponding to the standard CHM treatment that was offered in that study. Whilst it could therefore be regarded that treatment was individualised at the pattern-level in these three studies, there was no specific individualisation of the treatment at the patient-level. This is considered in general to be best practice by CM practitioners in both China and the UK. Therefore, the external validity of these studies could be brought into question and suggests that the results may not in fact reflect real-world CHM practice. However, this does also raise important questions relating to CHM practice in that if positive and significant results can be obtained with standardised CHM treatments such has been demonstrated in these studies, firstly would individualised treatments produce different results and if so, what size and direction would these effects be? Secondly would any difference that may exist in treatment effects between standardised and individualised treatments be in fact clinically meaningful? It is also interesting that 1 study did not report individualisation at the pattern-level as a requirement as the other 3 studies, suggesting that the CHM treatment in this study was given to all patients randomised to the CHM arm, regardless of their Chinese medicine diagnosis. Despite that this treatment was completely standardised in this study, significant improvements in objective measures of LH and testosterone in this population were still found. It is acknowledged that this was only in one of the four studies and certainly should not be regarded as conclusive evidence. Nonetheless, it does raise an interesting point to reflect upon in practice regarding the purpose of matching a patient to a CHM treatment in order to observe a clinical benefit.

3.4.3. Implications for research

It is disappointing that from 260 full texts retrieved and deemed potentially eligible, only 4 could eventually be included in this systematic review. The reasons for exclusion for all 256 studies are provided in Appendix 5 and range from methodological issues as well as study design considerations that were not consistent with the aims of this systematic review. Whilst the PRISMA flowchart in Figure 9 provides a relatively crude account for exclusions since some studies had multiple reasons for exclusion, it does nonetheless provide an indication as to some of the issues that were experienced when searching for studies. In this next section, I will now discuss the key issues and offer suggestions in which these could be addressed in future studies.

3.4.3.1. Use of PCOS diagnostic criteria

In this review, the most common reason for excluding studies was that the methods of diagnosis reported in publications were inconsistent with the Rotterdam criteria, seen in 91 of the 260 studies. Although the majority of these studies were published before 2003 and therefore prior to the availability of the Rotterdam criteria, the NIH criteria have been available since 1990 and either set of criteria were acceptable for this review. However, as the reader is aware by now from previous chapters, there has been considerable confusion surrounding the diagnostic criteria in the last three decades and which has led to difficulties in maintaining consistency in both the clinical practice of, and research into, PCOS. The issue surrounding diagnostic inconsistencies when screening for study eligibility in this systematic review is therefore perhaps of no great surprise given the uncertainties that continue to exist today surrounding the precise definition of PCOS. An additional finding during the review process was that despite references being made to original sources, the diagnostic criteria were frequently misquoted. The reasons for this are unclear and may suggest either misinterpretation of source material which is possible for example due to language restrictions, or that the source material was in fact not consulted. What is clear however is that there remains much room for improvement in terms of promoting more widespread use of internationally recognised PCOS diagnostic criteria within such studies. This would maximise the contribution that the results from these studies can provide to the current body of knowledge, and would also enable ethical standards to be upheld to ensure that meaningful results can be obtained in research when involving the participation of human subjects.

3.4.3.2. Randomisation and allocation concealment

Randomisation methods were frequently unreported in the studies that were screened, as was allocation concealment. After contacting 9 authors, 4 studies were excluded on the basis that their methods of randomisation did not appear to be truly random, despite being described as RCTs in the publications. This suggests that methodological training in the basic principles of RCTs is inadequate, although this appears to be an issue relating to research conducted in China in general and not specifically in CHM research (Wu et al., 2009b). Nonetheless, since most CHM research to date is conducted in China, this undermines the quality of many CHM systematic reviews and which is already evident from a number of reviews conducted to

date that have been unable to include the vast majority of, or in some cases any, studies in their review owing to methodological deficiencies (Zheng et al., 2009, Flower et al., 2009, Manheimer et al., 2009). The urgent need to improve methodological quality in Chinese-language studies has been consistently raised by authors and although there is evidence to suggest that the overall quality of trials is improving (Wang et al., 2007), this review provides yet further evidence to suggest that there remains much to improve upon. Examples of medium to long-term strategies to improve methodological quality include reporting to be guided by CONSORT (Schulz et al., 2010a), and associated elaboration upon CONSORT for herbal medicine trials (Gagnier et al., 2006), both of which have been published in Chinese for wider dissemination (Schulz et al., 2010b, Fei and Liu, 2008); increasing provisions for methodological training of researchers and clinicians; placing more emphasis on quality rather than quantity of publications; and the enforcement of peer review and of the requirement for protocol publication prior to study commencement which should be encouraged by journals and by funding institutions in order to improve transparency of reporting. In the meantime however, more immediate measures that have been undertaken by this review team and others such as author-contacting have been helpful to enable a more informed assessment of methodological quality of studies to be made. Although this review contacted only 9 authors, I found this overall to be a time-consuming process owing to many factors such as the unavailability of current contact details on publications and on institutional websites, and authors being difficult to reach and which often required numerous attempts to obtain further information. It is acknowledged that author-contacting may not be deemed feasible by some review teams, particularly where a large number of authors need to be contacted and where time and resources may be lacking. Nonetheless, for this review, this was deemed a reasonable and worthwhile undertaking, and I would recommend future reviewers of Chinese-language CHM studies to consider in the planning stages of the review whether sufficient time and resources can be allocated to contacting authors during the review process.

3.4.3.3. Participant, practitioner and assessor blinding

In the 4 studies included in this review, no placebos were used, and neither CHM practitioners nor assessors were blinded from treatment allocation. It

could be argued then that performance bias could arise as a result of systematic differences between groups owing to patient expectations, or differences in treatment delivery or in exposure to factors other than the treatments under investigation. Although this could explain a number of significant differences favouring CHM when looking at a number of subjective and objective outcome measures, there are a number of reasons to suggest why participant blinding may not have been incorporated in these 4 studies. In China, CHM is generally an accepted and acknowledged active treatment for symptoms of PCOS, and ethical concerns exist when offering a placebo in place of a treatment regarded to be active (Zaslowski, 2010). The administrative form of CHM treatment provided in 2 studies in this review were decoctions which are regarded by most CHM practitioners as being the most clinically effective form of CHM treatment. For decoctions, an adequate placebo has been typically regarded as being difficult to produce, although this has been overcome in a number of CHM studies in recent years (Flower et al., 2011b). In addition, decision-makers and government funding agencies in the West are now moving towards prioritising research in the form of pragmatic trials and comparative effectiveness research. Since provincial funding was reported in two of the four studies, it is possible that certain study design considerations such as participant blinding at least in these two studies may follow government research priorities and requirements prior to receiving state funding. However, despite these reasons as to why participant blinding may not have been incorporated in these studies, I regard it reasonable for blinding of practitioner and/or assessor to be conducted. This would be particularly important where outcome measures involve a subjective assessment of participant progress or response to treatment such as hirsutism. I acknowledge that researchers are likely to have reasonable justifications to support decisions regarding their choice of study design but maintain the importance of reporting these explicitly in publications, particularly in protocols that would be considered good practice to publish prior to study commencement.

3.4.3.4. Outcome measures

It was a requirement of this review that internationally validated outcome measures was used in the studies to be included. However, in all 4 studies there was lack of clarity regarding what specific outcome measures had been

planned for use before the study had started. This was owing to incomplete descriptions of methods as well as of specific aims and objectives of the study. Furthermore, selective outcome reporting was apparent in some studies which failed to provide results for some outcomes that they had reported measuring. This clearly could have been overcome by following CONSORT guidelines of reporting and by publishing a protocol prior to the study for readers to compare the final study publication against.

The primary outcome measure of this review, menstrual cyclicity, was poorly reported in the two studies that included this as an outcome measure, with data being usable only from one study. This problem is however echoed in conventional medical research where it is commonplace for different measures of menstrual cyclicity to be used. For example, some studies use dichotomous measures such as responders or non-responders (Essah et al., 2006), others have collected ordinal data such as eumenorrhoea, oligomenorrhoea and amenorrhoea (Morin-Papunen et al., 1998), whilst others have adopted continuous measures such as mean cycle lengths (Meyer et al., 2007). I acknowledge that measurement errors exist with any outcome measure and the nature of measuring menstrual data brings with it its own methodological issues. However the measurement of menstrual cyclicity is particularly interesting for a number of reasons. Firstly there are two dimensions to the measurement of this outcome in terms of cycle length as well as cyclicity and therefore stability of cycle patterns and this requires both clinical and statistical judgments to be made. Secondly, measuring menstrual cyclicity has been a topic of debate for many decades in women's health research and is a simple measure to record and yet there still remains a lack of a universally agreed standardised and clinically accepted outcome measure for menstrual cyclicity. As such, most studies have focused on the more clinically meaningful dichotomous or ordinal outcome measures by incorporating clinical definitions of eumenorrhoea, oligomenorrhoea and amenorrhoea. The results of these studies can however be difficult to interpret since clinical definitions vary between studies, between countries and over time, though the situation appears to be improving at least in the context of PCOS research. This is owing to recently published guidelines by an international PCOS consensus group which provided clinical definitions for variations in menstrual cyclicity (Fauser et al., 2012) and which provides a starting point for an international

working definition of menstrual cyclicity as a standardised outcome measure that is urgently required in this and other areas of research.

TCM outcome measures, which were reported in one of the 4 studies in this review, are often composite outcome measures and that may consist of otherwise internationally recognised outcomes such as menstrual cyclicity or BMI. However, the original raw data was rarely reported in publications and which this was one reason why many studies could not be included in this review. The use of TCM outcome measures may be considered to have potential clinical significance for practitioners but its meaning is limited by the fact that these outcome measures are not validated nor internationally accepted by neither the CM community nor the wider medical community. Furthermore, CM practitioners do not use TCM composite measures in clinical practice in order to monitor progress and instead focus on, amongst other evaluations, patient-reported status of symptoms and signs. It is therefore proposed that incorporating a validated HRQoL measure such as the PCOSQ or more generic measures as the SF36, EuroQol-5 dimension (EQ-5D) or Measure Yourself Medical Outcome Profile (MYMOP) in studies could provide more appropriate means of measuring patient-reported changes in health status than such composite TCM outcome measures. Although HRQoL was not measured in any of the studies included in this review, it would be an extremely useful addition in future PCOS CHM study designs that I would strongly recommend. Where researchers are interested in exploring health economic impact of CHM on PCOS and in calculating cost utilities, it may be helpful to note that the EQ-5D is the preferred measure of QoL as recommended by NICE.

I would also like to provide some comment on the importance of reporting on the adequacy of treatment duration for the outcomes to be measured, and also on the reporting and the adequacy of timepoints. This is clearly most important to address for the primary outcome measure for this review for which the treatment duration of 3 to 6 menstrual cycles found in the 4 studies in this review is generally regarded as adequate, although longer study designs of 6 or more menstrual cycles are preferable. However, for some of the secondary outcome measures reported in this review such as BMI and fasting blood glucose, the duration for the control intervention may not have been

deemed suitable in order for an effect to have been observed. This is also the case for choice of timepoints at which the measures were taken and upon which the study analyses had been conducted. This raises some questions regarding the results and conclusions of such studies and which, had there been more studies included, could have been addressed in this review by conducting sensitivity analyses.

3.4.3.5. *Statistical considerations*

This review found deficiencies in the reporting of many statistical aspects. For example, there was an absence, or inadequate reporting, of sample size calculations, and lack of clarity regarding the primary outcome measure and therefore of the primary analysis. It was also unclear how the authors had planned to treat missing outcome data statistically and the statistical approach used was not always explicitly reported. Per-protocol analysis was employed by two studies and it is possible that this approach could have led to exaggerated effect estimates when compared with an intention-to-treat approach. I also found subgroup analyses had been conducted but which had not been stated clearly as being pre-specified or post-hoc. These methodological issues are extremely important to address in future research as this has clear implications on the final results and overall conclusions and which must be placed into context regarding the statistical decisions that were reported to have been made.

3.4.4. *Strengths and limitations of this review*

There are number of strengths to this review. Two Chinese reviewers constituted part of this review team and since CHM studies are more commonly published in Chinese, this enabled this review not to be restricted from the Chinese language. This also meant that two reviewers were able to independently screen the full texts for this review as a means of minimising bias in study selection, and independently perform data extraction to improve on the reliability of the extracted data. Furthermore, access to the main Chinese-language and English-language databases was possible in order to conduct an extensive search of the literature, as was direct contact with study authors to obtain further information regarding their publications and which considerably improved the overall quality of this review.

There are however a number of limitations that need to be acknowledged. Only 4 studies could be included in this review, all of which were rated as having a high risk of bias following Cochrane methods of assessment and therefore considered to be low in methodological quality. Whilst this questions the quality of the evidence available and which has been consistently addressed throughout this review, I do not feel that this limits the usefulness of the data collected for the purposes of a secondary aim of this review which was to collate details of CHM treatments such as herbal ingredients, dosages and preparation methods. Furthermore, this review has enabled methodological issues to be brought forward as a means not only of critically evaluating the current available evidence, but also of identifying key issues within Chinese-language research that need to be urgently addressed in order to promote higher quality studies. A further limitation is that the studies were conducted in China and it is thus difficult to comment on the generalisability of these results to Western populations such as the UK. This is especially since the 4 studies were open trials and contextual effects such as expectation and the therapeutic relationship between patient and practitioner are highly likely to have influenced the observed treatment effect. One could argue then that these results would be skewed in a positive manner since it could be hypothesised that a more powerful contextual effect could be observed in a population in which CM was a culturally accepted treatment. However, there is growing evidence to suggest the contrary and that the younger Chinese generation may, for various reasons, be less likely to seek Chinese medicine and more inclined to opt for WM for their ailments. It is beyond the scope of this review to explore the evidence and the reasons for this in sufficient depth but it does nonetheless suggest that differences in treatment effects between Chinese and Western populations may be smaller than one might expect.

3.5. Conclusion

This review found limited evidence from one study to suggest that CHM plus Diane-35 versus Diane-35 only significantly improves menstrual cyclicity in women with PCOS at 6-months post-treatment (RR 2.60, 95% CI 1.06 to 6.39, $p=0.04$) (Zhou et al., 2010). As meta-analysis was not possible for the primary outcome measure of menstrual cyclicity, this should be considered a preliminary finding. Whilst results from the meta-analyses provide some evidence to suggest that CHM may influence testosterone and LH levels which

are key to the development and expression of PCOS symptoms, these findings should be interpreted with caution owing to the small number of studies included in each meta-analysis, the moderate to high levels of statistical heterogeneity and the high risk of bias found in all 4 studies.

There is also some limited evidence to suggest that CHM has no adverse effects on liver function, and that CHM is associated with fewer adverse events either when administered alone, or alongside Diane-35 compared to controls. However, this is based on sparse data from only two studies involving small sample sizes and larger studies need to be conducted in order that the issue of safety of CHM is addressed with more robust evidence.

The methodological deficiencies found in this review echoes the findings of other larger reviews of Chinese-language studies (Zheng et al., 2009, Shang et al., 2007, Wu et al., 2009b). In this review, I found a lack of clarity in terms of reporting the methods used for recruitment, randomisation and allocation concealment, primary and secondary outcome measures and justification of sample sizes. Although methodological quality appears to be improving gradually with increased reporting of funding sources and increased use of internationally validated outcome measures, the methodological quality of CHM PCOS studies remain in urgent need of improvement. This is important in order for patients, clinicians and CHM practitioners to be able to make informed decisions regarding CHM and which can be informed by the best available evidence to date.

This is the first systematic review of the literature for the effects of CHM on PCOS-related menstrual cyclicity and a number of other important measures such as testosterone and LH. This has enabled data to be synthesised for the effectiveness of CHM for PCOS and has allowed us to collate important information regarding the CHM interventions used. However, since the trials were conducted in China, it is possible that these results and interventions may not be relevant to Western populations. It was therefore important as part of this PhD to determine how CHM interventions are provided for Western PCOS populations in order to ensure that the design of the study would reflect CHM practice in the West. In this next chapter, I will describe the first empirical

study I undertook which involved a Delphi consensus-seeking study with a group of CHM practitioners.

Chapter 4: Developing clinical practice guidelines for the treatment of polycystic ovary syndrome with Chinese herbal medicine: A mixed-methods Delphi study

4.1. Introduction

The studies that were eventually included in the systematic review and meta-analysis enabled me to examine the strength of the evidence of effectiveness and safety of CHM for PCOS. The studies also enabled me to begin to formulate a treatment framework for PCOS in terms of TCM diagnoses, types of CHM used and the individual herbs and dosages that were used in the treatment of PCOS, at least in the context of clinical trials in China. However, it was not clear how these treatment methods performed by CHM practitioners in China and on a Chinese population would compare with everyday clinical practice for practitioners working in the West and on patients in Western populations. It has already been discussed in earlier chapters that CHM, as it is traditionally practiced, is highly individualised to each patient and their presenting symptoms and signs. Patients can present with differing patterns of symptoms and signs in CHM, despite receiving the same conventional medical diagnosis for a condition. These differing patterns in CHM can be caused by many factors, including those influenced by cultural and geographical differences such as diet and lifestyle. To maximise CHM model validity and to inform the CHM intervention in the proposed trial, it is therefore important for me to understand what CHM treatment methods are being adopted by practitioners in Western countries such as the UK. Accordingly, the main research question that I aimed to answer with the next study was:

- What constitutes good clinical practice for CHM practitioners treating PCOS?

More specifically:

- What symptoms and signs do women with PCOS present with in private practice?

- What diagnoses are commonly given?
- What and how is treatment offered, and how is it evaluated?

This next chapter describes the steps and processes of a Delphi study that was conducted to answer these questions.

4.2. Background to methods

In order that I could meet the study objectives within the timeframes of this project, and to create what I considered a useable output at the end of this study, I decided that a consensus method would be the most suitable.

The Delphi method and nominal group technique (NGT) are both formal consensus methods recognised by the National Institute for Health and Clinical Excellence (NICE) for developing clinical guidelines (2009). The Delphi methodology was the first to originate and came from a defence study of the RAND corporation in 1953 by Dalkey and Helmer (Dalkey, 1968, Linstone and Turoff, 2002). Shortly after in 1968, Delbecq and Van de Van developed NGT as a result of findings from a number of studies that had focused on the social psychology of group decision-making and participation in planning (Delbecq et al., 1975). Today, both remain widely adopted in medical and health services research, and are increasingly used in Chinese herbal medicine and acupuncture research (Schnyer et al., 2005, Flower et al., 2007, Cochrane et al., 2011, Smith et al., 2012, Smith and Betts, 2014).

Both Delphi and NGT essentially involve structuring group communication that enables the views of a panel of informed individuals to be considered, whilst at the same time minimising the drawbacks of collective decision-making (Jones and Hunter, 1995). However for this research question, the Delphi method had several advantages over NGT. For example, the initial idea-generating round in the Delphi typically involves distribution of a qualitative questionnaire, a series of small focus groups or one-to-one interviews. On the other hand, NGT typically involves physically gathering together all participants for this round to generate views, a task I felt would not have been feasible for this study where I was aiming to gather views from both UK and overseas practitioners.

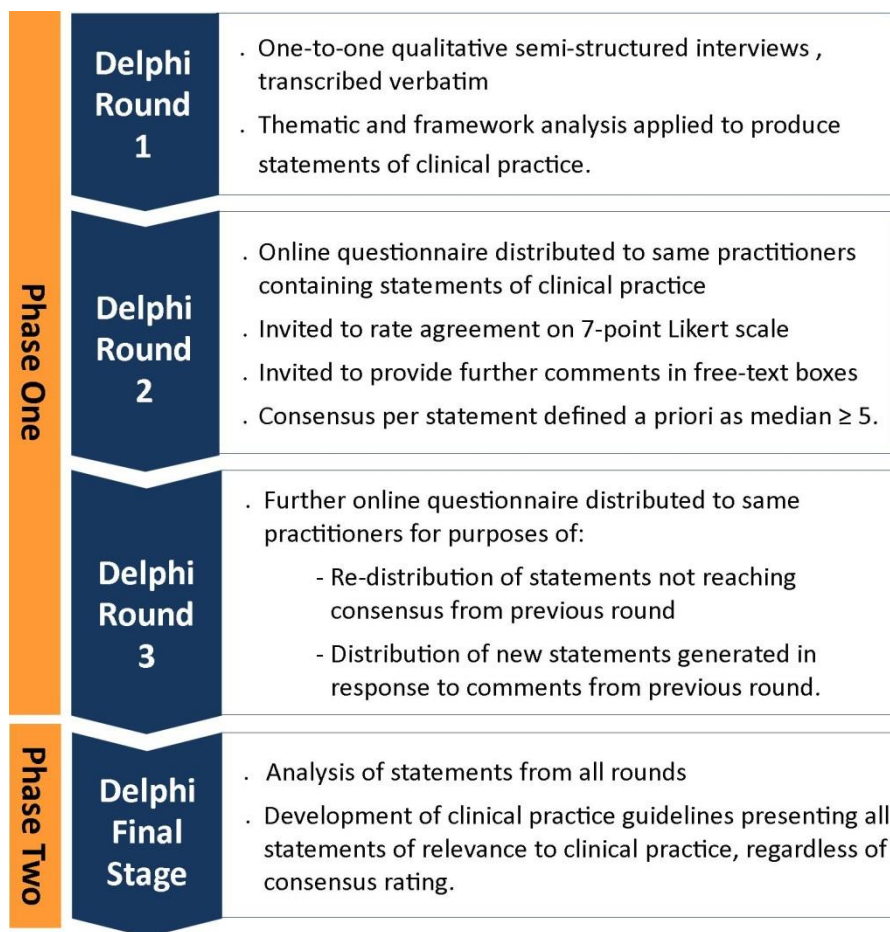
Additionally, most CHM practitioners are self-employed and I was not in a

position to financially reimburse CHM practitioners for time lost in clinical practice. In NGT, it is also common for a review of the literature to be presented to the panel prior to idea-generation, whilst in the Delphi this initial round tends to be much more open-ended. I felt that presenting the results of a literature review in the first instance could have led the CHM practitioners in this study to feel that their individual views were not being considered in their entirety. This could have led to response bias, potentially resulting in an artificial consensus being reached at the end of this study. This could also have reduced response rates for subsequent rounds and which would have affected the validity of the results, a criticism commonly made of all consensus method studies (Keeney et al., 2006). I felt that we could avoid these issues by adopting a more personal and open-ended approach from the outset to maximise participant buy-in and which other researchers have also found helpful as part of the Delphi method (Hasson et al., 2000, Flower et al., 2007, Schnyer et al., 2005, Alraek et al., 2011, Cochrane et al., 2011). I thus felt that this would be the most appropriate methodology to satisfy the overall aims of this study.

4.3. Methods

In order to meet the requirements of this study, I separated the methods of this study into two phases. Phase 1 involved data collecting with participants and which followed the stages of the Delphi process. Phase 2 involved analysing the data that was produced in order to fulfill the research objective of producing a set of clinical practice guidelines for CHM treatment of PCOS. An overview of the processes involved with each phase of the study can be seen in Figure 15. These will be discussed in further detail in subsequent sections.

Figure 15: Flowchart to show processes involved in Phases 1 and 2



The following section will now illustrate the methods that were used at each stage of Phase 1.

4.3.1. Phase 1

4.3.1.1. Recruitment

I aimed to recruit a suitable number of participants in order to foster diversity in opinion and which I estimated to be a sample of approximately 15 CHM practitioners. This is considered to be a suitable number of participants to encourage a diverse range of views, as supported by similar studies involving the Delphi method (Flower et al., 2007, Alraek et al., 2011, Smith and Betts, 2014). All practitioners in the study had to have been in practice for a minimum of 4 years prior to the start of the study, and have self-reported expertise in gynaecological conditions such as PCOS. To further foster diversity in opinion, I used expert and snowball sampling and purposively sampled for gender, CHM modality (traditional Chinese medicine/classical Chinese medicine), locality of CHM training (East/West) and current Western

country of practice (UK/Australia/Canada/US). This study was conducted in English only as we felt the time required to translate interview transcriptions and conduct qualitative analysis of the interview material was not feasible given the timeframes. Recruitment was thus restricted to Western countries only and which has been done in similar Delphi studies relating to the practice of CM (Smith et al., 2012, Smith and Betts, 2014). It is acknowledged that much of the expertise in CHM-prescribing is from within Eastern countries such as China and Japan and although I could not recruit from these countries for this study, I attempted to safeguard against this by sampling for locality of CHM training as mentioned above. This enabled me to include the views of English-speaking practitioners in this study who had at least received training in the East and who were applying these methods on a Western population.

Potential participants were identified by approaching CHM regulatory bodies of the following Western countries: the UK, the US, Australia and Canada. These bodies were provided with a brief background to the study and asked to put forward suggestions of approximately 10 potentially suitable practitioners. Practitioners were also asked to suggest names of other practitioners that they felt could be suitable for the study and those matching the sampling criteria were then approached. Since I was attempting to purposively sample for CHM modality and given that most practitioners registered with the regulatory bodies in the West are trained in traditional Chinese medicine, Five Element and Classical Chinese medicine practitioners were contacted directly as gatekeepers and asked to recommend suitable practitioners for the study. I also directly approached a number of practitioners who had published seminal texts on CHM and gynaecology and who were considered to be international experts in the field.

Contact with practitioners was initially made by telephone and an answer message left if there was no response. If there had been no reply to the invitation after 1 week, they were followed up with one more telephone call and a further answer message was left if we again received no response. Practitioners whose telephone number could not be retrieved were invited onto the study by email. An email and telephone script was used for all contact to ensure consistency in the information we provided to each practitioner and which are provided in Appendix 8 and Appendix 9 respectively.

Practitioners expressing an interest were posted or emailed an information pack which contained an official invitation letter, a participant information sheet, a consent form and a stamped self-addressed envelope to the research team. The literature suggests that Delphi studies can experience dropouts between consecutive rounds can be due to participants not feeling informed regarding the workload expected of them (Alraek et al., 2011, Hasson et al., 2000). For this reason, I felt it important to set expectations prior to recruitment onto the study in order to minimise drop-out from the study. Therefore during the recruitment process, I emphasised to practitioners the level of work that would be expected and offered practitioners the opportunity to ask further questions. Within the participant information sheet, I provided an approximate timeline for the study with a brief overview of the tasks that the researcher and the participant would be assigned at each stage. This ensured that practitioners were fully informed and those wishing to join the study were asked to return a completed consent form. The invitation letter, participant information sheet and consent form are provided in Appendix 10, Appendix 11 and Appendix 12 respectively.

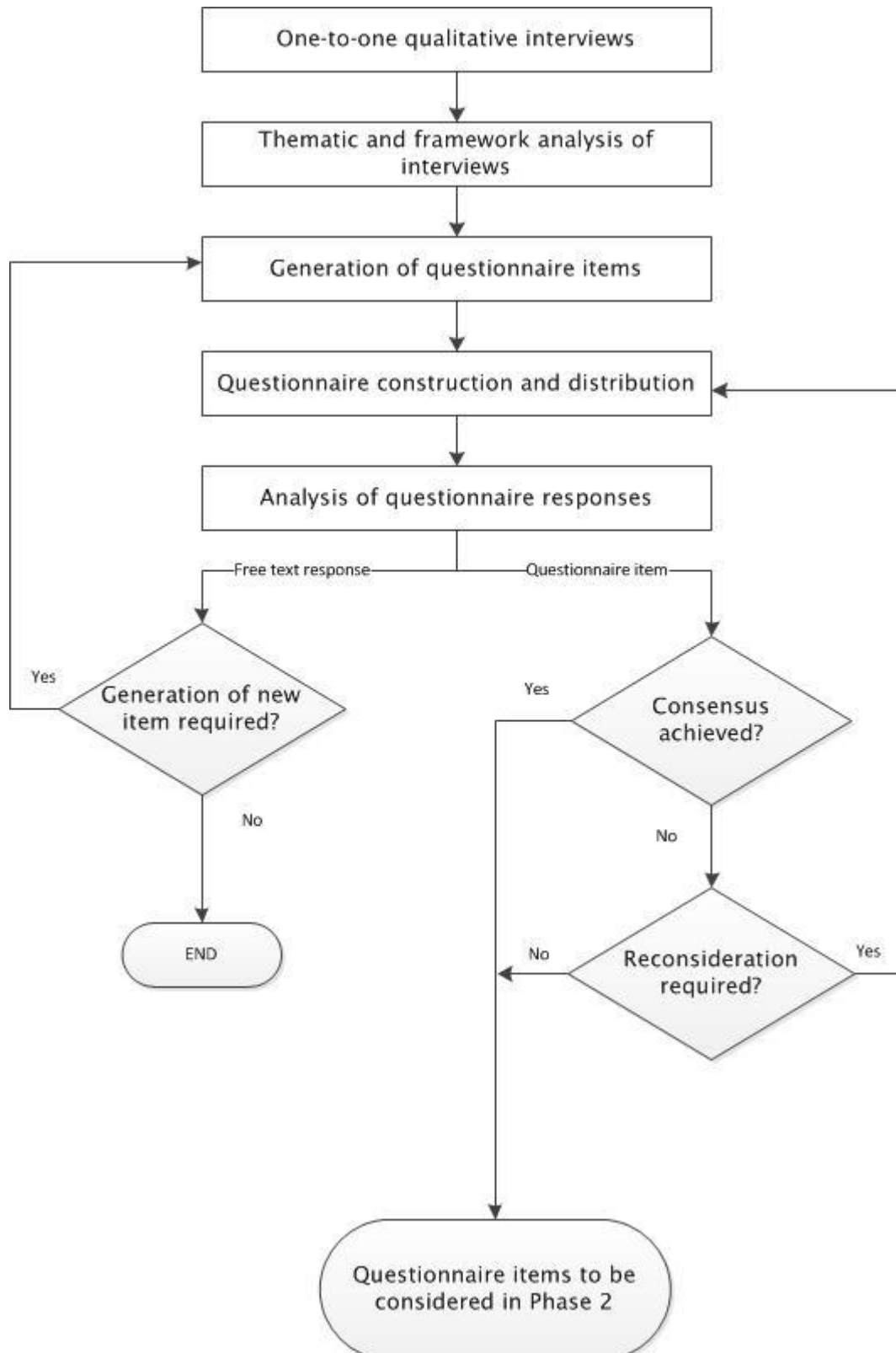
4.3.1.2. Initial round methods and data collection

An overview of the data collection methods and analysis that were eventually used in Phase 1 can be seen as a process flowchart in Figure 16. I had initially proposed to generate qualitative data using focus groups and in-depth interviews. I attempted to coordinate focus groups with participants located in the UK and where attendance of a focus group was not feasible, one-to-one interviews were offered.

The decision to use focus groups and in-depth interviews for the initial Delphi round was made by the study team. This was to be a modification of the conventional Delphi method that ordinarily uses existing literature to frame its questions to the panel in the initial idea-generating initial round. However, my view was that thoughtfully coordinated focus groups could enable a range of views to be generated and exchanged with other practitioners in order to generate group ideas or opinions regarding this topic. These group opinions would then be supplemented with individual opinions expressed through using

in-depth interviews for participants for whom it was not feasible to attend a focus group.

Figure 16: Overview of data collection and analysis in Phase 1



A focus group topic guide and an interview guide were devised and are presented in Appendix 13 and Appendix 14 respectively and which included open questions such as 'Could you tell me a little bit about your work?' and 'Would you tell me more about what you do when see a patient with polycystic ovary syndrome?'. This topic guide and interview guide were piloted on 2 CHM practitioner colleagues not involved in the study and prior to implementation to ensure that the focus group/interview questioning route was appropriate and to ensure phrasing of questions was appropriate, such as ensuring that questions were unambiguous and not leading. I employed a semi-structured design to my questioning style to ensure that I collected data that was relevant to my main research question, and also allowed me some flexibility in my questioning route to enable further exploration of relevant topics introduced by participants.

For focus groups, a neutral researcher who had no links to the CHM profession was available to facilitate focus group sessions. It was planned that these would last approximately 1½-2 hours and that I would have an observatory role by taking notes during the focus group discussion to feed back to the facilitator in case further elaboration of points was desired as well as to facilitate transcription of audio recordings. All in-depth interviews were conducted in person where possible, or by telephone, and were expected to last approximately 45-60 minutes. Focus groups and interviews conducted in person would be arranged at a location and time convenient to participants and, where travel costs had been incurred as a result of taking part in the study, these were reimbursed to the participant and stated clearly in the participant information sheet.

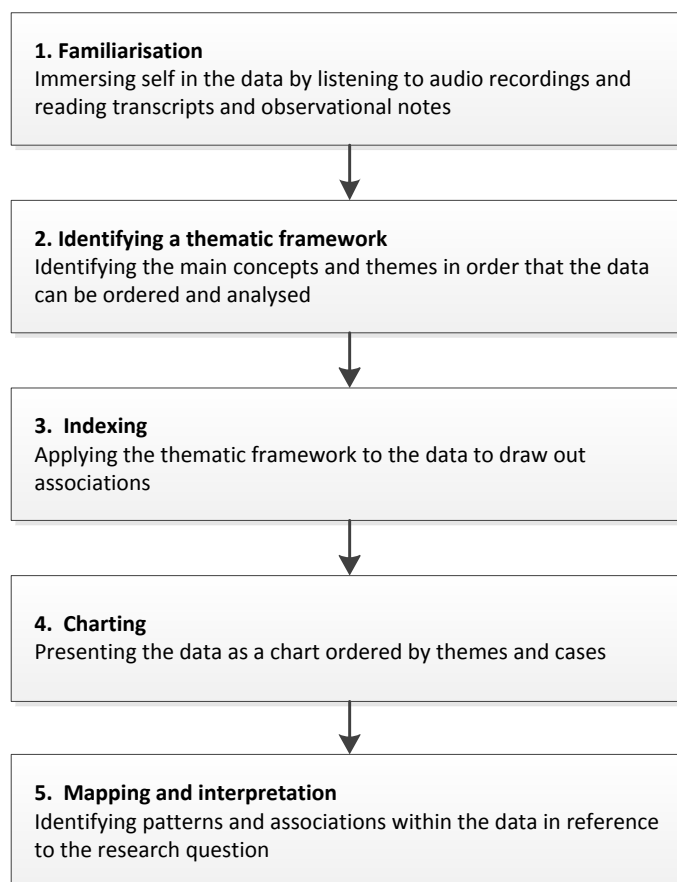
Qualitative data was collected by audio-recording interviews and by writing field notes and continued to be collected until data saturation was reached. Audio-recorded interviews were transcribed by me and by external transcription services. I checked all transcriptions against the audio recording for accuracy and removed participant identifiable data from the transcription. I also took field notes to record supplementary data considered relevant to the study, such as personal reflections of the interview, or conversations with participants that had taken place outside of the recording. It is widely recognised that field notes can provide further context that may not be

possible by using only transcriptions and I felt it important that these were recorded as part of the data collection process.

4.3.1.3. Initial round data analysis

Analysis of the qualitative data was conducted thematically and using the framework approach. Framework analysis was initially developed by a UK qualitative research unit within the Economic and Social Research Council (ESRC) that conducted applied social and public policy research (Ritchie and Spencer, 1994). Framework analysis is typically applied to contextual research that must meet specific objectives and within shorter timescales, making this method particularly suitable for me to adopt for the analysis at this stage of the study (Ritchie and Spencer, 1994). The framework approach follows five key stages of familiarisation, identifying a thematic framework, indexing, charting and mapping and interpretation and which are illustrated in Figure 17 (Ritchie and Spencer, 1994).

Figure 17: Stages of framework analysis



Reproduced from RITCHIE, J. & SPENCER, L. 1994. Qualitative data analysis for applied policy research. In: BRYMAN, A. B. & BURGESS, R. G. (eds.) *Analyzing qualitative data*. Abingdon: Routledge.

Following this approach, when I had conducted the initial interviews, I immersed myself in the data corpus by listening back to audio-recordings, reading my field notes and reading and re-reading the initial transcriptions (Braun and Clarke, 2006). I then conducted inductive thematic analysis using line-by-line open coding for three transcripts which involved capturing themes and subthemes from the data which I recognised as issues or concepts of potential relevance to the research question. During this process, these themes were identified at the semantic rather than latent level since an examination of surface meanings of the data, as opposed to its underlying theoretical assumptions, were required to answer the research question (Boyatzis, 1998).

The resulting list of inductively-generated themes and subthemes was then cross-referenced with the objectives of the research study in order to create a framework or index. This index consisted of a reduced list of themes that were of particular relevance to the research question and within which the data could be organised. Each theme and subtheme was allocated a number as an indexing reference and together formed the thematic framework. I then applied the index by annotating all transcripts with the indexing references in a systematic manner and by using Microsoft Word 2010 to annotate using the 'comments' function. As a result, paragraphs of text frequently contained a number of indexing references to indicate different themes being discussed. With this process of indexing, it was possible to begin to draw associations between themes and to see patterns emerging from within the data.

It is important here to note that the steps involved within identifying a thematic framework and of indexing are an iterative process that involves continually making judgments about each unit of data, reflecting on the research question and constant evaluation and re-evaluation of the material. The desired result is a framework that has been allowed the flexibility to continually evolve as more data is generated to inform it and as more time is spent immersed in the data.

After applying the index to all of my transcripts, a process of charting followed. This involved creating a chart within Microsoft Excel 2010 with

themes and subthemes as column headings, and participants as row labels. I then inputted into each field summaries of the annotated segments under the relevant theme and for each participant. These summaries involved taking annotated segments of the data from the transcripts and synthesising the information into a short phrase with the aim of retaining the main message as much as possible. The summary would also contain a reference to the transcript page number to enable the original source data be consulted if necessary. The chart that was created thus enabled the data set to be viewed and analysed as a whole as well as in segments by theme or by participant.

The resulting chart facilitated the final stage in the framework analysis process of mapping and interpreting the data set in its entirety. This involved comparing and contrasting the data by consulting my chart, transcriptions and field notes to seek patterns and structure within the accounts that were given by participants. It was also important to continually reflect on the research question to begin identifying the processes involved in providing CHM treatment for PCOS. This included for example structuring how CHM practitioners made decisions about care provision, identifying key characteristics of treatment effectiveness or searching for patterns of commonality or polarity within specific phenomena. By the end of this stage of the analysis, I had created an initial map of the form and nature of the phenomenon in question that was good CHM clinical practice for PCOS. This then formed the basis of the second round of the Delphi study and which constituted the next contact I had with study participants.

4.3.1.4. Second round methods and data collection

With the map that I had created of good CHM clinical practice for PCOS, I was able to identify key features and created a series of statements to reflect these.

Following the Delphi method, these statements constituted items within a quantitative questionnaire that would enable statistical assessment of agreement and subsequent evaluation of group consensus. This enabled the strength of consensus to be demonstrated using statistical measures of dispersion, which was considered to be more informative than simply presenting a list of consensus statements. I chose to use the Likert approach to scale responses as it is a validated scale that is easily understood by users,

frequently applied in Delphi studies and was appropriate to use for this Delphi study. A 7-point Likert scale was chosen that enabled a bi-polar scoring from between 1-7 and which included a description of the response corresponding to each point of the scale, such as '1, strongly disagree' (Edwards et al., 1997). I felt a 7-point Likert scale was sufficiently detailed to provide me with meaningful polarities in agreement or disagreement. This also ensured that a mid-scale score of '4, neither agree nor disagree' was available which I felt was important for participants not to feel forced into committing to either end of the polarity and which reflects appropriate interpretation of an opinion scale that can lie at the mid-point (Jackson and Furnham, 2000). Aside from the Likert scale responses, an additional response option of 'not-applicable' (NA) was available for each item. A free-text box was also available for additional comments to be made. As well as agreement ratings on statement items, demographic and clinical background information was additionally collected within this questionnaire. The decision to collect this information in the second round was made on the basis that I felt collecting for potentially sensitive information using a questionnaire could reduce response bias when compared with if I had asked for this information during the interview.

An initial version of the questionnaire was piloted with a CHM practitioner not involved in the study to check for clarity and ambiguity of item wording (Linstone and Turoff, 2002). This also enabled me to pilot data collection methods. I used Survey Monkey, a subscription-based online survey tool, to host and distribute questionnaires and to collect responses. A personalised email was sent to the original study participants providing a web link to the questionnaire and inviting them to provide their responses. Participants who did not respond within 2 weeks were followed up with a reminder email or telephone call.

4.3.1.5. Second round data analysis

At the end of data collection, questionnaire responses were downloaded from Survey Monkey into Microsoft Excel 2010. Demographic and clinical background data was collected as categorical, ordinal or interval data. For categorical and ordinal data, this was presented as counts per observation, and for interval data the mean and standard deviation (SD) were calculated.

For each statement item, the median, range and interquartile ranges (IQR) were calculated with group consensus evaluated per item. Participants who had responded to an item with 'Not applicable' (NA) were removed as a denominator in response for that item only. Agreement per item was defined a priori as being a median group rating of 5 or more, which I regarded as the level of group agreement that was acceptable for the purpose of this study. Items that achieved consensus in this round were accepted and reserved for consideration in the concluding set of clinical practice guidelines. Items not achieving consensus were, following the Delphi method, reserved for redistribution back to the participants via a further questionnaire round that will be described in further detail in the following section of this chapter.

As well as responses relating to item agreement, comments provided in the free-text boxes were also analysed. These could relate either to points regarding clinical practice, or to those regarding item construction and administration, for example relating to the wording of the item. Data regarding clinical practice issues could be presented as new information, or as emphasis on information already presented to me in the earlier round. Both types of data were analysed thematically and evaluated alongside the chart and thematic framework created in the initial Delphi round. This added to my original corpus of data and where deemed important to the research question, new items were generated for consideration within the next questionnaire round. Remaining comments pertaining to the wording or structure of the items or the questionnaire were considered separately in the analysis. These comments contributed to revisions of such items for redistribution to the participants where face-validity was queried (Linstone and Turoff, 2002). This illustrates the flexibility in enabling new data to be incorporated into the study, and an iterative approach to data analysis that are features of the Delphi process (Linstone and Turoff, 2002).

4.3.1.6. Third round methods and data collection

The next questionnaire that formed the third Delphi round firstly contained a brief summary of the items that had reached consensus from the previous round. Participants were then presented with items that had failed to reach consensus. For each item, the group consensus rating and the participants' own personal rating from the previous round were presented. Each participant

received a personalised questionnaire and could therefore not see individual ratings provided by other participants of the study. For each item that failed to reach consensus, every participant was invited to reconsider their original rating which they could accept or reject.

New and revised items that were introduced in this questionnaire were presented as in the previous round with an invitation to rate the level of agreement with each item.

As in the previous round, participants were emailed with an invite containing a link to their personalised questionnaire on Survey Monkey. Those who did not respond within 2 weeks were followed up by email or by telephone.

4.3.1.7. Third round data analysis

Items were analysed according to the same methods outlined in the previous round. Items that had been re-distributed that achieved consensus were accepted for the clinical guidelines. Those that again failed to reach consensus were not distribution again.

Newly introduced items that achieved consensus were accepted and it was planned that any of these items that did not achieve consensus in this round would be distributed for reconsideration in a fourth and final questionnaire. This means that for this study, I aimed for all items failing to reach consensus to be presented for re-consideration in one further questionnaire. I therefore stayed true to the Delphi method by presenting data for re-consideration, whilst minimising risk of questionnaire fatigue by limiting the Delphi rounds to four.

When all items had been distributed, and no new items were generated, this marked the end of the Delphi process and therefore of phase 1 of this study. At this point, I required no further data to be collected from participants who were notified by email that this part of the study was now complete.

The data that was collected from phase 1 was then evaluated further in phase 2. A description of the methods for this phase of the study will now follow.

4.3.2. Phase 2

Phase 2 constituted the development of clinical practice guidelines for the CHM treatment of PCOS.

Following phase 1, two lists of items regarding clinical practice were created - those that had reached consensus, and those that had not. I wished to produce a set of guidelines that were practical and accessible by both researchers and clinical practitioners. However, given the preliminary nature of this research, I felt it important to not only present key clinical practice points where consensus existed amongst participants, but also to illustrate the different levels of consensus and to enable the identification of particular items or themes where disparities in opinion were apparent and which could warrant further investigation as part of further research.

Following the principles of developing and presenting NICE guidelines that grade the overall strength of evidence per item, I felt it appropriate to present the guidelines in a similarly useful manner by grading each item according to the strength of the agreement. The grading classification was determined post-hoc in light of the results from phase 1. The strength of grading took into consideration the median ratings per item, and the IQRs that had been calculated per item as we felt it important to highlight the levels of dispersion and therefore of opinion. The criteria for determining grading within the classification are illustrated in Table 5.

Table 5: Clinical guideline criteria for classification of item grading

Grade	Description	Median	IQR*
A	Strong consensus	6 OR 7	≤ 2
B	Moderate consensus	6 OR 7	> 2
		5	≤ 2
C	Weak consensus	5	> 2
D	Consensus not achieved	< 5	

*IQR=Interquartile range

This created a framework which I could use to present the resulting items in a practical and clinically meaningful way within the concluding set of clinical guidelines. To my knowledge, this method of classification had not been done before and which I felt was more clinically appropriate and practical than listing a set of statements regarding clinical practice that had simply reached consensus.

The next section will now describe the results of this study.

4.4. Results

4.4.1. Phase 1

Phase 1 comprising the Delphi study itself took a total of three rounds of communication with participants; the first qualitative idea-generating round and two subsequent structured questionnaire rounds. I achieved 100% response rate throughout the process and the results from each round of the study will now be described in detail.

4.4.1.1. Recruitment

Professional bodies were contacted in February and March 2011 to begin collating lists of suitable practitioners to contact. Of the 4 bodies I contacted, 2 were able to provide a list of potentially eligible practitioners for this study – one in the UK and one in Canada. All practitioners were approached in July 2011 and since recruitment was closed only after I was satisfied that data saturation had been reached, recruitment finished shortly after the final interview was conducted in October 2011.

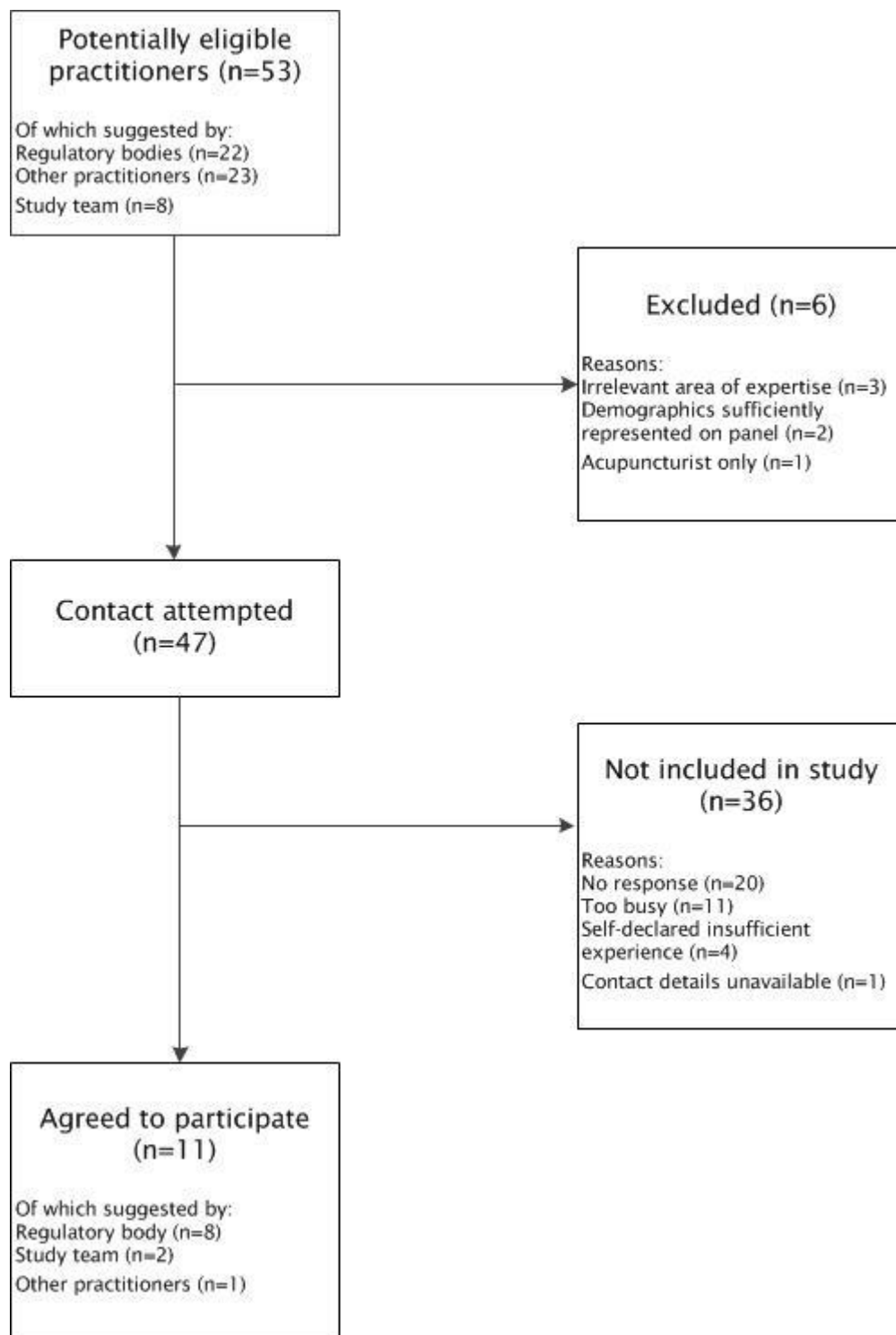
A flowchart of recruitment, recruitment methods and reasons for exclusion can be seen in Figure 18.

In total the names of 53 practitioners were obtained as potentially eligible for the study. These names came from three sources; suggestions from 2 of the 4 regulatory bodies who had been approached to assist this project (n=22); suggestions from other practitioners (n=23); and finally practitioners suggested directly by the study team (n=8) due to being widely published in gynaecology and PCOS clinical practice or research (n=5), or because they

practiced a particular modality of CHM as classical Chinese medicine (n=3) for which I did not have sufficient representation of within the panel.

Of these 53 practitioners, I attempted to contact 47 of these practitioners and did not attempt to contact 6 practitioners due to being CHM specialists not directly relevant to PCOS or gynaecology (n=3), their demographics being sufficiently represented in the panel at time of recruitment (n=2) and being trained only in acupuncture (n=1). Out of the 47 practitioners I attempted to contact, a total of 36 practitioners did not join the study for the following reasons: no response (n=20), too busy to participate (n=11), self-reported insufficient experience to participate (n=4) and current details could not be found to make contact (n=1). From the 47 practitioners contacted, 11 practitioners in total agreed and consented to participate and a 23.4% recruitment rate was eventually achieved.

Figure 18: Flowchart of recruitment process



The demographics of the 11 participants can be seen in Table 6. I was successful in recruiting a sufficiently heterogeneous mix of practitioners in terms of the majority of my purposive sampling criteria gender, CHM modality and country of CHM training. In terms of one sampling criteria 'current

Western country of practice' however, I failed to recruit from Australia, the US and Canada and all 11 practitioners eventually recruited were practicing in the UK. 'School of herbal training' and 'Setting of CHM provision' had not been pre-defined sampling criteria but are included in Table 6 to provide further background information.

Table 6: Demographics and characteristics of recruited participants

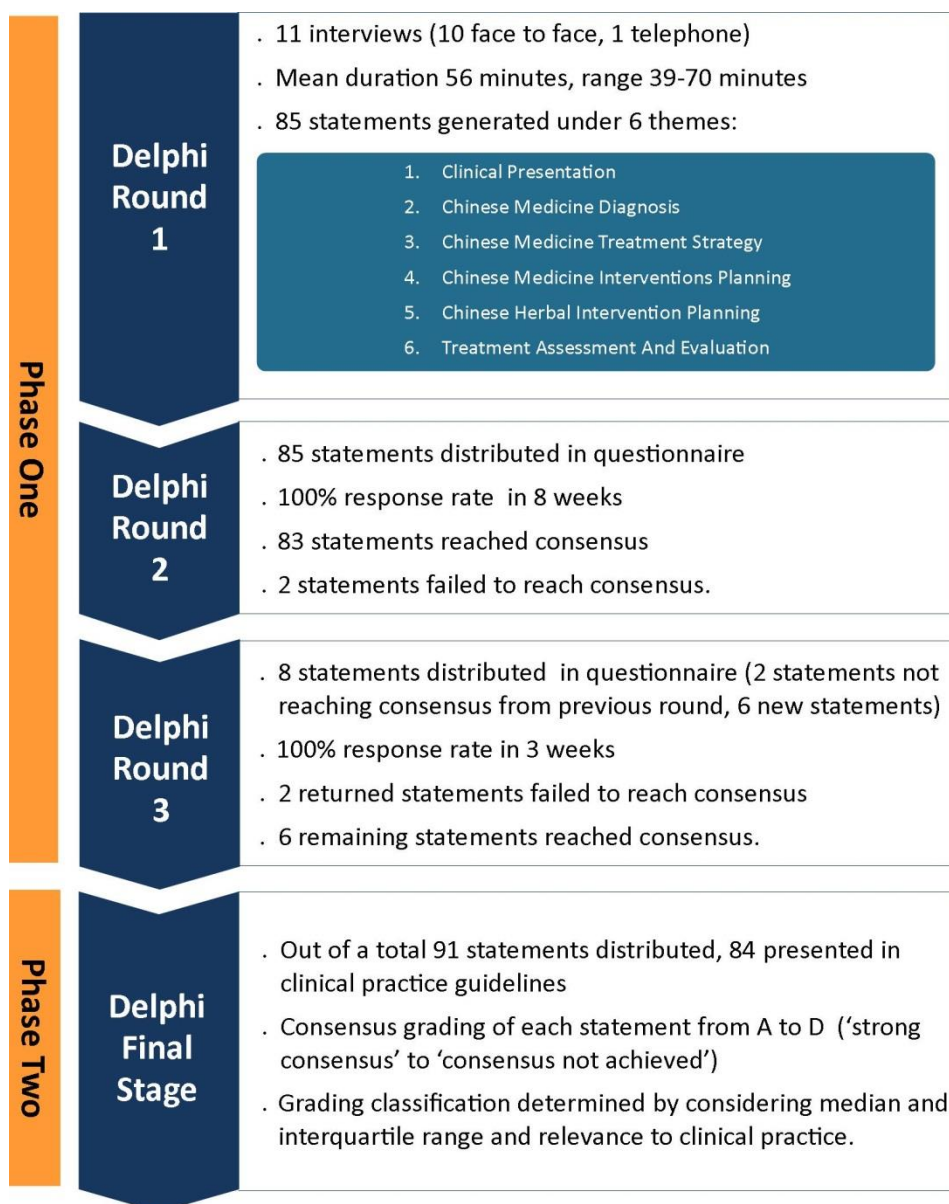
Characteristics	Number of participants (%)
Gender*	
Male	5 (45.5)
Female	6 (54.5)
CHM modality*	
TCM only	7 (63.6)
Classical only	1 (9.1)
Both TCM and Classical	3 (27.3)
Country* and school of herbal training*	
UK-trained	7 (63.6)
School of Herbal Medicine	1 (14.3)
Middlesex University	1 (14.3)
London College of Traditional Acupuncture	2 (28.6)
University of East London	1 (14.3)
London Academy of Oriental Medicine	1 (14.3)
College of Integrated Chinese Medicine	1 (14.3)
China-trained	4 (36.4)
Nanjing University	2 (50.0)
Beijing University	1 (25.0)
Henan University	1 (25.0)
Current country of practice*	
UK	11 (100)
Number of years in practice* (mean=18, range 4-34, SD=9.99)	
4-10	3 (27.3)
11-20	5 (45.5)
21-30	1 (9.1)
31-40	2 (18.2)
Number of PCOS patients per month*	
0	0 (0)
1-4	6 (54.5)
5-10	4 (36.4)
11-20	0 (0)
>20	1 (9.1)
Setting of CHM provision*	
Chinese medicine practice only	4 (36.4)
Multidisciplinary practice only	3 (27.3)
Chinese medicine practice and multidisciplinary practice	3 (27.3)
Chinese medicine practice, multidisciplinary practice, teaching clinic within academic institution	1 (9) [†]

*Purposive sampling criteria, *Information collected from second Delphi round,[†] Percentage rounded down to total 100%.

4.4.1.2. Initial round data collection

An overview of the results from Phases 1 and 2 is provided as a flowchart in Figure 19. These results will now be discussed in further detail in the subsequent sections.

Figure 19: Flowchart to show results of processes involved in Phases 1 and 2



Between August 2011 and October 2011, I conducted 11 one-to-one interviews. Although focus groups were initially offered to group members, concerns were raised by a number of practitioners such as time and availability

to travel to a location as well as uneasiness regarding participating in a group discussion. For this reason and because I deemed the number of interviews to be manageable within the timeframe, I decided that I would progress by conducting one-to-one interviews.

The interviews included 10 face-to-face interviews and 1 telephone interview and had a mean duration of 56 minutes, ranging from 39 to 70 minutes in length. For the 10 face-to-face interviews, I transcribed 2 of the interviews personally and with the remaining 8 transcribed by two external transcription services. For the 1 telephone interview, owing to technical failures, only the initial 10 minutes of the 65 minute interview was recorded and transcribed, and I took notes for the participant responses during the remainder of the interview. I personally checked all transcriptions for accuracy and field notes were taken for 9 of the 11 interviews and combined with the transcriptions during data analysis.

4.4.1.3. Initial round results

Thematic and framework analysis and statement generation for the questionnaire took a total of 3 months from the time of the first interview in August 2011 and until statement generation was complete in November 2011. Data analysis had taken longer than anticipated and all participants were sent a personalised email in October which, for some participants, had been 2 months since their interviews had been conducted. All participants were informed that data analysis was still underway and that the online questionnaire for the next phase in the study would be distributed within the next few weeks.

Exploring the data and attempting to capture the meaning of what participants were eluding to in their interviews was a challenging and rewarding process. Codes and themes that formed the basis of the thematic framework were continuously revised as new meanings and perspectives came to light with the addition of transcriptions and field notes to the data corpus. In order to maintain an emic perspective, and although I did not transcribe 8 of the 11 interviews, I remained close to the data by conducting all interviews and checking all transcriptions personally as well as by listening to the audio of each interview numerous times throughout data collection and analysis phase.

I felt that it was important to understand the viewpoints of each participant in the panel before attempting to draw out commonalities between members. This was a complex and lengthy process that took longer than originally anticipated but which, in true spirit of the Delphi process, enabled the analysis of the qualitative data and knowledge-creation to remain a truly iterative process.

During this process, it also became apparent how important it was for me to maintain reflexivity by remaining continuously mindful to the part that I as the researcher had personally played in the creation of the data. This is especially important in this study because of my professional background as a herbalist and because of pre-conceptions about providing clinical treatment for PCOS that I would have had as I started this study. As the researcher, I would also have had pre-study beliefs regarding which phenomena were, at least initially, to be explored. In addition because of the research question and because of the need to produce an output of a clinical guideline that had been clearly stated from the outset, this meant that the data was already and necessarily framed in this manner. There are clearly a multitude of advantages and drawbacks regarding these points which will be explored further in the discussion section of this chapter. However, at this stage it is important to highlight here that these points were necessary for me to reflect on and acknowledge throughout this process as the researcher attempting to construct new knowledge in this manner.

Developing the framework

Line-by-line coding of the transcripts from the first three interviews resulted in 52 initial codes being generated under 7 themes. These initial codes and themes can be viewed in Appendix 15. As analysis continued, it became apparent that 5 of these 7 initial themes were the most relevant to the research question and the codes of these 5 themes were then applied to the remaining 8 transcripts. The definitions of these codes under these 5 themes can be seen in Appendix 16 which additionally describes the positive and negative examples for each code, ensuring that these codes were mutually exclusive. Appendix 17 shows an excerpt from a coded transcript as an example of how coding was applied as numerical labels following framework analysis method.

After coding all the transcripts, a chart was devised to aid analysis and generation of statements. This chart consists of a spreadsheet with the codes and overarching themes along the top row, and the participants interviewed in the left hand column. The cells then contained summarised data for each code and for each participant where available, with a reference to the transcript page number for reference. Because the data is summarised in note form, and because of the layout of the chart, this enabled analysis to be conducted by participant as well as by theme. An excerpt of this chart can be viewed in Appendix 18: Chart For Framework Analysis which shows the data for all 11 participants under the 3 themes of Clinical presentation, Chinese medicine diagnosis and Chinese medicine treatment strategy.

Generating questionnaire statements

This chart was then used to facilitate my analysis of the data in order to ascertain what appeared to be the most important factors to consider when providing treatment for women with PCOS. This enabled me to generate statements about clinical practice that had been made by the participants and that I deemed relevant to the research question. From the 5 relevant themes that were initially generated from the corpus of data, 1 theme 'Chinese medicine treatment management' was separated into two themes 'Chinese medicine treatment strategy' and 'Chinese medicine interventions planning' for further clarity. The resulting 6 themes therefore were:

1. Clinical presentation
2. Chinese medicine diagnosis
3. Chinese medicine treatment strategy
4. Chinese medicine interventions planning
5. Chinese herbal intervention planning
6. Treatment assessment and evaluation

Under these 6 themes, 85 statements regarding clinical practice were generated for the second Delphi round. Figure 20 demonstrates the steps in which a statement was generated from the initial interview data that had been collected. Table 7 shows the number of statements that were generated by theme.

Figure 20: Generation of a statement from interview data

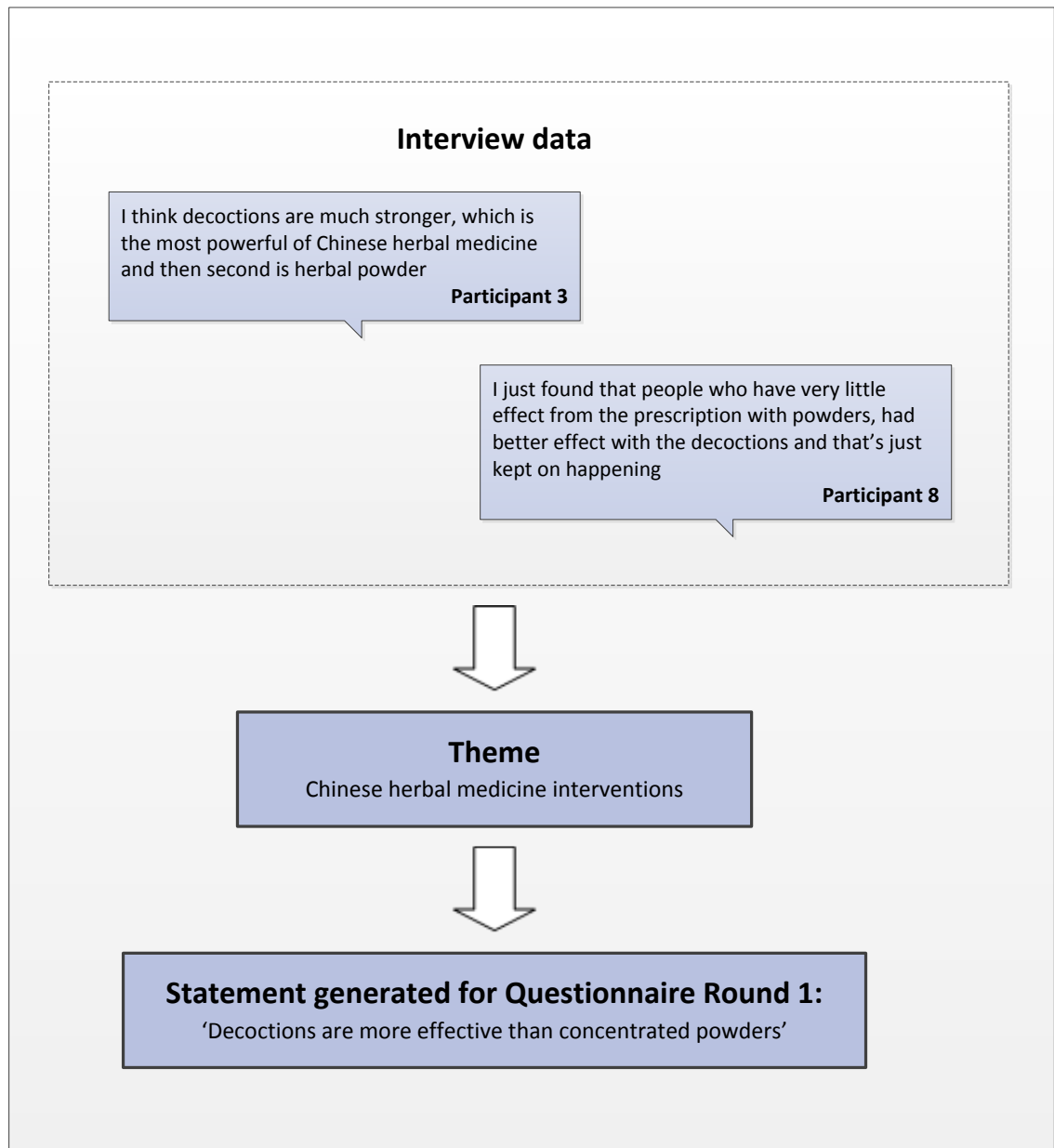


Table 7: Number of statements generated by theme for initial questionnaire

Theme	Number of statements generated
Clinical presentation	11
Chinese medicine diagnosis	12
Chinese medicine treatment strategy	4
Chinese medicine interventions planning	16
Chinese herbal intervention planning	17
Treatment assessment and evaluation	25
Total	85

It should be noted here that in the generation of the statements, the decision whether or not a statement was generated was not dependent on how many participants raised a similar point during their interviews but on the relevance to the research question. This means that even in cases where a minority of practitioners expressed a particular view, so long as this was relevant to the research question, this view would have still been returned as a statement for consideration by the entire panel.

These 85 statements were therefore prepared as part of the online questionnaire for distribution as part of the second Delphi round. These statements were presented in 16 sections and free-text boxes for additional comments were available at the end of these 16 sections. This questionnaire also included an additional 6 questions regarding clinical practice such as qualifications and country of training. Among these 6 questions was one that asked practitioners to state the typical daily dosage of concentrated herbal powders that they prescribed in PCOS. This was originally intended to be a statement item but I felt that could not be thoughtfully represented by such an item requiring agreement or disagreement. This was therefore instead presented as a question requiring participants to choose from a number of dosage ranges that had been generated from the interview data and that enabled categorical data to be collected.

The complete questionnaire that was distributed as part of the second Delphi round can be seen in Appendix 19.

4.4.1.4. Second round data collection

The questionnaire was distributed back to the original panel of 11 participants in late November 2011 via a personalised email containing a link to the questionnaire hosted on SurveyMonkey. 9 of the 11 participants (81.8%) responded within 2 weeks of distributing the questionnaire. Owing to public holidays in December, I followed up the remaining 2 participants in January 2012 with a telephone reminder and was successful in obtaining the remaining responses. A response rate of 100% had thus been successfully achieved within 8 weeks of the initial questionnaire distribution.

4.4.1.5. *Second round results and analysis*

There were three types of data that was collected and analysed from the second Delphi round: demographic and clinical background data, agreement ratings per statement item, and finally free-text responses that were offered by participants.

Demographic and clinical background data collected in the second Delphi round has already been presented within Table 6: Demographics and characteristics of recruited participants. For typical daily dosages of CHM powders prescribed in PCOS, 5 practitioners used 5-10g, 4 used 11-15g and 2 used 16-25g.

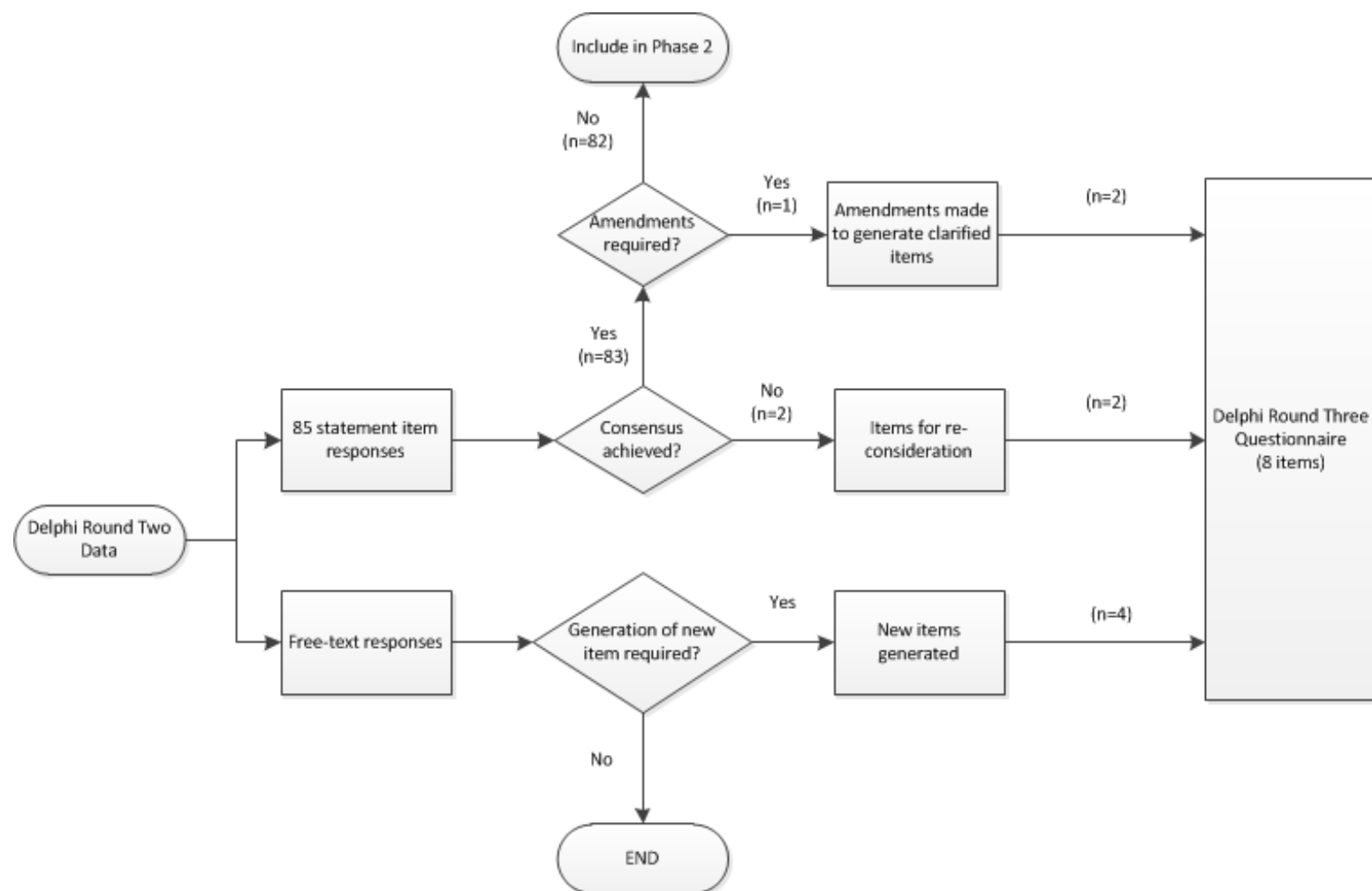
From the 85 statement items, group consensus existed in 83 items (97.6%) whilst 2 items (2.4%) failed to reach consensus. Free text responses were provided by one or more participants in 13 of the 16 free text boxes provided. These comments were considered alongside the responses to the statement items that were provided and also within the earlier thematic framework. This enabled me to see if the comments had already been taken into consideration by the interview data that had been collected and analysed and if not, whether the information was important for the panel to reflect upon in relation to the research question.

The 2 items that failed to reach consensus in the second round were automatically redistributed. From the 83 items that reached consensus, 82 of these were accepted for consideration for clinical guideline development in Phase 2 of this study. The remaining 1 item did reach group consensus. However, I received free-text responses from 3 participants indicating that the item required re-wording and clarification. For this reason, this item was separated into two new items and redistributed in the third round. The details of how this single item was treated in the data analysis are provided in Table 8. Free-text responses that were considered alongside the initial thematic framework also resulted in the generation of 4 new statement items. Figure 21 summarises the Delphi round two analysis by showing the flowchart of processes during data analysis and how this fed into the third Delphi round questionnaire.

Table 8: Clarification of original statement item by incorporating free-text responses

Delphi round two statement item	Free-text responses	Newly statement items for Delphi round three
Original item: Whilst patients are actively trying to conceive, Blood stasis removing herbs are not prescribed after CYCLE DAY 14	‘The perticular herbs with removing the blood stasis should be used around ovulation to promote ovulation's occurrence’ (Participant 1)	New item 1: Whilst patients are actively trying to conceive, Blood stasis removing herbs are not prescribed after OVULATION New item 2: Whilst patients are actively trying to conceive AND if they have a Blood stasis condition, it is suitable to prescribe Blood stasis removing herbs after OVULATION
	‘For question 6, my answer is "blood stasis removing herbs are not prescribed after ovulation" rather than "after cycle day 14", since pcos patients are often have irregular periods, they may not ovulate or ovulate late’ (Participant 2)	
	‘A tiny amount of blood moving herbs can sometimes be effective when a patient with an underlying condition of blood stasis is actively trying to conceive’ (Participant 11)	

Figure 21: Delphi round two data analysis and item preparation for Delphi round three



The questionnaire that was presented for the third Delphi round therefore consisted of 8 items in total; 2 items for reconsideration; 2 clarified items; and finally 4 new items. Free-text comment boxes were available at the end of 2 sections of this questionnaire and which allowed participants to volunteer further comment as necessary. Since the questionnaire for presentation in the third round was personalised to each participant as described in earlier sections, an example of a questionnaire for one of the participants is show in Appendix 20.

4.4.1.6. Third round data collection

The questionnaire for the third Delphi round was distributed to the original panel of 11 participants at the end of January 2012. All 11 participants responded within 3 weeks of distributing this questionnaire and a 100% response rate was thus achieved for the third Delphi round.

4.4.1.7. Third round results and analysis

There were 2 items that were redistributed for reconsideration by the group. For one item, 5 participants chose to re-rate the item. Analysis by taking into consideration the new ratings provided by these 5 participants and combined with the previous ratings given by the remaining 6 participants indicated that group consensus was not achieved with this item. For the remaining item, all 11 participants declined to change their ratings. This meant that the two returned items did not achieve group consensus after re-consideration and it was decided that no further redistribution of these items would be required.

For the 2 clarified items and the 4 new items, group consensus was achieved. Free text responses by one or more participants were obtained in both available sections. Analysing these responses in light of the thematic framework that had been developed, further amendments to current items and generation of new items was deemed unnecessary. These 6 items were therefore accepted for consideration in Phase 2 of the study.

After three Delphi rounds, comprising one interview round and two questionnaire rounds spanning over 7 months, the Delphi study was brought to a close in March 2012. All participants were informed of the study closure and thanked for their participation. At the study conclusion, a total number of 91 unique statement items had been distributed for consideration by the

panel, of which 89 (97.8%) reached consensus and 2 (2.2%) did not. The next section will describe in detail the processes that took place in Phase 2 to determine how these statements from Phase 1 were eventually incorporated into the development of a clinical guideline for CHM prescribing in PCOS.

4.4.2. Phase 2

It was important at the end of phase 2 for me to be able to present the data gathered from phase 1 into a single coherent and practical guideline. It was also important that this guideline could be used as an initial framework of good clinical practice and which, as guidelines ought to, could provide a sufficiently broad scope to capture the fundamental principles of good clinical practice but that was detailed enough to be clinically useful to practitioners. The concluding set of guidelines can be seen in Appendix 21. This next section will now describe the processes that took place in order to develop this set of guidelines.

When reviewing the 91 statement items, I decided that 84 (92.3%) of these items would be included in the concluding set of clinical guidelines. 7 items (7.7%) were thus discarded in total. One item required clarification and, as described in an earlier section, was replaced with two new items in Delphi round three and it was decided that as the two new items were modifications of the previous single item and accepted onto the guideline, that this original item would be discarded. For the remaining 6 items, these had been sufficiently represented by accepting associated items onto the guideline. These 6 were items under the theme of Treatment assessment and evaluation and Table 9 is an example illustrating how the decision to accept one item and discard 2 associated items was made by taking into consideration the median rating and IQRs per item.

Table 9: Retention and discarding of associated items in guideline development

Statement item	IQR*	Median	Action	Reason for action
When prescribing Chinese herbs for delayed periods in PCOS (cycles longer than 35 days), a regular menstrual cycle is observed:				Statement for 'Within 6 months' produced strongest agreement of the three statements in terms of IQR
Within 6 months	0	6	Retain for guideline	
Within 9 months	1.5	6	Discard	
Within 12 months	2	6	Discard	

*IQR=Interquartile range

For the 84 statement items, two of these statement items were combined together to form one item in the guideline as it was considered to be a more clinically useful way of presenting the information. This is illustrated in Table 10.

Table 10: Combining of two statement items for guideline presentation

Original items	Presentation in the guideline
When regulating menstruation in PCOS, a regular menstrual cycle is the observation of: 3 consecutive menstrual cycles	When regulating menstruation in PCOS, a regular menstrual cycle is the observation of 3 consecutive menstrual cycles, each 35 days or less in length
When regulating menstruation in PCOS, a regular menstrual cycle is the observation of: Menstrual cycles, each 35 days or less in length	

This meant that the data from 84 statement items was considered in the guideline and which were eventually presented as 83 guideline items, each of which were assigned a grading per item based on the strength of group consensus on this item using the methods described in earlier sections. At this point it is worth explaining that although this was a consensus-seeking study, I felt it important that items not achieving consensus were still presented within the guideline. Although it could be argued that such items may not be clinically useful if consensus failed to be reached, I felt that it was important to be able to reflect on and present diversity in some perspectives that clearly existed within the panel of practitioners. Furthermore, as there were only 2 items that failed to reach consensus, I felt that this would not have had a significant effect on the amount of space available in the final clinical guideline.

The remaining clinical practice points regarding typical prescribed dosages are presented firstly as a range across the two most commonly used dosage categories of 5-10g and 11-15g and secondly as a statement that dosages of up to 25g per day could be routinely prescribed. These 2 practice points are intended to illustrate both the complete as well as the typical range of dosages. As these had not been presented as statement items to the panel, there was no grading assigned to these two practice points.

The concluding set of clinical guidelines therefore consists of 83 statement items and 2 dosage practice points presented under 6 themes, totaling 85 guideline items. The majority of these items achieved A grading for strong group consensus (65 items in total, 76.5%) and the theme Treatment assessment and evaluation was the theme under which the highest frequency of guideline items were presented (28 items in total, 32.9%). Table 11 shows the composition of the complete clinical guideline by illustrating the frequency of guideline items by theme and by consensus grading.

Table 11: Frequency of guideline items by theme and by consensus grading

Theme	Consensus grading*					Number of guideline items n (%)
	A	B	C	D	NA	
Clinical presentation	8	1	2	0	0	11 (12.9)
Chinese medicine diagnosis	11	1	1	0	0	13 (15.3)
Chinese medicine treatment strategy	3	0	0	1	0	4 (4.7)
Chinese medicine interventions planning	15	3	0	1	0	19 (22.4)
Chinese herbal intervention planning	6	1	1	0	2	10 (11.8)
Treatment assessment and evaluation	22	5	0	1	0	28 (32.9)
Total n (%)	65 (76.5)	11 (12.9)	4 (4.7)	3 (3.5)	2 (2.4)	85

*where A=Strong consensus, B=Moderate consensus, C=Weak consensus, D=Consensus not achieved, NA=Not applicable since items were not distributed for rating

A sample of the clinical guidelines can be seen in Figure 22. The concluding set of clinical guidelines is available in Appendix 21.

Figure 22: Sample of the concluding set of clinical guidelines for the CHM treatment of PCOS

5. Chinese Herbal Intervention Planning	Consensus Grade
5.1. Decoctions are more effective than concentrated powders	A
5.2. Concentrated powders are suitably effective for PCOS	A
5.3. Individualised herbs are more effective than standardised herbs	A
5.4. Individualisation is important:	
5.4.1. To adapt to the specific needs of the patient	A
5.4.2. To prevent resistance to a herbal prescription	C
5.5. In Blood stasis, herbs for removing Blood stasis should be prescribed for use during menses	A
5.6. Whilst patients are actively trying to conceive:	
5.6.1. Blood stasis removing herbs should not be prescribed after ovulation	B
5.6.2. It is suitable to prescribe Blood stasis removing herbs after ovulation, IF patients also present with a Blood stasis condition	A
5.7. The prescribed daily dosage range of concentrated powders is 5g to 25g	NA
5.8. The most frequently prescribed daily dosage range of concentrated powders is 5g to 15g.	NA

4.5. Discussion

The main aim of this Delphi study was to find out what constitutes good clinical practice for CHM practitioners treating PCOS. This study adopted the Delphi approach to facilitate a systematic and rigorous practitioner-consultation exercise with 11 CHM practitioners based in the UK, resulting in the development of good clinical practice guidelines. These guidelines consist of 85 items illustrating key features of good CHM prescribing practice for PCOS, each of which have been assigned a grading of consensus strength. The guidelines also describe the range of symptoms and signs that women with PCOS present with, common CM diagnoses in PCOS and practice points regarding how treatment is planned, managed and evaluated. These guidelines will now be used to inform the design of the CHM intervention in a forthcoming RCT. The next sections will describe the strengths and weaknesses of this particular study, before placing the findings of this study into context within the existing literature, and also within this thesis.

4.5.1. Study strengths

4.5.1.1. *Qualitative interviews with panel members*

All 11 participants were interviewed qualitatively on a one-to-one basis in the first Delphi round. Though focus groups were offered for this round, it became apparent that this was not logistically feasible. The decision to use focus groups and interviews was a modification of the conventional Delphi which would typically present material from existing literature remotely via questionnaire or letter, and invite the panel for feedback in this initial round. The conventional method has been adopted in several CM protocol-development Delphi studies to date (Alraek et al., 2011, Smith et al., 2012, Smith and Betts, 2014) whilst other studies have modified the method by interviewing a small number of the Delphi panel qualitatively before presenting the results of these interviews to the remaining panel (Cochrane et al., 2011). One-to-one interviews with each panel member have been used in a Delphi study previously (Flower et al., 2007) and although I found it considerably more time-consuming to conduct interviews and analyse the interview data, this modification was adopted for good reason. Interviewing participants enabled me to gain deeper insight into the perspectives of each participant and which could be enhanced by asking for further elaboration, or exploring areas of particular interest or of minority views that would not have been possible by sending out a static open-ended questionnaire. This had the advantage of gathering more meaningful data by adopting an inductive approach and which enabled me to draw out commonalities more effectively for the subsequent deductive rounds. Interview data also enabled me to use the terminologies that practitioners had themselves used during interviews in order that I could depict as closely as possible the wording of clinical practice points whilst preparing statements for re-distribution. Using qualitative interviews therefore, in my view, enhanced the overall quality of the study and resulted in more accurate meanings of practitioners' accounts.

4.5.1.2. *Response rate*

Low response rates in Delphi studies can be particularly prevalent and previous studies have demonstrated that these could be enhanced by enabling participants to express their views through personalised contact in the initial round (McKenna, 1994). I feel that using interviews in this study did contribute towards the 100% response rate achieved in the Delphi questionnaire rounds,

perhaps through increasing participants' sense of ownership of the study. A further point is that had I only offered the option of attending focus groups to this particular panel, I feel that this could have affected response rates and recruitment rates adversely. In some cases this would have been due to practical reasons such as arranging a suitable time and location for busy practitioners. More interestingly however was that some practitioners appeared uneasy when I informed them that a focus group with other practitioners may be held. For these practitioners when the choice of arranging a one-to-one interview with me was offered, a sense of relief was apparent. Although this is speculative, this may have come about for example because of anxieties surrounding expressing personal views about practice that may differ from or oppose those held by other practitioners who they may feel are more experienced or more qualified. The CHM community in the UK is relatively small, consisting of several groups of practitioners and is a profession that is not yet accustomed to working together frequently, especially for research purposes. As such, the prospect of a mutual sharing of opinions and viewpoints and of open debates in a professional manner may be rather daunting to some practitioners. The flexibility of being able to offer interviews in this study therefore enabled the preservation of anonymity from one another and which appeared to be important to a number of practitioners on the panel. Participant anonymity is characteristic of the Delphi and it has been argued that anonymity could cause participants to take less responsibility when expressing views. It is my opinion however that anonymity in this particular panel of practitioners facilitated a sense of openness and mutual respect, creating an environment in which participants felt that minority views could be offered without judgment and which, where relevant, could be fed back in a systematic manner for consideration by the entire panel. Anonymity was therefore a key feature that was appropriately utilised in this Delphi study to facilitate as rigorous a scoping exercise as possible.

4.5.1.3. Administrative management

Delphi studies depend on the appropriate management of participants and on efficient administration throughout the course of the study, something that is widely discussed in the literature. It is perhaps particularly important in a study of this kind because of the duration and rounds of participation required of the practitioners (Linstone and Turoff, 2002). Strengths of this study

included personalised, appropriate and timely communication between the research team and practitioners, setting expectations with participants, managing issues that arose and the ability to respond flexibly to participant responses through the iterative nature of the Delphi process. This more personalised approach was possibly easier in this study because of the manageable sample size and because all practitioners resided in the UK. This nonetheless could have contributed participants to feeling valued and having their views acknowledged and thereby nurturing a sense of mutual trust and respect between practitioners and the research team. This could also have influenced the response rate achieved and although this personalised approach may not be possible for all studies, particularly larger or international Delphi studies, it is certainly worthwhile taking these factors into consideration in the planning stages.

4.5.2. Study Limitations

There are a number of limitations to this study that need to be acknowledged.

4.5.2.1. Panel representation

This study failed to recruit from a range of Western countries as intended and in the end I was successful only in recruiting practitioners working in the UK. This was for a number of reasons for example: professional organisations overseas having limited capacity to help with research; practitioners holding negative attitudes towards research due to beliefs or previous experience; and practitioners being too busy to participate. One could thus argue that this could limit the transferability of these results to practices in other Western countries. However, some practitioners on the Delphi panel reported using clinical methods described from a number of key CHM gynaecology texts. These texts had been written by two eminent CHM practitioners that I had attempted to recruit – one from the US and one from Australia. One could therefore argue that the views of these two practitioners could have been sufficiently represented by those using such clinical methods on the panel, a similar finding to an earlier Delphi study on acupuncture (Cochrane et al., 2011). Future research involving consultation of CHM practitioners such as in this study could benefit by developing links with, or scoping interest from, key practitioners at an earlier stage of the research project. This could be successful in generating interest and awareness about the research topic in order to minimise the number of ‘cold-calls’ that need to be made to busy

practitioners as well as in facilitating planning of the study by taking into consideration the schedules of these practitioners to maximise recruitment.

Owing to language restrictions and lack of resources, I could not recruit practitioners directly from East Asian countries such as China and Taiwan where CHM is widely prescribed. However, I had accounted for this in the planning stages by including a purposive sampling criterion for ‘country of CHM training’ and was successful in recruiting 4 UK practitioners who had received training in China from three different institutions. For the purpose of this study, I deemed this to be sufficient representation from East Asia. Although it would be preferable to recruit practitioners directly from East Asian countries, for research groups where this is not possible, I feel including ‘country of CHM training’ as a sampling criterion was an extremely helpful way of incorporating a wider range of CHM-prescribing views.

4.5.2.2. Selection of the panel

One of the most common criticisms of the Delphi relate to potential bias in the selection of participants and the definition of the informed individual.

Although I acknowledge that the purposive sampling method introduces a certain level of bias in the selection of participants, I attempted to minimise this by pre-specifying purposive sampling criteria. An example is the criteria to recruit practitioners from different CHM modalities in order to consider diversity in schools of thought that might exist. To protect from selection bias further, I approached third party organisations and individuals for practitioner recommendations. All recommendations provided by these parties were followed up and for further transparency, I have also provided clear justification for excluding other potential participants. It is possible for future studies to conduct a more systematic approach to panel selection such as sending a mailshot to a random selection of registered CHM practitioners. Although I lacked time to carry this out in the present study, this could be planned for in future studies to further minimise selection bias.

Others have argued that the commitment participants need to dedicate to a Delphi study requires them to have a vested interest in the research topic and which could in turn introduce selection bias as well as response bias. This may be a particularly pertinent issue in this study since I myself am a trained CHM

practitioner, with considerably fewer years of experience compared to the majority of the panel and am relatively unknown within the CHM community compared to the panel who mostly held informal or formal CHM teaching or research positions. This meant that practitioners could have seen taking part in this study as an opportunity to potentially influence the nature and direction of CHM research and practice by voicing thoughts and opinions to somebody who they perceived could understand their language, who could better relate to their concerns, and who at the same time could be considered junior enough for them to speak comfortably openly to. This is possibly influenced by the issue that research in CHM is scarce in the UK, particularly government-funded research as this study, and the novelty of being invited onto and being involved in such a research study may have influenced practitioners' decisions and motivations to participate. Furthermore, changes to EU legislation had imposed restrictions in the way CHM was practiced in the UK from April 2011 and that had created considerable confusion and uncertainty in the CHM community. The time of study recruitment had been only a few months since these changes had been enforced, and it is possible that this study recruited at a time when CHM practitioners were feeling particularly motivated to influence CHM practice by contributing to research. In these circumstances, response bias could be introduced since these participants could be particularly motivated to provide responses that they feel are desirable or necessary for what they perceive to be the purposes of the research study. However, I incorporated measures in an attempt to counter this. For example, I ensured the information provided in the participant information sheet regarding the purpose of the study was relatively broad. Furthermore, I did not provide an interview brief in advance to participants and informed participants that there was no right or wrong response. I also asked non-leading questions which ensured that responses were not contextualised by specific purposes of the study. These measures reduced the likelihood that participants could provide socially desirable responses during the interview process which could be considered a relatively naturally-occurring account in comparison to a questionnaire. This also maximised the credibility of the qualitative interview data upon which the subsequent Delphi questionnaires were based.

In my view, anonymity from other participants also encouraged participants to feel more comfortable in responding truthfully. In addition, the qualitative

data was analysed at a relatively manifest level for the purposes of this study. For example descriptions of patterns commonly presented by women with PCOS were drawn out for the clinical guideline which I feel are less likely to be influenced by social desirability, especially when compared with deeper and more meaningful qualitative information such as attitudes towards conventional medicine. Therefore, I feel it less likely that such responses would have significantly biased the information that I used to answer the main research question regarding the provision and delivery of CHM care.

4.5.2.3. Definition of consensus

Despite CHM being a complex intervention, I have demonstrated that it is possible for attain a high level of agreement regarding principles of good clinical practice amongst a panel of diverse CHM practitioners. The definition of consensus is a frequently raised issue with the Delphi design and which also affects validity. For Phase 1, consensus was defined a priori, and was determined per item. One of the reasons for this high level of agreement could be that statement items in both Delphi rounds two and three were positively-worded in order to aid analysis. Although this is widely used in Delphi studies, I acknowledge that a certain level of acquiescence response set could have been introduced, that is the tendency to agree rather than disagree throughout the set of questions, and which could have resulted in the high number of items that I found reached consensus. I would recommend future researchers to use both positively and negatively worded items within their questionnaires in order to protect against potential response sets in participants. However, I believe that practitioners were genuinely motivated in contributing to the study thoughtfully since further comments were offered in Delphi rounds two and three, suggesting that acquiescence bias may not have been as significant an issue.

It is also possible that despite apparent heterogeneity in the practice of CHM, high level of consensus can be achieved in certain aspects of CHM practice. I have successfully shown this to be the case in the present study topic of key practice principles and which may be because data analysis is occurring at the manifest 'face-value' rather than latent 'interpretative' content level. In this Delphi study, I have been seeking to draw out details of the process and transactional elements of practice rather than delving into the meaning and

reasoning of these processes. It is likely that research using this level of analysis has a greater potential to reach a high level of agreement as I found in this study and serves as a helpful reminder that research questions exploring more contentious or interpretative areas are probably be better suited to standalone qualitative, rather than consensus-seeking, methods.

4.5.2.4. Other reliability issues

The qualitative analysis was conducted by myself and checked by other members of the research team. I acknowledge that coding and/or further analysis of the same dataset by a second qualitative researcher could have improved the reliability of the results. However, this would have taken a considerably longer time and I had already experienced delays to the project during the qualitative analysis stage. Furthermore, one could argue that by attempting to capture participants' responses and summarising it within a statement item that was distributed to participants in Delphi round two, this could serve as a form of member checking or respondent validation. By enabling participants to provide further comment via free-text boxes, this served to facilitate participants' agreement or disagreement with my interpretation of the data, and thereby maximising the credibility of these findings.

Debate also exists over the reliability of results from Delphi studies, in that if two different panels were consulted in the same manner, would the same conclusion, or in this instance the same set of clinical guidelines, be reached? In some ways the arguments regarding reliability relate to issues that have already been explored in previous paragraphs, for example how informants were selected or how qualitative analysis was conducted which clearly have an influence on the degree of consistency of a study outcome. However, I have attempted to further safeguard against these issues concerning reliability by incorporating measures such as keeping an audit trail to document decisions and processes, and ensuring transparency and reflexivity in data analysis. These serve to increase the strength of the findings by reporting methods and decisions in a transparent manner that would allow others to critically evaluate.

4.5.3. Reflections on the Delphi process

This study has enabled identification and consensus of key aspects of CHM prescribing for PCOS and the sections so far have provided a critique of the

process and of the findings from a researcher's perspective. There are however a number of additional points to reflect upon from a clinical perspective and also within the wider context of CHM and CM research which I will now discuss further.

4.5.3.1. Modelling CHM as a complex intervention

It was important for this study to be able to provide scope and begin the process of identifying core principles of CM treatment and clinical management. The one-to-one qualitative interviews provided me the opportunity to do this by gaining deeper and more meaningful insight into each practitioner's perspective of treatment provision, but also how the varying fragments of data might relate to each other. During analysis, patterns in the data emerged in both the content of practitioner accounts, but also the way in which practitioners were presenting them. For example when practitioners were discussing carrying out treatment, it was clear that practitioners were triangulating many pieces of information presented by the patient in order to make important clinical decisions. This also shows that the six broad themes in which I have ordered the statements in the guideline are very much interlinked and related and should not be regarded as static and unrelated components. This highlights the complex nature of CHM treatment provision as it is practiced in the real-world, a finding in previous Delphi studies carried out in acupuncture and CHM (Cochrane et al., 2011, Flower et al., 2007). It does also raise concerns that this could lead to a reduction of this rich and highly descriptive qualitative data into static and more abstract clinical statements. Although I acknowledge this has happened to a certain extent in this study, I believe that deeper meanings have been appropriately captured in the data where this has been relevant to the research question, and that a certain degree of reduction in qualitative data was necessary to be able to produce practical and clinically useful guidelines that could also be used to inform the development of the trial protocol. Reflecting on the qualitative data that was obtained from the interviews however provides a useful reminder of the challenges that can be involved in attempting to model a complex intervention such as CHM and the role that consensus methods can play in shaping the definition of such a model.

4.5.3.2. Reflective practice

Through the interviews, the practitioners in this study described a range of contexts in which they provided treatment and also provided reflective accounts about their practice, successes and frustrations. Being able to reflect upon this by comparing these accounts to my own helped me as a practitioner to gain a broader perspective about clinical and patient management in PCOS. For example, the interviews provided me with new ideas for when adopting certain treatment strategies may be more appropriate; it helped me see alternative ways in which a conventional medical result could be interpreted from a CM perspective and acted upon in CHM prescribing; it enabled me unique access to an experienced practitioners' views on different combinations of herbs that could be administered for a particular symptom or CM pattern in PCOS. Obtaining these different perspectives challenged my own pre-conceptions about what I thought I knew and understood about PCOS and CM, but in the process also fostered a deeper sense of curiosity about the way in which CM treatment is provided and understood by other practitioners. Although CM textbooks and indeed good practice guidelines offer guiding principles for treatment, the clinical insight offered by individual practitioner accounts and patient case studies can be significantly more detailed and at times more clinically useful, and also emphasises the role that exchanging ideas with other practitioners in a non-threatening environment can play in encouraging reflective practice.

4.5.3.3. Possible directions for future work

This study has demonstrated that it is feasible to conduct a consensus study in order to inform the development of treatment protocols in CM research, echoing the findings of other Delphi and NGT studies in this area (Flower et al., 2007, Cochrane et al., 2011, Smith et al., 2012, MacPherson and Schroer, 2007). Qualitative methods are being increasingly incorporated into CM Delphi studies but this and the study by Flower et al. (2007) are the first to my knowledge that have conducted qualitative interviews with each of the panel members in the first Delphi round. Although I maintain that this was a strength of this study, I do acknowledge that there was a significant amount of additional work particularly in the qualitative analysis that increased this study's duration and that would affect this method's scalability in terms of

involving more practitioners in a future larger Delphi study. Obtaining qualitative data certainly can enrich the data and bring about more meaningful statements, but I believe that the method used by Cochrane et al. (2011) of conducting a smaller number of qualitative interviews and adopting an online forum to include the remaining Delphi participants could have enabled us to reach a similar output in less time and at less cost.

The range of consensus studies conducted to date shows that it is possible to achieve consensus in a number of clinical practice points despite the diversity in practice that clearly exists. Some of these practice points can be seen to be generic to CM e.g. 'Treatments in Chinese medicine are based on pattern differentiation', whilst others are more specific to the treatment or to the condition being investigated e.g. 'In PCOS, combined excess and deficiency patterns are found'. If consensus methods continue to be adopted to inform experimental research in CM, it may be a more effective use of resources to determine an internationally-agreed set of generic CM good-practice points relevant to both acupuncture and CHM. This research would not be without its own challenges owing to the diversity in the styles of CM practice cross-cultures, the interpretations of CM terminologies as well as the requirement for a number of research groups to co-ordinate such a project. If successful however, future CM research involving specific research questions could then build on this work by focusing efforts on determining the condition or symptom-relevant consensus statements to inform their project-specific treatment protocol.

Having undertaken a Delphi study, I believe that some of the data collected in the interviews could have been done so much more effectively using a CHM practice database. This could work along the same principles as the General Practice Research Database (GPRD) from which clinical and prescription data from anonymised patient records could be accessed and used for both clinical, monitoring and research purposes. Had information from such a database been available for this study, it is possible for this information to have been presented to practitioners for comment in the initial Delphi round and which could have significantly reduced the time required for this study. However, in the wider context of CM, this could present a significant opportunity in terms of timely provision of clinical information which, over time, could lead to larger

datasets from which observational studies could be conducted and which could have a potential role in informing the direction or format of forthcoming experimental CM research. A similar database has already been developed in Taiwan where the government provides reimbursement for CHMs and for which CM practitioners are required to submit patient-level data and prescription information. This has enabled nationwide data to be collected in Taiwan and which has led onto the evaluation of various aspects of CHM prescribing in Taiwan such as commonly prescribed herbs for certain conditions, commonly co-prescribed conventional medications and the safety of CHM (Chen et al., 2011, Lin et al., 2012). A similar project in the UK would be worthwhile considering and would be advantageous to a number of stakeholders in the UK including CHM practitioners, conventional medical professionals, researchers and policy-makers.

4.6. Conclusion

This Delphi study has been successful in identifying and achieving consensus in key features and components of CHM-prescribing for PCOS in order to produce guidelines for good clinical practice. The guidelines describe the range of symptoms and signs that women with PCOS present with, common CM diagnoses in PCOS and practice points regarding how treatment is planned, managed and evaluated. In the next chapter, I will demonstrate to the reader how the information gathered from this Delphi study and the resulting set of clinical guidelines were used in the protocol development of a planned placebo-controlled randomised clinical trial involving CHM treatment for PCOS in UK primary medical care.

Chapter 5: Development of a protocol for a placebo-controlled randomised feasibility and pilot study in primary medical care

5.1. Introduction

The purposes of the systematic review and the Delphi study had been to help develop and inform the protocol for a feasibility and pilot study which could potentially lead to a definitive and fully-powered main study in UK primary care. Unfortunately, the initial protocol for this study was necessarily revised owing to difficulties and challenges that I faced in obtaining information required for clinical study authorisation to be granted in a timely manner. Owing to the time constraints on the PhD, I and my supervisors decided a modification of the original protocol would be necessary and which will be presented detail Chapter 6.

In this present chapter, I will firstly discuss how the systematic review and Delphi study contributed to shaping key aspects of the trial protocol. I will then present in detail the issues that arose during the process of setting up the initial study and offer suggestions to mitigate against these from arising in future research.

5.1.1. Designing the study protocol

The systematic review and Delphi study provided key information regarding current research into and practice of CHM for PCOS. This made it possible for me to build this new information into the design of the feasibility study in three main ways:

1. Choice of outcome measures

The Delphi study results suggested that menstrual irregularities, hirsutism and weight issues were amongst some of the most commonly seen PCOS-related symptoms in private practice. Similar outcome measures were also reported in

the RCTs from the systematic review and which provided support for our choice of these measures in the feasibility study. It was particularly relevant that PCOS-related menstrual irregularities were reportedly commonly encountered in CHM practices. This appears to suggest demand from the patients' perspective and that practitioners are likely to be confident in offering CHM as a treatment option. In this way, this earlier work provided additional confidence in the choice of menstrual irregularities as the primary outcome measure.

2. Content of standardised CHM

The focus and subsequent contents of the standardised CHM was based on PCOS diagnostic patterns that were found in the review and the Delphi study. The Delphi guidelines suggest that a combination of excess and deficiency patterns are found in PCOS and that it would be important for a single standardised CHM remedy to address both types of patterns simultaneously. I then used the list of individual herbs that had been extracted from the RCTs in the systematic review and combined this with the excess and deficiency patterns put forward by the Delphi participants. This provided further focus for the standardised CHM and the final contents of the standardised CHM were agreed upon through a discussion with Dr. Flower as the senior herbalist within the research team. This process is detailed further in a later section 6.2.2 Study Medications, and in Figure 24: Decision-making process for contents of standardised CHM.

3. Administration of CHM

The Delphi results provided further information regarding the administration of the CHM intervention. For example, whilst decoctions were typically regarded as being the most effective administrative form for PCOS, participants appeared to agree that concentrated powdered CHMs were 'suitably effective' for PCOS. The prescribed dose of CHMs was also informed by the Delphi which appeared to suggest that although a prescribing range of 5-25g existed, typical daily dose appeared to be 10-15g. Anticipating some degree of non-adherence owing in part to the length of the study, I and Dr. Flower decided that the daily dosing range for the study would be 16g. The Delphi was also the main driver behind a revision in the initial study duration from the initially

proposed treatment course of 4 months to 6 months. 6 months had been deemed by Delphi participants as being the appropriate length of treatment for improvements to be observed in oligomenorrhoea. Given this was a feasibility study, I deemed this an important point to consider and the protocol was subsequently revised to reflect this.

The above account demonstrates that preliminary work through the systematic review and Delphi study was valuable in ensuring the study protocol was appropriately informed by the available evidence and clinical practice points. In the next section I will focus specifically on the process of setting up a feasibility study in NHS primary care, and discuss further the challenges that I was faced with in this process.

5.1.2. The initial study design

Since the design of the feasibility study would depend on the research questions for a definitive main study, it is necessary to firstly introduce the primary research question for this main study which is as follows:

- 1) Is CHM plus usual care superior to placebo plus usual care and to usual care alone for oligomenorrhoea and amenorrhoea in PCOS?

The secondary research questions for this main study are:

- 1) Does CHM reduce obesity or hirsutism in PCOS?
- 2) Does CHM improve quality of life in PCOS?
- 3) Is CHM safe?

My intention was to adopt an RCT design as the main study design as this would provide the most robust scientific evidence possible in order to answer my primary research question for the main study. However, the assessment was that there remained a great deal of uncertainty regarding how appropriate it would be to immediately conduct a fully-powered CHM trial in the UK and that important pieces of information were lacking such as data to support a suitable power calculation and uncertainty surrounding recruitment. For this reason, I and my supervisors felt that a feasibility and pilot study would be a necessary next step prior to a fully-powered RCT.

Feasibility and pilot studies are recognised as important research designs as part of the MRC complex interventions research framework and are typically adopted to gather valuable information for planning resources and reducing

uncertainties for a full-scale trial (MRC, 2000, Lancaster et al., 2004, Craig et al., 2008, Arain et al., 2010, Thabane et al., 2010). This is especially relevant when in this present situation of conducting a CHM trial in England for a number of reasons. Whilst prevalence of herbal medicine use remains high, CHM has suffered a tarnished public image in recent years owing to adverse media reports on its safety and it is unclear how this may affect the acceptability of the intervention to patients (Hunt et al., 2010). Furthermore, although a small number of CHM RCTs have been conducted in England (Sheehan et al., 1995, Flower et al., 2009), none have recruited specifically from a PCOS population and it is unclear how successful recruitment from this population would be. In addition, trials of complementary medical interventions and in particular trials conducted in NHS settings such as primary care require specific practical considerations such as willingness by GPs to recruit for such trials or patient preferences, and which I felt I would be unable to address without gathering preliminary information (van der Windt et al., 2000, Fransen et al., 2007, Bell-Syer et al., 2008). Owing to these uncertainties involved in planning a definitive trial, I and my supervisors agreed that initial investigation using a feasibility pilot study design was warranted which would enable important preliminary data be gathered regarding the study's feasibility and evaluation of the study techniques through a piloting process.

Set against the backdrop of these research questions for the main study, the aims of the feasibility study were as follows:

- To assess the feasibility of conducting an RCT in UK primary care using CHM for PCOS-related oligomenorrhoea and amenorrhoea
- To pilot and evaluate the study procedures such as randomisation and data collection.

My initial study design was in a primary care setting recruiting participants from NHS general practices using the Primary Care Recruitment Network (PCRN) and featured three parallel arms: standardised CHM plus usual care; placebo plus usual care; usual care alone. This design was chosen to enable an assessment of superiority in the main study by comparing specific effects (CHM plus usual care versus placebo plus usual care), contextual effects (placebo plus usual care versus usual care alone) and real-world effects (CHM plus usual care versus usual care alone). In order for authorisation to be granted for this study, approvals were required from NHS R&D and NHS

Research Ethics since the research was being conducted on NHS patients. Approval was also required from the Medicines and Healthcare products Regulatory Agency (MHRA) since both the standardised CHM and placebo preparations would be regarded as test and reference substances within the context of a clinical trial and therefore classified as investigational medicinal products (IMPs) according to European Legislation (Article 1, paragraph 2 of Directive 65/65 EEC). The subsequent classification of this study as a clinical trial of an investigational medicinal product (CTIMP) required a substantial amount of documentation for each IMP to include clinical and non-clinical data such as indications for traditional use of each herb, safe dosing ranges, details of the chemical extraction and other manufacturing processes and quality control procedures. I consulted at an early stage with a number of key stakeholders who would be involved in such a study set-up and which included the MHRA clinical lead, UK CHM distributors, overseas CHM manufacturing companies and a UK qualified person (QP), a legal representative who ensures all necessary documentation is present upon IMP importation.

In order to be vetted under the 'RCHM Approved Suppliers List', UK suppliers are required to demonstrate that the manufacturers who are sourcing their CHMs have received good manufacturing practice (GMP) approval and which ensures a minimum quality standard has been met. Most CHMs are manufactured in East Asia and predominantly seek GMP approval from China and Taiwan and it is these products that are most widely used in UK clinical practice. However, in research, Annex 13 states that IMPs in European trials need to have received GMP approval from a restricted list of countries which currently do not include China and Taiwan. This subsequently restricted the choice from a range of commercially-available products to just one that met the legal requirements for research conduct. This CHM product had received Australian GMP approval in addition to Chinese and Taiwanese GMP. This was appropriate for use in the EU since under Mutual Recognition Agreements (EMA/MRA/22/03), authorisations issued by regulatory authorities in Partner Countries such as Australia and Canada are also recognised in the EU. This strict requirement for IMPs to possess EU and equivalent GMP status was particularly frustrating and restrictive in practical terms, given that the premise of the research was based on CHM products that are already available for use in the public domain. These products are predominantly manufactured and

distributed in East Asia and would therefore seek GMP certification within these countries rather than from the EU. This makes CHM research particularly challenging owing to differences in the requirements for research and for public distribution. However, given that manufactured herbal products such as tablets and pills have in the past been linked with misidentification of herbs or contamination with heavy metals, it is entirely appropriate that a minimum standard of product quality is in place prior to use within a research context.

I and my supervisors began discussions in September 2010 regarding the study arrangements with all stakeholders and found discussions with MHRA and the QP fruitful and constructive. At the same time, we started communicating with the UK distributor stocking the one product line that was acceptable under the EU regulations and who communicated on our behalf with the Taiwan-based manufacturer. This manufacturer had previous experience in supplying for clinical trials in China and Taiwan and both distributor and manufacturer appeared to initially be extremely supportive of this study. Discussions from Spring 2011 however continued without a great deal of success during which time neither the distributor nor manufacturer had been able to provide us with basic information and documentation that the QP requested. It became clear that there were a number of factors that were hindering trial preparations and that broadly sit amongst two closely related themes of communication and environmental factors which I will now discuss in further detail.

When I first approached the UK distributor to scope interest for this project and to obtain an approximate quote, their discussions with the representative manufacturing company had initially been extremely positive and the manufacturer proposed supplying both CHM and placebo to the project free of charge. Although this was initially welcomed by all parties, it became clear that this placed the manufacturer in an increasingly difficult position. As discussions with the MHRA and the QP evolved, it became apparent that the requirements for the study design combined with EU regulatory requirements for QP sign-off and for authorisation to be granted required a much larger investment in time and human resources to dedicate to the project than both I and the manufacturer had initially estimated. Although the manufacturer had experience supplying for CHM clinical trials previously, we had specific

requirements for the study design that were different to those that this company had previously worked with. One example is that in the placebo formulation, I wished to add colourings and flavourings to the cornstarch base to increase security of blinding, a design that already been carried out successfully in an Australian CHM trial led by Professor Alan Bensoussan at the University of Western Sydney (Bensoussan et al., 1998). The company had initially replied that it would be possible to meet these requests and that they would be willing to source the colourings and flavourings from certified suppliers in order to preserve GMP status. However, it is my view that the additional resources required in negotiating and setting up contracts and in the supply of the goods placed the company in a position such that they felt no longer able to honour the initial agreement of providing the trial supplies free of charge. Further to this, the QP requested to see detailed technical information about the product to ensure it would indeed meet EU trial regulations upon arrival in the UK. It is clear that the manufacturer had not worked with an EU research group previously that was being asked to provide this level of information required legally by the QP to facilitate obtaining clinical trials and ethics approval. Given the sensitive nature of intellectual property in a competitive business environment, it is possible that the usual business practice of setting up contracts between involved parties would have facilitated a stronger and more trusting working relationship and easier exchange of information. It is clear that both parties, us as the research group and the manufacturer, were placed in a difficult situation that I and my supervisors could not rectify in a timely manner before my funding deadline. This is however likely to change in the future with clarification of EU legislative frameworks and policies that apply to research and herbal medicine provision.

This situation was further compounded by the difficulty I experienced in communicating directly with the manufacturer's R&D department. For the majority of the discussions, the UK distributor had been acting as our agent conveying our requests to the manufacturer. We had initially felt this would be a more appropriate and effective arrangement, owing to language restrictions and since we did not have an existing business relationship with the manufacturer. Although we provided clarity to the UK distributor regarding the technical requirements and our purposes for obtaining this information, it became apparent towards the end of the discussions that this had

unfortunately not been adequately conveyed to the Taiwanese manufacturer. It would have been ideal under this circumstance to have established a more direct line of communication with the manufacturer from the outset and to have worked more closely with a representative familiar with technical specifications of research and of GMP.

It is my view that the way in which the discussions were initiated may also have impacted the way the project was viewed from the manufacturer's perspective. As this was my PhD project, I was the point of contact from the research team and initial enquiries that I made were dealt with by administrative staff within the respective organisations and which were then escalated to senior members of the teams. This bottom-up approach was clearly appropriate for the initial scoping exercise of the study, and also for ongoing discussions regarding administrative tasks that involved handling technical and logistical details. However on reflection, given the differences in cultural and departmental management styles that existed across the parties, the inclusion of some elements of a top-down approach may have been beneficial for this particular project at certain time points and it is possible that discussions at an appropriate stage between senior members of all parties, in person or via conference calls, could have enabled both clarification and alignment of each party's stake in forging such a working relationship. Establishing such a relationship requires time to develop and it is acknowledged that this was particularly difficult for this project given time pressures. However, future researchers would benefit from developing working relationships at an early stage, preferably 6-12 months prior to the anticipated start date for a trial. This would enable the establishment of a shared working strategy that would be mutually agreed upon by senior management and which could have provided a sense of direction to other members of the teams and potentially fostered a more collaborative spirit for this project.

There were also factors external to the project that impacted the manner in which it progressed. The discussions occurred at a time when European legislation surrounding herbal product registration was being enforced and much confusion existed in terms of how CHMs would continue to be provided in the UK. This created uncertainty in the European market for manufacturers and a number of China-based manufacturers had already begun redirecting

their investments to other Western countries considered to have a less volatile market. It is likely that the focus of the company directors shifted from long-term business strategies such as research and investment in the EU, to more fundamental decisions surrounding the immediate preservation or withdrawal of their current stake in the EU. Although this can be seen as a business-related issue that we would not have been able to influence, it does provide additional context within which the discussions were occurring and highlight the importance of considering issues wider than the immediate project to hand.

Despite these setbacks, I took away from this experience a number of important lessons and that will equip me with more awareness in terms of how future CHM research could be managed and organised more effectively. It is natural that at the heart of these complex and frequently interrelated issues lie the establishment and management of effective relationships between research and industry partners. Within this project, we were seeking to establish new research territory by conducting a CHM trial in primary care under the current EU clinical trial regulations. The ambiguity of how such a trial could be conducted meant a great deal of consultation and co-ordination was required between involved parties, and the technical knowledge I gained and working relationships I have developed during the process have provided me with important skills, knowledge and network that will enable me to facilitate future research in CHM. Researchers conducting work in a similar area may find it helpful to take into consideration a number of points:

- Building relationships with stakeholders at the appropriate stage. This includes CHM manufacturers though I found it particularly helpful to consult the MHRA, the QP and the Southampton clinical trials unit at an early stage.
- Consulting other CHM research groups conducting similar work. For this project, consulting research groups based in Sydney and Melbourne in Australia who had experience in conducting CHM and acupuncture RCTs was particularly useful in the preparation and planning for this study.
- Managing communication more effectively. It is helpful to consider the cultural and institutional norms that may require different methods of communication throughout the process. Managing the logistics of this however can be challenging and depends on existing resources and relationships.

- Anticipating practical issues which could arise owing to organisational differences between research and industry. In this instance setting up contracts may have been helpful to ensure that intellectual property remained strictly confidential when exchanging information we required for research purposes.
- Building teams to maximise distribution of experience in different areas. For this project, having a member on both teams with technical experience such as the requirements of CTIMPs and of GMP would have been advantageous.
- Having clearer project management such as being clear as to what resources – human, financial and technical – are to hand and when they may be required to enable the team to prioritise available resources according to research objectives.

Although a number of difficulties were encountered during the set-up of this trial, it is likely that conducting such trials will become significantly easier in the near future owing to a number of factors. Recently proposed amendments to the EU Clinical Trials regulations under the Clinical Trials Regulation (CTR) EU No 536/2014 will enable the CTA procedure to be more harmonised via a single submission portal and will consider proportionality in terms of perceived risk of the trial intervention (2013). These amendments, which have been welcomed across the research community, are expected to come into force in 2016 and have the potential to facilitate future CHM research in the UK. Professional bodies such as MHRA will also become increasingly familiar with features of herbal medicine research and as a result be able to anticipate these challenges and work in collaboration with research groups such as ours to increase flexibility towards such trials. Furthermore, an increasing number of CHM manufacturers in China are seeking Western GMP status such as Australian GMP to expand their market potential and which is leading to an increased quality and thus availability of products suitable for use in UK clinical trials. This is likely to be accelerated with the introduction of statutory regulation of herbalists in the UK and which will increase the choice of manufacturers available to CHM CTIMP researchers in the UK.

In the next chapter I will provide details of the amended protocol for the feasibility study that forms the second and final empirical study to be

conducted as part of this thesis. I will demonstrate how the information collected from the systematic review and Delphi study informed the study design, elaborate on the eventual choice of study design and outcome measures, and provide justification as to how this final study will meet the initial aim of assessing the feasibility of conducting a CHM RCT in the UK.

Chapter 6: Protocol for a randomised feasibility and pilot study in private herbal practices

6.1. Introduction

The protocol for this feasibility study can be seen in Appendix 22: Revised Protocol For ORCHID Study. Ethics and insurance approvals for this protocol were granted by the University of Southampton Ethics Committee and Register of Chinese Herbal Medicine Research Ethics Committee in December 2012. The present study design did not require approval by the MHRA for which I received written confirmation for and which can be found in Appendix 23. The study was registered with the International Standard Randomised Controlled Trials Number (ISRCTN) in January 2013. This next chapter will now describe in detail the reasons for the final study design and outcome measures.

6.1.1. Research questions

It is helpful here to provide a reminder of the primary research question for this main study:

- 1) Is CHM plus usual care superior to placebo plus usual care and to usual care alone for oligomenorrhoea and amenorrhoea in PCOS?

The secondary research questions for the main study are:

- 2) Does CHM reduce obesity or hirsutism in PCOS?
- 3) Does CHM improve quality of life in PCOS?
- 4) Is CHM safe?

Although a feasibility and pilot study would still be appropriate, it was clear that the initial design of a placebo-controlled study in a primary care setting would not be possible. Set against the backdrop of the aforementioned research questions for the main study, the overall aims of the present feasibility study therefore were as follows:

- To assess the feasibility of conducting a definitive and fully-powered study in the UK using CHM for PCOS-related oligomenorrhoea and amenorrhoea;
- To pilot and evaluate the study procedures.

In order to meet the above aims of the study, the primary feasibility study question was:

- 1) Is oligomenorrhoea and amenorrhoea appropriate as the primary outcome measure for the main study?

The secondary feasibility questions were:

- 2) Are other measures more appropriate for investigation as the primary outcome measure for the main study?
- 3) What is the safety profile of CHM?
- 4) How should the CHM intervention in the main study be delivered?
- 5) Can a double-blind, randomised trial with CHM for PCOS be conducted?

It is necessary at this point for me to acknowledge that definitive feasibility 'criteria' can be useful in some circumstances and which has been recommended by some authors (Thabane et al., 2010). However, it is my view that for this particular study that is being used as a scoping exercise, it would be difficult to make a truly relevant assessment of feasibility using restrictive criteria. This is particularly important when the resources at this study team's disposal for the main study have not yet been defined and when it is possible for feasibility to be improved upon with relatively minor amendments to study procedures. For this reason, feasibility criteria have not been presented in this protocol. The end-of-study report(s) will instead document information gathered for the primary and secondary questions outlined and, where applicable, present comments and suggestions for changes that could be made to improve feasibility. Following recently published recommendations for the reporting of pilot studies, study objectives and endpoints where relevant will now be detailed with clear rationale provided in terms of how this data will inform a definitive study (Thabane et al., 2010).

6.2. Study objectives and endpoints

The primary objective of this feasibility study is:

1. To assess the suitability of oligomenorrhoea and amenorrhoea as the primary outcome measure for the main study and to provide scientific data to enable a sample size calculation to be made.

The secondary objectives are:

2. To explore other outcome measures that may be more appropriate for investigation in a main study;
3. To determine the safety profile of CHM;
4. To explore how the CHM intervention in the main study should be delivered;
5. To evaluate the feasibility of carrying out a double-blind and randomised trial in this population.

Specific feasibility and study objectives that are detailed in the protocol in Appendix 22 are provided further justification in Appendix 24.

6.3. Study design and rationale

To achieve the aforementioned objectives, I and my supervisors agreed that a pragmatic prospective multi-centre CHM service evaluation would be carried out and with nested randomised, parallel-group and double-blind components. This study was conducted in UK private CHM practices whereby participants were to be randomised with equal allocation to one of two treatment groups: individualised CHM versus standardised CHM which are both available in routine care in the UK. The option of including individualised CHM as a treatment arm was unavailable to me in the previous study design because such treatment was not possible in a primary care setting and when the research question focused primarily on comparing standardised CHM and placebo treatment. However, in this present study design, it was possible to explore differences that could exist between the two interventions, particularly since individualised CHM is typically regarded as 'gold standard' practice and which was further supported by the views of my Delphi study participants. Whilst this feasibility study would not be appropriately powered to detect statistically meaningful differences, the purpose was to obtain preliminary scientific data to explore potential differences that may arise to inform the choice of intervention for a main study.

Features of the main study would also be piloted in this present study. A prospective design using randomisation and parallel-group assignment was chosen to minimise selection and allocation bias. These protect against the occurrence of systematic error that would otherwise lead to incorrect conclusions be drawn from the statistical analysis. Double-blinding by blinding both participant and practitioner was also used to minimise performance bias which can occur if participants or practitioners are aware of their treatment

assignment and which can subsequently cause systematic differences between the groups in the care received or provided and which is not the treatment being tested in the study.

It should be noted that when following NIHR Research for Patient Benefit definitions of feasibility and pilot studies, this study would be considered a feasibility study {NIHR, #5361}. I have described this study as a pilot study since some of the processes that would be present in the main study were to be piloted such as consenting, randomisation procedures, providing treatment and collecting outcome measures. According to NIHR definitions however, pilot studies are a version of the main study that is run in miniature and the data for such pilot studies may contribute to the final analysis. Since the main study will include a comparator such as placebo or treatment as usual and which was not possible to include for this present study, this study should therefore be considered a feasibility study under NIHR definitions.

I have also described this study as a pragmatic rather than an efficacy study. There are a number of reasons why this was the case. For example the issues identified in the previous chapter prevented us from setting up the initial design which was an efficacy study in primary care. The most appropriate manner in which scientific data could still be collected on clinical effects of CHM on menstrual frequency was within a private practice setting. Another reason is that the protocol was relatively flexible in terms of inclusion criteria for both participants and volunteer CHM practitioners as well as in terms of the CHM intervention permitting co-interventions commonly used in private practice such as dietary and lifestyle advice. This enabled the clinical data to reflect as much as possible what is typically seen in private practices but also across the range of expertise amongst CHM practitioners. It follows then that this would be more appropriately described as a pragmatic design rather than efficacy. However, following work published by {Thorpe, 2009 #5362}, the pragmatic and efficacy nature of a study should in fact be considered as a continuum for a number of different domains, an analysis of which may be published alongside a study's main findings.

6.4. Study population

In order to obtain sufficient data to compute a sample size for a larger main study, this feasibility study required a sample size of 40. This sample size was calculated based on requiring approximately 15 participants per arm in order to obtain sufficient data to calculate an estimate of the treatment effect and associated variability of the treatment effect (Thabane et al., 2010).

Accounting for a 25% dropout rate from each treatment group based on data from similar studies (Flower et al., 2011b, Yasmin et al., 2011), 20 participants would be required from each group, totalling 40 participants.

6.4.1. Inclusion and exclusion criteria

Participants were eligible for the study if they satisfied the following criteria:

1. Female aged 18-44, considered reproductive age during which menstrual cycles are sufficiently stable following onset of menarche and prior to menopause;
2. Present with oligomenorrhoea, defined as intervals between periods of >35 days and <200 days, or with amenorrhoea, defined as intervals between periods ≥ 200 days, following recently published ESHRE/ASRM guidance (Fauser et al., 2012);
3. Diagnosed with PCOS consistent with the Rotterdam criteria which can be viewed in Appendix 25.

Participants were to be excluded if they:

1. Suffer from other causes of hyperandrogenism and menstrual irregularities such as acromegaly, congenital adrenal hyperplasia, androgen-secreting tumours of the ovary or adrenal gland, Cushing's syndrome, exogenous androgens, genetic defects in insulin action, primary hypothalamic amenorrhoea, primary ovarian failure, prolactin disorders and thyroid disease (2004);
2. Are pregnant, or suspected to be pregnant since the safety of CHM during pregnancy has not been confirmed;
3. Are breastfeeding within 6 months of study start date since this could influence study outcome measures;
4. Are receiving treatment that is prohibited for use within 6 months of the study start date as detailed in 5.10.2 Prohibited medications and interventions, that could influence the study outcome measures;
5. Are receiving prohibited medications, CHM and Western herbal medicines that could influence the study outcome measures or interact with the study medications as detailed in 5.10.2 Prohibited medications and interventions;
6. Have a history of liver or kidney pathologies such as cirrhosis, glomerulonephritis, pyelonephritis as a precautionary safety measure;

7. Have a history of psychotic illness, by asking potential participants whether they have ever had a psychotic illness such as schizophrenia, have ever seen a psychiatrist, or have ever been diagnosed with an eating disorder or hospitalised for a mental-health related incident. This is important owing to questionnaires being used as part of outcomes assessments which rely on the participant being emotionally and mentally stable in order for results to remain valid.
8. Have major depression, by asking potential participants whether they are currently depressed. If participants answer yes to this question, they will then be screened with the Patient Health Questionnaire (PHQ-9) (Spitzer et al., 1999), where a score of 15 is indicative of moderately severe major depression. This is also important to ensure participants are emotionally and mentally stable for questionnaire results to remain valid;
9. Have a current history of harmful and hazardous drinking. This will be determined firstly by screening using the Fast Alcohol Screening Test (FAST) where a score of 3 or more suggests a greater risk of harmful and hazardous drinking (Hodgson et al., 2002). If FAST screening is positive, an assessment will then be made using the Alcohol Use Disorders Identification Test (AUDIT) where a total score of 8 or more suggests hazardous and harmful alcohol use (Babor et al., 2001). FAST and AUDIT questionnaires can be viewed in Appendix 26 and Appendix 27 respectively. These will be used as a precautionary measure to minimise potential interactions between alcohol and the CHM product;
10. Have allergies to any one of the following common herbal ingredients that are contained within the standardised CHM product: nuts, citrus fruit peel, goji berry, licorice or cinnamon;
11. Do not have the spoken or written language skills necessary to take part. This is important since study assessments will be conducted in English and materials such as participant information sheets and questionnaires will only be available in English. This is owing to funding and other issues relating to limited resources at the study team's disposal;
12. Present with abnormal liver and/or kidney function at screening, defined as whole blood alanine aminotransferase (ALT) > 60 IU/l and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² as a precautionary safety measure.

6.4.2. Identifying participants

As this study was to be conducted in private practice, advertising for recruitment onto this study incorporated a variety of methods to seek both practitioner-referrals and patient self-referrals. These methods included, but were not limited to, those listed below:

- Recruitment posters and notices in study sites and public areas such as sports centres and community centres;
- Social networking sites such as Facebook and Twitter;
- Research posts on discussion forums and social networking sites such as those owned by charity organisations and patient support groups;

- Email circulars, articles and adverts via professional organisations such as the RCHM and ATCM and their journals;
- Presentations at conferences and other events attended by complementary medicine practitioners;
- Search engine optimised research study website;
- Press releases with local newspapers and magazines or newsletters from charity organisations and patient support groups.

An example of a recruitment flyer directly aimed at participants can be viewed in Appendix 28. An example of a request for practitioner referrals for potential participants can be viewed in Appendix 29. A screenshot for one the study website pages can be viewed in Appendix 30. All recruitment methods used in the study received ethical approval prior to the study's commencement.

6.4.3. Recruitment plan

I estimated that a consent rate of 10% of all initial enquiries would be achieved, based on consent rates in a recent Swedish acupuncture RCT recruiting from a PCOS population and on a feasibility search based in a Wiltshire GP surgery (Jedel et al., 2011). In order to recruit a total of 40 participants, it was estimated that 400 enquiries would need to be generated.

Recruitment was phased to ensure study personnel were not unduly burdened at the beginning of the study and to correct for any issues in the study processes that may be identified in the initial phase of the study. For this reason, recruitment targets were calculated according to the forecast below and according to when approvals for the study have been obtained to enable recruitment to begin.

For Month 1, recruitment target was 3 and which would rise during the subsequent months as the recruitment plan came into effect. I planned for a 7-month recruitment period and set recruitment targets for each month. Recruitment targets were reviewed each month and took into consideration seasonal availability of participants and study personnel, which could be reduced during holiday months over the summer months and during the Christmas period. Where targets were not met for two consecutive months,

the study team reviewed progress of recruitment to decide upon contingency measures that may be required and that are detailed in the protocol.

6.4.4. Screening

Screening of potential participants was conducted in three phases to minimise demand on study resources. Firstly an initial web-based screening, secondly a telephone screening interview and finally remaining screening criteria was to be checked at the baseline study visit.

1. Web-based screening

Women were asked firstly to read the participant information sheet (PIS) (Appendix 31) before completing a web-based screening questionnaire that was developed specifically for this study (Appendix 32). Women who were eligible at this stage were emailed a study invitation letter (Appendix 33), an additional copy of the PIS and consent form (CF) (Appendix 34). They were given a minimum of 24 hours to read through the material prior to telephone screening appointment in order to provide sufficient time for women to consider what would be required of them for this study.

2. Telephone screening interview

The purpose of the telephone interview was to ensure women meet further eligibility criteria before arranging a study visit, and to provide women with further information regarding study procedures. The purpose of this was to reduce unnecessary visits for those clearly ineligible and to promote participant commitment to the study. All reasons for ineligibility or for women declining to take part in the study following telephone screening were noted.

Where all criteria were met but a diagnosis of PCOS remained unclear, women were asked to provide further information from their GP or consultant, or to attend a private clinic for further assessment which could involve procedures such as a blood test or ultrasound scan for which women will be consented by clinic staff for as per routine practice.

Upon confirmation of eligibility and where women are satisfied with the study procedures involved, they were invited to attend a baseline visit at the clinic of one of the study practitioners.

3. Baseline study visit

At the initial baseline visit, eligibility assessments were completed. This included a liver and kidney function test to check for normal baseline levels. It was also possible that further information could be collected during this visit to confirm a PCOS diagnosis such as confirming menstrual cycle lengths or conducting a clinical assessment of hirsutism.

An overview of the eligibility criteria that was checked at each screening phase are presented in Table 12.

Table 12: A table to show eligibility criteria checked at each screening phase

	Web	Telephone	Baseline visit
Inclusion criteria			
Female aged 18-44	✓	-	-
Present with oligomenorrhoea or amenorrhoea	✓	-	-
Diagnostic criteria consistent with the Rotterdam criteria	✓	✓*	✓*
Exclusion criteria			
Other causes of hyperandrogenism/menstrual irregularities	-	✓	-
Pregnant, or possibly pregnant	✓	✓*	✓*
Breastfeeding in last 6 months	✓	-	-
Checked for permitted medications and interventions	✓	✓	✓*
Checked for prohibited medications and interventions	✓	✓	✓*
History of liver/kidney pathologies	-	✓	-
History of psychotic illness	-	✓	-
Current history of major depression	-	✓	-
Current history of hazardous drinking	-	✓	-
Known allergies to standardised CHM product ingredients	-	✓	-
Not fluent in English	✓	✓	-
Abnormal liver and kidney function	-	-	✓
Study-specific criteria			
Able to visit study centre	✓	✓	✓*
Interest in taking CHM daily for up to 6 months	✓	✓	✓*
Able to make scheduled study visits	-	✓	✓*

*as necessary

6.4.5. Consenting participants

Consenting procedures complied with the definition of informed consent stated in paragraph 3(1) of Part 1 of Schedule to the regulations, implementing Article 2(j) of the EU Directive 2001/20/EC. I also adhered to conditions applying to giving of informed consent by a capable adult as per Part 3 of Schedule 1 to the Regulations implementing Article 3(2) to the EU Directive. Women were instructed to read the PIS carefully and study processes were described in detail using a standard briefing document. At the baseline visit, the practitioner or researcher provided a sample of how the CHM granules would appear prior to reconstitution, and instructions on how to make the tea. Women were offered the opportunity at each contact to ask questions and if they were happy to participate, were asked to sign a consent form in the presence of a practitioner or researcher. After obtaining consent, women were considered recruited onto the study as participants and assigned a participant ID number.

After consenting to the study, participants were asked for their consent to the study team notifying the participant's GP of study participation. Where consent was obtained, a letter was sent to the GP providing notice of their patient being part of a clinical study with a brief description of the study, a copy of the PIS and contact details of the study team. A template of this letter is provided in Appendix 35. Where the participant declined to provide consent for GP notification, this was documented in a separate form. These participants' GP were not contacted and would not affect participants' eligibility for inclusion onto the study.

6.4.6. Randomisation

An independent statistician (PP) used a computer-generated random numbers table to provide an irregular block allocation sequence prior to the study. Block randomisation to either of the two groups, individualised or standardised CHM treatment, were performed with random block sizes of 4, 6 or 8 participants to ensure equal numbers in groups and to prevent the study team and the dispensary team from being able to predict a pattern to the randomisation. A treatment allocation ratio of 1:1 was used with equal chance of participants being randomised to either of the two groups.

Prior to and during the study, study practitioners and members of the study team had no knowledge of the randomisation sequence generated or of treatment allocation for each participant. Allocation codes describing group allocation were transferred to sealed opaque envelopes by the statistician and sent on to the study dispensary. The study dispensary was asked to keep the envelopes in the order in which it was sent to them.

After obtaining informed consent during the baseline visit and the CHM consultation had been carried out, the practitioner was asked to write an individualised CHM prescription for the participant as would be expected in routine practice. This prescription and corresponding participant ID number was forwarded onto the study dispensary.

Upon receiving the ID number of a new participant, a member of the dispensary team was instructed to open the envelope at the top, or at the front, of the pile of envelopes containing the allocation codes and treatment. A note of this information was made and stored in a password-protected secure and centralised document. The corresponding CHM prescription was then compiled for this participant.

For participants randomised to receive individualised treatment, the prescription provided by the study practitioner was then compiled by the dispensary. For those randomised to receive standardised CHM, the prescription provided by the study practitioner was ignored by the dispensing team and instead, the pre-determined standardised prescription compiled. The dispensing team were asked not to communicate any information to the study practitioner that could allude to the treatment allocation of the participant, unless in emergency situations. In emergency situations and where appropriate, it was planned that one of the study CIs would be contacted by the dispensing team for further advice.

For the remainder of the study, the named participant stayed within this allocated group and subsequent CHM prescriptions dispensed accordingly. The dispensing team was responsible for updating the centralised document that contained information of treatment allocation for each participant recruited onto the study. In case of emergency unblinding procedures, the

study team and the dispensing team had access at all times to an updated list of participant allocation throughout the study. The final list of allocation was downloaded at the end of the study to assist in data analysis. This final list was also checked against the original list of allocation codes to ensure allocation was performed as intended.

6.1. Patient and Public Involvement

2 patient and public involvement (PPI) representatives were consulted prior to study commencement and asked for feedback on the content and clarity of both the PIS and CF.

A number of amendments were subsequently made to these documents based on the PPI input such as:

Table 13: Amendments to documents from patient and public involvement feedback

PPI 1 comment	PPI 2 comment	Amendment
<i>Cost of herbs? Can you indicate how much free herbs they are getting?</i>	<i>On page 3 – can you add in here the approximate value of the herbs and consultations each participant will be receiving, as I imagine it's quite substantial and might motivate participation from some?</i>	Include information regarding potential saving costs in PIS

Further details regarding how the PPI comments contributed to other amendments made to these documents can be seen in Appendix 36.

6.2. Study Interventions

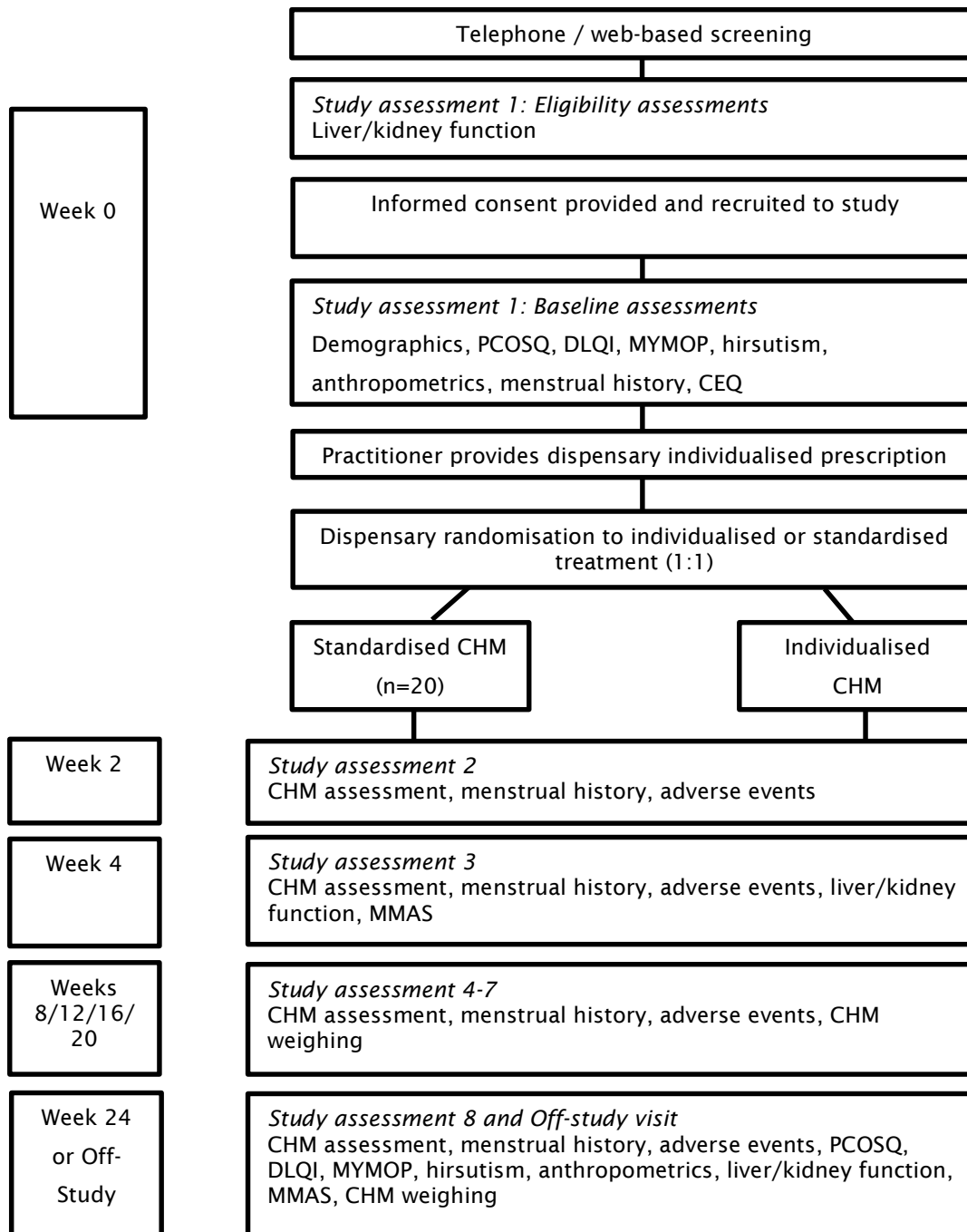
This section describes in detail the format and nature of the interventions and assessments in this study. All information presented fulfils the information

required of the CONSORT statement extension to the reporting of RCTs of herbal interventions (Gagnier et al., 2006), a copy of which can be seen in Appendix 37.

Participants randomised to either individualised or standardised CHM treatments were prescribed CHM for 24 weeks (6 months). This is regarded an appropriate length of treatment to obtain sufficient information to meet this study's primary objective of examining clinical effects on regulating menstruation in PCOS and supported by the earlier Delphi study results.

Participants were invited to 8 assessments in total over the 24 week period, of which it was considered compulsory to attend study visits at Weeks 0, 4, 8 and 12 as part of safety assessments and to check suitability for continued participation. Visits at Weeks 2, 16 and 20 were carried out as study visits or by telephone or email at the discretion of the study practitioner, considered routine practice that adheres to RCHM Codes of Conduct. The frequency and timing of the proposed study assessments can be seen in Figure 23.

Figure 23: Overview of feasibility study procedures



Abbreviations: CHM=Chinese herbal medicine; PCOSQ=Polycystic Ovary Syndrome Questionnaire;
DLQI=Dermatology Life Quality Index; MYMOP=Measure Yourself Medical Outcome Profile;
CEQ=Credibility/Expectancy Questionnaire; MMAS=Morisky Medication Adherence Scale

6.2.1. Study Practitioners and Study Sites

In order to be involved in this study, practitioners needed to:

- 1) Have a minimum 5 years' of clinical experience in order to be deemed suitably experienced;
- 2) Be registered with a professional body such as the RCHM or ATCM;
- 3) Provide a valid certificate for CHM professional indemnity and public liability insurance for the study site premises;
- 4) Have access to safety tests;
- 5) Be prepared to accept a minimum of 5 participants to maximise efficiency of pre-study training provided;
- 6) Agree to adhere to the study protocol

Mailshots to professional bodies and social media would be used to recruit practitioners onto this study. We also invited practitioners and practitioner-researchers directly who had previously worked with the study team.

It was planned that I would be the initial practitioner overseeing study-care in from named study sites in Hertfordshire and in London. Where practitioners joined the study and new study sites became involved, the study team ensured the above requirements for study practitioners were met and that relevant documentation such as evidence of Good Clinical Practice (GCP) training was in place prior to the study sites and practitioners being active. An example of a GCP training certificate by study personnel can be seen in Appendix 38.

6.2.2. Study Medications

Two active CHM interventions were directly compared in this study – individualised and standardised CHM - both of which are currently available in routine practice. All herbs dispensed in this study were compliant with the UK professional regulatory guidance for CHM offered by the RCHM and the European Directive on Traditional Herbal Medicinal Products (THMPD) 2004/24/EC. As such, no animal or mineral products were dispensed and only plant materials were used.

Individualised CHM

Following each consultation with the participant, the practitioner forwarded an individualised CHM prescription onto the study dispensary detailing the CHM

contents and dosages. To preserve patient-blinding, this prescription was not written in the presence of the participant and who was informed that they would be receiving their CHM shortly. Since each prescription was individualised to each participant, it was not possible to pre-determine the complete list of CHM that would be dispensed in the study. However, a list of commonly prescribed CHM in PCOS was collated from the systematic review as reported and which can be seen in Appendix 6.

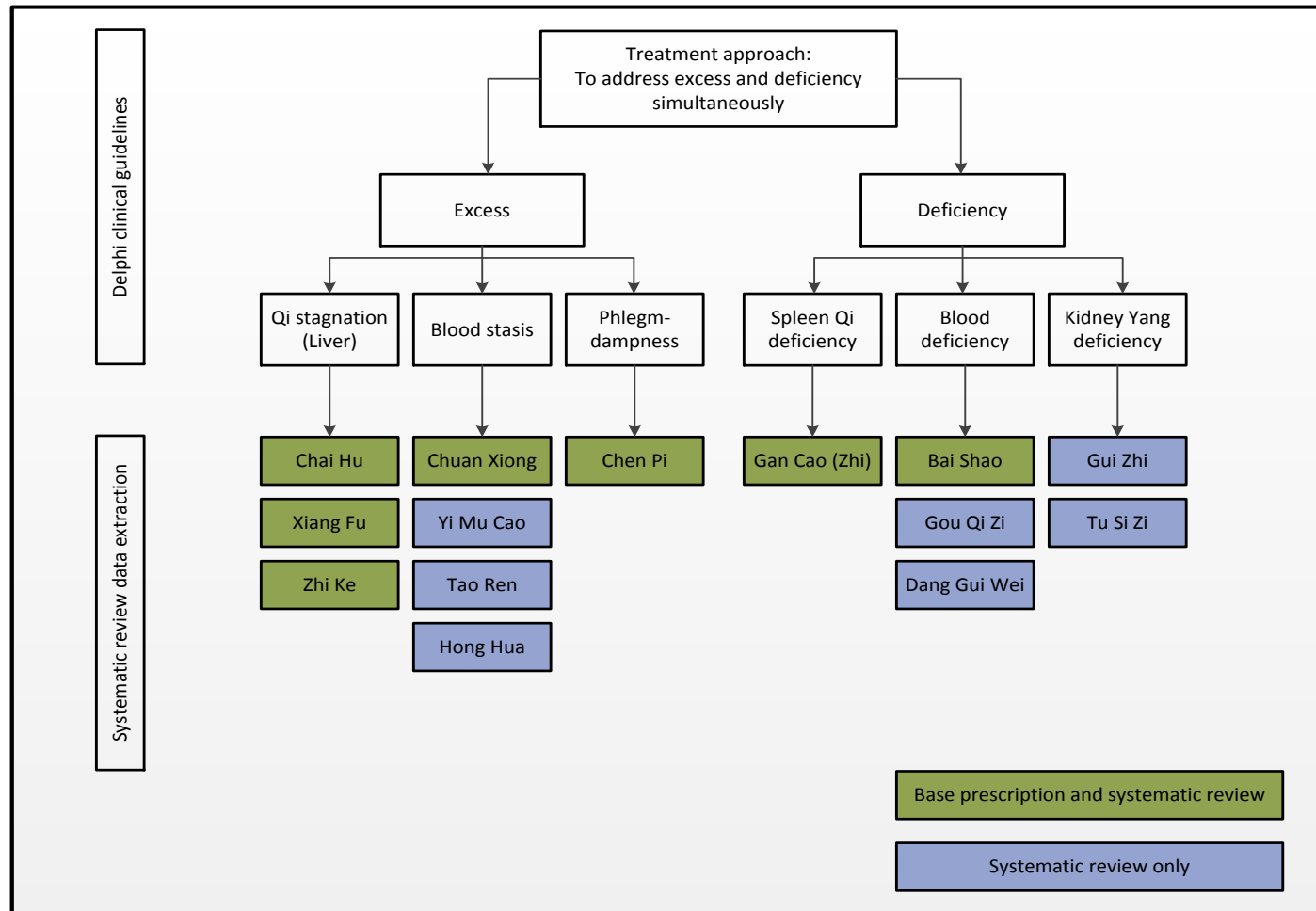
Standardised CHM

The standardised CHM prescription dispensed in this study consisted of a pre-defined formula of 14 single herbal granules which were chosen using an evidence-informed approach. This consisted of extrapolating frequently found Chinese medicine presentations and treatment strategies from the Delphi CHM practice guidelines (Appendix 21) and from extracting the individual herbs used within the RCTs in the systematic review. As the two experienced herbalists within the research team, I discussed this information with my CHM supervisor Dr. Flower. Given the standardised CHM would be prescribed over a period of 6 months and for oligo- and amenorrhoea in PCOS, we decided on an approach that addressed both excess and deficiency syndromes as suggested by the Delphi-derived clinical guidelines. The Delphi guidelines identified a number of excess conditions that were regarded as being important in PCOS and we agreed to focus in particular on the excess syndromes of Liver Qi stagnation, Blood stasis and Phlegm Dampness. Likewise a number of deficiency syndromes had been identified by the Delphi participants and Dr. Flower and I agreed that the deficiency syndromes Kidney Yang deficiency, Spleen Qi deficiency and Blood deficiency would be focused upon.

As a result, the standardised CHM prescription was based on a commonly-used 7-CHM base prescription known as Chai Hu Shu Gan San (Bupleurum Powder to Spread the Liver). This prescription contains 7 CHMs in total and which are directed at Liver Qi stagnation, Blood stasis, Phlegm-Dampness, Spleen Qi deficiency and Blood deficiency (Bensky and Barolet, 1990). To this we added a further 5 CHMs for greater emphasis on Blood stasis and Blood deficiency and introduced 2 CHMs for Kidney Yang deficiency. This resulted in a standardised prescription consisting of 14 CHMs in total. All 14 can be found in the list of commonly used CHMs that were extracted from the systematic review, but

have been decided upon with input from the Delphi-derived clinical guidelines in order to reach the final prescription. This evidence-informed decision-making process is outlined in Figure 24. The CHMs contained within the standardised prescription are listed with their corresponding granulated dosages in Table 14.

Figure 24: Decision-making process for contents of standardised CHM



Chapter 6

Table 14: Contents of standardised Chinese herbal medicine

	Chinese Pinyin Name	Common name	Family name	Part used	Botanical Name	Dried herbal daily dosage (g)	Percentage (%)
1	Bai Shao (Chao)	peony (dry fried)	Paeoniaceae	root	<i>Paeonia lactiflora</i> Pall.	15	10.64
2	Chai Hu	bupleurum	Umbelliferae	root	<i>Bupleurum chinense</i> DC.	9	6.38
3	Chen Pi	tangerine peel	Rutaceae	peel	<i>Citrus reticulata</i> Blanco	9	6.38
4	Chuan Xiong	Szechwan lovage rhizome	Umbelliferae	rhizome	<i>Ligusticum chuanxiong</i> Hort.	9	6.38
5	Dang Gui Wei	angelica extremities	Umbelliferae	root tail	<i>Angelica sinensis</i> (Oliv.) Diels	9	6.38
6	Gan Cao (Mi Zhi)	liquorice root (honey-fried)	Fabaceae	root	<i>Glycyrrhiza uralensis</i> Fisch.	6	4.26
7	Gou Qi Zi	goji berry	Solanaceae	fruit	<i>Lycium barbarum</i> L.	9	6.38
8	Gui Zhi	cinnamon twig	Lauraceae	twig	<i>Cinnamomum cassia</i> Presl.	9	6.38
9	Hong Hua	safflower	Asteraceae	flower	<i>Carthamus tinctorius</i> L.	9	6.38
10	Tao Ren	peach kernel	Rosaceae	seed	<i>Prunus persica</i> (L.) Batsch.	9	6.38
11	Tu Si Zi	Chinese dodder seed	Convolvulaceae	seed	<i>Cuscuta chinensis</i> Lam.	12	8.52*
12	Xiang Fu (Cu Zhi)	purple nutsedge (vinegar-fried)	Cyperaceae	rhizome	<i>Cyperus rotundus</i> L.	12	8.52*
13	Yi Mu Cao	motherwort	Lamiaceae	top	<i>Leonurus japonicus</i> Houtt.	15	10.64
14	Zhi Ke	bitter orange	Rutaceae	mature fruit	<i>Citrus aurantium</i> L.	9	6.38
Total daily prescription weight						141	

6.2.3. Summary of CHM Product Characteristics

For the lists of CHM provided in Appendix 6 and Table 14, details of common practice indications, contraindications and expected side-effects for each are provided in Appendix 39.

6.2.4. CHM Side-effects

CHM may be associated with adverse effects that include diarrhoea, nausea, loss of appetite and headaches which are not expected to last longer than 48 hours of initial administration. CHM can also be associated with a temporary aggravation of existing symptoms and which will be handled by the study practitioner according to their clinical judgment. Participants were informed of potential temporary side-effects and asked to contact their practitioner for further advice should they be concerned about their symptoms, or should their symptoms persist for longer than 48 hours.

In rare instances, adverse effects associated with CHM intake relate to impaired liver and kidney function (Patel et al., 2012). Symptoms and signs of impaired liver and kidney functioning were checked for as part of the Adverse Event (AE)/Serious Adverse Event (SAE) assessments during scheduled assessments and which are detailed in the protocol.

6.2.5. CHM Dispensary and Manufacturer

All CHM products provided in both treatment groups were dispensed by a UK distributor and dispensary approved by the RCHM and registered on the RCHM Approved Suppliers Scheme. A copy of the Approved Suppliers certificate can be viewed in Appendix 40 and a copy of the Dispensary and Pharmacognosy training certificate that a member of the dispensary team has completed in Appendix 41.

The manufacturer of the individual CHM single granules is Jiang Yin Tian Jiang Pharmaceutical Company Limited, located in mainland China. As a measure of quality assurance, the manufacturer possesses a certificate of Good Manufacturing Practice (GMP) for pharmaceutical products, granted by regulatory authorities from the People's Republic of China. A copy of this certificate can be viewed in Appendix 42. This ensures that the manufacturer

conforms to pre-determined standards in manufacturing processes to maintain consistency in quality of CHM and enables a systematic audit of CHM source, CHM identification, traceability and accountability of all procedures.

Certificates of analysis (C of As) were available for each batch of single CHM granules produced at this manufacturer. These analyses are typically performed within 7 days of manufacture and include details such as date of production and of analysis, batch number, expiry date, description of appearance, and conformity assessments for thin layer chromatography (TLC) identification of herb, moisture $\leq 6.0\%$ (%), solubility in water, heavy metal content i.e. Lead (Pb), cadmium (Cd), arsenic (As), mercury (Hg), microbiological ($<1000\text{cfu/g}$), fungal account ($<100\text{cfu/g}$) and *Escherichia coli* (absent in 1g). An example of a C of A of a CHM typically prescribed in PCOS is provided in Appendix 43. At the end of the study, C of As for all batches of single CHM granules dispensed in this study will be compiled. A voucher specimen was retained for each batch of single herbs that was used for the standardised and the individualised group. These are kept as part of routine dispensary practice in a storage area separate from the dispensary room at the dispensary site.

6.2.6. Stability data

Since the CHM used in this study were not pre-manufactured, no formal stability data for the finished products was available. Stability data for the products in this study were not collected due to limited resources available to the study team for analysis.

6.2.7. Labelling and Packaging

Both the individualised and standardised CHM were packaged by the CHM dispensary in white pharmaceutical grade plastic bottle containers with a tamper-evident seal as in routine practice. Each container was labelled with information consistent with Annex 13 Labelling for IMPs, an example of which is provided in Appendix 44. To preserve patient and practitioner blinding, no information was provided on the label regarding the ingredients prescribed. It was the manufacturer's recommendation that the CHM products for this study are not stored above 30°C and that it should be kept away from bright light and moisture (Appendix 45).

6.2.8. Justification for expiry dates

An expiry date of 3 months from date of dispatch was assigned by the study dispensary to each prescription. Single CHM granules manufactured at Jiangyin Tianjiang Pharmaceutical Company possess expiry dates 5 years from production, as supported by C of As provided with each batch of single CHM granules that is produced. Owing to the manufacture that takes place at the UK dispensary and mixing together the single CHM granules to form each prescription for this study, the manufacturer and dispensary deemed it appropriate that a 3 month use-by date is assigned to these prescriptions, as can be seen by the letter provided in Appendix 45.

6.2.9. Study Medication Distribution and Disposal

Participants received their CHM after each consultation with the study practitioner and which were distributed as per usual practice following processes that adhere to RCHM guidance. The prescription weight and frequency of CHM sent were identical regardless of the treatment allocation.

Participants were asked to bring all CHM prescription pots received to their Week 12 and final study visit to calculate weights of unused CHM. Participants had the option of keeping their unused CHM or to leave with the study team to be disposed as per RCHM codes of practice. Where participants chose to continue using their CHM, they were strongly advised to continue under the supervision of a registered CHM practitioner and were forwarded information directing them to the relevant professional bodies in the UK.

6.2.10. Dosing regimen and instructions

CHM treatments in both arms were prescribed for participants to self-administer orally at a dosage of 8g of CHM granules per dosage, two dosages daily, totalling 16g per day for the study duration of 24 weeks.

Participants were instructed to prepare the CHM as in usual practice which involved using the plastic measuring spoon provided by the dispensary with each prescription pot to measure the granules and reconstituted with hot water and taken as a tea. Participants were advised to drink the tea whilst warm and approximately 30-60 minutes after meals. Administration prior to a meal was permitted, though participants were informed that this could increase the likelihood of developing aforementioned temporary digestive side effects.

Participants were advised to leave at least one hour either side of taking the CHM when administering other medications or supplements permitted on this study, and to take CHM approximately 3 hours either side of having alcohol. This recommendation follows usual practice in order to reduce the likelihood of possible interactions.

Where participants were finding it difficult to take the recommended dose of CHM because of taste, participants were permitted to make the prescription more palatable at the study practitioners' advice as is usual practice. This included, though was not limited to, adding up to a tablespoon of honey or sugar, or making a mixture consisting of 25% fruit juice such as apple juice and 75% water.

6.2.11. Participant Adherence

Participant adherence was examined in terms of adherence to the protocol and to the study intervention.

To be considered adherent to the CHM as prescribed, participants must have taken CHM at the minimum recommended dosage of 5g per day, for a minimum of 18 of the 24 weeks of the study and with a break from CHM administration of no more than 7 days at a time. Adjustments and reasons for adjustments were noted in study records to inform feasibility of the intervention as prescribed and to explore potential dose-responses. Dose adjustments were monitored by the study practitioner for the remainder of the study and return to recommended dose was attempted where deemed clinically appropriate.

To be considered adherent to the protocol, participants had to physically attend a study visit at Weeks 0, 4, 8 and 12 as part of safety assessments and to check suitability for continued participation.

Participant adherence to the CHM intervention was not a compulsory requirement since the statistical analysis for the main study was planned to be based on an intention-to-treat approach. Non-adherence to the CHM

intervention therefore was insufficient grounds alone for withdrawing a participant provided they demonstrated adherence to the study protocol.

The study team and practitioners attempted to maximise adherence to the intervention by discussing at baseline with each participant the use of memory aids and prompts, and during on-study assessments where relevant.

Adherence to the intervention was assessed as part of the feasibility criteria and to provide further information to aid the design of the main study and was assessed using both self-reported means and observer-reported means.

Participants were administered the 8-item Morisky Medication Adherence Scale (MMAS-8) at Weeks 4 and final study visit to assess for self-reported medication adherence. MMAS-8 is a validated questionnaire where a total score of 0 to <6 suggests low adherence, 6 to <8 medium adherence and 8 high adherence (Morisky et al., 1986, Morisky et al., 2008). The questionnaire can be viewed in Appendix 46.

For observer-reported measures, participants were asked at each study assessment non-leading questions regarding how they have been finding administering the CHM. The frequency and size of CHM orders and re-orders were recorded. At Week 12 and at the end of the study, participants were asked to return all prescription pots to enable the study team to calculate total CHM usage during the study. This was clearly specified at the baseline visit and instructions placed on the prescription labels not to dispose of containers.

6.2.12. Changes to CHM prescription

Changes to the CHM prescription contents between scheduled study assessments were not permitted in this study owing to resource constraints. Post-randomisation changes in study practitioner were not permitted, although where a study practitioner offered study consultations at more than one location, it was permissible for a participant to change the location at which she received this consultation.

6.2.13. Excessive dosing

Where participants reported taking a higher than prescribed dose, participants were asked to contact a member of the study team or a medical doctor

immediately for further advice. Excessive dosing was defined in this study as taking more than twice the standard daily dosage for this study i.e. more than 32g per day. This has been determined by taking into consideration the routine practice dosage range of 5g to 25g reported in the CHM guidelines provided in Appendix 21.

6.2.14. Prior and concomitant medications and interventions

6.2.14.1. *Permitted medications and interventions*

The following medications, supplements and interventions were permitted for use at all times prior to, and at any point during, this study:

- Analgesics e.g. Aspirin, paracetamol;
- Antidepressants such as amitriptyline or SSRIs;
- Vitamin, mineral and selected natural supplements e.g. Coenzyme Q10, Evening Primrose Oil, B vitamins, Zinc, magnesium, milk thistle, mint;
- Weight loss interventions e.g. Exercise, diet.

Whilst it was recognised that the administration of these medications, supplements or interventions could potentially have an effect on the outcome measures in this study, these are used commonly amongst women with PCOS and the study team, after careful consideration, regarded these as acceptable for use within this pragmatic study.

The following medications were permitted in this study, provided they had been administered for 6 months or longer at the start of the study:

- Insulin-sensitising agents e.g. Metformin;
- Oral contraceptives e.g. Diane-35;
- Anti-androgens e.g. Spironolactone;
- Acupuncture.

The above interventions were permitted since 6 months was deemed a sufficient period of time to have lapsed in order for clinical improvements from such treatments to have stabilised prior to administering CHM. These medications and interventions have been used safely and without record of serious adverse events from previous RCTs involving CHM for PCOS (Hao, 2010, Li et al., 2011a, Zhou et al., 2010).

During the study, participants may have started taking the above medications and interventions or found to have been taking these within 6 months of starting the study. Since these participants would have been randomised and

were likely to have been receiving study CHMs for a period of time, it was planned that these participants would not be withdrawn from the study, but would be considered separately in the analysis.

6.2.14.2. *Prohibited medications and interventions*

The following medications and interventions were not permitted at any point during this study due to potential interaction with study medication or due to potential effects on the study outcome measures:

- Anticoagulants such as heparin and warfarin;
- Anti-hypertensives;
- Diuretics;
- Cardiac glycosides (Digoxin);
- Ciprofloxacin;
- Corticosteroids;
- Lithium;
- CHM and other herbal supplements that have a potential action on symptoms of PCOS or could interact with the study medication e.g. St Johns Wort, black cohosh, vitex agnus castus, saw palmetto;
- Ovulation-inducing agents e.g. Clomiphene citrate, letrozole, tamoxifen;
- Fertility procedures e.g. In vitro fertilization, intrauterine insemination;
- Laparoscopic ovarian cauterization.

6.2.15. Concomitant advice

Study practitioners were permitted to provide participants with additional advice according to Chinese medicine theory, including advice on lifestyle, stress-management or general wellbeing which is commonplace in routine CHM practice. It is acknowledged that offering additional advice could be a potential confounder of this study. However, concomitant advice was offered to both treatment groups as part of pragmatic routine practice and was considered by this study team as an acceptable co-intervention.

Such advice was recorded in clinical notes for analysis and study practitioners were asked to not offer additional advice outside that which is given in a typical CHM consultation.

6.2.16. Study Restrictions

As there is no available safety data of CHM use during pregnancy, participants were strongly advised against trying to conceive whilst being administered

CHM in this study. Participants were advised that it would be safe to conceive after completing on-study CHM treatment.

6.3. Outcome measures

6.3.1. Safety Assessments

6.3.1.1. Liver and kidney function

Although the herbs contained within both standardised and individualised prescriptions were widely prescribed by CHM practitioners, the safety profile of these CHMs is unknown. Liver and kidney function was therefore monitored during this study by measuring alanine aminotransferase (ALT), and creatinine to determine estimated glomerular filtration rate (eGFR). These were conducted by using serum blood tests or the Reflotron Desktop Analyzer, a validated point-of-care test device involving finger prick blood (Thue and Sandberg, 1993). These tests were to be conducted as part of the eligibility criteria at baseline and to monitor safety during the study at Week 4 and at final study visits. Attendance at study visit Week 4 was therefore a compulsory requirement in order that study practitioners could check for safety prior to further prescribing.

6.3.1.2. Adverse Events and Serious Adverse Events

During all study assessments and withdrawal assessments, participants were checked for AEs and SAEs as part of safety monitoring.

6.3.2. Chinese medicine clinical assessment

Study practitioners conducted a CHM assessment with each participant at each study assessment involving a clinical overview of symptoms and signs, providing an appropriate Chinese medicine diagnosis and treatment principle(s) where relevant and details of other assessments such as tongue and pulse observations where these were carried out. The clinical record form was developed for this study and piloted prior to study commencing and can be seen in Appendix 47.

6.3.3. Study Assessments

This following section describes the content and timing of study-related assessments. Permission was checked and obtained where required for use of questionnaires.

6.3.3.1. Screening criteria

As part of the inclusion and exclusion criteria, participants underwent an assessment for hazardous drinking through the FAST questionnaire and a blood test to confirm normal baseline liver and kidney function. Where FAST score is positive, the AUDIT questionnaire was used. Copies of the FAST and AUDIT questionnaire can be viewed in Appendix 26 and Appendix 27 respectively. Where diagnosis of PCOS was unclear, further assessments such as ultrasound scans or blood tests may be required. A demographics questionnaire was administered at baseline (see Appendix 48).

6.3.3.2. Menstrual history

As there was no run-in period, participants were asked to recall a minimum of 6-month menstrual frequency data at baseline and to score on a Likert scale of how confident they were in this data's accuracy. During the study they were asked to keep a menstrual diary and which was recorded by the study practitioner at each assessment.

6.3.3.3. Anthropometric measurements

Measurements for height, weight, waist and hip measurements were taken at Week 0 and at final visit using clinically validated instruments such as constant-tension stretch-resistant measuring tapes and weighing scales that are minimum class III. Standard Operating Procedures (SOPs) were followed to maximise consistency in measuring of anthropometric data.

6.3.3.4. Quality of life

This was assessed using the following standardised questionnaires: the polycystic ovary syndrome questionnaire (PCOSQ), Dermatology Life Quality Index (DLQI) and Measure Yourself Medical Outcome Profile questionnaire (MYMOP) (Cronin et al., 1998, Finlay and Khan, 1994, Paterson, 1996). These

were administered at Week 0 and at final visits. Copies of the DLQI and MYMOP are provided in Appendix 49 and Appendix 50 respectively.

6.3.3.5. Modified Ferriman-Gallwey questionnaire

The modified Ferriman-Gallwey (mFG) questionnaire is a standardised and validated questionnaire that involves observer-assessment of hirsutism where 9 body areas are scored between 1 and 4 (Ferriman and Gallwey, 1961). A copy of the questionnaire can be viewed in Appendix 51.

This assessment was carried out at Week 0 and at final visits. This may also have been carried out as part of the inclusion criteria in order for participants to be diagnosed with PCOS where an mFG score of ≥ 6 was clinically accepted as being indicative of hirsutism (Yildiz et al., 2010).

6.3.3.6. Practitioner blinding questionnaire

Practitioner-blinding was assessed by asking study practitioners to fill out a simple 3-item questionnaire which has been recommended for use to assess success of blinding in controlled trials and has previously been used in acupuncture studies (Bang et al., 2004, Kolahi et al., 2009, Enblom et al., 2011).

Study practitioners were asked 'Do you feel this participant was assigned to standardised, or to individualised CHM?' (Response: Standardised/individualised). They were then asked 'How sure are you of your answer?' (Response: Not at all sure, just guessed/Fairly sure/Entirely sure). The final question asked to provide reasons for their answer (Free text).

This questionnaire was administered at Week 4, Week 12 and final visit. A copy can be viewed in Appendix 52.

Patient blinding was not monitored as participants were unaware of the difference in group assignments.

6.3.3.7. Chinese medicine treatment details

Anonymised clinical notes for each study assessment were collated to provide individualised prescription data and additional Chinese medicine advice offered by study practitioners.

6.3.3.8. Credibility/Expectancy Questionnaire

To obtain a measure of treatments expectancy and rationale credibility, participants were administered a short 6-item credibility/expectancy questionnaire (CEQ) provided in Appendix 52 (**Deville and Borkovec, 2000**). This was administered immediately following their baseline visit and prior to receiving their CHM. As instructed by the questionnaire developers, this questionnaire was modified for this study by substituting the word in the original questionnaire of ‘therapy’ for ‘treatment’, and the word of ‘trauma’ with the word ‘PCOS’. Study practitioners were kept blind from the answers provided to protect against potential subsequent care effects from the practitioner.

6.3.3.9. Morisky Medication Adherence Scale (MMAS-8)

Self-reported medication adherence was recorded using the MMAS-8 administered at Weeks 4 and at final visits (Morisky et al., 1986, Morisky et al., 2008). This questionnaire was adapted for this study by substituting the word in the original questionnaire of ‘medicine’ with ‘herbs’, and the word ‘patient’ with ‘participant’.

6.3.3.10. End-of-study evaluation

Semi-structured questionnaires to evaluate study participation were administered to each participant at the end of their participation, and to study practitioners and CHM dispensary at study close. These were used to evaluate the experiences of taking part in this study and were designed specifically for the study (Appendix 54 and Appendix 55).

Table 15 provides a summary of all study assessments and method of assessment.

Table 15: Summary of study assessments

Study Assessment	1	2	3	4	5	6	7	8	Withdrawal number
Study week	0	2	4	8	12	16	20	24	
Visit/Remote	V	V/R	V	V	V	V/R	V/R	V	V/R
Demographics	✓	-	-	-	-	-	-	-	-
FAST	✓	-	-	-	-	-	-	-	-
CEQ	✓	-	-	-	-	-	-	-	-
PCOSQ	✓	-	-	-	-	-	-	✓	✓
DLQI	✓	-	-	-	-	-	-	✓	✓
MYMOP	✓	-	-	-	-	-	-	✓	✓
Blinding	-	-	✓	-	✓	-	-	✓	✓
Hirsutism	✓	-	-	-	-	-	-	✓	✓
Anthropometric measurements	✓	-	-	-	-	-	-	✓	✓
Liver and kidney function	✓	-	✓	-	-	-	-	✓	✓
Adherence	-	-	✓	-	-	-	-	✓	✓
CHM assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
Menstrual history	✓*	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	-	✓	✓	✓	✓	✓	✓	✓	✓

*in last 12 months

FAST=Fast Alcohol Screening Test, CEQ=Credibility/Expectancy Questionnaire, PCOSQ=Polycystic Ovary Syndrome Questionnaire, DLQI=Dermatology Life Quality Index, MYMOP=Measure Yourself Medical Outcome Profile

6.4. Proposed Analyses

Primary analysis consisted of a descriptive analysis of clinical and process data.

The primary objective of this study was:

1. To explore the suitability of oligomenorrhoea and amenorrhoea as the primary outcome measure for the main study and to provide scientific data to enable a sample size calculation to be made.

I proposed to assess this by collecting the following data:

- Is CHM effective for regulating periods in PCOS?

- Treatment effects in menstrual frequency and variability of cycle length, calculated from recording the mean and standard deviation of the number of days between menses during the 6-month treatment period and during the final 3 months of the treatment period. This is because some herbalists in the Delphi study expressed views that menstruation may not improve until after 3 months of treatment whilst others felt an improvement within the first month was possible. By analysing menstrual cycle data collected during the 6-month treatment period and that collected during the final 3 months, I will be able to conduct an exploratory analysis and choose an appropriate measurement for the main study. An improvement due to treatment in this study was determined as a reduction from baseline in standard deviation to reflect stability in the variability of cycle length, and a reduction from baseline in the mean number of days between menses towards a 21-35 days interval which is clinically accepted as a regular cycle length. This analysis was conducted for between-group and within-patient comparisons before and after treatment.
- Can menstrual data be obtained?
 - Percentage of missing menstrual data, collected at baseline as recall data for at least 6 months, and at the end of the treatment period.
- Is regulating menses important to women with PCOS?
 - Ranking of oligomenorrhoea and amenorrhoea amongst self-reported symptoms that are important to women with PCOS recorded in MYMOP. Where available, relevant data will be extracted from end-of-study participant feedback questionnaires.

The secondary objectives of this feasibility pilot study and subsequent data that would be used were:

1. To explore other outcome measures that may be more appropriate for investigation in a main study by looking at:
 - Frequency and rank order of self-reported symptoms regarded as being of importance to women with PCOS which will be recorded in MYMOP;
 - Relevant data provided from end-of-study participant feedback questionnaires;
 - Treatment effects at 6 months by obtaining point estimates and variance in the following:
 - Body mass index (BMI) and classified according to WHO cut-off points for normal range (18.50 – 24.99), overweight (25 – 29.99) and obese (≥ 30);
 - Weight (kg) where a clinically significant loss in weight for overweight and obese patients is determined as a loss of $\geq 5\%$ of initial weight (Moran et al., 2010);
 - Waist circumference, classified following WHO cut-off points for increased risk of metabolic complications ($>80\text{cm}$), or substantially increased risk of metabolic complications ($>88\text{cm}$) (2008);

- Waist hip ratio, classified following WHO cut-off points for substantially increased risk of metabolic complications (≥ 0.85) (2008);
- Hirsutism using mFG score, where a score of ≥ 6 signifies hirsutism (Yildiz et al., 2010).
- PCOSQ score for health-related quality of life in 5 domains of body hair, infertility, menstrual dysfunction, emotions and weight, where a minimally important difference in the score of 0.5 on the 1 to 7 scale per domain represents the smallest change in score that women feel is important in their daily lives (Cronin et al., 1998);
- DLQI, a dermatology-specific quality of life measure owing to dermatological complaints such as acne that are frequently found in PCOS but the impact of which are not covered in PCOSQ. The minimal important difference for general skin conditions is a change in DLQI score of ≥ 3.2 points (Finlay and Khan, 1994, Basra et al., 2008). An observer-assessment of acne will not be conducted since there is currently no agreed standard or reliable method of acne assessment;
- MYMOP where the minimal important difference for the change in score is 1.0 (Paterson, 1996, Guyatt et al., 1998).

2. To evaluate the safety and tolerance of CHM:

- Number, nature, severity, seriousness and expectedness of adverse and serious adverse events arising which have been assessed as being possibly related to CHM use for all participants in the study and by treatment group;
- Relevant data from end-of-study participant feedback questionnaires.

3. To inform the CHM intervention for the main study:

- Comparison of treatment effects and of safety between individualised CHM and standardised CHM;
- Doses prescribed of individual herbs to enable a preliminary exploration of dose-response and of safe-dosing parameters. A definitive evaluation of this will not be attempted since different doses of CHM will not be prospectively prescribed as part of this feasibility study;
- Frequency and rank order of individual CHM prescribed in individualised prescriptions, to enable a list of individual herbs and CHM combinations be collated;
- Frequency and rank order of diagnoses of participants in the study, to enable a list of the most frequently observed diagnoses be collated;
- Content of additional lifestyle and dietary advice that is typically offered within a CHM consultation for PCOS;
- Data relevant to the choice of CHM intervention from end-of-study participant feedback questionnaires.

4. To evaluate the feasibility of conducting a double-blind, randomised trial with CHM for PCOS and to pilot the study procedures;

- Eligibility rate from those responding to recruitment methods, and to assess reasons for ineligibility which will help evaluate the restrictiveness of eligibility criteria;
- Percentage of participants requiring further assessment in order to confirm diagnosis of PCOS and breakdown of type of assessment required e.g. ultrasound scan, assessment of hyperandrogenism. This will help evaluate the number of diagnosed and undiagnosed women who are recruited;
- Overall and monthly consent rate by study site and by recruitment method. This will provide useful data in terms of variation in rates based on geographical location of study sites, cost-effectiveness of recruitment methods and time lag between initiation of recruitment method to participant enrolment;
- Overall and monthly consent rate from those eligible, and assess reasons for ineligibility and those declining participation. This will help in ascertaining the overall recruitment for the duration of the study, and the initial acceptability of the study to participants after being provided information regarding the intervention and of the study procedures;
- Randomisation rate from those consenting and assess reasons for refusing randomisation. This will enable exploration of the acceptability to participants of being randomised;
- Retention rate, and withdrawal rate and numbers lost to follow-up and assess reasons for withdrawal and loss-to-follow up. This will enable an evaluation be made regarding acceptability to participants of the intervention and of the study procedures;
- Percentage of missing data by data collection method, which will enable a comparison be made of the efficiency of different methods of data collection;
- Security of practitioner-blinding by assessing Bang Blinding indices (BBI) over time and between groups, which will assess the value of attempting to blind in this study design (Bang et al., 2004);
- Security of the randomisation and allocation procedures, by comparing the allocation of participants at end-of-study with the allocation list initially generated by the statistician;
- Adherence to CHM administration using observer-reported methods and self-reported measures such as the MMAS-8 (Morisky et al., 1986, Morisky et al., 2008). Reasons affecting CHM adherence will also be recorded and will provide an initial exploration of the acceptability of the CHM and of the dosing regimen;
- Adherence to the study protocol by measuring study assessment rates and compulsory and non-compulsory study visit rates, and reporting on reasons affecting assessment rates. This will allow an initial assessment be made of the feasibility of study participants being seen as would be expected in routine practice;
- Number and percentage of participants unable to continue with full and minimum study doses.
- Impact on study outcomes of covariates such as baseline BMI, severity of menstrual irregularity, rationale credibility and expectancy score at baseline using the CEQ (Deville and Borkovec, 2000);
- Number and percentage of participants providing menstrual data and assessment of self-reported accuracy;
- Time taken for study processes such as study visits to provide data for resource planning and costing for the main study;

- Data relevant to feasibility from end-of-study feedback questionnaires administered to participants and study personnel;
- Piloting and evaluation of the following study components:
 - Recruitment methods;
 - Eligibility screening methods;
 - Data collection methods;
 - Statistical analysis;
 - Involvement of CHM dispensary;
 - Involvement of study practitioners.

6.4.1. Statistical methods

For statistical analysis, principles of intention-to-treat were adopted by keeping participants within their allocated treatment for analysis. Formal data imputation was however not conducted, although an exploration of the suitability of data imputation for the main study was planned. The main statistical analysis in this study was therefore an available-case analysis which analyses the data for every participant for whom the outcome was obtained.

Statistical analysis was piloted in this feasibility study to check its suitability for the main study and was conducted by myself and a statistician independent of the study team named in the protocol. This analysis tested for within-patient and between-group differences at Week 0 and at Week 24 and which analysed for clinical treatment effects using the variables as outlined above. Continuous variable comparisons were assessed at Week 24 adjusted for baseline assessments for the two groups using analysis of variance, or an analysis of covariance to include the effects of BMI, WHR, severity of menstrual disorder, demographic variables, CEQ score and adherence as appropriate.

Menstrual data were analysed from the first menses since randomisation onto the study.

Investigating the effects of these variables is important to initially explore whether groups of participants were likely to experience different treatment effects. Since these statistical analyses were piloted in this feasibility study and as no formal power calculations have been carried out, results from the statistical analysis presented as part of the feasibility study findings should be considered preliminary and must be interpreted cautiously (Lancaster et al., 2004).

Clinical notes detailing lifestyle and dietary advice given by study practitioners were analysed using content analysis.

Study-evaluation questionnaire data were analysed using content analysis for text-responses and descriptive summaries for Likert scales.

In the next chapter I will describe the findings from conducting out the feasibility study as described in this chapter, and discuss these results and analyses in context of the overall thesis.

Chapter 7: Results of a randomised feasibility and pilot study in private herbal practices

7.1. Introduction

Ethical approval was applied for in August 2012 and, following acceptance of amendments, was eventually granted 4 months later in December 2012 by the University of Southampton and the Register for Chinese Herbal Medicine research ethics committees (Approvals ID 3977). This trial was registered with an international trials registry in January 2013 (ISRCTN 31072075) and the trial protocol published in March 2014 (Lai et al., 2014) and which can be seen in Appendix 56. This next chapter will detail the results and findings from the conduct of this study.

7.2. Recruitment

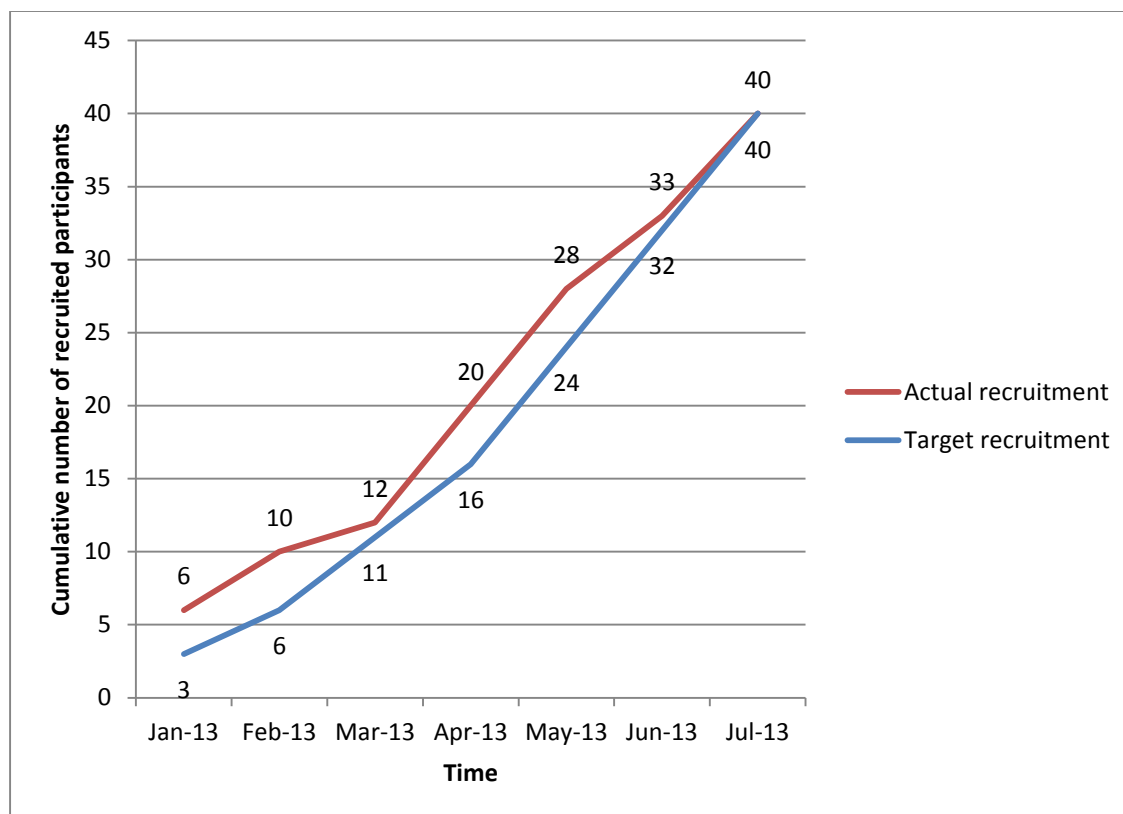
7.2.1. Recruitment of practitioners

I received a poor response from the majority of the practitioner community regarding helping to see participants in the study. Three practitioners responded with a desire to help but who were eventually not able to for reasons such as lacking access to safety testing (n=1) and lacking time (n=2). This resulted in me being the only practitioner providing treatment on this study and recruiting from two clinical sites, one in Primrose Hill in North London, and one in Hemel Hempstead in Hertfordshire.

7.2.2. Recruitment of participants

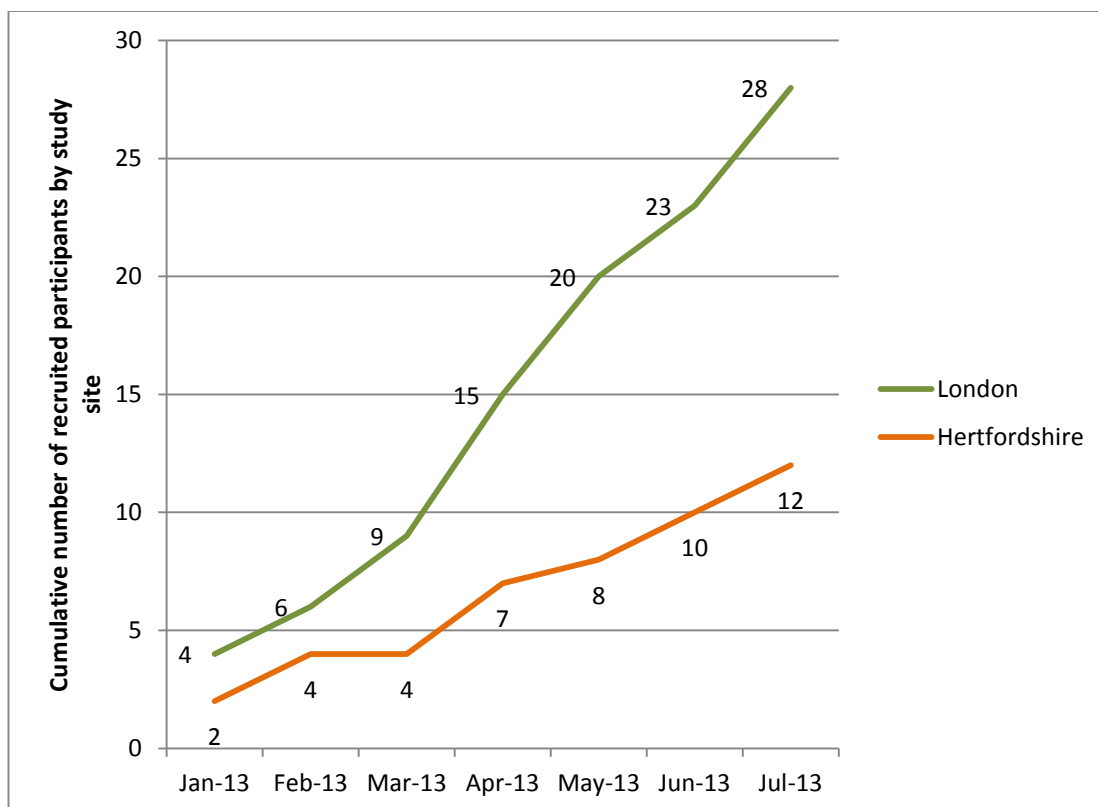
Participant recruitment commenced in January 2013. I received a total of 245 enquiries and reached the recruitment target of 40 participants within my planned 7 month recruitment period (16.3% eligibility rate). Figure 25 shows the target and actual cumulative recruitment targets over the 7 month period.

Figure 25: Target and actual cumulative recruitment numbers



Comparing recruitment between the two clinical sites, the London clinic site was more successful, recruiting 28 participants (70%) compared with 12 participants (30%) in Hemel Hempstead. Figure 26 displays the cumulative recruited participants by site.

Figure 26: Cumulative recruited participants by study site



I recruited directly from the community and not through primary care pathways and as a result, I used a number of resources to facilitate the recruitment process. Table 16 and Figure 27 show from the proportion of the final recruits which recruitment method had prompted their original enquiry.

Table 16: Number and percentage recruited by recruitment method

Method	Enquiries received (n)	Recruited from this method (n)	% recruited from method
Participants	5	5	100
Poster or flyer	13	7	53.8
Social networking site	2	1	50
Internet search	7	3	42.9
Chinese medicine practitioner	24	7	29.2
Online forum	82	9	11
Direct (Study website/email)	90	8	8.9
Newspaper article	14	0	0
Other healthcare professional	5	0	0
Family and friends	3	0	0
Totals	245	40	

Figure 27: Percentage of enquiries generated by recruitment method

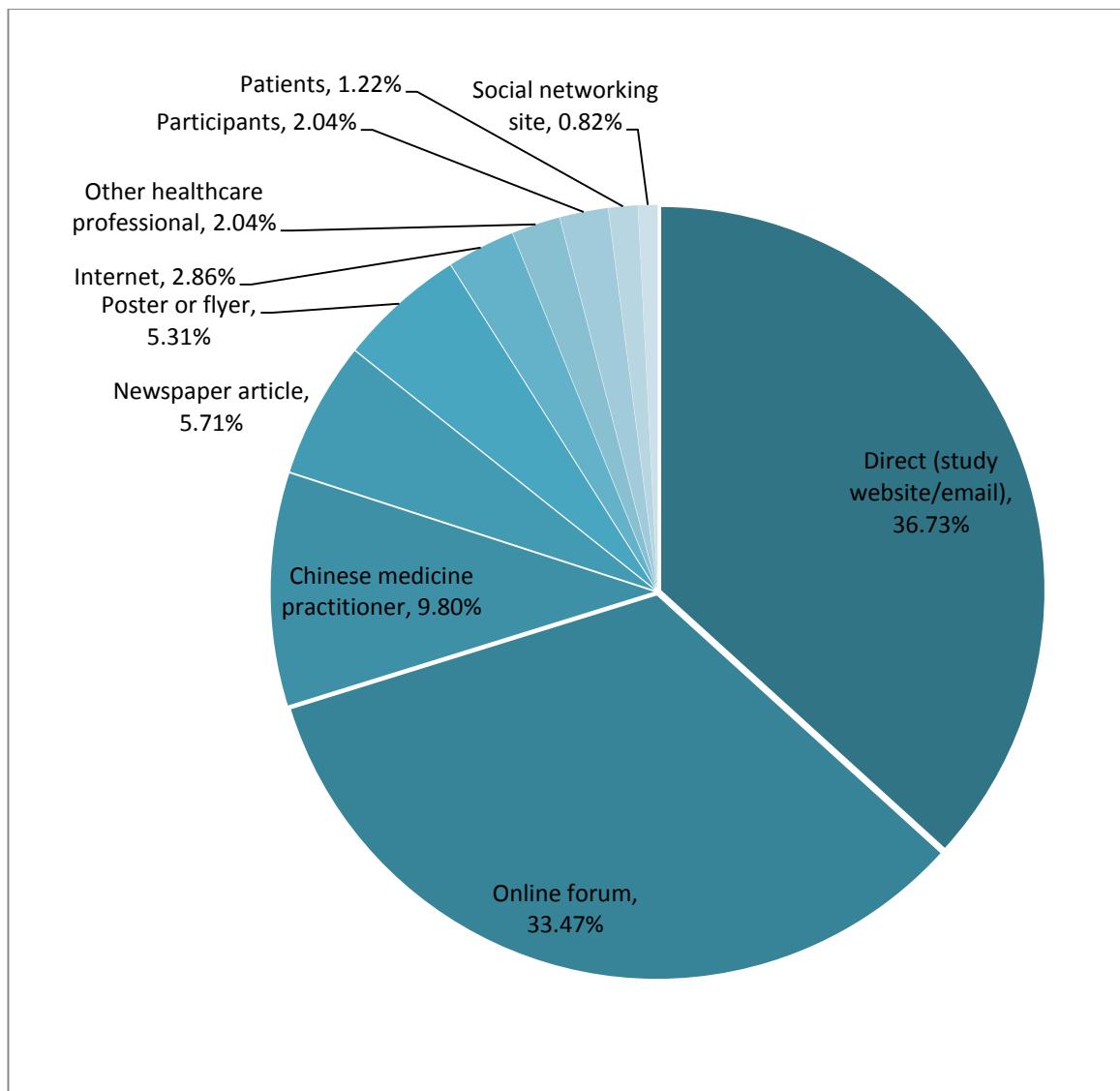
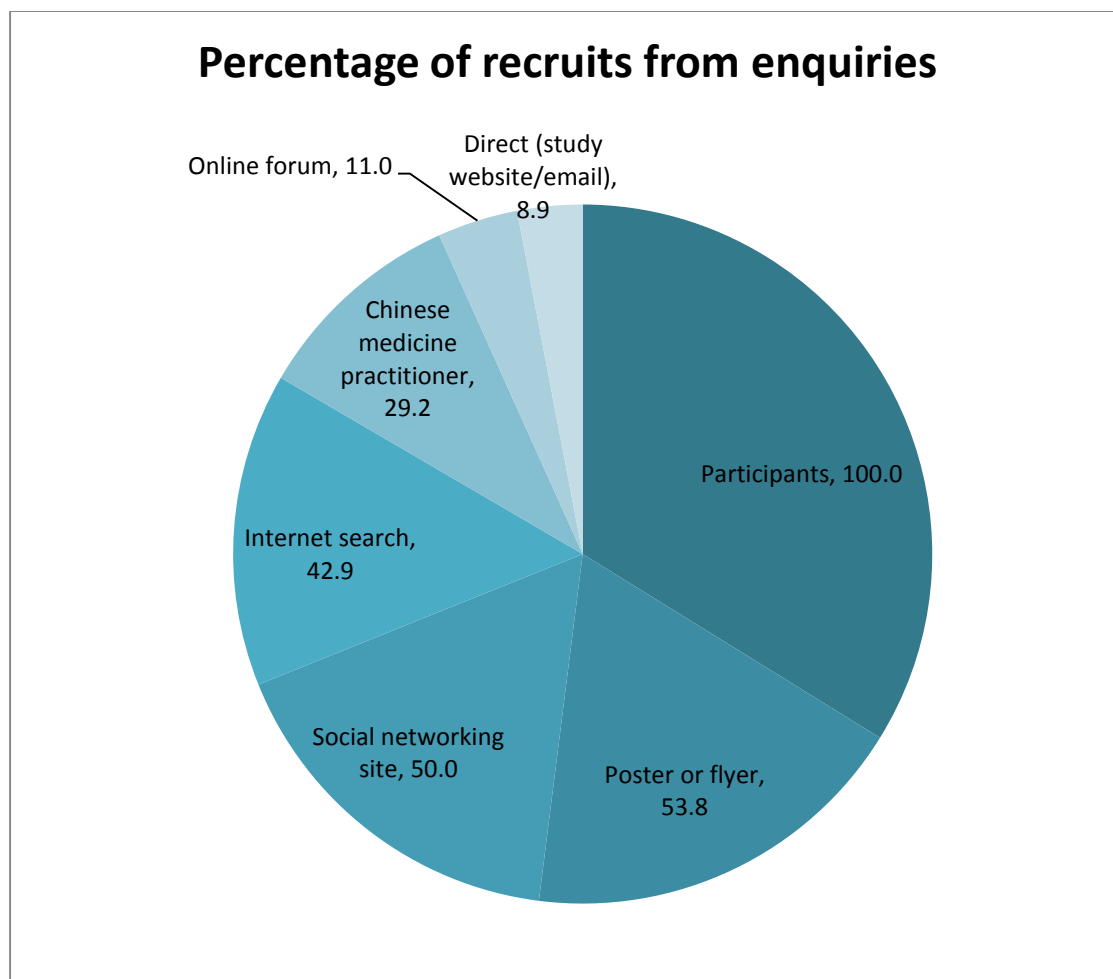


Figure 28: Percentage recruited by recruitment method



I calculated the time lag between initiation of each recruitment method by the study team to first enquiry generated and are provided in Table 17, ranked by time to first enquiry.

Table 17: Ranking of recruitment method by time lag between initiation of recruitment method to first enquiry

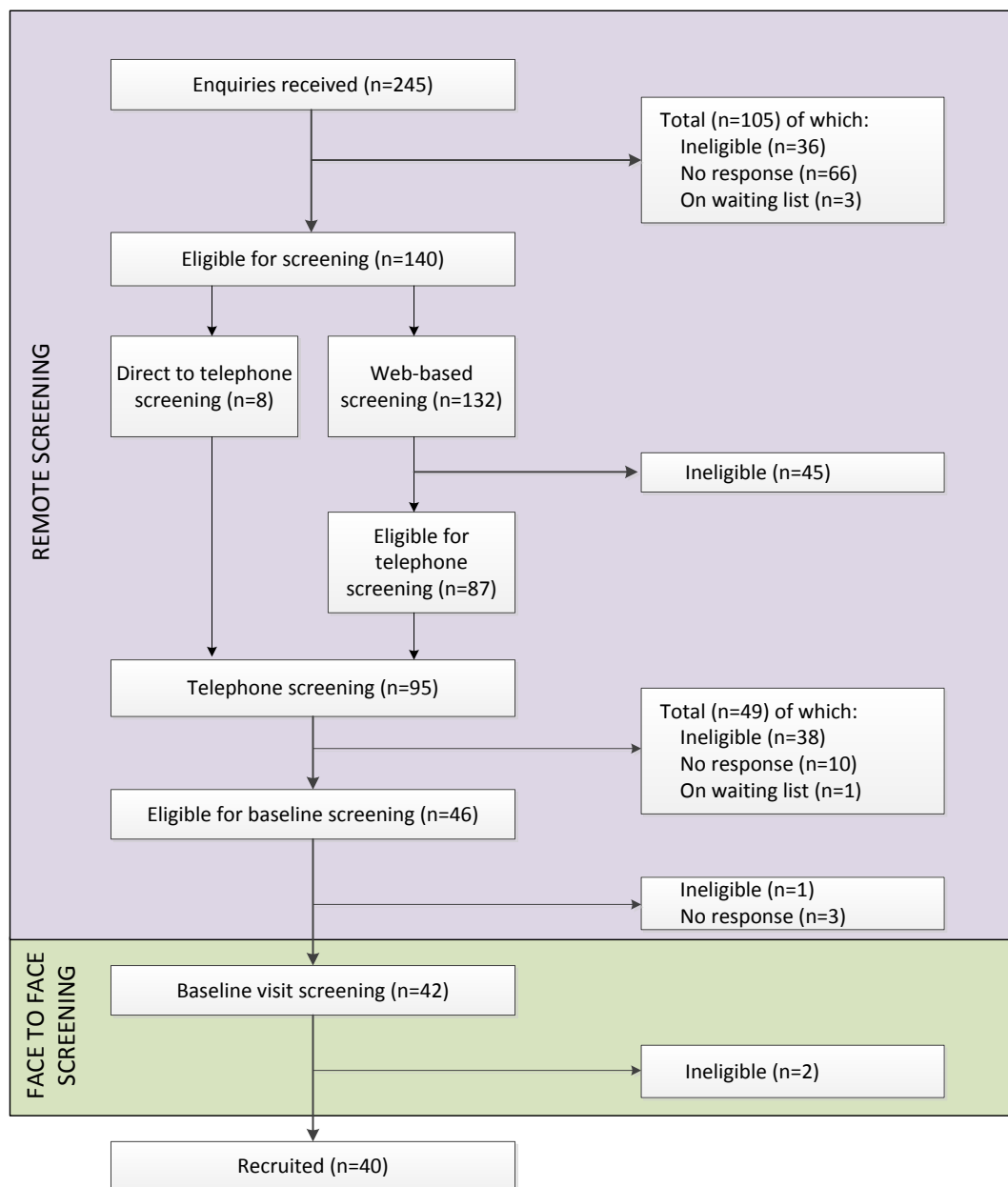
Recruitment method	Initiation of recruitment method	First enquiry received	Time to first enquiry
Chinese medicine practitioner	01/08/2012	01/08/2012	Within 24 hours
Newspaper	01/11/2012	01/11/2012	Within 24 hours
Online forum	28/01/2013	28/01/2013	Within 24 hours
Social media	07/10/2012	09/10/2012	2 days
Internet	07/10/2012	20/10/2012	13 days
Posters and flyers	01/10/2012	24/10/2012	23 days

The recruitment methods shown were not necessarily mutually exclusive – for example, posters and flyers were used at Chinese medicine conferences to invite referrals from Chinese medicine practitioners. This data nonetheless provides a preliminary estimation of time to first enquiry and will be helpful for other researchers drawing out recruitment plans for similar community-based studies.

7.3. Eligibility

Of the 245 enquiries received, 40 were eventually recruited, indicating a 16.3% eligibility rate. The flowchart in Figure 29 also displays the stage at which ineligibility was detected.

Figure 29: Eligibility flowchart



The eligibility flowchart demonstrates the majority of ineligible or non-responding enquirers (99%, 199 of 201 ineligible) were screened out during the remote screening procedures and prior to scheduling a baseline visit. I had no participants decline to participate after attending the baseline visit screening and no participants refusing randomisation after providing consent.

Reasons for ineligibility were reported as completely as possible and permitted multiple reasons for ineligibility per enquirer where this data was available. The frequency and rank order of these reasons are presented in Table 18.

Table 18: Frequency and rank order of reasons for ineligibility

Rank order and reason	Count
1. None provided - No response following provision of further details about the study	79
2. Prohibited medication or treatment	34
3. Regular periods	27
4. Distance	22
5. Trying to conceive	13
6. Contraindicated medical condition	10
7. Diagnosis inconsistent with Rotterdam	10
8. Further information required not available to complete eligibility assessment	9
9. Personal reasons	5
10. Expenses not covered	4
11. On waiting list	4
12. Currently breastfeeding/pregnant	3
13. Allergies	2
14. Outside of age range	2
15. Hazardous and harmful drinking	1
16. Improvement of symptoms	1
17. Abnormal baseline liver/kidney function	1

7.3.1. Further assessments required

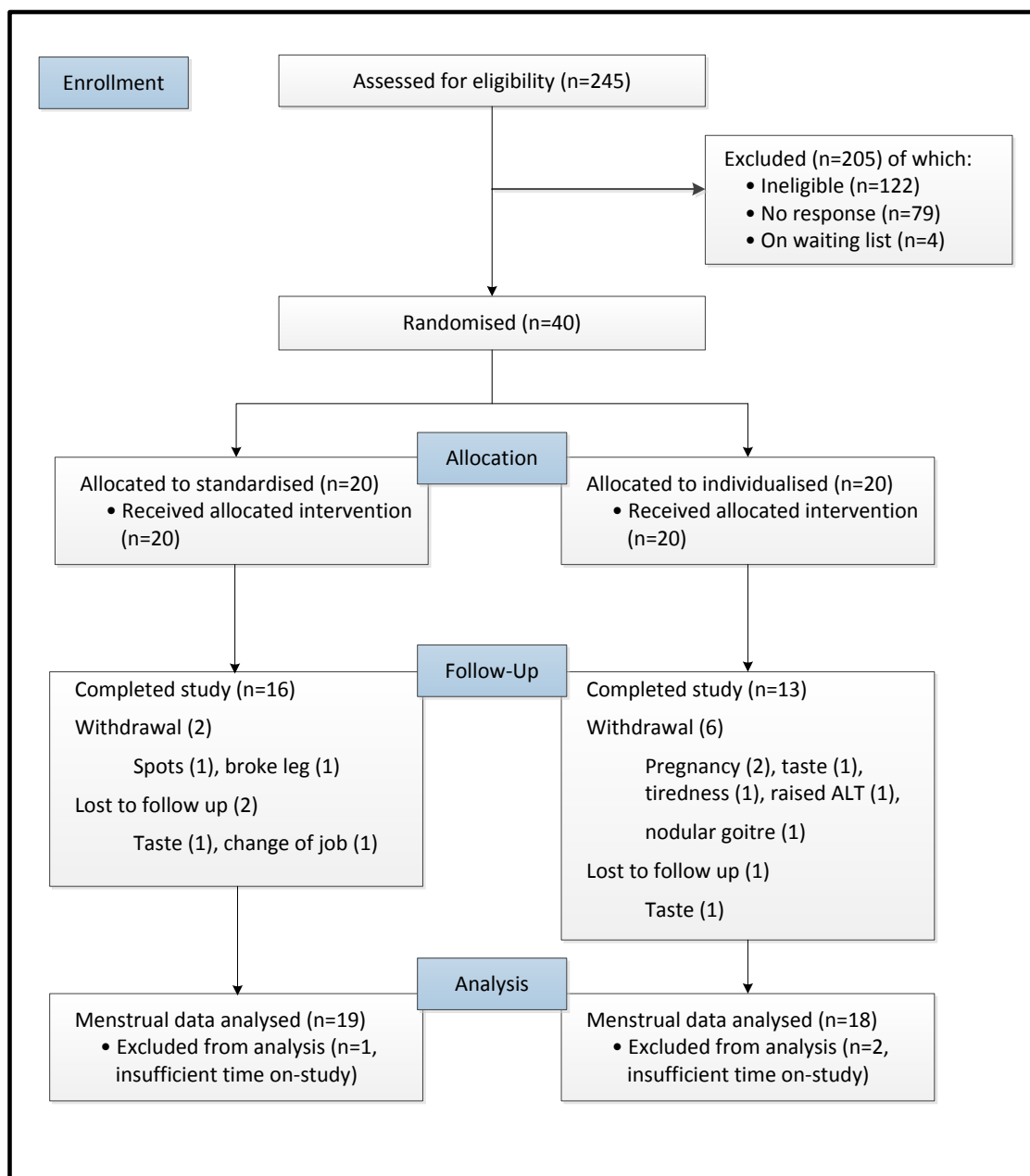
3 potential participants were referred to a private fertility clinic in London for further investigations to ensure that the Rotterdam criteria for PCOS diagnosis were fulfilled. All three potential participants required blood tests to confirm the absence of other hormonal causes for menstrual irregularities and other causes of hyperandrogenism. One of these participants additionally required an ultrasound scan to check ovarian status. These investigations were paid for by the research team and copies of results provided to each participant and, at the participant's request, to their respective GPs.

7.3.2. Retention and withdrawal

Figure 30 shows the flow diagram of the participants during the study. Of the 40 participants, 29 (72.5%) completed the 6-month treatment course, 8 (20%) withdrew from the study and 3 (7.5%) were lost to follow-up. The mean days of study participation was 160 days (range 13 to 237 days).

Reasons for withdrawal were pregnancy (n=2), serious adverse event (n=2), adverse event (n=1), adverse reactions (n=2) and taste (n=1). For the 3 who were lost to follow-up, the following issues were raised at point of last contact: taste (n=2), change of jobs (n=1).

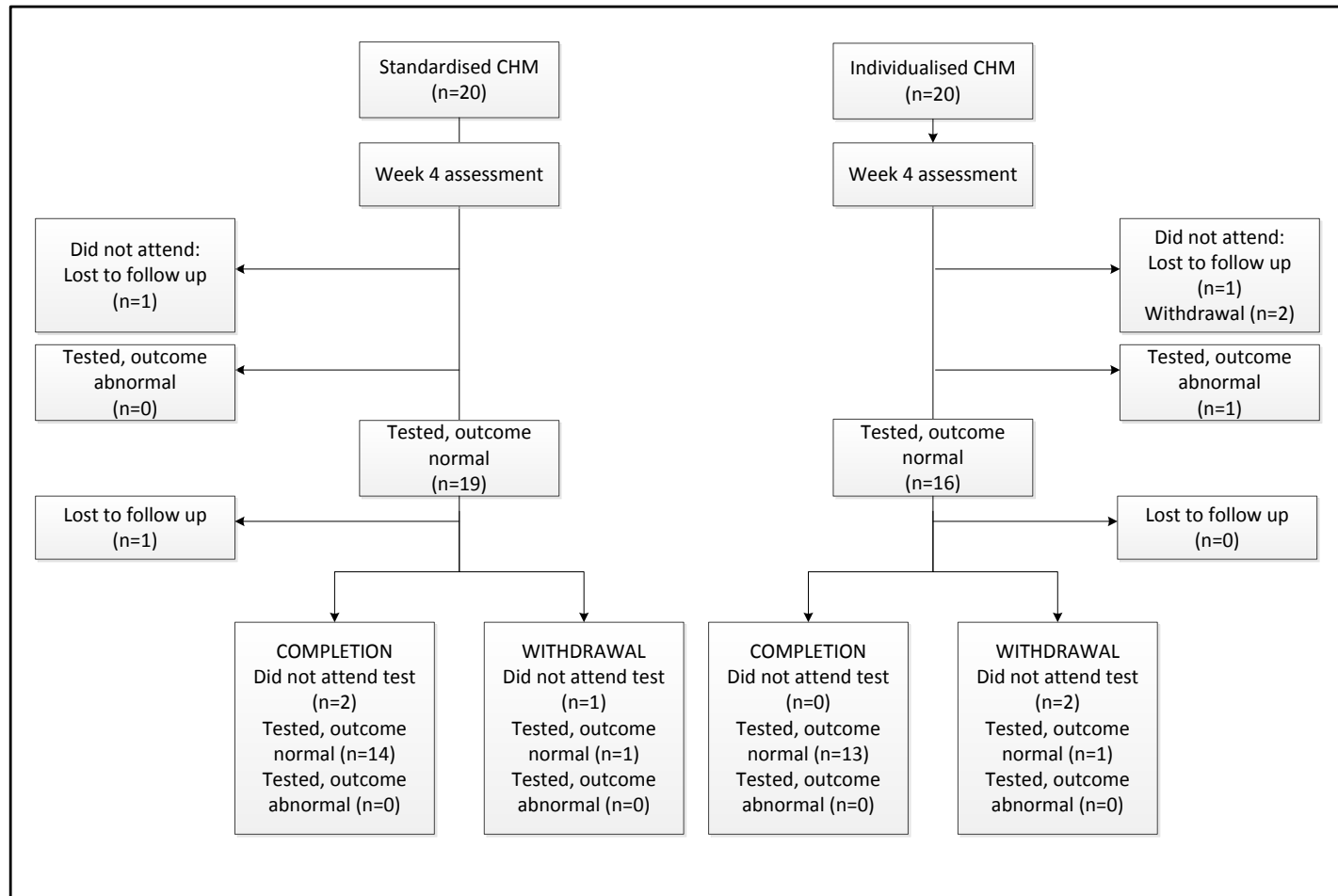
Figure 30: CONSORT participant flow diagram



7.4. Safety and adverse events

Liver and kidney function data taken at Week 4 and at final visit are summarised in Figure 31.

Figure 31: Flowchart to show safety assessments and outcomes by treatment group



There were two serious adverse events reported. One participant allocated to the individualised CHM was diagnosed with nodular goitre at study week 12. This participant was subsequently withdrawn and the consultant assessment of causality was that it was unrelated to the study treatment. One participant allocated to standardised CHM was on holiday abroad and reported a leg fracture which required hospitalisation. Causality was independently assessed as being unrelated to study treatment. For the single adverse event, one participant allocated to individualised CHM presented with an abnormal ALT reading at study week 4 and was subsequently withdrawn from the study. This adverse event was later assessed as being related to alcohol-intake which the participant reports experiencing on a previous occasion prior to joining the study. This reaction was assessed as being unrelated to study treatment.

Table 19 shows the frequencies of adverse reactions for each treatment group i.e. adverse events where there is at least a reasonable possibility of a causal relationship between the CHMs and the unintended response.

10 participants in total (4 from individualised and 6 from standardised) reported experiencing adverse reactions. When compared using Pearson Chi-Squared test, the number of participants reporting an adverse reaction in each group did not reach statistical significance, $\chi^2(1, N=40)=0.53$, $p=0.72$.

A total of 17 adverse reactions were reported amongst these 10 participants, with gastro-intestinal symptoms being the most commonly reported. All 17 were assessed as having a reasonable causal relationship with the allocated treatment and all 17 were assessed as being mild in severity, expected and not serious. When assessing duration of adverse reactions, 2 (loose stools and bloating) were persistent for 2 participants from the standardised treatment group who experienced these reactions with continued CHM administration. For the remaining 15 reactions, 14 lasted a median of 4 days (range 1-74) and 1 reaction had an unknown duration since this participant was lost to follow-up.

Table 19: Nature and frequency of adverse reactions compared between groups

Symptom	Standardised (n)	Individualised (n)	Total reporting by symptom (n)
Bloating	1	3	4
Nausea	2	1	3
Loose stools	1	2	3
Spots	1	0	1
Vomiting	1	0	1
Ovulation pain	1	0	1
Tiredness	0	2	2
Light-headedness	0	1	1
Headache	0	1	1
Total events reported by treatment group	7	10	17

7.5. Clinical data

End of study data was collected at withdrawal or final visit as specified in the protocol. The exception is menstrual data which was collected throughout study participation and which enabled analysis according to time since randomisation.

Data were analysed using SPSS version 21. Normality of the data was checked visually by histogram and using the Shapiro-Wilk test which is considered suitable for sample sizes smaller than 50 as in this study. Continuous measures were analysed using ANOVA where assumptions for normality were met and using Mann Whitney U test where this was not the case. For categorical variables, Chi-squared test was used. Where small numbers within

categories violated assumptions required for Chi-squared, I used Fisher's Exact test. Significance levels were set at $p < 0.05$ (two-tailed), unless otherwise specified.

7.5.1. Baseline demographics and variables

Baseline demographics of study participants are displayed in Table 20.

Demographics were shown to be comparable between groups at baseline and were analysed using Pearson's Chi-squared test apart from 'Age' and 'Years since diagnosis', analysed by one way ANOVA, and 'Menstrual presentation' and 'Parity' analysed by Fisher's Exact test. Due to the number of analyses carried out exploring baseline demographics and variables and to protect against detecting spurious significant results, I set significance levels for these analyses to $p < 0.01$.

Table 20: Baseline demographics of ORCHID study participants

Baseline demographics, n (%) unless specified otherwise	Standardised (n=20)	Individualised (n=20)	χ^2 statistic	P value
Age, mean (SD)	28.5 (6.0)	30.4 (6.6)	0.96*	0.33
Years since diagnosis, mean (SD)	7.1 (4.8)	9.3 (6.7)	1.45*	0.24
Menstrual presentation				
Oligomenorrhoea	15 (75)	17 (85)	NA	0.70^
Amenorrhoea	5 (25)	3 (15)		
Current conventional medication use				
Yes	1 (5)	2 (10)	0.36	0.55
No	19 (95)	18 (90)		
of which previously tried conventional medication#	16 (80)	11 (55)	NA	
Prior use of				
CAM: Yes	14 (70)	16 (80)	0.53	0.47
Acupuncture or CHM: Yes	8 (40)	12 (60)	1.60	0.21
Parity ≥ 1				
Yes	4 (20)	1 (5)	NA	0.34^
No	16 (80)	19 (95)		
PCOS phenotype#				
Type A: Menstrual disturbances, hyperandrogenism and polycystic ovaries	15 (75)	10 (50)	NA	
Type B: Menstrual disturbances, hyperandrogenism	0	1 (5)		

Type C: Menstrual disturbances and polycystic ovaries	5 (25)	9 (45)	
Employment status#			
Full time employment	12 (60)	11 (55)	NA
Part time employment	2 (10)	3 (15)	
Self-employed	2 (10)	2 (10)	
Student	1 (5)	3 (15)	
Homemaker	1 (5)	1 (5)	
Out of work, looking for work	2 (10)	0	

*F statistic, #Not compared as a baseline demographic, ^ Fisher's Exact Test

Baseline variables were also found to be comparable at baseline, as shown in Table 21. Values are shown as means and SDs unless otherwise specified.

Table 21: Comparability at baseline between treatment groups

Baseline characteristic	Standardised (n=20)	Individualised (n=20)	F statistic	P value
Menstrual rate, n per 28 days	0.38 (0.28)	0.51 (0.28)	2.00	0.17
Modified Ferriman-Gallwey score	8.1 (6.0)	7.6 (6.5)	0.05	0.82
Anthropometrics				
Weight (kg)	74.5 (17.1)	78.2 (23.7)	0.32	0.57
BMI (kg/m ²)	27.2 (5.8)	28.1 (7.9)	0.16	0.70
Waist hip ratio	0.82 (0.07)	0.82 (0.06)*	0.03	0.86
Waist circumference (cm)	87.4 (14.8)	90.3 (20.0)	0.27	0.60
Quality of life questionnaires				
MYMOP Score 1	4.60 (1.05)	5.15 (0.88)	3.25	0.08
MYMOP Wellbeing	3.37 (1.6)*	3.20 (1.7)	0.10	0.76
DLQI	2.75 (3.4)	5.10 (6.6)	2.00	0.17
PCOSQ Total	18.2 (5.6)	17.3 (5.6)	0.30	0.59
Credibility and Expectancy				
Q1. How logical does treatment seem? (score 0-9)	6.85 (1.8)	7.55 (1.4)	1.99	0.17
Q2. Think – how successful in reducing symptoms? (score 0-9)	6.00 (1.4)	6.25 (1.4)	0.32	0.58
Q3. How confident to recommend? (score 0-9)	6.25 (2.2)	6.40 (1.7)	0.06	0.81
Q4. Think – improvement by end of treatment? (score 0-100%)	0.55 (0.2)	0.54 (0.2)	0.01	0.94
Q5. Feel – treatment will reduce symptoms? (score 0-9)	5.70 (1.5)	6.35 (1.8)	1.50	0.23
Q6. Feel – improvement by end of treatment? (score 0-100%)	0.55 (0.2)	0.61 (0.2)	0.74	0.40

*Data for 19 participants in this group; Abbreviations: BMI=Body Mass Index, MYMOP=Measure Yourself Medical Outcome Profile, DLQI=Dermatology Life Quality Index, PCOSQ=Polycystic Ovary Syndrome Questionnaire; Equal variances assumed

7.5.2. Primary outcome measure: Menstrual cyclicity

To enable mean menstrual cycle length and associated variability be computed as was initially proposed, the dates of at least three periods needed to be provided prior to the study as the baseline assessment and on-study for the final assessment. I was aware prior to the study that this data could be difficult to obtain and my concerns were founded as this amount of data was not possible for 6 participants at baseline and for 13 participants for the on-study assessment. Since excluding these participants' data would have resulted in biases in treatment comparisons, I and the study statistician (PP) agreed that another measure should be used that was closely related to the interval between menses and which would enable us to analyse as many of the participants' data as possible. I therefore re-defined menstrual cyclicity as menstrual rate per month (28 days), an approach that has been used in other PCOS trials (Moggetti et al., 2000, Essah et al., 2006) and enabled me to use all menstrual data provided by the participants.

The initial endpoint had been pre-specified in the published protocol as menstrual cyclicity up until 6 months (168 days) post-randomisation. In addition to this, for 26 of the participants, the actual number of days on-study was greater than 6 months (168 days) owing to logistical issues relating to arranging appointment times for the end of study visit. This meant menstrual data continued to be collected up until the final visit and led to additional menstrual data for 13 participants. As this was a significant proportion of the study cohort, I chose to explore this in a post-hoc analysis to explore the effects of taking this additional data into consideration. This means that I will present menstrual data at the 6 month timepoint, and also at the end of study timepoint.

3 participants withdrew or became lost to follow up within 21 days post-randomisation and we were unable to obtain any on-study menstrual data from these participants. On-study menstrual data was therefore available for analysis from 19 participants in the standardised CHM group and 18 participants in the individualised group.

The descriptive statistics for menstrual data at baseline and unadjusted at 6 months and at End of study are provided in Table 22.

Table 22: Unadjusted menstrual rates at 6 months, at End of study, and change from baseline for Standardised and Individualised CHM treatment groups

Assessment	Standardised group menstrual rate (menses/28 days)		Individualised group menstrual rate (menses/28 days)	
	n	Mean±SE (95% CI)	n	Mean±SE (95% CI)
Baseline	20	0.38±0.06 (0.25 to 0.52)	20	0.51±0.06 (0.38 to 0.64)
6 months	19	0.58±0.05 (0.47 to 0.70)	18	0.75±0.07 (0.59 to 0.90)
End of study	19	0.65±0.06 (0.52 to 0.78)	18	0.83±0.08 (0.66 to 1.01)
Change from baseline at 6 months	19	0.20±0.07 (0.05 to 0.35)	18	0.25±0.07 (0.09 to 0.40)
Change from baseline at End of study	19	0.27±0.08 (0.10 to 0.43)	18	0.34±0.09 (0.16 to 0.52)

This data suggests that standardised CHM improves mean menstrual rate by 0.20 menses/28 days in the study population and that we can be 95% certain that the true population improvement is from 0.05 to 0.35 menses/28 days. In comparison, the individualised CHM improves mean menstrual rate by 0.25 menses/28 days in the study population and, again, we can say with 95% certainty that the true population improvement is from 0.09 to 0.40 menses/28 days. Since the confidence intervals for change from baseline for both analyses at 6 months and at End of study do not cross 0, this indicates that changes are statistically significant from baseline for both groups.

I explored this further by comparing the menstrual rates between the two groups and adjusting for covariates as was stated in the protocol. ANCOVA

test of between subject effects at 6 months showed that the covariate baseline menstrual rate was significant ($p=0.01$) as well as age ($p=0.03$). Table 23 shows the adjusted mean menstrual rates at 6 months, at End of study and change from baseline adjusted for baseline menstrual rate and age. ANCOVA was performed to compare the adjusted mean menstrual rates between-group at 6 months and at End of study and results from this analysis can also be seen in Table 23.

Table 23: ANCOVA of menstrual rate at 6 months and at end of study

Assessment	Menstrual rate (menses/28 days)						
	Standardised group		Individualised group		Between group		
	n	Adjusted mean $\pm$ SE (95% CI)	n	Adjusted mean $\pm$ SE (95% CI)	Adjusted mean difference $\pm$ SE (95% CI)	F statistic	p value
6 months menstrual rate*	19	0.62 $\pm$ 0.06 (0.50 to 0.73)	18	0.71 $\pm$ 0.06 (0.60 to 0.83)	0.10 $\pm$ 0.08 (-0.07 to 0.26)	1.33	0.26
End of study menstrual rate*	19	0.69 $\pm$ 0.06 (0.56 to 0.82)	18	0.80 $\pm$ 0.07 (0.66 to 0.93)	0.10 $\pm$ 0.09 (-0.09 to 0.29)	1.24	0.27
Change from baseline at 6 months*	19	0.18 $\pm$ 0.06 (0.06 to 0.29)	18	0.27 $\pm$ 0.06 (0.15 to 0.39)			
Change from baseline at end of study*	19	0.25 $\pm$ 0.06 (0.12 to 0.38)	18	0.35 $\pm$ 0.07 (0.22 to 0.49)			

*Adjusted for baseline menstrual rate and age at these timepoints

7.5.2.1. Menstrual data analysed on-study and up to 6 months

Table 23 shows that after adjustment for baseline differences in menstrual rates and age, there is no statistically significant difference between the two treatment groups at 6 months (MD 0.10±0.08, 95% CI -0.07 to 0.26, $F(1,33)=1.33$; $p=0.26$). The changes from baseline suggest that the standardised CHM group improves mean menstrual rate by 0.18 menses/28 days in the study population and that we can be 95% certain that the true population improvement is from 0.06 to 0.29 menses/28 days. The individualised CHM on the other hand improves mean menstrual rate by 0.27 menses/28 days in the study population and we can express with 95% certainty that the true population improvement is from 0.15 to 0.39 menses/28 days. As these confidence intervals do not cross 0, this indicates statistically significant improvements from baseline in both groups at 6 months.

7.5.2.2. Menstrual data analysed on-study and up to end of study participation

For menstrual data at End of study, although the adjusted means and mean changes from baseline appear more favourable compared with the 6 month data, the same conclusion as in the primary analysis is reached. This is shown in Table 23 that demonstrates after adjustment for baseline differences in menstrual rates and age, there is no statistically significant difference found between the two treatment groups at End of study (MD 0.10, 95% CI -0.09 to 0.29, $F(1,33)=1.24$, $p=0.27$). In terms of changes from baseline, the standardised group saw a mean change from baseline of 0.25 menses/28 days (95% CI 0.12 to 0.38) whilst the individualised group saw a mean change from baseline of 0.35 menses/28 days (95% CI 0.22 to 0.49). Once again, these indicate statistically significant improvements from baseline in both groups at End of study.

7.5.2.3. Responders vs non responders

In the absence of a minimum clinically important difference for menstrual rate, I attempted to enhance the clinical relevance of our findings post-hoc by dichotomising menstrual cyclicity data into responders and non-responders. I followed definitions of a response to treatment from other PCOS studies (Moggetti et al., 2000, Essah et al., 2006) and which define response as a change from amenorrhoea to oligomenorrhoea or eumenorrhoea, a change

from oligomenorrhoea to eumenorrhoea, or as achieving pregnancy. The results can be seen in Table 24.

Table 24: Responders and non-responders to CHM treatments

	Standardised n, column %	Individualised n, column %	Total
Responder	10 52.6%	13 72.3%	23
Non responder	9 47.4%	5 27.8%	14
Total	19	18	37

There was a slightly higher odds of responders in the individualised treatment in terms of menstrual rate (OR 1.37, 95% CI 0.82 to 2.29) which was not statistically significant between group ($\chi^2(1, N=37)=1.51, p=0.22$).

It is important to note that the latter two of the analyses of the menstrual data up to end of study participation and as a dichotomised variable were post-hoc. Although interesting exploratory analyses are presented, these should be interpreted with caution.

7.5.3. Secondary outcome measures

ANCOVA of the secondary outcome measures are shown in Table 25 and which show mean differences between and within group, adjusted for age and corresponding baseline value for each variable.

Table 25: ANCOVA comparing secondary outcome measures within and between group

Outcome measure	Standardised group		Individualised group		Between group		
	n	Adjusted mean difference from baseline $\pm$ SE (95% CI)	n	Adjusted mean difference from baseline $\pm$ SE (95% CI)	Adjusted mean difference between-group $\pm$ SE (95% CI)	F statistic	p value
MYMOP 1	17	2.04 $\pm$ 0.39* (1.24 to 2.84)	18	2.02 $\pm$ 0.38* (1.24 to 2.80)	-0.02 $\pm$ 0.57 (-1.12 to 1.14)	0.001	0.98
MYMOP2	17	0.87 $\pm$ 0.39 (0.07 to 1.67)	18	1.46 $\pm$ 0.38* (0.68 to 2.24)	0.59 $\pm$ 0.55 (-0.53 to 1.71)	1.15	0.29
MYMOP Activity	11	2.38 $\pm$ 0.43* (1.49 to 3.26)	15	1.59 $\pm$ 0.36* (0.84 to 2.34)	-0.78 $\pm$ 0.58 (-1.98 to 0.41)	1.85	0.19
MYMOP Wellbeing	16	0.92 $\pm$ 0.32 (0.28 to 1.57)	18	0.90 $\pm$ 0.30 (0.30 to 1.51)	-0.02 $\pm$ 0.43 (-0.90 to 0.87)	0.001	0.97
PCOSQ Total	17	5.17 $\pm$ 1.0 (3.09 to 7.25)	18	3.74 $\pm$ 1.00 (1.72 to 5.77)	-1.43 (-4.33 to 1.49)	1.00	0.33
<i>PCOSQ Emotions</i>	17	0.97 $\pm$ 0.22* (0.53 to 1.42)	18	1.06 $\pm$ 0.21* (0.63 to 1.49)	0.09 $\pm$ 0.31 (-0.54 to 0.72)	0.09	0.77
<i>PCOSQ Body Hair</i>	17	0.84 $\pm$ 0.26* (0.31 to 1.38)	18	0.32 $\pm$ 0.26 (-0.20 to 0.83)	-0.53 $\pm$ 0.37 (-1.27 to 0.22)	2.09	0.16
<i>PCOSQ Weight</i>	17	0.79 $\pm$ 0.32* (0.15 to 1.44)	17	0.56 $\pm$ 0.31* (-0.06 to 1.19)	-0.23 $\pm$ 0.44 (-1.13 to 0.68)	0.26	0.61
<i>PCOSQ Infertility</i>	17	1.17 $\pm$ 0.25* (0.66 to 1.68)	18	0.77 $\pm$ 0.24* (0.27 to 1.27)	-0.40 $\pm$ 0.35 (-1.12 to 0.32)	1.30	0.26
<i>PCOSQ Menstrual</i>	17	1.40 $\pm$ 0.24* (0.91 to 1.88)	18	1.03 $\pm$ 0.23* (0.56 to 1.50)	-0.37 $\pm$ 0.33 (-1.05 to 0.31)	1.23	0.28
DLQI	16	-1.97 $\pm$ 0.66 (-3.32 to -0.62)	18	-0.36 $\pm$ 0.62 (-1.63 to 0.91)	1.61 $\pm$ 0.93 (-0.29 to 3.50)	3.02	0.09

BMI	15	-0.41±0.46 (-1.40 to 0.54)	15	-0.26±0.48 (-1.25 to 0.72)	0.15±0.67 (-1.23 to 1.53)	0.05	0.83
Weight (kg)	15	-1.13±1.30 (-3.80 to 1.54)	14	-0.77±1.34 (-3.53 to 1.99)	0.36±1.88 (-3.51 to 4.23)	0.04	0.85
Waist circumference (cm)	15	-0.80±1.28 (-3.45 to 1.85)	13	-2.96±1.38 (-5.81 to -0.11)	-2.16±1.90 (-6.08 to 1.75)	1.30	0.27
Waist hip ratio	15	0.002±0.01 (-0.02 to 0.02)	12	-0.04±0.01 (-0.06 to -0.01)	-0.04±0.02 (-0.07 to -0.01)	6.41	0.02
Hirsutism	15	-2.52±0.42 (-3.40 to -1.65)	14	-1.44±0.44 (-2.35 to -0.54)	1.08±0.61 (-0.18 to 2.34)	3.11	0.09

*achieved minimum clinically important difference (MCID) *

For MYMOP 1 and MYMOP activity, both treatment groups achieved a minimum clinically important difference (MCID) of 1.0 by the end of the study. However, the difference between groups in MYMOP 1 at end of study (MD -0.02, 95% CI -1.12 to 1.14) was not statistically significant, $F(1,31)=0.001$ ($p=0.98$). This was also found in the difference between groups in MYMOP activity at end of study (MD -0.78, 95% CI -1.98 to 0.41) which was not statistically significant, $F(1,22)=1.85$ ($p=0.19$). PCOSQ Total scores also improved from baseline in both treatment groups with mean improvements in standardised and individualised groups of 5.17 (95% CI 3.09 to 7.25) and 3.74 (95% CI 1.72 to 5.77) respectively. Again, between-group differences (MD -1.43, 95% CI -4.33 to 1.49) did not reach statistical significance, $F(1,31)=1.00$ ($p=0.33$). Apart from PCOSQ Body Hair score for individualised CHM, all other PCOS domain scores for both groups reached the MCID of 0.5 by the end of the study. Statistical significance was also reached within-group in almost all PCOSQ domain scores with the exception of Body Hair and Weight domains for individualised group only. Changes from baseline PCOSQ domain scores did not reach statistical significance between group.

MYMOP 2 achieved MCID for the individualised group only, although statistical significance from baseline was reached within-group for both groups. Between-group differences (MD 0.59, 95% CI -0.53 to 1.71) did not reach statistical significance, $F(1,31)=1.15$ ($p=0.29$).

There were small improvements observed in both treatment groups for BMI and weight, but these were neither clinically nor statistically significant within or between groups. For waist circumference, individualised CHM experienced appeared to experience a significant change from baseline (MD -2.16, 95%CI -5.81 to -0.11) whilst standardised CHM did not (MD -0.80, 95%CI -3.45 to 1.85) and which was not significant between-group ($p=0.27$). For waist hip ratio, standardised CHM group experienced no significant change from baseline (MD 0.002, 95% CI -0.02 to 0.02) whilst individualised CHM group improved significantly from baseline (MD -0.04, 95% CI -0.06 to -0.01). This reached statistical significance between groups favouring individualised treatment, $F(1,23)=6.41$ ($p=0.02$). Improvements in DLQI and hirsutism scores were also observed in both groups. Hirsutism scores were significantly improved from baseline in both standardised group (MD -2.52, 95% CI -3.40 to -1.65) and individualised group (MD -1.44, 95% CI -2.35 to -0.54) but which did not reach between-group significance, $F(1,25)=3.11$ ($p=0.09$). There was a significant change observed in DLQI scores from baseline in standardised treatment (MD -1.97, 95% CI -3.32 to -0.62) though not in individualised treatment (MD -0.36, 95% CI -1.63 to 0.91) and which was not statistically significant between-group, $F(1,30)=3.02$ ($p=0.09$).

Although this data suggests some encouraging preliminary findings, these results must be interpreted cautiously owing to the amount of missing data found in a number of these measures, most notably in MYMOP activity and waist hip ratio.

7.5.4. MYMOP ranking

The frequency and rank order of MYMOP 1 and 2 symptoms are shown below in Table 26. These symptoms were then combined into one list and the frequency and rank order are shown in Table 27.

Table 26: Frequency and rank order of MYMOP 1 and 2 symptoms

MYMOP 1		MYMOP 2	
n	Symptom	n	Symptom
9	Weight/Regularity of periods	11	Hirsutism
8	Hirsutism	8	Mood
5	Acne	7	Weight
2	Mood/Period pain/Tiredness	5	Acne
1	Bloating/Infertility/Weak periods	3	Regularity of periods
		2	Bloating
		1	Period pain/Infertility/ Excessive sweating/Body odour

Table 27: Frequency and rank order of MYMOP 1 and 2 symptoms combined

MYMOP 1 and 2 combined	
n	Symptom
19	Hirsutism
16	Weight
12	Regularity of periods
10	Acne/Mood
3	Bloating/period pain
2	Tiredness/Infertility
1	Weak periods/excessive sweating/body odour

Weight and regularity of periods ranked highest in terms of being a main concern for study participants whilst hirsutism was the next highest ranking symptom. When the data was combined, hirsutism, weight and regularity of periods ranked in the top 3 most distressing concerns.

7.5.5. Practitioner-blinding assessment

The practitioner-blinding questionnaire was administered at three time-points in the study and at least one blinding questionnaire was completed for 38 participants. Blinding data was available for analysis at Weeks 4 (n=36), 12 (n=31) and end of study (n=36).

Table 28 shows the Bang Blinding Index (BBI) results by group and by time of administration. BBI was calculated for each treatment group using the following formula:

$$BI = \frac{\text{correct guesses in group}}{\text{total guesses in group}} - \frac{\text{incorrect guesses in group}}{\text{total guesses in group}}$$

A BBI of negative value indicates a tendency towards an opposite, i.e. incorrect, guess. The BBI at each of the three timepoints was at Week 4 standardised -0.11 (95% CI -0.35 to 0.14) and for individualised 0.47 (95%CI 0.23 to 0.71). At Week 12, BBI was for standardised -0.24 (95%CI -0.54 to 0.07) and for individualised 0.50 (95% CI 0.12 to 0.88). At End of Study, this was for standardised -0.56 (95% CI -0.91 to -0.20) and for individualised 0.61 (95% CI 0.30 to 0.92). When interpreted as suggested by Bang et al. (2004), practitioner guessing at Week 4 was standardised random/individualised unblinded, at Week 12 standardised random/individualised unblinded and at End of Study standardised opposite/individualised unblinded.

Table 28: Practitioner-blinding results using Bang Blinding Index

	Standardised	Individualised	Row total
Week 4			
Stated: Standardised	2	0	2
Stated: Individualised	4	8	12
Not at all sure	13	9	22
Total	19	17	36
Bang Blinding Index (95% CIs)	-0.11 (-0.35 to 0.14)	0.47 (0.23 to 0.71)	
Week 12			
Stated: Standardised	2	2	4
Stated: Individualised	6	9	15
Not at all sure	9	3	12
Total	17	14	31
Bang Blinding Index (95% CIs)	-0.24 (-0.54 to 0.07)	0.50 (0.12 to 0.88)	
End of study			
Stated: Standardised	3	2	5
Stated: Individualised	13	13	26
Not at all sure	2	3	5
Total	18	18	36
Bang Blinding Index (95% CIs)	-0.56 (-0.91 to -0.20)	0.61 (0.30 to 0.92)	

The reasons practitioners provided for treatment guesses were categorised and Table 29 shows the frequency counts for each treatment group and corresponding guesses. As each treatment guess could involve more than one reason, column totals do not equate to the total number of guesses.

Table 29: Frequency table of reasons for practitioner-treatment guess

	Standardised treatment			Individualised treatment			Row total (n)
Reasons for treatment guess	Stated: Standardised (n)	Stated: Individualised (n)	Not at all sure (n)	Stated: Standardised (n)	Stated: Individualised (n)	Not at all sure (n)	
Presence of effects	0	12	12	0	21	10	55
Presence of side-effects	0	4	3	0	1	1	9
Lack of effects	5	0	6	3	0	3	17
Lack of side-effects	0	0	0	0	0	0	0
Participant reported changes in taste and/or smell between prescriptions	0	8	1	0	5	0	14
Lack of participant reported changes in taste and/or smell between prescriptions	1	0	1	0	0	1	3
Participant reported difficult taste	0	0	1	0	2	1	4
Administrative error by pharmacy	1	0	0	1	1	0	3
None given	0	0	1	0	0	0	1
TOTALS	7	24	25	4	30	16	106

This table shows that ‘Presence of effects’ was the most commonly provided reason for guessing treatment allocation in both the standardised (24 of 56 guesses; 43%) and the individualised groups (31 of 50 guesses; 62%). ‘Lack of effects’ was the next most commonly provided reason and constituted 11 of 56 guesses (20%) in the standardised group, and 6 of 50 guesses (12%) in the individualised group. The third most common reason was ‘Participant reported changes in taste and/or smell between prescriptions’ and constituted 9 of 56 (16%) guesses in the standardised group and 5 of 50 guesses (10%) in the individualised group.

7.5.6. Security of randomisation and allocation procedures

To compare the security of randomisation and allocation procedures, I obtained the randomisation log from the CHM dispensary and a sample of 89 (39.9%) prescription invoices from a total of 223 invoices that were placed. Each participant recorded in the pharmacy-generated randomisation log was allocated to the treatment group that was consistent with the randomisation list provided by the study statistician, indicating that randomisation was successfully conducted as intended. The available prescription invoice data was triangulated with the randomisation list and indicated that all participants received the assigned treatment intervention as intended.

7.5.7. Adherence to CHM administration

7.5.7.1. MMAS

Table 30 shows the group means for MMAS scores at Week 4 and at end of the study. The mean score differences for the groups are also shown to explore changes in self-assessed adherence during the course of the study.

Table 30: MMAS scores by treatment group and by assessment

	Group	n	Mean (SD)	95% CI for mean		p value between groups
				Lower	Upper	
MMAS Week 4	Standardised	18	3.2 (1.5)	2.8	4.0	0.37
	Individualised	17	2.7 (1.8)	1.8	3.7	
MMAS End of study	Standardised	17	4.0 (1.7)	3.1	4.9	0.68
	Individualised	17	3.7 (2.3)	2.5	4.9	
MMAS Score difference	Standardised	17	0.9 (2.2)	-0.3	2.0	0.86
	Individualised	16	1.0 (1.4)	0.3	1.8	

Table 30 indicates that a slight increase in self-assessed adherence was evident in both groups, shown by the positive value in the difference scores. The mean change in MMAS score was statistically significant from baseline in the individualised group only (1.0, 95% CI 0.3 to 1.8). There was no statistically significant differences between-groups in the mean change score ($p=0.86$).

I explored changes in adherence as a categorical variable using the MMAS scale with a score of <6 to reflect low adherence, 6 to <8 medium adherence and 8 high adherence. The variable 'Adherence change' was computed with 0 indicating no change in adherence and 1 indicating an improvement in adherence, reflecting a change from low adherence to medium or high adherence, or a change from medium adherence to high adherence. No cases were assessed as a worsening of adherence by category. The frequency counts for no change from baseline adherence and improvement from baseline can be seen for each treatment group in Table 31. When using Fisher's Exact test, there was no statistical difference found between groups in the adherence change ($P=0.99$).

Table 31: Between-group changes in categories of adherence using MMAS

Treatment group	Adherence - No change from baseline n, column %	Adherence - Improvement from baseline n, column %	Totals n	P value between groups
Standardised	13 52%	4 50%	17	0.99
Individualised	12 48%	4 50%	16	
Total	25	8	33	

7.5.7.2. CHM weighing data and compliance

To calculate the proportion of CHMs that were taken by the participants, I asked for prescription pots to be returned for weighing at two points of the study. Complete data was provided for 15 participants (37.5%) who returned 100% of the prescription pots for weighing. No weighing data was available for 10 (25%) participants who had either withdrawn from the study before the first weigh-in at Week 12 (n=7), or who were unable to bring in prescription pots at either weigh-ins (n=3). Incomplete data was available for the remaining 15 participants (37.5%) for whom I could account for a mean of 58% (SD 25) of prescribed CHMs.

Owing to incomplete data, I chose to estimate the proportion of CHMs used during the study only from participants for whom 75% or more of their CHMs had been accounted for. Data from 21 participants (52.5%) was thus used to estimate that a mean of 65% (SD 21.2) of prescribed CHMs were administered by participants. I defined good compliance to the CHM interventions as administering 75% or more of prescribed CHMs, and 6 (15%) participants were able to demonstrate this. Owing to the amount of missing weigh-in data, I was not able to calculate the number of participants who were unable to administer the minimum study dose.

7.5.8. Study assessments: Adherence

I explored study assessment attendance rates by considering all participants eligible at each assessment and therefore removing from the denominator withdrawals and those lost-to-follow-up. Results are shown in Table 32.

Table 32: Attendance rates by study assessment

Study assessment week number	No. participants followed up/ No. eligible for assessment (%)	Contact method			
		Visit	Telephone	Email	Text
2	40/40 (100)	0	40	0	0
4*	36/36 (100)	36	0	0	0
8*	33/34 (97)	31	2	0	0
12*	33/33 (100)	33	0	0	0
16	29/31 (94)	0	29	0	0
20	30/30 (100)	0	28	1	1
24*	29/29 (100)	27	1	1	0
Withdrawal*	7/11 (64)	2	4	1	0
Total assessments	237/244 (97)	129	104	3	1

*compulsory assessments

I maintained a mean assessment rate of 98.5% on-study and achieved a 100% assessment rate at Week 24 and 64% assessment rate for withdrawals, indicating a reasonably high protocol adherence rate.

7.5.9. Study assessments: Resource usage and management

Out of the 237 assessments conducted, the most frequently used format were study visits (129, 54.4%) and telephone (104, 43.9%), with a minority of assessments by email (3, 1.3%) and by text (1, 0.4%).

All baseline assessments were study visits and which had a mean duration of 59 minutes (SD 11, range 40-80 mins). For on-study assessments between weeks 2 to 20 inclusive, study visits had a mean duration of 25 minutes (SD 7, range 10-45 mins) whilst telephone assessments had a mean duration of 15 minutes (SD 8, range 1-40 mins). For week 24 and withdrawal assessments, study visits had a mean duration of 45 minutes (SD 11, range 25-60 mins) whilst telephone assessments had a mean duration of 22.5 minutes (SD 8, range 17-28 mins).

I had 19 missed clinic visits by 14 participants and which were scheduled at Week 4 (9 appointments), Week 8 (1 appointment), Week 12 (4 appointments), Week 24 (1 appointment) and at withdrawal (4 appointments). Reasons for missing clinic visits were forgot (n=10), no reason provided (n=4), unwell (n=3), other reasons (n=2).

Although the nature and duration of the assessments were planned as part of the study arrangements, the actual resource usage and reasons for missing appointments presented above remains helpful to plan resources for a larger-scale trial.

7.5.10. CHM intervention

223 prescription orders were placed over the duration of the study. As an individualised prescription was prepared for each of the 40 participants, a total of 161 unique individualised prescriptions were generated featuring 118 individual herbs in total. The frequency, rank order and mean daily dose of the 20 most frequently prescribed herbs are shown in Table 33.

Table 33: Frequency, rank order and mean daily dose of 20 most frequently prescribed CHMs

Rank	Count	Herb Name	Latin Name	Dried herbal weight (mean daily dose)
1	158	Xiang Fu (Cu Zhi)	<i>Cyperus rotundus</i> L.	10.8
2	151	Bai Shao	<i>Paeonia lactiflora</i> Pall	10
3	139	Chai Hu	<i>Bupleurum chinense</i> DC.	10.3
4	130	Chuan Xiong	<i>Ligusticum Chuanxiong</i> Hort.	6.7
5	124	Bai Hua She She Cao	<i>Hedyotis diffusa</i> Willd.	10.5
6	123	Gan Cao (Mi Zhi)	<i>Glycyrrhiza uralensis</i> Fisch.	6.0
7	96	Mu Dan Pi	<i>Paeonia suffruticosa</i> Andr.	9.9
8	96	Shu Di Huang	<i>Rehmannia glutinosa</i> Libosch.	9.3
9	91	Gan Cao	<i>Glycyrrhiza uralensis</i> Fisch.	5.8
10	91	Gui Zhi	<i>Cinnamomum cassia</i> Presl	8.5
11	91	Dang Gui	<i>Angelica sinensis</i> (Oliv.)Diels	9.3
12	88	Fu Ling	<i>Poria cocos</i> (Schw.)Wolf	11.7
13	82	Chi Shao (Chao)	<i>Paeonia lactiflora</i> Pall.	9.5
14	82	Dang Gui Wei	<i>Angelica sinensis</i> (Oliv.)Diels	9.4
15	68	Chen Pi	<i>Citrus reticulata</i> Blanco	9.2
16	62	Sheng Di Huang	<i>Rehmannia glutinosa</i> Libosch.	9.2
17	60	Zhi Zi	<i>Gardenia jasminoides</i> Ellis	9.1
18	60	Yan Hu Suo (Cu Zhi)	<i>Corydalis yanhusuo</i> W.T.Wang	9.8
19	59	E Zhu (Cu Zhi)	<i>Curcuma kwangsiensis</i> S.G.Lee et C.F.Liang	5.7
20	55	Dang Shen	<i>Codonopsis pilosula</i> (Franch.)Nannf.	9.5

For each participant, a primary CHM diagnosis was given at the baseline assessment and which could contain more than one pattern of CM disharmony. 19 patterns of disharmonies in varying combinations were recorded for the 40 participants and the frequencies and rank order of these patterns are displayed in Table 34.

Table 34: Frequency and rank order of CM patterns of disharmony diagnosed at baseline

Rank	Count	Pattern of disharmony
1	13	Blood stasis
2	10	Stagnated Liver Heat
3	8	Blood Heat
4	7	Liver Qi stagnation Phlegm-damp accumulation Spleen Qi deficiency
5	5	Blood deficiency
6	4	Spleen Yang deficiency
7	3	Kidney Yin deficiency Stagnated Lung Heat Kidney Jing deficiency
8	2	Damp Heat in Chong and Ren
9	1	Excess Cold in Uterus Liver Yang rising Heart Yang disturbance Stagnated Heat in Stomach and Gallbladder Damp Heat in Blood Heart Qi deficiency Kidney Qi deficiency

7.5.11. Lifestyle and dietary advice

Self-care advice generally came under two themes of lifestyle advice and dietary advice, given out 23 times and 62 times respectively. The sub-categories and count data are shown in Table 35.

Table 35: Types and count of lifestyle and dietary advice recorded on-study

<i>Advice</i>	<i>Count</i>
Lifestyle	
Exercise	9
Use warmth and massage	5
Promote relaxation	2
Other self-care advice specific to symptoms	7
Dietary	
Increase protein	8
Promote warm and cooked foods	7
Use herbs and spices in cooking and in drinks	7
Increase vegetable and fruit intake	6
Avoid deep fried and greasy foods	6
Reduce caffeine, sugar and red meat	6
Reduce dairy intake	4
Reduce carbohydrate intake	4
Maintain water content in foods by steaming/stewing	3
Eat breakfast and eat regularly	2
Use dietary management strategies	2
Increase fibre intake	1
Use dried fruit, nuts and seeds	1
Reduce alcohol intake	1

7.5.12. Piloting and feedback data

I planned to evaluate the piloting of key aspects of the clinical trial by collecting feedback data from participants and by study personnel to include CHM dispensary staff and study practitioners. I was successful in obtaining end-of-study feedback data from 35 participants and by 1 CHM dispensary staff member.

7.5.12.1. Participant Feedback Questionnaires

In response to the first question to participants 'Would you agree to participate in a study like this again?', 23 (57.5%) responded 'Definitely', 9 (22.5%) responded 'Probably', 1 (2.5%) responded 'Not sure' and 2 (5%) responded 'Probably not'. I had 5 (12.5%) non-responses to the participant feedback questionnaire.

An open-ended follow-up question to this first question asked participants 'Please provide reasons for your answer'. A further three open questions followed: 'What do you feel could have been done better about this study?', 'What did you particularly like about taking part in this study?' and finally 'Do you have any other comments you would like to add?'. The responses to these 4 questions were analysed thematically as part of the study evaluation from the participants' perspectives and which fell under 5 broad themes of:

- Appraisal of the CHM intervention
- Managing practicalities of research participation
- Empowerment and enablement
- Management of care
- Quality of care

These themes and associated data will now be presented with quotes provided alongside pseudonyms.

- Appraisal of the CHM intervention

Participants most frequently assessed the value of the CHM interventions by describing improvements observed in symptoms they were seeking help for:

'I have enjoyed taking part and believed the herb has help with my periods which was the main thing along with my weight' (Debra)

'Have seen a massive improvement in my periods (regular) and facial hair growth' (Mina)

However, participants also provided accounts of negotiating benefits gained from CHM against the perceived safety risks and side-effects:

'...only disadvantage is that I did not know what I am taking and that it may not work well for me, but I think that risk that something could go wrong is low.' (Elsa)

'I was worried about the safety of herbal medicine and how it would affect me and make me feel.' (Anne)

- Managing practicalities of research participation

Besides perceived safety risks and side-effects of the interventions themselves, participants described needing to take into consideration the practical consequences of trial participation. For example, factors such as convenience, flexibility and length of appointments and study location were important to participants when appraising their participation in the study:

'If possible, provide opportunities for more flexibility with tests and appointments, in case of emergencies/unforeseen incidents happening with patients' (Susan)

Some concerns were also raised regarding the frequency of CHM administration and the taste of CHMs which influenced participants' experiences of the study:

'I found it difficult taking the herbs every day as required because of the taste.' (Phoebe)

'Maybe change the tea to a tablet, if poss. I really did not like the taste.' (Justine)

- Empowerment and enablement

Participants described feelings of empowerment and enablement as a result of participating in the study. Some reported for example an increased sense of hope and of control over their condition through being presented with another treatment option and through gaining knowledge about PCOS and about CHM:

'New experience...Have learnt a bit about it [herbal medicine] and has led me to take more control over my PCOS' (Yvonne)

'Not only do I feel better taking the herbs but the daily use of them has focused my attention on my health and the fact that I needed to make changes to feel better, which I've done over the last 6 months' (Emily)

For some, the study provided an opportunity to access CHM treatment for financial reasons whilst other participants referred to participating in the study as an opportunity to contribute to the ‘common good’ and to further knowledge of PCOS:

‘It feels lucky to be able to contribute to a study, which may help women with PCOS like myself. And I would do it again because it is important to progress in understanding and treatments of PCOS’ (Bella)

- Management of care

There were a number of aspects of care management that participants reported attaching particular importance to during their trial participation. The desire for self-care, for example, was particularly evident in participants:

‘Being closely monitored by a herbalist has helped me to reflect on my lifestyle and how I deal with my condition, i.e. my exercising and diet choices’ (Kelly)

‘...the daily use of them [herbs] has focused my attention on my health and the fact that I needed to make changes to feel better...’ (Emily)

Participants were appreciative of the holistic and personalised approach of the treatments and there were suggestions that meeting others with PCOS could be helpful:

‘I felt that taking the herbs helped not just my PCOS but other aspects of my health as well’ (Gwen)

‘The opportunity to discuss my concerns about PCOS and finding out about how it affects so many other areas of my health/wellbeing that I wasn’t aware of’ (Rachel)

‘It would’ve been motivating for the participants to meet each other. This could help them.’ (Kelly)

Participants remarked that study treatment length was appropriate whilst others made suggestions that a longer treatment course or a longer term follow up could have been helpful.

- Quality of care

A feature of the study that participants attached particular importance to was the quality of care that they had received from the trial staff. Participants for example described staff as being approachable, non-judgmental and knowledgeable:

'[NAME OF HERBALIST]'s approach and her ability to explain and talk through things with me' (Andrea)

'[NAME OF HERBALIST] has been a great support throughout the trial, open and easy to talk to and it's great to be honest and not judge over anything you say or do' (Tara)

Compassion and trust were also highlighted by participants as being particularly important to them in the care that they received:

'It's also great to be listened to and valued and not just advised to 'go on the pill' like most GPs do' (Tara)

'Very friendly and accommodating, didn't ever feel uncomfortable' (Judith)

7.5.12.2. Study Personnel Data

I had initially planned to use feedback questionnaire data from study practitioners and dispensary staff as part of the study evaluation. However, I was unsuccessful in recruiting study practitioners and received one response only from the dispensary team. As practitioner recruitment had failed before participant recruitment commenced, I planned prospectively to use comments logs data as an alternative data source and which are one of the CRFs used routinely by research staff to record any information during the study felt to be of potential relevance to the evaluation of a study. I incorporated this comments log data with the open-ended responses from the feedback

questionnaire returned by the one dispensary team member and analysed this dataset using principles of thematic and framework analysis. This was used to identify themes and subthemes relevant to evaluating the piloting and feasibility of this study and also with particular consideration for issues relevant for the planning of a future study. An overview of these themes and subthemes are provided below and are described in detail in the subsequent section:

Improving participant experience

- Consideration for participant experience when undergoing assessments
- Discussing practicalities of trial requirements
- Feeding back on progress
- Providing timely information

Improving trial conduct and management

- Improving efficiency of data collection
- Maximising use of automated processes
- Better management of time and of communication

Design considerations for future research

- Blinding
- CHM design considerations
- Other outcome measures

Improving participant experience

- Consideration for participant experience when undergoing assessments

Trial staff reported that participants experienced discomfort and anxieties when undergoing certain clinical assessments, particularly relating to anthropometric and hirsutism assessments, and finger-prick blood tests:

‘Participant expressed awkwardness when stepping on scales and commented ‘I hate doing this bit’ before stepping on, and commenting ‘I feel huge next to you’.’ (Celia – logged comment)

‘Participant wishes to get blood test at EOS (end of study) visit ‘over and done with’ first. Comments would have preferred venepuncture as finger-prick seems to hurt more.’ (Gwen – logged comment)

- Discussing practicalities of trial requirements

The management of the CHMs in this study was complex and it was apparent that arrangements surrounding CHM administration and weighing could have been discussed in more detail with participants:

‘Participant had not stopped taking the previous prescription when new prescription arrived. Clearer explanation required.’ (Mina – logged comment)

‘Participant commented that the CHM looks like a big pot but actually goes down very quickly – consider measuring out doses for next study?’ (Christina – logged comment)

Participants appeared to actively seek tailored advice regarding the practicalities of administering CHMs with staff. This was not only in terms of developing personalised strategies for managing CHM administration, but participants also wanted professional reassurance that they were taking CHMs correctly in relation to other medication or to drinking alcohol:

‘(Participant) Misses evening dose frequently, can’t take CHMs hot so skips morning dose sometimes. Could prepare evening before and refrigerate and have in morning.’ (Gwen – logged comment)

‘Participant asked if okay to skip a few doses because of drinking alcohol and uncertainty re calculating 3 hours between medications and having alcohol.’ (Rachel – logged comment)

This study required participants to use barrier contraceptive methods for the duration of the study as the safety of herbs had not yet been confirmed in pregnancy. Staff recalled that some participants raised concerns regarding this requirement and which was at times conflicting with information they had been provided by other healthcare providers:

‘Participant commented that she has never had to worry about using contraception before as was told by doctor she would never fall pregnant without medical help. Found study requirement to use condoms quite

difficult to comply with and to discuss with husband.’ (Celia – logged comment)

- Feeding back on progress

Staff comments suggested participants wished to receive feedback during the study and at the end of the study as a way of appraising their progress, particularly with regards to anthropometric measurements and to help alleviate anxieties regarding safety:

‘Participant very interested in seeing if had lost weight and took picture of pre and post WC (waist circumference), HC (hip circumference) and weight measurements.’ (Phoebe – logged comment)

‘Participant appears very anxious re blood test due to discomfort and results. (Appears) Positive that results are immediate.’ (Monica – logged comment)

It was also apparent that participants were curious with how the study was progressing overall and expressed a desire to compare their experience with those of other women on the study:

‘Participant asked if any other women on the study so far have experienced benefits.’ (Christina – logged comment)

‘Participant query re if she is on the type of CHM where women are noticing changes to symptoms.’ (Julie – logged comment)

- Providing timely information

There were reports that participants raised a number of queries during the trial that centred on wishing to be provided with more information and to have certain concerns addressed. For example, participants had questions regarding the background to the research project and wished to have further clarification. It was also reported that participants had raised concerns pre-

study regarding safety in reference to the liver and kidney function assessment and potential side-effects of the CHMs:

‘Participant asked re safety of the CHMs and whether herbs had been quality checked’ (Tara – logged comment)

‘Participant queried if herbs have been used before and whether this was why we need to check for liver and kidney function.’ (Sonia – logged comment)

Some anxieties were expressed by participants when the issue was broached regarding GP notification of study entry. GP notification was not an eligibility criteria of the study but participants were concerned that GPs would respond negatively and that the study team would have access to their medical records:

‘Feels very uncomfortable with research team notifying GP of study participation. Appeared concerned about us accessing her medical records and worrying GP would respond negatively to her participation in the study. Assured we do not have access to records.’ (Sonia – logged comment)

As participants were approaching the end of the study, it became increasingly clear that they wished to clarify arrangements with the research team post-trial and what they could expect in terms of continuation of symptom-improvements:

‘Feeling anxious about leaving study because weight loss and periods have never been as good/regular as it is now.’ (Yvonne – logged comment)

‘Participant remarked she would like to know what herbs she is taking in case she’d like to carry on for a few months after the study.’ (Bella – logged comment)

- Improving efficiency of data collection

There were a number of external factors identified that affected the measurement of a number of outcomes and the management of these factors were identified on-study. For example, hirsutism assessment was very difficult with a number of participants owing to recent use of hair removal techniques. Despite coming off contraceptive medication for the required 6 months prior to joining the study, some participants' hirsutism status had not yet stabilised at point of study entry and which also made it difficult to conduct an appropriate assessment. Difficulties were reported with clarity of completing some outcome measures such as MYMOP and calculating eGFR. Repetitive data capture was also apparent in some areas and which could be improved upon by reviewing study procedures.

- Maximising use of automated processes

The theme of using automated processes recurred throughout the study. Suggestions included having apps on handheld mobile devices for calculating eGFR and menstrual cycle length for convenience and which would potentially help streamline study processes.

- Better management of time and of communication

Herbalists reported feeling frustrated that the required research activities impinged on time for the clinical consultation '*...finding it frustrating that has limited to time to conduct lifestyle/dietary advice since limited time and has study processes that need to be checked*' (General – logged comment)

'Travelling to sites means carrying paperwork or equipment re extra consideration and time wasted. Ideal if practitioner already works on site and seeing participants fitted into normal schedule' (General – logged comment)

The frequency of participant communication could also have been reduced by directing participants to a website providing answers to FAQs. It had also been recognised that screening during off-peak hours and requesting questionnaire completion prior to clinic visits could further improve efficiency.

Design considerations for future research

- Blinding

Patient-blinding appeared to have unintended effects on the practitioner who found it restrictive and deceptive not to discuss the herbs or prescription changes with participants:

‘As a practitioner finding it restrictive not being able to discuss the herbs, what actions are and the changes I am making or not making. Being deliberately vague makes me feel that I am being deceptive.’ (General – logged comment)

‘Unable to have conversation with patients regarding how their CHM works from a theoretical perspective, and that may be individualised and how this is decided upon – pragmatic CHM care not completely reflected in this trial design?’ (General – logged comment)

Participants also raised concerns regarding placebo use who asked for clarification that no placebo would be used at the start of the study and commented that it was ‘good there is no placebo’.

- CHM design considerations

There were a number of issues identified that could impact the design of the CHM itself in a future study. For example, some key CHMs were not permitted on-study due to being in a different price bracket and individualisation was not permitted any more frequently than once per month after the first month on-study had passed. These aspects were recognised to deviate from pragmatic practice and could be considered in future CHM trial designs.

On the other hand, consideration for a more pragmatic design also led to practical issues. For example, the provision of individualised treatments meant that practitioners would require access to clinical data throughout the study. Furthermore, individualising treatments and the requirement to complete trial paperwork could also affect practitioner buy-in.

- Other outcome measures

There were a number of comments that suggest the possibility of including other outcome measures in a future study. Some of this centred on biochemical investigations such as ovarian status and biochemical tests to follow up on their PCOS status. A number of other measures were also suggested by participants who commented on the improvement of symptoms such as balding, quality of periods and control of appetite.

A number of problems were also identified with the current gold standard hirsutism assessment and which could warrant exploration of a new and more adequate measure of hirsutism to be developed. With the present assessment, issues were identified such as the lack of consideration for the rate of hair growth and the thickness of hair:

'Difficult to score hirsutism since should account for rate of hair growth, thickness and freq of hair removal that may reflect QoL assessment better than objective appearance assessment' (Celia – logged comment)

'Hirsutism assessment should consider speed of hair growth as well as distribution for this patient as rate of growth and hair removal req(uired) clearly distressed, and (was) important to, (this) participant' (Bella – logged comment)

Participants also reported being distressed by hair growth in areas not represented in the mFG assessment diagram such as in the lower back, breast and nipples and other areas of the face.

7.6. Discussion

I return to the feasibility study questions presented in Chapter 6 to structure the discussion of these results. These questions are as follows:

1. Is oligomenorrhoea and amenorrhoea appropriate as the primary outcome measure for the main study?

The secondary objectives are:

2. Are other outcome measures more appropriate for investigation in a main study?
3. What is the safety profile of CHM?
4. How should the CHM intervention in the main study be delivered?
5. What is the feasibility of carrying out a double-blind and randomised trial in this population?

These questions will now be discussed in further detail reflecting upon the results provided in the previous section. This will then be followed by a critical assessment of the strengths and limitations of this work including comparison with previous or existing work, and finally a discussion regarding how best to take this work forwards.

7.6.1. Is oligomenorrhoea and amenorrhoea appropriate as the primary outcome measure for the main study?

In the primary analysis of the menstrual data at 6 months, significant improvements from baseline were seen in menstrual rates for both standardised CHM treatment (mean change 0.18 menses per 28 days, 95% CI 0.06 to 0.29) and individualised CHM treatment (mean change 0.27 menses per 28 days, 95% CI 0.15 to 0.39). There was no difference observed between groups (MD 0.10±0.08, 95% CI -0.07 to 0.26; p=0.26). This provides preliminary clinical data to support the notion that beneficial effects in menstrual regulation can be observed with both standardised and individualised CHMs and provides support for menstrual regulation as the primary outcome measure for a main study. To compare this with the PCOSQ menstrual domain scores, both groups reported a clinically meaningful improvement in QoL scores with respect to menstrual issues. This was statistically significant within group for both standardised CHM (mean change 1.40, 95% CI 0.91 to 1.88) and individualised CHM (mean change 1.03, 95% CI 0.56 to 1.50) and which was not statistically significant within group (MD -0.37, 95% CI -1.05 to 0.31; p=0.28). This suggests that the QoL data is in agreement with the clinical data for this specific outcome and provides additional data to facilitate triangulation of these findings. Despite this

encouraging data, it should be emphasised that this is very preliminary evidence, given that no comparison could be made in the absence of a placebo or usual care arm. This data should therefore be interpreted with caution.

When assessing whether menstrual regularity is of concern for PCOS patients, the MYMOP data indicated that 'Regulating menses' was the third most important concern to participants after 'Weight' and 'Hirsutism'. However this needs to be considered in light of the fact that participants had already been screened based on presenting with sufficiently severe menstrual irregularity and were aware that this was one of the key measures of interest. Given that I recruited successfully for this study, this also suggests a large proportion of women with PCOS in the community find their menstrual symptoms are not satisfactorily managed by conventional treatment and who are sufficiently distressed by their symptoms to seek help using other treatments. Indeed this was the case for 67.5% of participants who had previously sought conventional treatment and who had stopped treatment due to lack of effect or due to side-effects. This suggests that regulating menses would also be important from a patient's perspective, particularly in those who were found to be resistant to first-line conventional management of menstrual irregularities. This provides further support for it as a primary outcome measure for a main study.

7.6.2. Are other measures more appropriate for investigation as the primary outcome measure for the main study?

There were a number of other symptoms that participants described as having a negative impact on their QoL and which could be worthy of further investigation as the primary outcome. 'Weight' and 'Hirsutism' concerned participants most according to the MYMOP data, ranking higher than 'Menstrual regularity' and it is worthwhile turning to the corresponding data that was collected to evaluate these as potential outcome measures for a future study.

7.6.2.1. Weight

To evaluate 'Weight', I turn to data on BMI, weight and waist-hip-ratio as well as the quality of life data from the PCOSQ weight domain. The changes from baseline for BMI are unremarkable within-group for both standardised CHM (mean change -0.41, 95% CI -1.40 to 0.54) and individualised CHM (mean

change -0.26, 95% CI -1.25 to 0.72) and was not statistically significant between-group (MD 0.15, 95% CI -1.23 to 1.53; $p=0.83$). This was the same for weight where standardised CHM saw a slightly greater mean loss of 1.13kg (95% CI -3.8 to 1.54) compared with a mean loss in the individualised CHM group of 0.77kg (95% CI -3.53 to 1.99), but which was not statistically significant between group (MD 0.36, 95% CI -3.51 to 4.23; $p=0.85$). For waist-hip-ratio however, individualised CHM led to a statistically significant reduction from baseline of -0.04 (95% CI -0.07 to -0.01) whilst there was an unremarkable change observed in the standardised CHM of 0.002 (95% CI -0.02 to 0.02). This appeared to be a statistically significant difference between groups favouring individualised treatment (MD -0.04, 95% CI -0.07 to -0.01; $p=0.02$). With the exception of waist-hip-ratio data for which there appeared to be a favourable result for individualised CHM, the overall picture from the objective anthropometric measurement data suggests little difference observed within and between-group. Interestingly, PCOSQ scores in the weight domain showed that the MCID was achieved for both treatment groups although within-group statistical significance was seen only in the standardised group which saw a mean improvement of 0.79 (95% CI 0.15 to 1.44). These are encouraging findings in terms of impact on QoL but which appear not to be in agreement with the anthropometric data. However, given that this study was not powered to address weight issues and that the composition of both CHM treatments specifically targeted regulating menses as opposed to weight, further work in this important outcome would certainly be warranted and should be explored further at least as a secondary measure in subsequent work.

7.6.2.2. Hirsutism

The hirsutism data suggested statistically significant within-group improvements in both the standardised group with a mean score difference of -2.52 (95% CI -3.40 to -1.65), and in the individualised group with a mean score difference of -1.44 (95% CI -2.35 to -0.54). This was not statistically significant between-group ($p=0.09$). However, the PCOSQ body hair domain scores show that only the standardised group saw a clinically meaningful improvement (mean change 0.84, 95% CI 0.31 to 1.38) when compared with the individualised group (mean change 0.32, 95% CI -0.20 to 0.83). It is difficult to interpret these results given issues with power as well as measurement issues

with hirsutism assessment reported in the process feedback. Again, the issues discussed in the previous section remain relevant regarding insufficient power for this outcome and inappropriate targeting of CHMs. Further to this, clinical treatment for hirsutism is typically advised for longer than 6 months. Given the encouraging preliminary results that were obtained then in the relatively short timeframe, further work is certainly warranted for this distressing complaint and for which there remains limited treatment options.

7.6.2.3. *Quality of life*

Besides the PCOSQ weight and hirsutism domain scores discussed in the previous sections, improvements in quality of life were seen in a range other measures and domains. For example, MCID as well as statistical significance was achieved within-groups in both groups for the following quality of life domains: MYMOP 1 (standardised MD2.04±SE0.39, 95%CI 1.24 to 2.84; individualised MD 2.02±SE0.38, 95%CI 1.24 to 2.80), MYMOP activity (standardised MD2.28±SE0.43, 95%CI 1.49 to 3.26; individualised MD 1.59±SE0.36, 95%CI 0.84 to 2.34), PCOSQ emotions (standardised MD0.97±SE0.22, 95%CI 0.53 to 1.42; individualised MD 1.06±SE0.21, 95%CI 0.63 to 1.49), PCOSQ infertility (standardised MD1.17±SE0.25, 95%CI 0.66 to 1.68; individualised MD 0.77±SE0.24, 95%CI 0.27 to 1.27) and PCOSQ menstrual (standardised MD1.40±SE0.24, 95%CI 0.91 to 1.88; individualised MD 1.03±SE0.23, 95%CI 0.56 to 1.50). For a small sample, these are impressive effect sizes but owing to the lack of control for contextual effects, it is also extremely difficult to interpret these findings. However, these effects should not be dismissed as being unimportant and given that patient-centred outcomes such as increased QoL is increasingly emphasised, these measures are certainly worth considering including in future work. It is possible for additional Patient and Public Involvement (PPI) work here to be carried out with patient representatives advising on outcome measures that would be particularly important to them.

7.6.2.4. *Other outcome measures*

A number of other outcome measures were proposed from the process and feedback data that appeared to be important to women with PCOS. Participants expressed a desire for their ovarian status and hormonal profiles to be followed up alongside their clinical symptoms at the end of the study and

which would additionally provide mechanistic data that could potentially explain the effects of CHMs. This would be possible to incorporate in future work and that may be ideally executed in collaboration with a reproductive endocrinology unit. Improvements in appetite control were also noted and regarded favourably by participants and it would be possible to assess this further with validated questionnaires such as the Three Factor Eating Questionnaire (Stunkard and Messick, 1985) that assesses dietary restraint, disinhibition and hunger. Female pattern hair loss was also raised as a concern by some participants and although clinical measures exist to assess this, these scales appear to have similar limitations as hirsutism assessment (Ludwig, 1977, Savin, 1994, Yip and Sinclair, 2006). Participants also reported valuing assessing the quality of periods using factors such as flow, clotting, colour and consistency of menstrual bleeding. Some of these factors can be assessed with measures such as the Pictorial Blood Assessment Chart or the Menorrhagia Impact Questionnaire (Bushnell et al., 2010). To my knowledge, colour and consistency of bleeding are not considered in menstrual impact questionnaires or in the PCOSQ menstrual issues domain. Further work may therefore be warranted exploring the feasibility of incorporating these factors within a more holistic menstrual impact questionnaire.

7.6.3. What is the safety profile of CHM?

The safety data containing both objective and subjective assessments provides preliminary data to suggest that the individualised and standardised CHM treatments used in this study were safe. The ALT and creatinine data suggests that administration of CHMs in this study were not associated with adverse liver and kidney functioning when monitored at 4 weeks or at end of study participation. I recorded 1 serious adverse event and 1 adverse event, both assessed as being unrelated to the study treatment by attending medical professionals who were independent to the research study. 2 participants in the individualised arm who withdrew due to pregnancy reported healthy and uneventful pregnancies, both of which resulted in live births and healthy deliveries. This provides preliminary data to suggest that administration of individualised CHMs at time of conception did not result in risk to pregnant women or their children. When looking at the adverse reaction data, I found no differences between the two treatments in the number of ARs and the number of dropouts as a result of ARs. These were assessed as having

reasonable association with CHMs but which were considered to be mild and not serious. The majority of these were expected and related to digestive complaints such as bloating, nausea and loose stools, were mostly well-tolerated and had a relatively short median duration of 4 days. Although this provides preliminary encouraging data regarding safety and is in concordance with findings of other CHM trials (Flower et al., 2011b, Grant et al., 2013), it should be acknowledged that this study was not powered to detect clinically significant differences in adverse event rates nor pregnancy-related risk. Safety and adverse event data unfortunately remains almost completely absent given the widespread use of CHM and assessing safety should remain of critical importance in ongoing CHM research.

7.6.4. How should the CHM intervention in the main study be delivered?

7.6.4.1. Standardised or individualised

The scientific and pilot data from this study provides further insight into choosing the design of the CHM intervention for a main study in terms of standardised or individualised treatment. Both treatments provided similar improvements in menstrual outcomes and had similar safety and adverse effects profiles. This may initially appear contrary to widespread belief amongst practitioners that individualised treatment is typically more effective and leads to fewer side-effects. However, this lack of difference in effect is partly due to the lack of power as post hoc power calculations suggest this study had only 18% power to detect differences in menstrual rates between these two interventions. Although between-group differences were analysed as stated in the study protocol, these need to be interpreted cautiously given underpowering and given the feasibility nature of this study.

After taking into account the aforementioned methodological considerations, it is also possible that the apparent lack of difference can be partly explained by the suitability of the standardised CHM in targeting the patterns of disharmonies that were diagnosed in this cohort. This is unsurprising since the standardised CHM prescription was drawn up with guidance from the Delphi-derived Good Clinical Practice guidelines, enabling us to focus the standardised CHM on the most frequently occurring patterns of disharmonies that the panel of practitioners reported diagnosing in PCOS. This is a powerful endorsement for the Delphi process as an important precursor to a clinical trial

and which enabled the design of the standardised intervention in this study to be grounded in pragmatic practice.

7.6.4.2. Dosage and administrative form

I regarded the overall compliance to CHM in this study as acceptable. Participants administered a mean of 65% (SD 21.2) of prescribed CHMs and good compliance defined as administering 75% or more of the CHM intervention was demonstrated by only 6 participants (15%). This suggests the proposed powdered CHM dosage of 16g per day (8g b.i.d) over a 6 month treatment course would not be feasible for a future study. Despite the majority of participants took a reduced dosage of CHMs during the study, encouraging preliminary treatment effects were observed in menstrual cyclicity at 6 months. It is possible that reducing the dosage to 65% of the dose (10-11g) per day would lead to similar effect sizes and which could at the same time increase compliance amongst participants. The initial powdered CHM dosage was chosen based in part on available financial resources and on the recommended daily prescribing range of 5g to 25g according to the Good Clinical Practice guidelines developed from the Delphi study. This suggests that reduction from 16g per day to 10-11g per day would still be considered to be within the guideline recommendations.

In the feedback data, participants reported issues with convenience and taste of the CHMs due to dosing frequency and taking the powders as a tea. Consistent with findings in the wider clinical literature, the feedback data suggests compliance could be improved upon by reducing the frequency of administration to once daily and by changing the administrative form to tablets or capsules (Jin et al., 2008, Lakatos et al., 2010, Caldeira et al., 2014, Flower et al., 2011a).

7.6.5. Can a double-blind, randomised trial with CHM for PCOS be conducted?

This study provides reasonable evidence that a main study using CHMs for PCOS would indeed be feasible. To help put these results into context I will now discuss the feasibility aspects according to different stages of the study.

7.6.5.1. Recruitment and screening

There are a number of important points to discuss regarding feasibility in terms of recruitment and screening methods. I recruited to target within the planned recruitment period and this data suggests that word-of-mouth referrals by participants and healthcare providers could be a particularly promising area of focus in future recruitment work. The phased screening procedures enabled me to maximise efficiency of resources and keep to a minimum the costs of screening and further diagnostic assessments. It is possible for screening efficiency to be improved upon in future by examining reasons for ineligibility at each stage, and ensuring clear, and timely delivery of, information regarding the study and eligibility criteria. In terms of location of recruitment sites, a higher proportion of recruited participants attended the site in London compared to Hertfordshire (70% vs 30%) which is located just 25 miles away. Recruitment for a main study could therefore involve adopting more sites in London and distancing the sites further by having additional sites in the North of England and the Midlands.

This study had a reasonable level of acceptability of procedures as no eligible enquirers refused to consent or to be randomised. The novelty and relative expense of the CHM intervention in private practice may partly explain why procedures appeared to be highly acceptable to participants. However, it is likely that the high degree of acceptability was due to participants being aware that there was no risk of being allocated a placebo or usual care arm and that all would receive one form of active CHM treatment. The participant feedback data suggests that, in agreement with similar literature, the incorporation of a placebo-control as was initially planned is likely to affect recruitment and dropout rates adversely, at least in this population and for an intervention of this duration (King-Fai et al., 2008). This is however a limitation of this study in that it was not possible in this design to assess the feasibility of an RCT that compared a usual care or placebo arm against CHM. It is possible in future work to maximise acceptability by offering delayed treatment to those randomised to either usual care, or to placebo as CHM studies have done previously (Flower et al., 2011b).

7.6.5.2. Study processes

The data from this study suggests that randomisation and allocation procedures were successfully and securely carried out by the CHM dispensary.

This was partly due to the fact that stringent requirements must be met by CHM dispensaries prior to receiving RCHM approval and which enabled us to ensure that the duties I required of them deviated as little as possible from their usual practices and processes. My experience suggests that involving a UK CHM dispensary for future research would indeed be feasible, especially where project goals are aligned, where good communication exists and where RCHM approval has already been granted for the dispensary. However, it would also be important to identify, and plan for, capacity issues for a larger-scale trial, especially where individualised rather than standardised CHMs are featured in the study design.

Assessment of practitioner-blinding suggests that, consistent with the present literature, blinding in this study can be interpreted as being secure (Moroz et al., 2013). It has been argued that the standardised random/individualised unblinded scenarios, which I saw in Weeks 4 and 12, may be problematic and could be interpreted that treatment effects exist in the individualised group and that the absence of effects in the standardised group meant that as a practitioner I did not know what to expect and which led to random guessing. However, this should be viewed in conjunction with the finding that ‘presence of effect’ consistently led to a guess of ‘individualised treatment’ or ‘not at all sure’, and ‘absence of effect’ consistently led to a guess of ‘standardised treatment’ or ‘not at all sure’. Since the End of Study blinding scenario was standardised opposite/individualised unblinded and given that treatment effects in both groups became increasingly apparent as treatment progressed, the findings from these blinding data should be unsurprising. This supports my view that the ‘wishful thinking’ scenario was evident which has been previously described in the blinding literature (Moroz et al., 2013, Enblom et al., 2011). This is when I as a practitioner had a tendency to believe that any treatment administered was perceived to be the individualised treatment and which is further supported by the fact that the presence and absence of treatments effects led to my guesses of individualised and standardised treatments respectively. These findings are limited to my experiences as the single practitioner in this study and it would have been helpful for this to have been assessed with the involvement of more practitioners as intended. However, this pilot work has highlighted patterns of practitioner behaviour that could be expected, and enabled an exploration of what information

practitioners use to guess treatment allocation. This can be used to help improve security of practitioner-blinding in future work.

7.6.6. Strengths and limitations of this study

There are a number of strengths and limitations that need to be acknowledged with this study.

7.6.6.1. Evaluation of the standardised CHM

The analysis of these preliminary results appear to suggest that statistically significant improvements from baseline in menstrual regularity were seen in both standardised and individualised CHM. These results however should be interpreted with caution owing to the lack of placebo and usual care treatment arms and being unable to subsequently correct for regression to the mean, natural history or contextual effects. Although this study was not powered to detect differences between these two interventions, it does appear to provide preliminary evidence to suggest the suitability of this standardised CHM prescription for PCOS-related menstrual dysfunction. It also gives weight to the background work undertaken to reach this prescription which consisted of combining systematic review evidence with the clinical practice points generated from the Delphi practitioner-consultation exercise. This approach has been used in acupuncture and CHM research previously and which has successfully informed the protocols of subsequent clinical trials (Smith et al., 2012, Flower et al., 2007). However, to my knowledge this is the first time this approach has been applied to generate a standardised CHM prescription for further evaluation in a clinical study. This study provides encouraging clinical data as a means of evaluating the strength of this dual evidence and practitioner-informed approach and should be replicated in future work as a method of maximising model validity within research.

7.6.6.2. Participant recruitment

I was successful in recruiting the target participant sample size required for this study and within the planned time period. Given that trial recruitment remains one of the most challenging areas to address in both primary care and complementary medicine trials, this suggests that community-based recruitment methods such as those used in this study were a key strength to this study. It should however be acknowledged that success in recruiting for this study is likely to have been affected by our study design since all

participants would be randomised to one of two active CHM treatments. Because participants were aware there was no risk of being assigned placebo, this unfortunately limits the interpretation of feasibility in terms of recruitment for a placebo-control RCT.

Recruiting in this manner means it remains unclear how representative this study population is in comparison to that in primary care. Although basic demographic data such as employment status was recorded, no further socio-demographic data was collected in this study and which limits the interpretation of our findings. From the information available however, it can be seen that 80% of participants were in employment and which raises questions regarding how these results may be generalised to the wider PCOS population. Furthermore, 75% of our participants reported prior CAM use whilst 50% reported prior use of acupuncture or CHM. Although these figures appear higher than the average lifetime prevalence of CAM use in the UK of 51.8%, 92.5% of our participants were not using conventional medication at entry onto the study (Posadzki et al., 2013b). This is partly due to the fact that we did not permit the use of a number of medications as co-interventions but 67.5% of all participants reported previously using conventional medication and discontinuing medication for various reasons. Although this appears to suggest a selective group of women with PCOS, it is not unreasonable to assume that CAM use within this population is likely to be high given the limited pharmacological options available to them from primary care. This suggests these results may be particularly relevant to those who are resistant to, or otherwise unsuitable for, first line treatments for regulating menses such as the OCP or metformin. Although this would enable a treatment to be targeted for a specific subset of the PCOS population, this does have implications for generalisability. In a future study recruiting from primary care, it is possible to recruit women who have recently been diagnosed and who are having initial discussions with their GP regarding treatment options. This will enable recruitment of participants who may be less likely to already be using CAM treatments. It is also possible to exclude those who had used CHM previously, or to incorporate a subgroup analysis comparing those who had used CHMs previously against those who had not. A multi-centre trial recruiting from different areas of social deprivation would also enable findings to be more generalisable in terms of sociodemographic status.

7.6.6.3. Practitioner recruitment

I was unsuccessful in recruiting practitioners to this research study given the limited time and resources at my disposal and this unfortunately meant I was the sole practitioner providing care in this study. Although this may threaten the generalisability of these results based on care given by other CHM practitioners, treatment adhered to the good practice principles according to our Delphi guidelines where this was permitted within the study protocol. For example, tailored dietary and lifestyle advice were provided where relevant and treatment progress was evaluated at appointments by following up on symptoms such as menstrual clotting and emotional wellbeing. This ensured that treatment provided on-study reflected pragmatic care following pre-defined principles of best practice as much as possible. Future studies would still benefit from seeking the help of practitioners especially in the area of comparative effectiveness research where head-to-head comparisons are made of pragmatic treatments. In future work, it would be important to maximise convenience for practitioners to take part, reimburse practitioners for their time and allow for more time in the recruitment period to canvas interest from the practitioner community. This experience also suggests that further work regarding practitioner views and experiences of research is warranted that could help identify facilitators and barriers to participating in research and which could be used to help the planning stages in future trials.

7.6.6.4. Menstrual data collection and analysis

Baseline menstrual data relied on recall data in this study and which highlights a limitation in my analysis of this proposed primary outcome measure. It is acknowledged that incorporating a run-in period to collect menstrual data prospectively would have added to the strength of the study findings. However, similar studies have found high levels of dropouts in waiting-list controls (Flower et al., 2011b, Brown et al., 2009) which I anticipated could occur in this study with a substantial run-in period. It was therefore decided that the limited time and resources would not enable us to incorporate this within this feasibility study. This highlights an important limitation of menstrual regularity since it is based on subjective reporting as opposed to objective data, particularly in the absence of a run-in phase to the study. Although it could be argued that this reduces the robustness of the primary outcome measure, menstrual regularity remains an important aspect of PCOS for patients and for healthcare professionals. Despite there being potentially

more drawbacks in terms of measurement in comparison to objective measures such as testosterone and LH, menstrual regularity remains one of the three Rotterdam diagnostic criteria and which should emphasise further its importance. These limitations in operationalising the definition of menstrual regularity highlight the need for a definition to be agreed upon amongst experts in the field and which could help to provide further clarification for patients, professionals and researchers.

It was not possible to use the pre-defined method of assessing menstrual regularity using means and standard deviations owing to missing menstrual data at baseline and at end of study. A strength of this study was that our planned analyses were published in our protocol (Lai et al., 2014) and this transparency enables readers to identify our initial approach and reasons for deviating from this planned analysis. I and the study statistician instead adopted alternative methods of assessing menstrual data as used in other PCOS studies by calculating a menstrual rate per month and by dichotomising to responders and non-responders. This enabled us to apply both approaches to analysing the data which reached the same conclusion that statistically significant improvements were observed within-group in the standardised and the individualised groups but not between-groups.

7.6.6.5. Safety data

A considerable strength of this study was the prospective collection of safety data. I monitored adverse event data as part of usual clinical trial reporting requirements but also obtained objective liver and kidney function data at pre-specified timepoints throughout the study. Given that the treatment was administered at a moderate dosage of 16g per day for 6 months, this provides preliminary medium-term data regarding clinical safety for a typical dose of CHMs. Importantly, the CHMs in this study featured multi-herb combinations as would ordinarily be prescribed in usual practice and typically featuring in excess of 10 different herbs per prescription. It is a frequent criticism that the high number of CHMs per prescription would lead to adverse events. Although one serious adverse event and one case of raised ALT was reported in this study, these incidents were judged by an independent physician to be unrelated to the study medications. Whilst safety data from this study appears

to suggest CHM is safe, I acknowledge that this was a small scale study and that further research on safety should certainly be welcomed.

7.6.6.6. *Feasibility and process data, adherence and dropouts*

This study was designed specifically to test the feasibility of a main study and to pilot procedures. The resource usage data will enable a more precise estimate of costs in a future study. Furthermore, the feasibility and feedback data has helped to identify potential issues relating to future work. One example is the CHM weighing data which showed that a mean of 65% (SD 21.1) of prescribed CHMs was being taken and which I regarded as an acceptable level of adherence. Given that beneficial effects were evident in both groups, this suggests a reduction from 16g used in this study to 10-11g of CHMs per day may be sufficient in order to obtain a beneficial effect. This has tangible implications for improving adherence to the intervention in a larger study, but which will also translate to reduced costs for CHM treatment.

Excellent adherence to study visits and follow ups were observed in this study. Although a 27.5% dropout rate was observed which was slightly higher than the anticipated rate of 25%, this remains comparable to other CHM studies of similar duration (Ho et al., 2009, Flower et al., 2011b) and lower than lifestyle modification studies in the same population (Brown et al., 2009, Turner-McGrievy et al., 2014). Furthermore, the process data suggests a number of practical measures could be adopted to reduce dropout rate such as improving flexibility of appointment scheduling, amending the CHM administration to capsules or tablets and including the collection of ovarian sonography and biochemical testing data. Had further resources been available to this study, qualitative interviews with participants and staff would have been helpful as part of the study evaluation.

7.6.7. Directions for further work

7.6.7.1. *Contextual effects*

Given that both treatments provided similar improvements, these results appear to suggest that standardised CHM could be suitably effective to be trialled in a main study. This is a particularly strong argument when the aim is to seek a treatment that is more cost-effective and that can be more readily integrated to the NHS and offered by GPs and nurses. Besides the specific effects of the CHMs however, it is also sensible to be cognizant of the

contextual effects that featured in the delivery of the CHMs in this trial. Contextual effects in trials for regulating menses have been demonstrated by a Cochrane review comparing the effects of metformin against placebo or no treatment in PCOS {Tang, 2012 #5360}. This showed that metformin improved ovulation rates with an OR of 1.81 (95% CI 1.13 to 2.93, 15 RCTs, 1208 participants) {Tang, 2012 #5360}. Furthermore, when specifically looking at comparative risks for ovulation rate, the review authors reported that the relative effect of metformin versus placebo or no treatment was OR 1.81 (95% CI 1.13 to 2.93). The corresponding risk for metformin was 332 per 1000 (95% CI 237 to 446) compared to the assumed risk for placebo or no treatment of 215 per 1000. Although the overall conclusion here is that there is evidence of a clinical effect over that of placebo or no treatment, this also highlights the contribution of contextual or non-specific effects towards the overall effect sizes for menstrual frequency and for ovulation rate. Comparing this with menstrual response rates obtained in this study of 52.6% and 72.3% in the standardised and individualised CHMs respectively, this suggests that an important proportion of the effect size could be explained by contextual effects.

Though it is difficult to make direct comparisons of these results, it does highlight the importance of using an appropriate control group in a future study to enable this analysis to be carried out. Contextual effects were evident in this study since both standardised and individualised CHM treatments were provided with the expertise and attention of a CHM practitioner who was monitoring participants regularly. Furthermore, additional information and support was provided to participants and which included tailored lifestyle and dietary advice according to CM principles and which could in part be responsible for the large effect sizes seen in a range of QoL scores. As practitioners were blinded to allocation and provided tailored care to both groups, it is likely that these contextual effects would be reduced where standardised CHM was to be provided by non-CHM practitioners. Participants reported valuing these features of the intervention and it would be sensible to explore further the influence of different modes of delivery on overall treatment effect by, for example, comparing CHM practitioner-led support against conventional nurse-led support. This provides further argument to

return to the placebo-control design that was initially planned in order to evaluate the scale of both contextual as well as herb-specific effects.

7.6.7.2. Comparative-effectiveness design

For both groups, 6 month and end of study menstrual datasets point to a shift in menstrual presentation towards eumenorrhoea, defined as 0.80 to 1.33 menses per 28 days which was also observed when dichotomising our data as responders vs nonresponders. To compare this data with conventional treatments, Cochrane review evidence recommends Diane-35 as the pharmacological treatment of choice where regulating menses is the primary treatment (Costello et al., 2007a). However, evidence remains lacking in terms of assessing speculated adverse effects of increasing triglyceride levels and is not always well-tolerated by patients (Costello et al., 2007a). An open long-term study exploring effects of metformin in PCOS found that it significantly improved menstrual rates in terms of menses per month from baseline 0.23 (SE 0.04) to 0.59 (SE 0.07) ($p < 0.001$) (Moggetti et al., 2000). This suggests that both CHM interventions in this study deliver comparable benefits in terms of regulating menses and present promising alternatives to metformin for this outcome. Although metformin has additional benefits for reducing fasting insulin which this study did not collect data on, it is also associated with a higher incidence of severe adverse gastrointestinal effects that frequently requires stopping medication, limiting its overall effectiveness (Costello et al., 2007a). This suggests that a main study could be conducted which would make a head-to-head comparison of these treatments to enable comparative effectiveness data to be generated.

7.6.7.3. Addressing the requirement to use barrier contraception on-study

Participants were required in this study to use barrier contraceptive methods since the safety of herbs during pregnancy had not yet been ascertained. Some participants reported concerns regarding the impact of this requirement on intimacy and 2 participants became pregnant on-study. These 2 pregnancies resulted in healthy children but as the use of barrier contraception this was a safety requirement, it remains important that this issue is appropriately addressed in future work. Measures to maximise the effectiveness of barrier contraception could include supplementing use with spermicide (MHRA, 2010). Participant adherence to this requirement could

additionally be increased by incorporating a more in-depth discussion during the consenting process regarding justification for contraceptive use as a study requirement and which could involve planning with participants how these requirements could be best met. Signature certification of participants understanding contraceptive requirements has also been reported in the literature (Cain et al., 2000) and which could be a simple and sufficiently effective measure in future work. Given that this is a common requirement in research studies where risk for pregnancy is potentially high in this population, it would be helpful to explore participant views in this area and which may lead to better strategies for managing this in future work.

7.6.7.4. RCT in a secondary care setting

Although long-term care for PCOS patients is provided in primary care, it is possible that a main study is better suited for in a secondary care setting. There are several advantages to this. For example, identification of participants and screening for presence of contraindicated conditions could be much easier with authorised access to secondary care data, whereas the ability to identify PCOS patients in primary care could be limited by coding efficiencies in primary care databases. Recruitment of PCOS patients may also be more successful in a secondary care setting where diagnosis is typically made, though this may result in bias towards recruiting certain sub-populations such as those with subfertility. Despite this, recruiting at the point of diagnosis may enable results to be more generalisable since recruitment would be taking place before any treatments – WM or CAM – would have been administered by the medical professional. This could require further feasibility work since trial authorisation, recruitment, screening and data collection procedures are likely to be different between primary and secondary care settings. However, it is possible to consider a range of strategies based within the community as well as in primary and secondary care in order to maximise potential for recruitment success in future trials.

7.7. Conclusion

I have demonstrated within this study that it is feasible to conduct a CHM trial for oligo- and amenorrhoea in PCOS. This evaluation supports the use of menstrual regularity as a primary outcome measure for a main study, and suggests that individualised and standardised CHMs present with similar safety profiles and similar clinical effects on menstrual regularity. Although these

results are promising, they do need to be interpreted with caution owing to obvious limitations that have already been discussed such as not incorporating a placebo or usual care treatment control group.

Future work should incorporate an appropriate control group such as a placebo group to enable specific effects to be evaluated, or a usual care group to enable head-to-head comparisons be made of effectiveness and which would maximise research impact for policymakers, healthcare providers and patients alike

Chapter 8: Discussion

8.1. Introduction

The objective of this PhD was to explore the use of CHM in primary care for oligo- and amenorrhoea in PCOS. This was carried out over three phases. The first phase was a systematic review and meta-analysis of Chinese-language RCTs; the second a Delphi consensus study with CHM practitioners to produce a set of good clinical practice guidelines; and finally a feasibility and pilot study to explore the effects of CHMs on regulating menses in PCOS.

8.2. Summary of findings

My systematic review included only 4 RCTs owing predominantly to methodological issues. Only 1 RCT reported on menstrual cyclicity as an outcome measure and which showed that at 6-months post-treatment, a significantly greater number of eumenorrhoeic women were found with CHM plus Diane-35 when compared with Diane-35 alone (Zhou et al., 2010). Pooled comparisons suggest CHM has beneficial effects on hormonal parameters key to PCOS, with CHM leading to significantly greater reductions in total testosterone when used alone or in combination with Diane-35. CHM alone also demonstrates equivalence to other pharmacological treatments in terms of LH reduction, and appears to lead to significantly greater reductions in LH when combined with Diane-35 compared with Diane-35 alone. In terms of safety, CHM appears to have no adverse effects on liver function and is associated with fewer adverse events when compared with pharmacological treatments. I emphasise the importance of interpreting these findings with caution owing to the small number of studies included in each meta-analysis, the moderate to high levels of statistical heterogeneity and high risk of bias found. Nonetheless, this review does provide some preliminary evidence to suggest CHM is likely to be safe and that it has important effects on testosterone and LH that are comparable to other pharmacological interventions and which would be worthy of further investigation.

The aim of the second phase of the project was to develop good clinical practice guidelines for CHM prescribing in PCOS and which could be used to inform the protocol of the feasibility study as a way of maximising CHM model

validity. The Delphi approach was used in this study to facilitate a systematic practitioner-consultation exercise that was conducted over three Delphi rounds. Qualitative interviews with 11 UK CHM practitioners were used in the first Delphi round to develop clinical practice items. These items were distributed back to the same panel of practitioners via questionnaire who were invited to rate their agreement with each item. The concluding set of guidelines consist of 85 items that describe the range of symptoms and signs that women with PCOS present with in CHM practice, common CM diagnoses in PCOS and practice points regarding how treatment is planned, managed and evaluated. Unique to this study is the presentation of consensus grading within the guidelines. I chose to adopt this in the spirit of GRADE used by NICE to grade strength of recommendations in guideline development, and to convey information transparently as a way of maximising applicability to clinical practice and research. These guidelines were subsequently used to inform various aspects of the protocol for the feasibility study, including the choice of herbs for the standardised CHM, the dosage of CHMs and the length of CHM treatment.

The initial plan for the third phase was to conduct a placebo-controlled feasibility study in primary care comparing three treatment arms: standardised CHM plus usual care, placebo plus usual care versus usual care alone. Unfortunately the time that the CHM manufacturer required to collate the extensive information necessary for clinical trial approvals was inconsistent with the funding deadlines. This necessitated a revision in the original protocol to involve a feasibility study in the community comparing two treatment arms: standardised CHM versus individualised CHM. I successfully recruited 40 women to the study and my assessment suggests that it is feasible to conduct a CHM trial for oligo- and amenorrhoea in PCOS. Both standardised and individualised CHMs appeared to be safe and showed statistically significant improvements from baseline in menstrual regularity following a 6-month treatment course. This evaluation supports the use of menstrual regularity as a primary outcome measure for a main study and recommends the inclusion of additional secondary outcomes such as biochemical profiling and ovarian ultrasonography. Furthermore, this demonstrates the successful combination of both an evidence and practitioner-informed approach to inform the study protocol. This approach not only

helped to inform the standardised CHM prescription, but also ensured that the dosage and length of treatment was appropriate according to usual clinical practice. This demonstrates the importance of such an approach as a way of maximising model validity within clinical research.

8.3. Reflections as a practitioner-researcher

I had been practitioner CHM and acupuncture for 5 years prior to embarking upon this PhD. Having seen firsthand how Chinese medicine had benefited patients, I was, as most enthusiastic healthcare professionals, passionate about sharing my work and creating a greater impact. Thus the decision to pursue research was fuelled partly by a desire to increase the amount of high-quality evidence relevant to the UK, and partly by an eagerness to understand how evidence can be implemented into practice. Whilst pursuing both these goals, I have been afforded the opportunity to reflect upon my roles as a clinical practitioner and budding researcher, and now have a more nuanced appreciation of the implications this research has on all the stakeholders involved - patients, CHM practitioners, conventional medical doctors, researchers, commissioners and manufacturers. This PhD has brought to the fore the importance of working together cross-disciplines towards a common goal of increasing the evidence-base for CHM, and indeed other CAMs. It has also highlighted the importance of an adequate infrastructure to facilitate this process such as that in Australia where government-backed research funding and statutory regulation are present to protect the public, increase professional accountability and to maximise safety and consistency in professional standards.

My own understanding of CHM and acupuncture has been challenged from the moment I started my PhD and I'm pleased to say continues to be the case. I do not see this as a weakness and does not mean that I no longer value my work or my patients. Rather, it is the result of a deeper understanding of how knowledge and truth is framed, and the ability to be self-critical in all aspects of my work. I am fortunate to have worked alongside some of the best academics in CAM and primary care and have seen that the best researchers of any kind are those who are genuinely interested in knowledge creation and in creating an impact. They thoughtfully take on criticism and understand the

limitations of knowledge, a mindset that is not embraced as widely in CHM as it could be. There are lots of reasons at play here. One of the most helpful actions CHM professionals can take is to change the discourse from one that predominantly highlights the benefits of CHM to one where limitations are also discussed – and proactively addressed - in an open and thoughtful way. This change will take time and requires appropriate leadership for it to be truly effective. I have had the opportunity to speak to many practitioners and researchers regarding this matter during my PhD. Given the thoughtful contributions that they have made towards this issue, I feel this is certainly a change that the CHM profession feels is worthwhile and is prepared to embrace.

8.4. Recommendations for future research

I have demonstrated within my PhD that it is indeed feasible to use CHMs for PCOS-related oligo- and amenorrhoea and that it would be appropriate to use this pilot data to support further research in this area. This PhD has provided me with much insight and I intend to incorporate the following recommendations for future research into my forthcoming work:

- Future CHM research should place increased emphasis on safety and cost-effectiveness and which has already been highlighted in recent guidance documents relating to CM and CAM research (Pilkington and Boshnakova, 2012, Witt et al., 2014, Fischer et al., 2014). Given its biological plausibility and potential to interact with conventional medications, it should remain a priority that the safety of CHMs be rigorously monitored and evaluated. This could be carried out in a number of ways such as conducting large-scale observational studies or the establishment of a CHM prescription database that has the potential to be linked with NHS health records and which previous work in CAM has already demonstrated to be possible in primary care (Peters et al., 2000). Cost-effectiveness data regarding CHMs remains scarce in the literature and will be an important area to address as public spending on interventions becomes increasingly scrutinized.
- Related to the former point, I intend in my future work to evaluate the potential role of emerging technologies and social communities in the

delivery and evaluation of care and generation of data for research purposes. During my PhD I have taken advantage of my understanding of technology and how communities are forged and used this alongside traditional routes of conducting research, for example in the recruitment of my feasibility study. Although there is an increasing amount of research being conducted in emerging technologies and online communities in primary care and some areas of CAM, it remains to my mind undervalued as a way of improving efficiency of research, increasing the global impact of our work and also in the engagement with relevant communities. Technology will have an increasingly important role in research, not only in aspects such as generating and collecting large datasets, but also in the way that patients and healthcare professionals engage with each other and in the delivery and evaluation of healthcare. There remains much that is unknown in this area and current methods of research will inevitably move along with these developments in technology and which I intend very much to embrace and incorporate within my own work.

- It is important for CHM researchers to continue to work collaboratively and engage with other CM and CAM researchers, but I wish to emphasise here the importance of prioritizing engagement with the medical community. My PhD was undertaken within a primary care institution and provided me with a rare opportunity to grasp the wider issues and challenges faced by the primary care community. This enabled me to identify issues that could become relevant to the future of CHM practice and also provided me with the chance to engage with practicing GPs about my work at both an academic and clinical level. Despite obvious differences, it continues to – pleasantly – surprise me how much commonality exists between CHM and conventional medicine which goes unrecognized, fuelled in part by a lack of communication as well as a lack of desire to engage with one another. I have found academia invaluable as a way of seeking common ground with clinicians and to start long overdue conversations about CHM which begin to clear a myriad of common misconceptions about both CHM practitioners and the patients who attend CHM consultations. I intend to continue these conversations with the medical community in my ongoing work and

envisage a day where practitioners from multiple disciplines respect and learn from each other's differences to provide healthcare that is fluid, integrated and firmly patient-centred.

Given the increasingly widespread use of CHM and generally of CAM in the UK, it cannot be emphasised enough that the body of scientific evidence in these areas should continue to grow. As with all evidence for healthcare professionals, CHM evidence provides insight into the effectiveness and safety of treatments but it also has a vital role in informing, not replacing, clinical practice and expertise. It is also important to remember that 'real' evidence-based medicine in the provision of care to patients does not seek to replace the humanistic interchange between patient and healthcare professional with mindless, black and white, algorithm-based processes that has come to plague some aspects of conventional medicine. Instead I hope for research evidence to facilitate a more careful and thoughtful examination of treatment options whilst keeping at the heart of these discussions the needs and wishes of the patient as the most important person in such medical interactions. After all, in the words of Hippocrates:

'It is far more important to know what person the disease has, than what disease the person has.'

Appendices

Appendix 1. Phenotypes According To Each Criteria

Criteria	Phenotypes						
	A	B	C	D	E	F	G
Hyperandrogenism	+	+	+	-	+	-	-
Oligo- or anovulation	+	+	-	+	-	-	+
Polycystic ovaries	+	-	+	+	-	+	-
Satisfaction of corresponding criteria							
NIH criteria	✓	✓	✗	✗	✗	✗	✗
Rotterdam criteria	✓	✓	✓	✓	✗	✗	✗
AES criteria	✓	✓	✓	✗	✗	✗	✗

Adapted from: MORAN, L. & TEEDE, H. 2009. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. *Hum Reprod Update*, 15, 477-88.

Appendix 2: Search Strategy

For the systematic review, I searched via Ovid the following databases:

MEDLINE (1946 to 'July week 3 2011'), EMBASE (1947 to '2011 July 25'), AMED (1985 to 'July 2011') and psychINFO.

- 1 exp Polycystic Ovary Syndrome/
- 2 exp polycystic ovary disease/
- 3 polycystic ovar\$ syndrome.tw.
- 4 polycystic ovar\$ disease.tw.
- 5 PCOS.tw.
- 6 PCOD.tw.
- 7 stein leventhal.tw.
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7
- 9 exp Medicine, Chinese traditional/
- 10 exp Drugs, Chinese herbal/
- 11 exp medicine, east asian traditional/
- 12 exp herbal medicine/
- 13 exp phytotherapy/
- 14 exp plant preparations/
- 15 exp plants, medicinal/
- 16 (herb\$ medicin\$ or medicin\$ herb\$).tw.
- 17 (medicin\$ adj (chines\$ or orient\$ or tibet\$)).tw.
- 18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
- 19 8 and 18
- 20 limit 19 to (clinical trial or randomized controlled trial or controlled clinical trial)
- 21 limit 20 to human.

Appendix 3: Script For Email Contacting

Dear Dr. <insert surname in English>

<insert surname in Chinese> 醫生您好:

I am a Chinese medicine PhD student in England, UK at the University of Southampton. I am currently conducting a systematic review titled 'Chinese herbal medicine for polycystic ovary syndrome (PCOS): A systematic review'. Your paper <insert article title in English> is very important to this systematic review. As part of the systematic evaluation of papers, I have some important questions I would like to ask you in order that clinical research into Chinese medicine for PCOS can be further disseminated.

我是英國的 Southampton 大學的一名中醫博士研究生，目前我正在進行一項關於中草藥治療多囊卵巢綜合症（PCOS）的系統綜述‘Chinese herbal medicine for polycystic ovary syndrome (PCOS): A systematic review’。您發表的 <insert article title in Chinese>對這篇系統綜述很重要，目前關於您的這個研究，我有一個問題需要向您請教以便通過該系統評價，讓中醫藥對 PCOS 的臨床研究成果得到更廣泛的傳播。

1. From reading your article, we can see that you randomised the patients in your trial. Can you describe clearly the process of randomisation that you carried out?
1. 通過文章我們了解到您應用了隨機方法對入組的患者進行了隨機分組，請問您能否詳細說明你使用的隨機方法？
2. Could you describe the method with which you used to recruit patients?
2. 您是否可以描述一下納入患者的過程？
3. Your paper states that for women who wished to conceive, fertility treatment was provided. Since our review is looking at the effectiveness of Chinese herbal medicine for regulating periods without use of fertility treatment, can you provide us with the data for the women who did not receive fertility treatment?
3. 您在論文中提到，對於那些希望受孕的婦女，提供生育治療。由於我們的研究是在尋找中草藥調節無生育要求時期對調節月經週期的有效性，您能夠提供沒有接受生育治療的這部分患者的數據？

Your help in this matter is greatly appreciated. If there is anything that is unclear, please don't hesitate to let me know. I look forward to receiving your reply and thank you once again for your time!

非常感謝您的幫助。如果有任何問題，也歡迎您和我聯繫，非常期待您的回復！再次感謝！

Yours sincerely,

Lily Lai

黎宛芸

BSc (Hons) TCM, BM (Beijing), MRCHM, MATCM
Registered Acupuncturist and Chinese Medical Herbalist
NIHR School for Primary Care Research Training Fellow
Faculty of Medicine
Complementary and Integrated Medicine Research Unit
University of Southampton
England, UK

Appendix 4: Script For Telephone Contacting

Introduction

‘Hello Dr. X. My name is X, I’m a PhD student calling on behalf of a review team based in UK, Australia and Beijing and we are currently doing a review on Chinese herbal medicine for PCOS. We came across your paper published in the <year of publication> and was wondering if we could ask you a few minor questions about it?’

Questions

To check for randomisation methods: ‘Could you give me some more information about what happened when you randomised the patients in your trial?’

To check for randomisation and allocation concealment methods: ‘Could you tell me what happened in the trial when a patient joined the trial? How did you decide the group that a patient would join?’

To check for diagnostic criteria: ‘Could you let us know which diagnostic criteria you used for your trial?’

Closing

‘Thank you very much for taking the time to speak with me, your help in answering these questions is greatly appreciated.’

Appendix 5: Reasons for exclusion for remaining studies

Study ID	Reason for exclusion
An XQ 2009	No outcome measures of interest
Anderson RA 2008	Non-randomised study, population includes non-PCOS
Bao WY 2009	Inadequate randomisation
Bei GZ 2010	Inadequate randomisation
Bloomgarden 1996	Technical review of nutritional therapy
Cai PP 2003	Inconsistent with Rotterdam
Cao WP 2010	Unacceptable control/treatment intervention: fertility
Chai LH 2006	Population outside of age range
Chang P 2011	Inconsistent with Rotterdam
Chen JL 2004	Unacceptable control/treatment intervention: CHM as control
Chen JL 2006	Complete data unavailable for measures of interest
Chen L 2006	No outcome measures of interest
Chen LS 2005	Inconsistent with Rotterdam
Chen LX 2008	Systematic review
Chen XP 2008	Population outside of age range
Cheng MX 2009	Population outside of age range
Chu JZ 2009	Inconsistent with Rotterdam
Cui W 2006	Inconsistent with Rotterdam
Deng AL 2008	Inconsistent with Rotterdam
Dong BL 2004	Complete data unavailable for measures of interest
Dong CY 2009	Inconsistent with Rotterdam
Dong CY 2010	Inadequate randomisation
Dong L 2010	Inconsistent with Rotterdam
Duleba AJ 2009	Not relevant to review (clinical review of conventional treatment)
Dong Q 2010	Complete data unavailable for measures of interest
FACT 2009	No articles of relevance in short reports
FACT 2010	Systematic review of acupuncture
Fang RD 2004	Inconsistent with Rotterdam
Fang RD 2009	No outcome measures of interest
Farnoosh 2010	Unacceptable control/treatment intervention: Acupuncture
Feng CF 2009	Inconsistent with Rotterdam
Feng CF 2009 (1)	Inconsistent with Rotterdam
Gao FY 2009	No outcome measures of interest
Gao ZQ 2009	Inconsistent with Rotterdam

Guo LC 2007	Inconsistent with Rotterdam
Guo LC 2008	Inconsistent with Rotterdam
Guo TL 2009	Unacceptable control/treatment intervention: CHM as control
Han CF 2009	Inconsistent with Rotterdam
Han YQ 2008	Inconsistent with Rotterdam
He HL 2009	Inconsistent with Rotterdam
He P 2010	No outcome measures of interest
He QH 2007	Inconsistent with Rotterdam
He XF 2006	Complete data unavailable for measures of interest
He Y 2010	Systematic review
Hou JW 2000	Inconsistent with Rotterdam
Hu XD 2010	Unacceptable control/treatment intervention: Acupuncture
Hu ZR 1999	No outcome measures of interest
Hua L 2003	Inconsistent with Rotterdam
Huang LY 2006	Unacceptable control/treatment intervention: fertility
Huang M 2007	No outcome measures of interest
Huang XO 2010	No outcome measures of interest
Huang YB 2004	Inconsistent with Rotterdam
Huang YL 2004	Non-PCOS participants included
Huang YY 2006	Inconsistent with Rotterdam
Jia Y 2008	Inconsistent with Rotterdam
Jia Y 2010	Inconsistent with Rotterdam
Jia YQ 2004	Inconsistent with Rotterdam
Jiang WH 2007	Inconsistent with Rotterdam
Jin LL 2003	No outcome measures of interest
Jin LN 2006	Not CHM
Jones A 2008	Non-CHM retrospective study
Lai MH 2010	Complete data unavailable for measures of interest
Lai YQ 2006	Inconsistent with Rotterdam
Li B 2010	Inconsistent with Rotterdam
Li FY 2010	Complete data unavailable for measures of interest
Li FY 2010 (1)	Not CHM
Li J 2009	Unacceptable control/treatment intervention: Acupuncture
Li J 2009 (1)	Inconsistent with Rotterdam
Li J 2009 (2)	Inconsistent with Rotterdam
Li SP 2010	Inadequate randomisation
Li SZ 2010	No outcome measures of interest
Li XB 2002	Inconsistent with Rotterdam

Li XB 2007	Inconsistent with Rotterdam
Li XH	Inconsistent with Rotterdam
Li XL 2009	Inadequate randomisation
Li XL 2009 (1)	Inconsistent with Rotterdam
Li XP 2005	Inconsistent with Rotterdam
Li XW 2009	Unacceptable control/treatment intervention: CHM as control
Li YS 2010	Inconsistent with Rotterdam
Li ZZ 2010	Inconsistent with Rotterdam
Lian F 2008	No outcome measures of interest
Liang RN 2008	Unacceptable control/treatment intervention: fertility
Lin Y 2005	Complete data unavailable for measures of interest
Lin Y 2009	Unacceptable control/treatment intervention: Inconsistent treatment
Liu BJ 2009	Inconsistent with Rotterdam
Liu GY 2010	Unacceptable control/treatment intervention: Acupuncture
Liu RX 2011	Population outside of age range
Liu SY 2009	Inconsistent with Rotterdam
Liu X 2009	No outcome measures of interest
Liu XX 2010	Unacceptable control/treatment intervention: fertility
Liu YH 2010	No outcome measures of interest
Lu J 2010	Inconsistent with Rotterdam
Lu R 2006	Inconsistent with Rotterdam
Lu W 2008	Inconsistent with Rotterdam
Lu XH 2007	Inconsistent with Rotterdam
Luo J 2010	Population outside of age range
Lv LP 2009	Inconsistent with Rotterdam
Lv SM 2009	Complete data unavailable for measures of interest
Lv XP 2007	Unacceptable control/treatment intervention: Acupuncture
Ma HX 2009	Unacceptable control/treatment intervention: Acupuncture
Ma HX 2009 (1)	No outcome measures of interest
Ma HX 2009 (2)	No outcome measures of interest
Ma LS 2010	Systematic review
Ma MH 2010	Inconsistent with Rotterdam
Mao YX 2003	No outcome measures of interest
Ni YY 1999	No outcome measures of interest
Nie SX 2009	No outcome measures of interest
Ouyang ZT 2010	Inadequate randomisation
Pan LM 2010	Unacceptable control/treatment intervention: Acupuncture

Peng SF 2009	Inconsistent with Rotterdam
Qiu HN 2006	Inconsistent with Rotterdam
Qiu RQ 2008	Unacceptable control/treatment intervention: fertility
Ran XM 2007	No outcome measures of interest
Ran XM 2008	No outcome measures of interest
Ran XM 2010	No outcome measures of interest
Ren QL 2006	Inconsistent with Rotterdam
Ren QL 2008	Inconsistent with Rotterdam
Ren XQ 2002	No outcome measures of interest
Sang HL 1998	Complete data unavailable for measures of interest
Sang HL 2000	Inconsistent with Rotterdam
Shao DY 2004	Inconsistent with Rotterdam
Shao F 2009	Inconsistent with Rotterdam
Shao MX 2006	Inconsistent with Rotterdam
She XH 2009	Inconsistent with Rotterdam
Sheng PJ 2010	Unacceptable control/treatment intervention: Acupuncture
Shi F 2010	No outcome measures of interest
Shi Y 2009	Population outside of age range
Shi Y 2009 (1)	Population outside of age range
Siu MF 2011	Inconsistent with Rotterdam
Sun B 2004	Animal study
Sun J 2009	Inadequate randomisation
Sun JL 2009	Unacceptable control/treatment intervention: fertility
Sun W 2010	Unacceptable control/treatment intervention: Acupuncture
Sun WF 2009	Population outside of age range
Sun Y 2008	Complete data unavailable for measures of interest
Tan MH 2005	Inconsistent with Rotterdam
Tan Y 2009	Inconsistent with Rotterdam
Tao LL 2005	Population outside of age range
Tao LL 2008	Unacceptable control/treatment intervention: CHM as control
Tao LL 2009	Unacceptable control/treatment intervention: CHM as control
Tao LL 2010	Unacceptable control/treatment intervention: Acupuncture
Tian BY 2003	Inconsistent with Rotterdam
Wan ZX 2009	Not randomised
Wang CP 2007	Inconsistent with Rotterdam
Wang DM 2002	Unacceptable control/treatment intervention: CHM as control
Wang HF 2009	Unacceptable control/treatment intervention: fertility

Wang HM 2007a	Inconsistent with Rotterdam
Wang J 2006	Inconsistent with Rotterdam
Wang J 2009 (1)	Population outside of age range
Wang LY 2009	Complete data unavailable for measures of interest
Wang N 2004	No outcome measures of interest
Wang Q 2010	Inconsistent with Rotterdam
Wang S 2010	Inadequate randomisation
Wang T 2006	Inconsistent with Rotterdam
Wang W 2009	Inconsistent with Rotterdam
Wang YF 2011	No outcome measures of interest
Wang YH 2010	No outcome measures of interest
Wang YX 2007	Inconsistent with Rotterdam
Wei CL 2011	Population outside of age range
Wei X 2008	Inconsistent with Rotterdam
Wu MY 2010	Insufficient detail to make assessment
Wu N 2008	Inadequate randomisation
Wu XX 2010	Inconsistent with Rotterdam
Xia XJ 2004	No outcome measures of interest
Xia XJ 2007	Population outside of age range
Xie GZ 2005	Inconsistent with Rotterdam
Xie XY 2010	Insufficient detail to make assessment
Xu DW 2010	Complete data unavailable for measures of interest
Xu F 2009	Inadequate randomisation
Xu HO 2008	Inconsistent with Rotterdam
Xu JB 2007	Unacceptable control/treatment intervention: Inconsistent treatment
Xu JH 2008	Inconsistent with Rotterdam
Xu XQ 2010	Inconsistent with Rotterdam
Xu Z 2006	Complete data unavailable for measures of interest
Xue XW 2004	No outcome measures of interest
Yan LF 2003	Complete data unavailable for measures of interest
Yan W 2009	Not randomised
Yang GM 2010	Inconsistent with Rotterdam
Yang P 2010	Inconsistent with Rotterdam
Yang YH 2005	Unacceptable control/treatment intervention: Acupuncture
Yang YS 1985	Inconsistent with Rotterdam
Yang ZQ 2010	Inadequate randomisation
Yao ML 2007	Inconsistent with Rotterdam
Yao XH 2009	Population outside of age range

Ye DM 2007	Inconsistent with Rotterdam
Ye LQ 2004	Inconsistent with Rotterdam
Ye TZ 2010	Insufficient detail to make assessment
Yi SG 2005	Complete data unavailable for measures of interest
Yin J 2004	Unacceptable control/treatment intervention: Acupuncture
Ying ML 2008	Population outside of age range
Ying XP 2007	Complete data unavailable for measures of interest
Yu LJ 2007	Inconsistent with Rotterdam
Zhang CH 2009	No outcome measures of interest
Zhang CL 1999	Not CHM
Zhang F 2004	Complete data unavailable for measures of interest
Zhang FC 2007	Population outside of age range
Zhang FC 2008	Inconsistent with Rotterdam
Zhang H 2007a	No outcome measures of interest
Zhang H 2007b	Inconsistent with Rotterdam
Zhang HM 2011	Population outside of age range
Zhang JM 2002	No outcome measures of interest
Zhang L 2010	No outcome measures of interest
Zhang LM 2003a	Inconsistent with Rotterdam
Zhang LM 2003b	Inconsistent with Rotterdam
Zhang N 2010	Non-PCOS participants included
Zhang Q 2010	Not randomised
Zhang SC 2008	Complete data unavailable for measures of interest
Zhang T 2010	Complete data unavailable for measures of interest
Zhang XN 2010	Complete data unavailable for measures of interest
Zhang Y 2007	Inconsistent with Rotterdam
Zhao CP 2006	Inconsistent with Rotterdam
Zhao H 2008	Inadequate randomisation
Zhao H 2009	Inadequate randomisation
Zhao XL 2010	No outcome measures of interest
Zhao Y 2006	Unacceptable control/treatment intervention: Acupoint injection
Zhou YH 2010 (1)	Include in review
Zhao YL 2007	Inconsistent with Rotterdam
Zheng JQ 2008	Complete data unavailable for measures of interest
Zhong XL 2006	Inconsistent with Rotterdam
Zhong XL 2009	Inconsistent with Rotterdam

Zhong XM 2007	Not CHM
Zhou FQ 2008	Population outside of age range
Zhou FQ 2009	Inconsistent with Rotterdam
Zhou J 2009	Inconsistent with Rotterdam
Zhou JB 2010	Unacceptable control/treatment intervention: Acupuncture
Zhou MF 2007	Unacceptable control/treatment intervention: fertility
Zhou XY 2007	Complete data unavailable for measures of interest
Zhu BZ 2009	Inconsistent with Rotterdam
Zhu WX 2010	Clinical guideline
Zhu Y 2009	Inconsistent with Rotterdam
Zhuang XY 2008	Complete data unavailable for measures of interest

Appendix 6: Commonly Prescribed Chinese Herbal Medicines In Polycystic Ovary Syndrome Randomised Controlled Trials

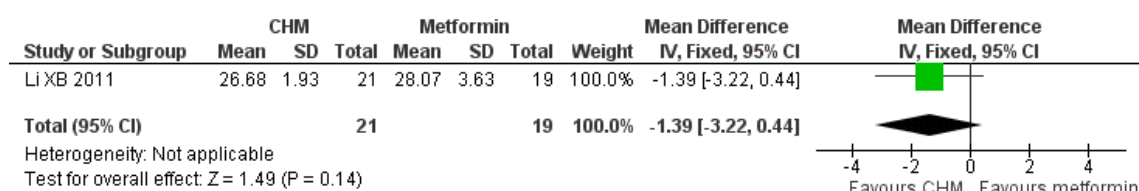
Chinese pinyin name	Botanical name
Ba Ji Tian	<i>Morinda officinalis</i> How
Bai Jie Zi	<i>Brassica alba</i> (L.) Boiss.
Bai Shao	<i>Paeonia lactiflora</i> Pall
Bai Zhu	<i>Atractylodes macrocephala</i> Koidz.
Bu Gu Zhi	<i>Psoralea corylifolia</i> L.
Cang Zhu	<i>Atractylodes lancea</i> (Thunb.) DC.
Chen Pi	<i>Citrus reticulata</i> Blanco
Chai Hu	<i>Bupleurum chinense</i> D.C. or <i>B. scorzoneraefolium</i> Wild.
Chuan Niu Xi	<i>Cyathula officinalis</i> Kuan
Chuan Xiong	<i>Ligusticum chuanxiong</i> Hort.
Da Zao	<i>Ziziphus jujube</i> Mill. Var. <i>inermis</i> (Bge.) Rehd.
Dan Shen	<i>Salvia miltiorrhiza</i> Bge.
Dang Gui	<i>Angelica sinensis</i> (Oliv.) Diels
Dang Shen	<i>Codonopsis pilosula</i> (Franch.) Nannf.
Fa Ban Xia	<i>Pinellia ternata</i> (Thunb.) Breit (prepared)
Fu Ling	<i>Poria cocos</i> (Schw.) Wolf
Gan Cao	<i>Glycyrrhiza uralensis</i> Fischer
Gou Qi Zi	<i>Lycium barbarum</i> L. or <i>L. chinense</i> Mill.
Gui Zhi	<i>Cinnamomum cassia</i> Blume
Han Lian Cao	<i>Eclipta prostrata</i> L.
Hong Hua	<i>Carthamus tinctorius</i> L.
Nu Zhen Zi	<i>Ligustrum lucidum</i> Ait
Shan Zhu Yu	<i>Cornus officinalis</i> Sieb.et.Zucc.

APPENDICES

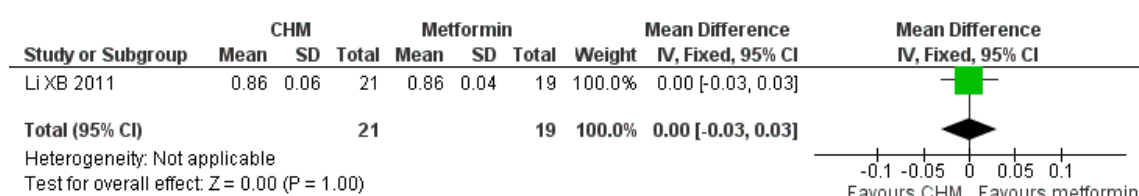
Shu Di Huang	<i>Rehmannia glutinosa</i> (Gaertn.) Libosch. or <i>R. glutinosa</i> Libosch. f. <i>hueichingensis</i> (Chao et Schih) Hsiao
Su Mu	<i>Caesalpinia sappan</i> L.
Tao Ren	<i>Prunus persica</i> (L.) Batsch. or <i>P. davidana</i> (Carr.) Franch.
Tu Si Zi	<i>Cuscuta chinensis</i> Lam.
Xian Mao	<i>Curculigo orchioides</i> Gaertn.
Xiang Fu	<i>Cyperus rotundus</i> L.
Yi Mu Cao	<i>Leonurus heterophyllus</i> Sweet
Zhi Ke	<i>Citrus aurantium</i> L. (Rutaceae)

Appendix 7: Forest Plots For Non Meta-Analyses

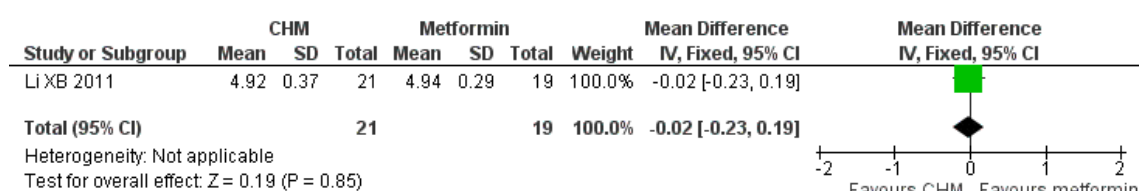
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Body mass index



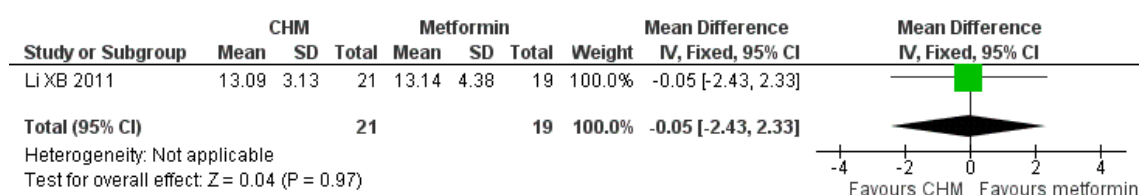
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Waist hip ratio



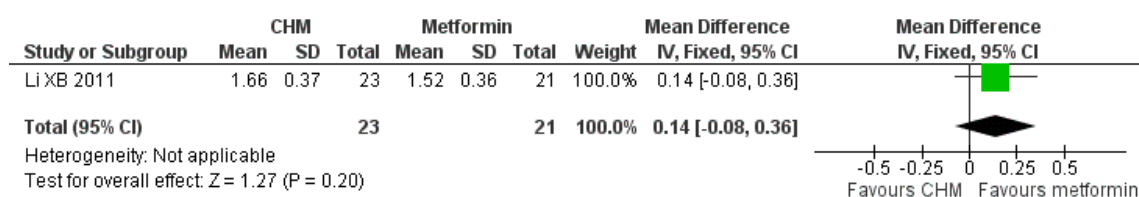
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Fasting blood glucose



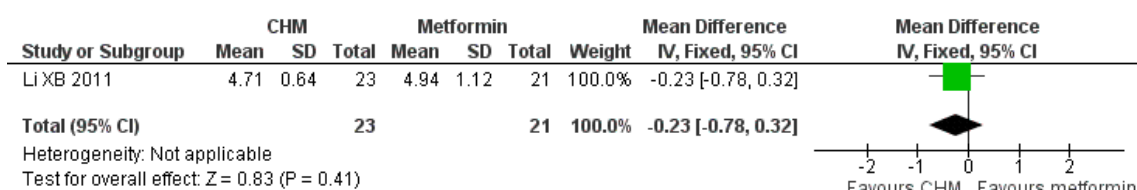
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Fasting insulin



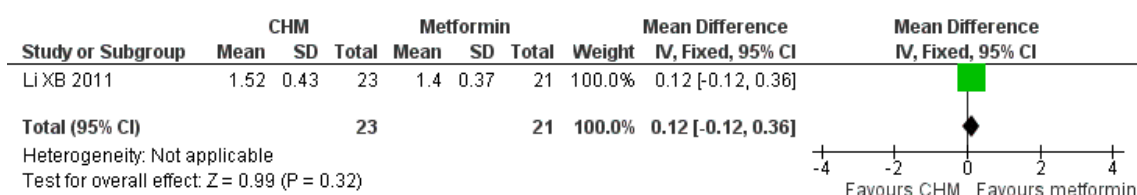
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Triglycerides



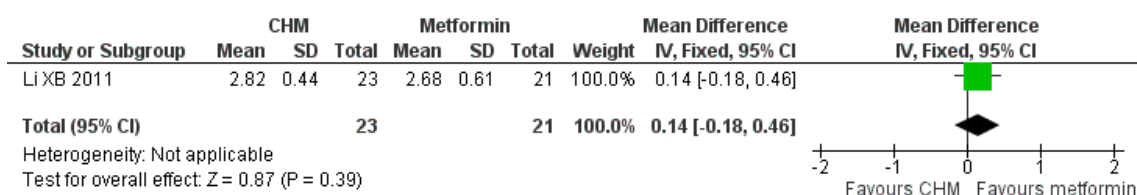
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Total cholesterol



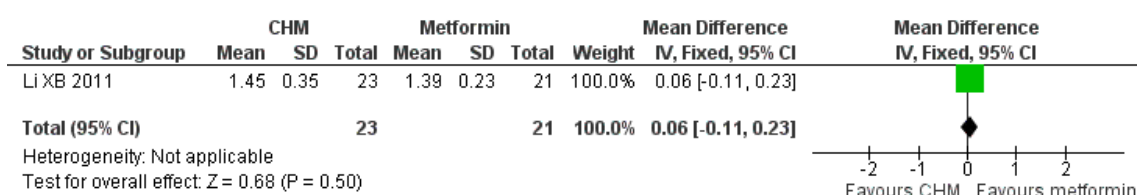
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: High-density lipoprotein cholesterol



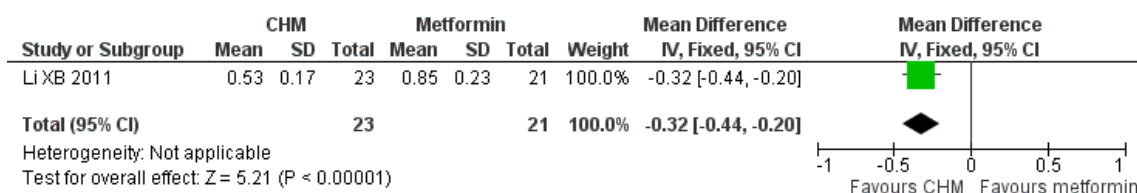
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Low-density lipoprotein cholesterol



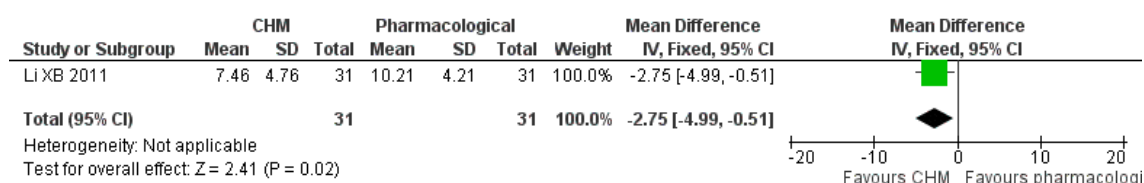
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Apo-lipoprotein A



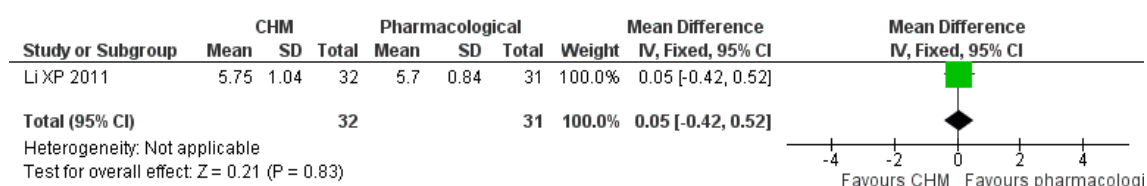
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Apo-lipoprotein B



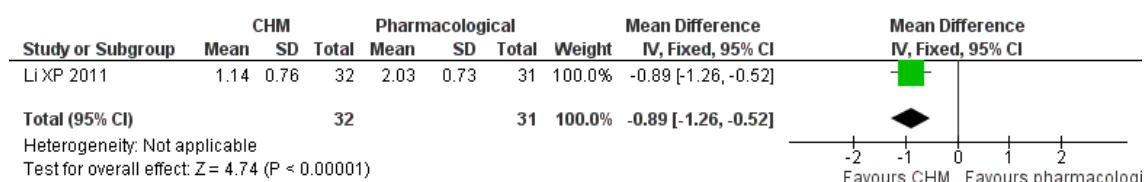
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Traditional Chinese Medicine syndrome score



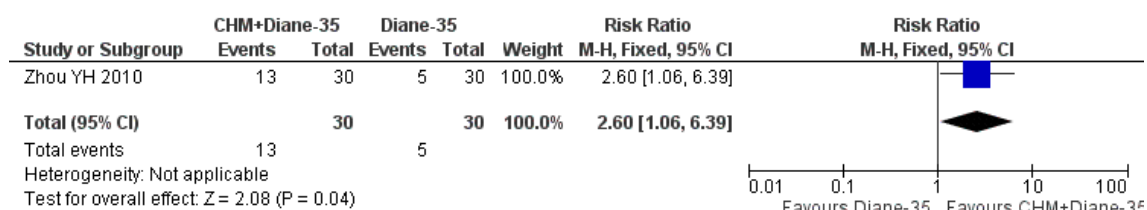
Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Hirsutism



Analysis: Forest plot of comparison CHM alone versus pharmacological treatment alone for outcome: Acne



Analysis: Forest plot of comparison CHM plus Diane-35 versus Diane-35 alone for outcome: Menstrual regularity (responders)



Appendix 8: Email Script To Potential Delphi Study Participants

Dear <insert participant name>,

My name is Lily Lai and I am carrying out a PhD in Chinese herbal medicine with the University of Southampton in England, United Kingdom. I would like to invite you to take part in a research study looking at the use of Chinese Herbal Medicine in the treatment of polycystic ovarian syndrome (PCOS) which forms part of my PhD project.

I am seeking the views of herbalists from various countries who have a minimum of 4 years' clinical experience with Chinese herbal medicine and who frequently treat gynaecological conditions. Please note you do not have to specialise in PCOS to be considered for this study and that different backgrounds in training and modalities of Chinese herbal medicine practice will also be considered. You have been selected for this study as I have approached Chinese herbal medicine regulatory bodies and individuals in various countries to suggest names of suitable herbalists.

This study will involve several 'rounds' of questionnaires and a brief interview with me. At this stage, I would appreciate hearing from you if you are willing to consider participating in this study. To register your interest in participating, please send an email to lywl1g10@soton.ac.uk with the subject heading 'Agree to be contacted' and I will be in touch shortly regarding the next steps.

Thank you for taking the time to read this information and I hope to hear from you soon.

Kind regards,

Lily

Lily Lai
PhD Research Student
School of Medicine
Complementary and Integrated Medicine Research Unit
University of Southampton
Aldermoor Close
Southampton
SO16 5ST

Email: lywl1g10@soton.ac.uk
Website: www.cam-research-group.co.uk

Appendix 9: Telephone Call And Message Script To Potential Delphi Study Participants

Telephone call script

Hello there, my name's Lily Lai, I'm a PhD student from the University of Southampton and am ringing to invite you onto a research study into Chinese herbal medicine. I was wondering if I could take a few minutes of your time to give you a little bit of background information to the study to see if you may be interested or available to take part?

The study is looking to consult Chinese herbalists who are considered to have clinical experience in the field of Chinese herbal medicine. The study will be asking about treatment of symptoms relating to Polycystic Ovarian Syndrome. The aim of the study is to try to get an overall industry opinion on the practice of Chinese herbal medicines in treating PCOS if this is at all possible and you've been shortlisted as one of the practitioners who would be suitable to participate.

Could I tell you a little bit more about what kind of work might be involved if you agree to being part of the study?

The study is set in 2 phases. The first phase will be a one-to-one interview that I will carry out with you where I will be just asking for your thoughts on providing treatment for symptoms of PCOS and the approaches you might use.

For the interviews, I am very happy to travel to you, or for us to meet in a suitable location and to arrange a time and date that suits you.

The second phase will involve 3 online questionnaires, and one will be sent out every 6 weeks. These questionnaires shouldn't take more than 30 minutes of your time to complete each time.

Does this sound like something you think you might be interested in taking part in?

If so, could I take a postal address or an email address so that I can send you an information pack?

Thank you very much for your time. I will be in touch again in the next few days with the information pack.

Telephone messages script

Hi there, my name's Lily Lai. I'm a Chinese medicine herbalist and PhD student with the University of Southampton looking to carry out a piece of research into Chinese herbal medicine for symptoms of Polycystic Ovarian Syndrome. I was ringing to invite you onto a research study that looks at the use of Chinese herbal medicine for Polycystic Ovarian Syndrome and wondered if I could take a few minutes of your time to give you a bit of background into the study?

Would it be possible for you to drop me a quick call back on <insert phone number>, and I can provide you with some more details. Many thanks, and I hope to speak with you soon.

Appendix 10: Delphi Study Invitation Letter



Research Study Invitation Letter

Study Title: Chinese herbal medicine in the treatment of polycystic ovarian syndrome (PCOS): Developing clinical practice guidelines with Chinese medical herbalists

5th October 2011

Dear

I am a PhD research student based in the UK and am looking into the use of Chinese herbal medicine for polycystic ovarian syndrome (PCOS). My research is with the Complementary and Integrated Medicine Research Unit at the School of Medicine at the University of Southampton and I am funded by the National Institute for Health Research (NIHR).

As part of my research, I am conducting an interview and questionnaire study and am looking for the help of Chinese herbal practitioners like you to find out your views on the management of symptoms of PCOS with Chinese medicine. I have approached Chinese herbal regulatory bodies and individuals for names of practitioners who they felt would be suitable for this study and you have come recommended, hence my writing to you now to invite you onto this study.

This research study will firstly involve a one-to-one interview that will last no longer than 60 minutes. This is followed by completing a maximum of 3 rounds of online questionnaire surveys. Each questionnaire should take no longer than 20-30 minutes of your time at approximately 4-6 week intervals. The study duration between the interview and the last questionnaire is expected to last no more than 4 months.

I have attached a participation information sheet which provides you with further details about this study and what to expect if you decide to take part. If you have any questions or concerns about the study, please do not hesitate to contact me for further clarification, either by email on LYWL1G10@soton.ac.uk, or by telephone on +44 (0) 7815 885 947. If you decide you would like to participate, please email me with 'Research: Agree to Take Part' in the subject title. I will then email you back to make further arrangements.

Thank you for considering taking part in this study, and I hope to hear from you soon.

With kind regards,

Lily Lai

Lily Lai

PhD Research Student
Complementary and Integrated Medicine Research Unit
Telephone: +44 (0) 7815 885 947
Email: LYWL1G10@soton.ac.uk

Please reply to:
Complementary and Integrated Medicine Research Unit
School of Medicine, University of Southampton, Aldermoor Health Centre, Aldermoor Close
Southampton SO16 5ST, United Kingdom

Version 4.2, 30/08/2011

Appendix 11: Participant Information Sheet for Delphi Study



Participant Information Sheet

Study title: Chinese herbal medicine in the treatment of polycystic ovarian syndrome (PCOS): Developing clinical practice guidelines with Chinese medical herbalists

Researcher: Lily Lai

Ethics Number: SOMSEC094.11

This is an invitation to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. If you are happy to participate, you will be asked to sign a consent form stating that you have read this information.

What is the research about?

Chinese herbal medicine (CHM) has long been used in China to treat gynaecological conditions such as polycystic ovarian syndrome (PCOS). However, practice guidelines are lacking which are needed to ensure that methods used within clinical trials reflect those used in clinical practice. You have therefore been invited onto a research study that aims to develop clinical practice guidelines for treating symptoms of PCOS with CHM by determining, if possible, a consensus in opinion amongst practitioners like you.

This research study is conducted in association with the University of Southampton in the UK and forms part of the researcher's PhD project investigating the feasibility of Chinese herbal medicine (CHM) for Polycystic Ovarian Syndrome (PCOS). The results of this research study will help to guide the methods used for a proposed clinical trial to be conducted as part of this researcher's PhD project.

Why have I been chosen?

Central to this research study are the views of CHM practitioners like you who come from a variety of training backgrounds. Practitioners ideally will have interest or expertise in gynaecological conditions such as PCOS. The researcher has approached CHM regulatory bodies and practitioners in a number of countries to put forward names of practitioners they would recommend for this research study. You have been identified as a potential practitioner who may be interested and have therefore been sent an invitation to join this research study.

What is expected of me for this study?

This research study will consist firstly of a one-to-one interview with the researcher followed by a multiple-round online questionnaire survey.

During the interview, you will be invited to share your views regarding appropriate treatment methods using CHM and also about your clinical experience. This interview will be conducted either face-to-face at a time and location convenient to you, or by telephone.

Version Number 4.2, 18/08/2011

After the interview, you will be invited to complete several 'rounds' of online questionnaires. Each round should not take any more than 20-30 minutes of your time at approximately 6 week intervals. Within these questionnaires, you will be asked to 'rate' your level of agreement with statements generated from the information provided during the interviews. You will also be asked some information regarding your background and clinical experience.

The information from each questionnaire round will be analysed by the researcher to prepare subsequent questionnaires. Therefore to ensure that the experience of the research study is as smooth as possible for you and fellow participants, it would be advisable to have convenient access to your email and to the internet.

What should I expect to happen if I decide to take part?

The expected timeline for the study is as follows:

Week		Time (mins)
1	You receive an invitation by email and by letter to research study. If you agree to participate, you should email the researcher with the subject title 'Research: Agree to Take Part'. Researcher will email you back and ask for your consent to the study.	
4	The researcher contact you to arrange a one-to-one interview.	
6-8	The researcher will meet you for an interview.	60
12	You will receive email invite to complete questionnaire round 1.	20-30
18	You will receive email invite to complete questionnaire round 2.	20-30
22	If a further round is required, you will receive email invite to fill out questionnaire round 3.	20-30
23	Researcher will email you informing you of close of study.	

Do I have to take part?

Taking part in this research is entirely voluntary.

What happens if I change my mind?

You can withdraw from this study at any time without any consequence. The researcher may ask for a reason for withdrawal but you do not need to offer one. If you decide to withdraw from the study, the information that you have provided in the study up to that point will contribute to the final analysis in this study. However, you will not be contacted for further information, or invited to further rounds of questionnaires.

Are there any benefits in my taking part?

Whilst you may not experience immediate benefits from taking part in this study, your participation will contribute to the development of CHM treatment guidelines for symptoms of PCOS. This will be helpful for practitioners and for guiding the design of future trials in CHM.

Are there any disadvantages or risks involved?

All information you provide on this study will be held by the University of Southampton in accordance with the Data Protection Act 1998. Your information will be coded, placed on a password-protected computer and kept strictly confidential. You will not be identifiable from any information you provide that is disseminated and will remain anonymous from other participants throughout this research study. Only the researcher will be aware of your identity.

The researcher will be able to arrange an interview location most suitable for you. However, if the interview requires you to travel to a mutually convenient location and which will incur travel costs, these will be reimbursed to you.

Who is organising or funding this research?

This research is conducted within the Complementary and Integrated Medicine Unit on behalf of the University of Southampton in the UK. The researcher's PhD position is funded by the UK's National Institute of Health Research (NIHR).

What happens if something goes wrong?

If at any point of the study you have cause for concern or complaint, please contact:

Lead Researcher

Lily Lai
PhD Research Student
Complementary and Integrated Medicine
Research Unit
University of Southampton
Aldermoor Health Centre
Aldermoor Close
Southampton
SO16 5ST
United Kingdom

+44 (0) 7815 885 947
LYWL1G10@soton.ac.uk

Research Governance Office

Dr Martina Prude
Head of Research Governance
Research Governance Office
Corporate Services
George Thomas Building 37
Room 4055
University of Southampton
University Road
Highfield
Southampton
SO17 1BJ
United Kingdom

+44 (0) 23 8059 28848
M.A.Prude@soton.ac.uk

Where can I get more information?

If you have any further questions, please email or call the researcher directly on LYWL1G10@soton.ac.uk, or by telephone on +44 (0) 7815 885 947.

How can I register to participate?

Please email the researcher Lily Lai on LYWL1G10@soton.ac.uk and include in the subject heading 'Research– Agree to Take Part'. Lily will be in contact shortly after for you to ask further questions and to arrange a consent form to be completed.

Thank you for taking the time to read this Participation Information Sheet and for considering taking part in this study.

Appendix 12: Consent Form for Delphi Study

UNIVERSITY OF
Southampton
School of Medicine

Consent Form

Study title: Chinese herbal medicine in the treatment of polycystic ovarian syndrome (PCOS): Developing clinical practice guidelines with Chinese medical herbalists

*Please write your **initials** on the dotted lines beside each statement:*

1. I have read and understood the participant information sheet provided to me about this study (version 4.2, dated 18/08/2011). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
Please initial
2. I understand that my participation is voluntary and I am free to withdraw at any time without giving any reason.
Please initial
3. I understand that direct quotations may be used in reporting the study but that these will be anonymised.
Please initial
4. I consent to my participation in interviews to be recorded and transcribed and understand that the audio recording will be destroyed following verification of transcriptions.
Please initial
5. I understand that my identifying information will be stored securely and that data will be stored anonymously.
Please initial
6. I agree to take part in the above study.
Please initial

Signature:

Name of participant:

Date:

Ethics approval number: SOMSEC094.11

Please return this completed consent form to the researcher directly:

- By email to LYWL1G10@soton.ac.uk with a digital copy or scan of your completed and signed consent form attached, or
- By fax to +44 (0)2380 701 125, or
- By post. A stamped self-addressed envelope is provided in postal information packs. If you were emailed an information pack, this can be provided at your request.

Many thanks.

Lily Lai
Complementary and Integrated Medicine Research Unit, School of Medicine, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, SO16 5ST, United Kingdom

Version 4.2, 18/08/2011

Appendix 13: Delphi Study Focus Group Topic Guide

Focus Group Topic Guide

Total Participant time required: 60 – 90 minutes

Aims of the Focus Group

The purpose of the focus group discussion is to collect information from Chinese herbalists relating to:

- Effectiveness of Chinese herbal medicine (CHM) for symptoms of Polycystic Ovarian Syndrome (PCOS);
- CHM treatment strategies and approaches for treating PCOS;

Introduction

- Welcome and thank participants, and introduce self.
- This study is being carried out as part of my PhD looking at the use of CHM for PCOS. This research has been funded by the National Institutes for Health Research which is a government led research body.
- This purpose of this group discussion is to explore the experiences that herbalists have of working with patients with PCOS in the UK. In particular, there will be a focus on your experiences of appropriate treatment methods and explore clinical effectiveness of CHM for these women.
- This is a very important part of researching CHM to ensure that I can consider what issues and factors are involved in the clinical practice of CHM in order to inform the design of appropriate future research in this area.
- This is one of several focus groups being carried out with herbalists in the UK and information taken from today's session will be considered as a whole rather than on an individual basis. None of your names will be used in the analysis of the discussion.
- The purpose of today is to encourage a free dialogue and a relatively informal discussion about the topics I've raised. This is an opportunity to make your views known and to influence research in CHM so please do speak openly and honestly, and respond directly to each other's comments directly without feeling like you must wait for me to step in to ask you.
- If we seem to be going off topic, I may interrupt you just to make sure we get the chance to cover everything in our discussion. I would also really like to make sure everyone gets the opportunity to contribute and have their say, so if I can see that you want to say something, I might directly invite you to comment. If I do this, don't feel bad about it, it's just so that I can make sure everyone's perspective is taken into account.
- To encourage open and honest discussion, I do ask you to keep each other's identities, participation and remarks private.
- This discussion will be recorded to make sure that I don't miss any of your comments. This recording will be locked away and only I and another member of staff in the

Version 1, dated 03/06/2011

department will have access to it. After it's been transcribed and checked, the recording will be destroyed.

- Introductions within the group

Issues for focus group exploration

1. Which signs and symptoms related to PCOS do you feel that CHM, used without acupuncture, can be effective for?
 - Why these signs and symptoms in particular?
 - How would effectiveness be determined?
 - How important are changes in Chinese medical observations like the tongue and pulse when considering the effectiveness of the treatment?
2. What do you do as a practitioner when you give a CHM treatment?
 - What does the patient experience as a recipient of CHM treatment?
 - Are there other aspects of the CHM treatment that you feel are important for the overall effectiveness of CHM? I.e. is clinical effect just down to the effects of the herbal medicine itself?
 - How does offering CHM by itself influence overall effectiveness when compared with offering the 'whole package' of CHM and acupuncture etc.
3. How does the conventional medical diagnosis of PCOS affect your decision to treat a patient with CHM?
4. What sorts of CHM treatment approaches or strategies are appropriate for women with PCOS?
 - How different are approaches/strategies for different signs and symptoms?
 - How long is optimal CHM treatment?
5. What factors affect how compliant patients are with taking CHM?
 - How important is 100% compliance and why?
6. What is the most appropriate choice of CHM administration for this group of women?
 - When and how should concentrated powders or decoctions be used?
 - Why does it matter?
 - Does the administration type influence clinical effectiveness?
 - What is the most appropriate dosing schedule?

7. How frequently should a patient taking CHM for PCOS be reviewed for optimal effectiveness?
 - Is this dependent on symptoms, their CM diagnosis?
 - How are patients reviewed and how regularly? Face-to-face or telephone consultations?
 - What happens during a review? What are you looking for as a practitioner? What is it telling the patient?
8. What is the optimal duration of CHM treatment before a clinical effect should be expected?
 - Why?
 - How should patients be managed after the treatment has been clinically effective?
9. What sorts of CM syndromes in PCOS are commonly observed in your experience?
 - How effective do you feel CHM is at treating these syndromes?

Closing

- Thank participants.
- Inform participants that other focus group discussions will be taking place before data from all the discussions is analysed and then summarised for feedback from participants via a questionnaire.
- Questionnaire will be sent out in approximately 6-8 weeks by email and should take no longer than 20-30 minutes of their time.

Appendix 14: Delphi Study Interview Topic Guide

Interview Topic Guide

Total Participant time required: 60 minutes

Aims of the Interview

The purpose of the interview discussion is to collect information from Chinese herbalists relating to:

- Symptoms commonly seen in practice;
- Patterns seen in PCOS;
- Strategies to prescribing CHM;
- Chinese herbs used in these patterns;
- Duration of treatment to get a clinical response.

Version 3.1, dated 08/09/2011

Interview Guide

What is it that you do? (Txs, types of patients seen, advice/counselling/support etc)

- And what sorts of treatments do you offer in your clinic?

If you could think back to a patient you've seen with PCOS. Could you tell me more?

- Her background
- How she came about to decide to have acupuncture/CHM (signs and symptoms)

When you treat a patient like this, what are you doing with this information? (patterns x 3)

Could you tell me more about what you do to help women with PCOS? (tx)

- When might you use CHM

How do you feel about the different forms of CHM?

- Dosage
- Convenience and adherence
- Treatment strategy
- Following up
- Frequency of changing base formula
- Treatment duration to see clinical effect

Herbs/formulas

One symptom/one pattern

Anything else?

Closing

- Thank you very much again for your time and letting me interview you. It's been a real pleasure to discuss these issues with you and you've really helped me gain some interesting insight that will be useful for this study.
- I just need to conduct the rest of the interviews over the next few weeks. After the interviews are finished, the information will be gathered together and you will be emailed a link to an online questionnaire.
- Hopefully I will be able to get the questionnaire to you in around 6-8 weeks and will take approximately 20-30 minutes of your time.
- Do you have any questions for me before we finish?

Appendix 15: Initial Codes Generated From Line-By-Line Coding

Delphi: Initial codes and initial themes

1. Characteristics of good practitioners

- 1.1. Length of experience
- 1.2. Qualifications
- 1.3. Learning from experienced practitioners/schools
- 1.4. Teaching positions in formal institutions
- 1.5. Use of biomedical information or knowledge
- 1.6. Personal attributes
- 1.7. Other

2. Characteristics of patients with PCOS

- 2.1. Patient experience with WM
- 2.2. Patient beliefs and expectations of WM
- 2.3. Timing of seeking CM use
- 2.4. Patient beliefs and expectations of CM
- 2.5. Endorsement by a third party
- 2.6. Symptoms and signs
- 2.7. Other

3. CM Understanding of PCOS

- 3.1. Definition of illness
- 3.2. Definition of PCOS
- 3.3. Defining severity of an illness
- 3.4. Causes of PCOS
- 3.5. Pathological mechanisms leading to PCOS
- 3.6. Diagnostic types in PCOS
- 3.7. Clustering of diagnostic types in PCOS
- 3.8. Biomedical information used in understanding illness
- 3.9. Other

4. CM Management of Patient

- 4.1. Core features of good practice in CM
- 4.2. Offering choice of treatments
- 4.3. Reasons for choice of treatment
- 4.4. Practitioner's role with reference to patient management
- 4.5. Contact with WM in the context of a patient's care
- 4.6. CM treatment strategies
- 4.7. Use of biomedical information to inform decision making
- 4.8. Other

5. CHM Treatment

- 5.1. CHM administration types and reasons for choice
- 5.2. Dosage of raw herbs
- 5.3. Dosage of concentrated powders
- 5.4. Formulas
- 5.5. Herbs
- 5.6. Length of treatment
- 5.7. Timing of treatment
- 5.8. Other methods adopted alongside CM
- 5.9. Reasons for other methods adopted alongside CM
- 5.10. Other

6. Assessment

- 6.1. Determining response
- 6.2. Frequency of re-assessment
- 6.3. Definition of effectiveness
- 6.4. Reasons for effectiveness
- 6.5. Reasons for non-effectiveness
- 6.6. Other

7. Research in CM

- 7.1. Role of research in CM
- 7.2. Role of interviewer within research in CM
- 7.3. Role of interviewee within research in CM
- 7.4. Other

APPENDICES

Appendix 16: Coding Manual

Theme (description)	Sub-theme	Description	Excludes	Positive example	Negative example
Clinical presentation	Symptoms and signs	Symptoms and signs that practitioners report women with PCOS presenting with	Biomedical information such as blood tests, laboratory investigations which should be coded under 'Biomedical information'	'She – had kind of very heavy periods, so kind of severe dysmenorrhea, irregular periods, also noticed recent weight gain, hirsutism; also noticed that she was becoming more aggressive as well...'	'we'll always do a blood test for testosterone, and for SH – sex hormone binding globulin, SHBG? And oestrogen'
	Biomedical information	Biomedical information such as laboratory investigations and medical procedures that a practitioner reports	Symptoms and signs that women with PCOS describe and which should be coded under 'Symptoms and signs'	'I send people for scans because, for example, with polycystic ovaries, of course, being able to see the ovary and to see the proportion of stroma to cysts is really important – for me – in defining the herbal formula I use.'	'Horrendously obese...sodden skin, overweight'
Chinese medicine diagnosis	Process of diagnosing	How a practitioner uses, processes and orders	Simple descriptions of symptoms and signs	'There <u>is</u> no condition of polycystic ovaries in	'But in many cases has an aspect of Kidney

APPENDICES

		information to reach a diagnosis	which should be coded under the subtheme 'Symptoms and signs', and excludes naming of diagnosis which should be coded under 'Diagnostic types'	TCM...But the defining disease category for polycystic ovaries is long cycles. So...late menses and that's the consistent pattern...But in TCM terms, that's where it fits in the disease category. And then the pattern discrimination inside that disease category...There are four or five other patterns in that disease category which you come across and you have to treat according to the pattern discrimination'	Yang deficiency and Phlegm'
	Diagnostic types	Names of CM syndromes diagnosed in PCOS	Biomedical diagnoses or descriptions regarding PCOS phenotypes which are of biomedical origin	'Well I split my polycystic ovaries into Yin and Yang type..she's so thin and very wiry, and very Yin xu...And yet the other end of the spectrum which is the really bad Yang xu'	'Also they are worried about – you know – the future implications of not treating it, like diabetes, heart disease and stuff like that'

APPENDICES

Chinese medicine treatment management	Treatment strategies	Description of the Chinese medicine approach to managing the treatment for a woman with PCOS	Factors influencing decisions regarding specific treatments such as acupuncture or Chinese herbal medicine which should be coded under 'Choice of CHM administrations' and 'Other treatments'	'I would have had to deal with all her stagnations and excesses far more...more quickly. I would begin by clearing as much as I could of excess conditions and then doing the long slow job with the deficiencies'	'I just found the people take powders very easily and very well and they just seem to work'
	Factors influencing treatment strategy	Reasons and scenarios for and against a treatment strategy	Factors influencing decisions regarding specific treatments such as acupuncture or Chinese herbal medicine which should be coded under 'Choice of CHM administrations' and 'Other treatments'	'I think she was very stressed when she came, very stressed – you know – a lot of digestive problems like diarrhoea, constipation – a lot of pain – just very, very, very stressed, very – kind of Liver, very wiry...I tried just to – you know – regulate the Liver and basically try and move Blood as well, slowly, and start with that.'	'So that's equivalent to 18, 20 grams of raw herbs a day. And for gynae that's pretty...you know normal BMI people, that's pretty good. Sometimes we'll go up to 6, 9 grams a day.'
Chinese herbal intervention planning	Choice of CHM administration	Descriptions of different CHM administration	Descriptions of CHM formulas and herbs	'I think decoctions are much stronger, which is	'The initial formula I gave her was a

APPENDICES

		types and factors influencing this choice	rather than of the administration type and which should be coded under 'CHM formulas and herbs'	the most powerful of Chinese herbal medicine and then second is herbal powder, but decoctions actually – herbal decoctions – have some disadvantages; for example taste very strong, very smelly and troublesome – you know – you have to boil up, you have to drink'	modification of Jia Wei Xiao Yao San'
	Dosage	Description of dosages for prescription CHM such as raw herbs, herbal granules and concentrated powders	Descriptions of non-standardised dose measures	'Normally I just give about six days supply – if I say – 50 grams a day, so a week – I give them six days. So that's 300 grams – around 300-350 grams a week...The powder is about 10 grams a day...I just give then like – five grams each time, twice a day'	'I think, initially, she was boiling bags twice a week'
	CHM formulas and herbs	Description of CHM formulas and individual herbs used in PCOS	References to practitioners or texts, or brand names for pre-manufactured CHM for	'you just move Qi, you know, based on Si Ni San or Chai Hu Xiao Yao San, Chai Hu, Huang	'I mean there is an interesting book. Have you come across her? [shows text book] I

APPENDICES

			which the formula of origin or herbal contents are unknown	Qin, Zhi Qiao, Chen Pi, Chuan Xiong'	mean she is very precise and very interesting because she bridges the two.'
	Timing	Information regarding timing of the administration of prescribed CHM and factors influencing this	Information regarding timing of patients seeking CHM treatment, or of other interventions such as biomedical or pharmacological treatments	'For example, that from day 4 or 5 till day 14, that should be follicular phase – sorry – til day 13 should be the follicular phase; from day 14 till – 17 is ovulation phase and then of course from day 18 till day – well you could say till day 28 or towards the end of the cycle, that's called the luteal phase, and then, again, from day 1 or the day before, is like – bleeding period. So hence the herbs are different.'	'So often they come to me after they've been trying unsuccessfully for some years including failed IVFs, IUI.'
	Other treatments	Description of other interventions (Chinese medicine or non-Chinese medicine) endorsed or actively prescribed/used	Interventions such as pharmacological treatments already received by the patient	'Because I put her on quite a strict dietary regime as well, so I cut out all starch,	'She'd tried six sessions of clomiphene citrate, which is Clomid and she'd had ovarian drilling'

APPENDICES

		by the practitioner alongside CHM	prior to visiting the practitioner	carbohydrates and made her do exercise.'	
Treatment assessment and evaluation	Determining response	How practitioners determine response to Chinese medicine and CHM treatment	Descriptions of response to biomedical and pharmacological treatments	'I mean her periods were better...they were less painful and they were more regular, but they were still irregular'	'When taking contraceptive pills, artificial oestrogen support. So period coming regularly.'
	Determining effectiveness	How practitioners determine effectiveness of Chinese medicine and of CHM treatment	Descriptions of effectiveness of biomedical and pharmacological treatments	'So we did that for another two months and then she got pregnant...Yeah. So it was 5...5, 6 months - maybe 5 ½ months' treatment'	'Combined oral contraceptive pill called Dianette which has got a particular progesterone type which is good for skin'
	Factors moderating response and effectiveness	Factors practitioners describe as being responsible for the response or effectiveness of Chinese medicine and CHM treatments prescribed	Factors practitioners describe as being responsible for the response of effectiveness of biomedical treatments	'You see it depends on how compliant the patient is, as well, because I don't think it's just the herbs, I think the exercise and diet is very important as well. And the stress that people are under as well'	'She came off the pill, I can't remember, 8-9 months ago and since then she hasn't had any periods. She's been given metformin and again she is resistant to that.'

Appendix 17: Excerpt From A Coded Transcript

[Interview 4 (13/09/2011:10am-11.40am:38m32s): Transcribed SM, Proofed LL]

132 do that; I pay more attention to what the body – body temperature and also the signs
133 and symptoms really – and how people are feeling as well, because I think – if they
134 are still feeling very tired and having blood sugar swings – then I have to change the
135 formula really. So – I only give it a month or two months before I would change, if I
136 do change it).

Comment [LL35]: 5.6

Comment [LL36]: 6.1

137 I: Yes, sure. And with this patient – you did change it after two months? (P: Yeah I did)
138 What was the reason for that?

139 P: ...I think the pattern changed, I think she was very stressed when she came, very
140 stressed – you know – a lot of digestive problems like diarrhoea, constipation – a lot
141 of pain – just very, very, very stressed, very – kind of Liver, very wiry; you know –
142 the tongue was quite red around the sides. There was a coating but I just thought
143 there was more – they were Liver symptoms really and I tried just to – you know –
144 regulate the Liver and basically try and move Blood as well, slowly, and start with
145 that. Because – yeah I mean I suppose, in a way, people say – it's Kidney Yang, I
146 found in this patient, it was more Liver. So I started off with the Liver first of all and
147 there was a bit of a Blood deficiency as well, so I started off with that formula and
148 then I changed because I think there was still coldness and I still think maybe there
149 was – I think the Yang deficiency became more apparent but I think I was trying to
150 warm the Liver and move Blood and drain Dampness second and I think the pattern
151 had changed. She was less stressed and feeling a bit more kind of relaxed).

Comment [LL37]: 4.7

152 I: Yes, so with her, she actually – her condition had almost changed and –?

153 P: Well I think it had and she was more chilled out; I think she did other things as well
154 like meditation) and – you know – but, yes, it was – it was difficult because I think –
155 she had problems boiling the herbs – as you know – [laughter from I] -and – I'm not
156 sure that granules were around then, I don't think they were, or I wasn't using them
157 initially – because I think, initially, she was boiling bags twice a week but I then went

Comment [LL38]: 5.8

APPENDICES

Appendix 18: Chart For Framework Analysis

Theme	Clinical presentation		Chinese medicine diagnosis			Chinese medicine treatment management		
Subtheme	Symptoms and signs	Biomedical information	Process of diagnosing		Diagnostic types	Factors influencing treatment strategy		
Code (s)	2.6. Symptoms/signs/QoL	3.8. Biomedical information	3.3. Defining severity of an illness	3.4. Causes of PCOS/disease	3.5. Pathological mechanisms leading to PCOS/disease	3.6/3.7 Diagnostic types, diagnostic clusters	4.2/4.3 Offering choice of treatments and reasons for choice of treatment	4.4. Role as practitioner
1	Missing period, delayed period (3)(21), easily tired, loose bowels or constipation in Qi and Kidney deficiency (14), heavy body, darker complexion, suppurative acne, teethmarks with white coating, weak pulse with Kidney Yang and Spleen Qi deficiency (18), acne (introduced term) (17), moodiness, wiry pulse, upset and crying if Liver Qi stagnation and Kidney Yin deficiency (18).	Progesterone (7), ovary lump (8), oestrogen (9)	Biologically detectable/diagnosable by WM (3), real vs pre-clinical disease (3), presence/absence of symptoms (7), what level of CM treatment is required for response (acupuncture and moxibustion being low level) (8), severity of symptoms eg. deviation of menstrual cycles from the norm of 28 days (8), multiple pattern presentations (19)	Western lifestyle, Pill, delaying starting for family (for fertility) (5), prolonged stress (21), physical exertion/high achievers (21).	Pill forces hormones to be on standby for length of time, function is lost though form may be present (5).	Kidney Yin deficiency with Liver Qi stagnation, Kidney Yang deficiency with Spleen Qi deficiency (6), Blood stasis and Heat (18), Kidney Yin deficiency with Liver Qi stagnation and Liver Heat (18), sometimes a combination of all the above - and then treat the Liver (19), Dampness stagnation (21)	Matching strength of treatment with severity of condition (8)	Refer patients to WM if not yet seen by a doctor (3); making connections with WM (5); Improving effectiveness of CM by understanding role within integrated medical practice (2), explaining to patient what CM involves and supporting them (5), matching patient's requests/demands, continued monitoring, building confidence in CM and in practitioner (9), integrative working style (4), attentive to patient (15), not being distracted by personal problems (15), giving time to taking pulse (15).
2	Delayed periods and amenorrhoea (1), desire to conceive (2), stress (10), depression (11), emotional upset (11), irregular periods (50-70 days) (1,16)	Poor response to IVF, IUI treatments (1,3), egg quality and blastocyst embryos (2), ovulation (5), progesterone (6).	The form of CHM shown to offer the quickest response (8), delay in seeking help from CM (10), having received WM already? (10), age (10), time since experiencing problem (10), comorbidities? (10), combined patterns? (10), even in serious gynaecological conditions eg. tubal blockage (15)	Damp and Cold UK weather aggravating existing PCOS condition of Dampness and Phlegm (10,11), delay in seeking help with CM (10), stress and frustration with failing to conceive (10), diet and living environment (10), stress with IVF due to cost (11).		Kidney Yang and Spleen Qi deficiency with accumulation of Dampness and Phlegm (most common) (7), Liver Qi stagnation with Kidney Yin deficiency and Blood deficiency (less common) (7), Heat Phlegm and Blood stasis (even less common) (7)	Advises both for PCOS (3), herbs more important (3), herbs treat wider range of problems than acupuncture (3), distance prevents patients from returning regularly, hence herbs more appropriate (9), acupuncture more acceptable to patient (12), patient more aware of acupuncture (12), patients believing acupuncture is more natural and without medication therefore safe without side effects (12), negative reports about Chinese herbs and concerned about (safety?) (13), preparation involved in herbs (13), tasting herbs (13), consultants/gynaecologists not minding/supporting patients having acupuncture but not herbs (13), patients being asked to stop taking any other medications when starting IVF (14), difficulties in co-prescribing during IVF treatment (14), consultants not being aware that patients are taking herbs (14), consultants not knowing how herbs work and not wanting them to interfere with IVF drugs (14), consultants hearing negative reports about CM (14), consultants believing CM are placebo (14), consultants not interested in finding out more about CM (14), patient reading information about herbs/acupuncture to make own decision (14), affordability affecting access to range of treatments (15)	Clarity for patient (4), treating patient with CM seen to be linked though separate to counselling role (12), helping to change attitude to deal with stress (12), discuss treatment choice and plan with patients to consider affordability and what treatments they need (15)

APPENDICES

3	Eczema (1), irregular periods, mostly delayed periods 8-12 week cycles, severe dysmenorrhoea, excessive hairiness on arms face and legs (2), very tired (kidney deficiency) (2), fertility (2), greasy tongue coating (Dampness) (2), food intolerance, bloating with gas (Dampness) (3), severe Blood stasis symptoms like very painful periods, clots in period, purplish spots on the tongue (14), yellow tongue coating is Damp Heat and inflammation (12).	ovulation (14), cysts (15)	By amount of herbs required to see a response (9), strength of the categories of herbs required (9), working at a certain 'level' eg. Qi level or Blood level (11), length of time of symptom being evident (16), presence of obesity = Damp/Phlegm (16), depends on 'kind' of PCOS (16).	NA	NA	Spleen deficiency, Kidney deficiency (2nd most common), Blood stagnation, Qi stagnation, Phlegm and Damp accumulation (3rd most common) (4, 10), combinations of 2-3 patterns (5), 80% of symptoms related to Blood stasis 20% deficiency (10), Damp Heat (12)	Herbs for internal organ problems and for channel problem like pain, acupuncture more suitable (12), acupuncture requires once weekly treatment (12), young patients (17-18 years old) would not like needles and have to persuade her/parents to accept (12), parents needing to take patient to frequent visits (12), herbs require less intensity of treatment 4-6 weeks (12), herbs more effective at treating internal organ complaint eg. gynaecological conditions (12).	Warn patient of consequences of PCOS re fertility (2), recognise difficulties with decoctions for patients (9), explain differences in treatment strengths (9), warn re side effects of diarrhoea, nausea and vomiting (9), quick treatment progress is important than constant slight improvements (4), we can help but cannot give you guarantee (8), close and attentive follow up esp at initial stages of prescribing herbs (9), despite severity of condition, must treat because you are there to help patients - need to set expectations and to explain it will require a long course of treatment (17).
4	trying to conceive (1), improve health in relation to PCOS (1), very heavy periods, dysmenorrhoea, irregular periods, recent weight gain, hirsutism, more aggressive, worried about TTC (1), swollen face, 70% fertility-related 30% other problems eg. weight issues, mood issues, congestive dysmenorrhoea, hirsutism (4), finding condition debilitating and find it hard to lose weight (4), feel it's better/healthier to have a regular cycle (4), body temperature, tiredness, blood sugar swings (6), Liver symptoms: very very stressed, digestive problems eg. diarrhoea and constipation, tongue with red around sides (6), hard to determine most important symptom with PCOS because everybody is different (15).	progesterone (2), ovulation (5),	NA	Dietary (2, 3), health/illness and PCOS being a continuum eg. re-introducing the dietary cause of this patient's PCOS reintroduced symptoms again (5), external factors like cold in the abdomen and cold in the liver perhaps a root cause of PCOS (17), diet and lifestyle (17), differentiating from kidney Yang deficiency (17), invasion of cold esp in this part of the world and Dampness (17), environment (17)	Life we live today, stress, adrenaline (16)	Phlegm (2), Spleen, Phlegm Lung, Heart (8), Liver Qi stagnation (8), Cold in the Liver (8), Kidney Yang deficiency (8), Cold and Liver deficiency (17), different to textbooks which discuss more kidney Yang deficiency (17)	Japanese acupuncture always used, twice per month before ovulation and before period to reduce pain or invigorate Qi or Blood (10), use Hara diagnosis involving feedback to check hormonal points and reflexes to choose acupuncture points (10), Acupuncture removes some symptoms and signs to give a clearer picture to be able to see what herbs you should use (11), acupuncture by itself difficult to treat PCOS (11), herbs and the acupuncture much easier (11), you need less sessions of acupuncture if having herbal medicine as well (11), acupuncture used prior to onset of some pain symptoms so they feel better beforehand and is immediate (12), herbs can take a while to kick in (12), acupuncture can influence the cycle quite quickly (12).	Patients seeking advice on when appropriate or inappropriate to integrate CM with WM (2), ensuring partner had sperm test (2), accounting for patients' busy lifestyle (2), using tools eg. BBT charts to monitor ovulation (3), educational (3), empowering patient with knowledge and ability to do things for themselves (5), being attentive to changing symptoms in a patient and adapt treatment accordingly (5), not relying solely on hormonal tests (using for guidance) (5), paying attention to body, temperature and signs and symptoms (6), can influence cycle quickly with acupuncture if you're good (12), being on the ball with recognising syndrome and patterns and attentive to patients continuing to eat badly and not exercise (12).
5	women's problems, fertility, menopause, dysmenorrhoea, amenorrhoea (5), uncontrolled episodes of PMS causing lot of stress in marriage (4), slim and very attractive-not typical PCOS (4), irregular periods (5), trying to conceive (5), distress from trying to conceive (5), changed personality quite radically, very sharp tempered and moody, could not function in normal life (5), no depression (5), thirst and urination (5), nervous and tending to sleep badly (6), lassitude and fatigue (7), morning sickness during pregnancy (13), re-strengthen patient following ectopic pregnancy (13), heavier with weight problems though not always obese, loose puffy flesh with sallow complexion and sticky coat if Phlegm is more common in PCOS with amenorrhoea (22)	severe polycystic ovary (5),	Severe PCO, inability to conceive without metformin (5), not yet having severe diabetic symptoms such as hypo (6), disturbed hormonal picture that she definitely would not have conceived (6), diagnosis of PCOS (17), length of treatment required (17), complete absence of menstruation (18).	Western lifestyle (12), eating sugary greasy fatty dairy products that create Spleen Dampness and damage Spleen and create Phlegm and fluids (28).	Spleen very damaged (5), when cycle is delayed tremendous build-up of tension (23).	Complex (7), Blood deficiency, kidney Yin deficiency (6), Blood stagnation and Phlegm (11), Liver Qi stagnation (12), Kidney Yang xu = Qi and Blood movers (24).	Initially acupuncture because what people know about (1), over 50% will have herbs once they understand what it can do (1), difficult delivering medicine, getting regular attendance with herbs (3), internet helpful in emailing for following up (5), people with amenorrhoea and dysmenorrhoea need daily treatment if possible and when trying to move Blood, more effective with herbs (3), most effective treatment is required to ensure patients don't become despondent if symptoms don't change (4), important to reduce timescale for women who need to see a quick result and considering you only have symptom once per month (4), acupuncture is less effective at clearing phlegm and dampness compared with herbs (16), severity and degree of condition and cyclical nature means herbs are considered more effective than acupuncture (19), herbs are better for severe deficiency and because they are 'material' and can give daily (20), provision of treatment on a daily basis not feasible in UK vs China 'western problem' (21).	Helping patients understand how treatments can help them, pinpoint something that herbs will be more effective at treating or help speed the treatment up (1,2), educating about herbs, taking extensive Chinese medicine and medical history (3), needing to ensure change of symptoms to prevent patients from becoming despondent (4), suspected diabetic connection because of Spleen damage and having trouble with thirst and urination (5), referral to gynaecologist specialising in PCOS (5), role alongside WM (7), happy to combine WM and CM in order patients get well (8), when to refer to WM (8), when practitioner feels CM can do 'just as well' (8), teaching/gently teasing to take time off (9), importance of a relationship transcending any discomfort patient might experience of treatment such that they'll come back (9), assessment of how good somebody will be with herbs (9), remaining personable and remembering the patient despite few visits (13), 'What I have got to do is try to be as effective as I can within the limits of people coming and their lifestyle and what they'll do' (21), patients expect acupuncture and know acupuncture so initial visit spurred on by interest in this (23), practitioner will then educate patients re herbs if certain patient really needs herbs or is better off with herbs than acupuncture (23), meeting patient's expectations (23), people in area not in contact with other people with herbs so herbal popularity/awareness less evident (23), important for patient to understand consequence of using Blood movers in initial stage of treatment and not TTC during this time (27), not being prescriptive or scaring patients (28), better communication between medical profession and us so everyone working together - helpful for patients and so that everybody feels like they are working for the same purpose and patient knows as much as possible about what's going on (30, 31).

APPENDICES

6	Fertility (3), history of chocolate cysts (3), rarely people who want to sort themselves out and not motivated by fertility (4), 56 day cycle with 3 week bleed (3), bleeding constantly after childbirth (5), painful periods (severely affects QoL for patients) (21)	Scan (3), proportion of stroma to cysts on ovary (3), pre-androgen index (3), chocolate cysts (3), AMH (5), thyroid (5), progesterone (5), ovulation (5), follicular phase (10), lupus or arthritis (11), thyroid (11), autoimmune thyroiditis or hashimoto's disease (11), auto-immune response (11), natural killer cells (11), Hughes syndrome (11), cysts (17), free androgen index (17), proportion that LH is raised above FSH (18), progesterone (18), scans, stroma versus follicle growth or cyst growth (18), day 2 FSH, LH, oestrogen (18), free androgen index (19), progesterone (19),	Requiring medical intervention (4,5), deviating from the 'norm' (4), excessively high hormone levels (5), co-existing medical conditions (5), obesity (6), mental exhaustion from chronicity of condition (6), duration of symptoms (6), lack of stability in symptoms (6), age (6), requiring raw herbs (14)	Pill (5), Damp Cold weather (19),		Yin and Yang types based on body shape, plus diagnosis of differentiating factors (5), Yin xu thin, very wiry, very pale, doesn't sleep that well (6), Yang xu obese, sallow skin, overweight, very difficult to lose weight (6), Blood stasis as primary (8), Blood stasis symptom as spotting, brown pre-period (8), BBT chart does not fall down properly at beginning of cycle, bloating, sore breasts, mood swings, stuck in liver (8,9), Blood stasis: pre-period and mid-cycle spotting, mittelschmerz, brown trailing start to period, dusky skin with liver spots, sublingual veins, purple tongue, PMS (10), other diseases eg. rheumatoid or auto-immune issues, lupus and arthritis which are Blood stasis related (10), recurrent miscarriage as Blood stasis (11), natural killer cells, Hughes syndrome suggest Blood stasis (11), Cold in the uterus and Phlegm Cold (17), Blood xu (19), Phlegm Damp in Uterus, Blood stasis, kidney Yang and Blood xu (22), always a combination of deficiency and excess (22),	Patients accepting that they need mental help (6), acupuncture alone insufficient, acupuncture and herbs better (11), herbs works continually vs acupuncture (12),	Biomedical information informs herbal treatment (3), re-educating patients, bringing hope, empowering patients (4), helping the body re-communicate (4), encouraging patient to see positively (4), not accepting patients who aren't going to comply (7), getting patients to sign form saying will use barrier method whilst on herbs eg. Blood stasis (7), partnership with patient - expecting patient to do their bit (13), teaching self and being pro-active in seeking out teachers (1), challenging self and discuss ideas with colleagues (2), thinking outside the box (1), being too reliant on textbooks (20),
7	Amenorrhoea, dysmenorrhoea, fertility (1,2), hair loss, hirsutism (2), spots (2), difficulty in controlling weight (2), obesity (2), abdominal pain during intercourse (2), irregular periods (3), facial hair (4), young girls: facial hair, spots, weight and women over 25 fertility more dominant (4), heavy period (6), period pain (19),	pituitary gland (9), polycystic (9), thyroid (9), hormones (9), circulation system (9), nerve system (9), endometriosis (21),	Diagnosis of PCOS for long time (2), seeing numerous specialists (2), having IVF multiple times (2), stages of PCO affecting patient (3), suffering a long time (3), disease entering Blood level vs Qi level (3), stubborn when internal pathogen Phlegm involved (7), Phlegm-Blood stasis most stubborn pathogen (7), affecting hormones of the whole body eg. PCOS and pituitary gland problem (9),	Lifestyle and dietary problem (5), late nights (5), young girls dressed inappropriately (5), women think they are busy in UK but China women are a lot busier (13), women in China a lot more pressure and responsibility (13), China less deficiency problems because they look after themselves, keep reasonably warm, pay attention to food and daily living (13), exposing feet in cold weather (14), exhaustion with commuting to London and heavy social life (14), unrealistic expectations of hoping a miracle will happen (14), PCOS masked by contraceptive pills (20), contraceptive pill masks problems like pain or irregular period to help girls through certain periods of time but difficult to treat when on pill for over 10 years (20),	When hormone becomes imbalanced, water retention and metabolism disorder makes body produce Phlegm (7), Phlegm and Blood stasis together (8), in China higher levels of toxicity (13), high insulin and male hormones (14), coffee and smoking (14), Spleen produces Blood so if deficiency in Blood will tonify Spleen (14), Blood stasis can cause Blood deficiency (15),	Blood stagnation, Qi stagnation (3), deficiency always present in PCOS (5), Qi stagnation + Blood stagnation combined common (7), internal pathogen of Phlegm can affect when PCOS gets stubborn (7), Phlegm and Blood stasis combined being the most stubborn pathogen you can treat (7), UK women more deficiency - Qi/Blood/Yang due to less attention to lifestyle aspect (13), younger women or early stage PCOS may have more Qi stagnation with toxicity and gently tonify as Qi stagnation more dominant than Blood stagnation (16), rare to see Heart and Lung pathologies in gynaecology (16), cannot generalise to one pattern because every patient is different (19), though formula will focus on Liver, Spleen and Kidney (20),	Offering acupuncture and herbs to treat PCOS (9), herbs to treat the root (9), acupuncture preserves results of herbs and helps with Qi stagnation, heat symptoms (spots) and psychological impact (9), severity of a hormonal problem such as PCOS requires herbs and acupuncture for results (9, 10), NHS should offer treatments to girls with PCOS younger and increase awareness in younger generation (20), educating of doctors and parents as girls follow their advice (20), offering treatments at younger age because less work required (21),	Educational role in helping patients look after themselves (4), being honest to patients, helping them understand what is going on in their body, set expectations and how they can improve from their perspective (5), lay out a plan of treatment (6), guiding patient psychologically to retain confidence in the treatment so they do not panic or become impatient with treatment (6), reassurance when 'side-effects' happen (6), they know you are 100% in charge (6), comforting patient who are struggling to deal with psychological impact (8), boosting confidence and diverting attention to other things, joke (8,9), frequent sessions ensure close monitoring and guidance for a better chance of success (9), bonding between patient and practitioner after weekly treatments of once a week for 4-6 weeks (10), waste of patients' money and our energy if not prepared to engage in treatment (11), China patients do not have time or privacy to speak about pressure/stress as UK patients do (12), patients in UK like therapist to take lead and to take control (13), patients in China more active in seeking help, or will use initiative and question therapist more because they feel more in charge (13), educate patients about looking after themselves to prevent illness or keep at bay (14), telling patients to slow down (14), having passion and desire to see quick results does not always work as can drive patients away (18), GPs being too short-sighted and not dealing with the matter at hand (21), prescribing pill economically saves government money and easier for GP to prescribe (21),
8	Amenorrhoea, irregular periods, erratic periods who are trying to conceive (4), infrequently women with weight problems and acne (4), amenorrhoea for 3 years (5), cold hands, cold feet, lower back pain, frequent urination (8), Qi stagnation signs such as tongue with red rim, stress, abdomen quite tight and tense (8), IBS (19),	not ovulating (6), hormonally active (14), hormone receptors (15), follicles, anti-inflammatory (15), insulin resistance (18),	NA	Women working too hard (8), constitutional tendency towards PCOS (8), emotional suppression (13), busy tense women (13),	Stagnation obstructs Blood, Chong and Ren Mai and menstrual cycle becomes blocked (7), importance in getting things moving but underneath obstruction there being an underlying deficiency (7), deficiency is often a Spleen or kidney deficiency (7), once you have started to get things flowing, you can put more emphasis on tonifying deficiency (7), Kidney Yang deficiency that weakens the ovulatory process (8), possible that Blood deficiency due to not having periods but no real signs of Blood deficiency (8), strong emotional component in gynae problems with pushing down emotional tension of anger, frustration or fear getting locked into pelvis (12), women having a smiley outward persona and suppressing emotions that are deemed unacceptable (12), root cause of some problems like endometriosis and PCOS (13), acne coming from Heat in blood that may arise from Qi stagnation (18), insulin resistance and obesity would raise questions re Spleen function (18),	Complex patterns, Liver Qi stagnation and stagnant Blood with Phlegm, Spleen deficiency, slight Blood deficiency, Qi deficiency, Dampness (7,8), Kidney Yin deficiency less common, Kidney Yang deficiency more common (8),	Acupuncture and herbs (2), herbs more accessible such as pre-cooked decoctions improving compliance though expensive (2), more confident about what works and better prognosis with herbs (2), treating physical as well as emotional things to ensure things move and changes are made (12), addressing what you see ie. Spleen depleted, Liver stagnant (12), changing how patients live the world (12), discomfort with acupuncture (14), herbs only if patients have limited resources as herbs can go deeper and have a more hormonally active effect than acupuncture (13), herbs stronger treatment (14), herbs operate more pharmacologically and activate hormone receptors, break down adhesions and dissolve residual follicles, have an anti-inflammatory effect (15), herbs are physiologically clear in WM terms whilst acupuncture more at Qi moving and circulating (15),	To set expectations that it could be a lengthy intervention of several months and to encourage them (10), be persistent and not give up on the patient despite lack of apparent response (10), staying confident and being persistent (11), recognising easy for patients to feel uneasy when paying lots of money, taking something tasting horrible and nothing apparently happening (11), having experience to tell patient what happens (12),

APPENDICES

9	Fertility (1), late menses (2), long cycles (11), skin problems, hair growth (11),	Anovulatory (2), scans, blood tests and BBT charts (3), polycystic (3), scan (4), blood test for testosterone and for SHBG (4), polycystic ovaries (4), BBT chart (4), normal biochemistry (4), normal scan (4), diabetes (5), insulin resistance (5), antibiotics (6), normal BMI (9), too much testosterone, too much oestrogen, not enough progesterone, not ovulating, not producing eggs (12), androgens (12),	Age (1),	Damp and Cold in UK than in China (10), environmental and genetic effect (10),	Combined oral contraceptive pill Dianette good for skin but makes the PCO condition worse by shutting down ovaries (11,12),	Kidney Yang deficiency and Phlegm (2), Damp and Cold (2),	Herbal medicine, diet and exercise combined (1), herbal medicine alone not much success (2),	Treating the presenting symptoms and signs even if not a WM diagnosis (4), integrating treatments by prescribing WM and CM appropriately, safely and legally (6), responsibility in protecting patients from unknown contraindications and side effects in mixing prescriptions of WM and CM (6), patient should be treated properly in their teens so they are not mistaken to thinking their PCO is resolved with the pill (12),
10	Digestive symptoms (17), irregular periods (17), lower abdominal bloating, sluggish bowels, IBS-like symptoms, urgent bowels (30),	cysts (28), scan (28), endometriosis (28), polycystic ovaries (41), underactive thyroid (41)	Gynaecology problems quite deep set due to chronic nature (16),	NA	Water metabolism problems lead to problems with Blood (10), Small Intestine is source of Yang for Lower Jiao which helps metabolise Water, if injured will require supplementing (10),	If a pulse fits into a Jin Gui 'chapter', will diagnose according to patterns show in chapter (5), If does not fit chapter, will diagnose according to the pulse (5), pathologies 'on top' of other pathologies (5), PCOS as a Blood and Water based disease (6), Blood stasis (6), Blood and Water mutually congesting (8), Jue Yin pattern with Shao Yang on top esp coming up to period (16), fertility (30), general tiredness and not feeling refreshed in the morning (30), frequent urination and clear urination (31), dry mouth (31), palpitations (31), Gui Zhi Fu Ling Wan pattern (42), Jue Yin Tai Yang = Blood and Water (42), Wen Jing Tang plus Gui Zhi Fu Ling Wan (42),	NA	NA
11	Menstrual difficulties (2), fertility issues (2), getting health sorted (2), not menstruating regularly (2), painful menstruation (2), fertility (3), primary or secondary infertility (3), very emotional (3), overweight (3), very hairy (4), bad relationship (4), menstrual irregularities as being an issue for women trying to get pregnant (5), younger patients more concerned with obesity and hirsutism (5), 30-40 day cycles seen to be only slightly irregular (8),	ovulation (5), sinocapillaries (5), progesterone (6), receptors (6), don't tolerate metformin (7), would like access to results from blood tests and scans (8)	Having numerous factors working against patient eg homesick, problematic periods, duration of problems, stressed, busy (7),	NA	NA	Phlegm and Blood stasis with Blood deficiency (7), possibly Kidney and Spleen Yang deficiency and Qi deficiency (7), thin patients may be Yin and Jing deficient but less common in UK (7),	NA	Taking time to go through herbs with patients (8), encouraging ways to get patient to participate eg BBT chart so they can see progress (8), stopping BBT charts if patients get anxious or obsessive (8),

Appendix 19: Questionnaire Distributed In Delphi Round Two

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

An interview and questionnaire study with Chinese medical herbalists

In this questionnaire, you will be asked to rate a number of items. These items consist of statements that you and other herbalists have made about Chinese herbal medicine as well as Chinese medicine as a whole system.

For this reason, the following definitions have been made in this questionnaire:

'Chinese medicine' refers to the system that includes acupuncture and Chinese herbs.

'Chinese herbs' refers to Chinese herbal medicine alone.

Thank you for your continued participation.

Background

Please provide some information about your background and experience by filling in the following questions.

1. Please state below the research code you were provided in your email.

2. Please list your qualification(s) relevant to Chinese medicine including the name of the institution.

Qualification	
Institution	
Qualification	
Institution	
Qualification	
Institution	

3. In what setting(s) are your Chinese medicine treatments carried out? (please tick all that apply)

- ☐ Chinese medicine practice
- ☐ Multidisciplinary practice
- ☐ Teaching clinic within academic institution
- ☐ Other (please specify)

4. Which system(s) of Chinese medicine do you practice? (please tick all that apply)

- ☐ Traditional Chinese medicine (TCM)
- ☐ Classical Chinese medicine
- ☐ Other (please specify)

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

5. In a typical month, how many patients with PCOS-related complaints do you treat?

- ☐ 0
☐ 1-4
☐ 5-10
☐ 11-20
☐ > 20

6. How many years have you been prescribing Chinese herbs for?

Diagnosis and treatment strategy

7. In the clinic, patients with PCOS present with:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Delayed periods (cycles longer than 35 days)	☐	☐	☐	☐	☐	☐	☐	☐
Absent periods (no period for 6 months or more)	☐	☐	☐	☐	☐	☐	☐	☐
Infertility	☐	☐	☐	☐	☐	☐	☐	☐
Painful periods	☐	☐	☐	☐	☐	☐	☐	☐
Heavy periods	☐	☐	☐	☐	☐	☐	☐	☐
Weight management issues	☐	☐	☐	☐	☐	☐	☐	☐
Acne	☐	☐	☐	☐	☐	☐	☐	☐
Hirsutism (excessive facial and body hair)	☐	☐	☐	☐	☐	☐	☐	☐
Pre-menstrual syndrome (PMS)	☐	☐	☐	☐	☐	☐	☐	☐
Emotional issues	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

8. Please rate how much you agree or disagree with the statements below regarding diagnosis and treatment planning in Chinese medicine:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Chinese medicine is an integrated system of interventions and self-care measures tailored to the individual	☐	☐	☐	☐	☐	☐	☐	☐
In PCOS, knowledge of a patient's biomedical status, such as status of ovaries or testosterone levels, informs the Chinese medicine treatment	☐	☐	☐	☐	☐	☐	☐	☐
Treatments in Chinese medicine are based on pattern differentiation	☐	☐	☐	☐	☐	☐	☐	☐
In PCOS, combined excess and deficiency patterns are found	☐	☐	☐	☐	☐	☐	☐	☐
With combined excess and deficiency patterns in PCOS, Chinese medicine treatments address both simultaneously	☐	☐	☐	☐	☐	☐	☐	☐
In PCOS, treatments initially prioritise clearing excess patterns	☐	☐	☐	☐	☐	☐	☐	☐
In PCOS, when excess patterns start to clear, treatments prioritise nourishing deficiencies	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

9. The following excess patterns are found in PCOS:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Blood stasis	☐	☐	☐	☐	☐	☐	☐	☐
Liver Qi stagnation	☐	☐	☐	☐	☐	☐	☐	☐
Excess Cold in the Uterus	☐	☐	☐	☐	☐	☐	☐	☐
Stagnated Liver Heat	☐	☐	☐	☐	☐	☐	☐	☐
Phlegm Damp accumulation	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

10. The following deficiency patterns are found in PCOS:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Kidney Yin deficiency	☐	☐	☐	☐	☐	☐	☐	☐
Kidney Yang deficiency	☐	☐	☐	☐	☐	☐	☐	☐
Spleen Qi deficiency	☐	☐	☐	☐	☐	☐	☐	☐
Spleen Yang deficiency	☐	☐	☐	☐	☐	☐	☐	☐
Blood deficiency	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Treatment Provision

11. When providing Chinese medicine treatment for PCOS, the following are recommended:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Acupuncture	☐	☐	☐	☐	☐	☐	☐	☐
Chinese herbs	☐	☐	☐	☐	☐	☐	☐	☐
Dietary changes	☐	☐	☐	☐	☐	☐	☐	☐
Advice on exercise	☐	☐	☐	☐	☐	☐	☐	☐
Stress management techniques	☐	☐	☐	☐	☐	☐	☐	☐
Appropriate work-life balance	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

12. Acupuncture has the following advantages over Chinese herbs:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Provides rapid relief of pain	☐	☐	☐	☐	☐	☐	☐	☐
More effective for emotional issues	☐	☐	☐	☐	☐	☐	☐	☐
Moves Qi rapidly	☐	☐	☐	☐	☐	☐	☐	☐
Provides direction for Qi	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

13. Chinese herbs have the following advantages over acupuncture:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
More effective for hormonal conditions	☐	☐	☐	☐	☐	☐	☐	☐
More effective for chronic conditions	☐	☐	☐	☐	☐	☐	☐	☐
More effective for severe patterns of deficiency	☐	☐	☐	☐	☐	☐	☐	☐
More effective for severe patterns of excess	☐	☐	☐	☐	☐	☐	☐	☐
Can be administered more readily on a daily basis	☐	☐	☐	☐	☐	☐	☐	☐
Have a longer-lasting effect	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

14. Please rate how much you agree or disagree with the following statements regarding Chinese herbal prescribing.

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Individualised herbs are more effective than standardised herbs	☐	☐	☐	☐	☐	☐	☐	☐
Individualisation is important to adapt to the specific needs of the patient	☐	☐	☐	☐	☐	☐	☐	☐
Individualisation is important to prevent resistance to a herbal prescription	☐	☐	☐	☐	☐	☐	☐	☐
Decoctions are more effective than concentrated powders	☐	☐	☐	☐	☐	☐	☐	☐
Concentrated powders are suitably effective for PCOS	☐	☐	☐	☐	☐	☐	☐	☐
Whilst patients are actively trying to conceive, Blood stasis removing herbs are not prescribed after cycle day 14	☐	☐	☐	☐	☐	☐	☐	☐
In Blood stasis, herbs for removing Blood stasis are prescribed for use during menses	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

15. A daily prescription of concentrated powders for PCOS is:

- ☐ < 5g
- ☐ 5-10g
- ☐ 11-15g
- ☐ 16-25g

If you would like to make any further comments about this item, please use the box below

Treatment Evaluation

16. Chinese herbs are effective for the following PCOS-related symptoms:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Delayed periods (cycles longer than 35 days)	☐	☐	☐	☐	☐	☐	☐	☐
Absent periods (no period for 6 months or more)	☐	☐	☐	☐	☐	☐	☐	☐
Infertility	☐	☐	☐	☐	☐	☐	☐	☐
Painful periods	☐	☐	☐	☐	☐	☐	☐	☐
Heavy periods	☐	☐	☐	☐	☐	☐	☐	☐
Weight management issues	☐	☐	☐	☐	☐	☐	☐	☐
Acne	☐	☐	☐	☐	☐	☐	☐	☐
Hirsutism (excessive facial and body hair)	☐	☐	☐	☐	☐	☐	☐	☐
Pre-menstrual syndrome (PMS)	☐	☐	☐	☐	☐	☐	☐	☐
Emotional issues	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

17. In PCOS, initial response to Chinese herbs is determined by assessing:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Cycle length	☐	☐	☐	☐	☐	☐	☐	☐
Period pain	☐	☐	☐	☐	☐	☐	☐	☐
Menstrual clotting	☐	☐	☐	☐	☐	☐	☐	☐
Colour of menstrual blood	☐	☐	☐	☐	☐	☐	☐	☐
Heaviness of menstrual flow	☐	☐	☐	☐	☐	☐	☐	☐
Duration of menstrual bleeding	☐	☐	☐	☐	☐	☐	☐	☐
Emotional wellbeing	☐	☐	☐	☐	☐	☐	☐	☐
Basal body temperature chart	☐	☐	☐	☐	☐	☐	☐	☐
Tongue appearance	☐	☐	☐	☐	☐	☐	☐	☐
Pulse palpation	☐	☐	☐	☐	☐	☐	☐	☐
Abdominal palpation	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

18. In PCOS, an initial response to Chinese herbs is observed:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Within 1 month	☐	☐	☐	☐	☐	☐	☐	☐
Within 3 months	☐	☐	☐	☐	☐	☐	☐	☐
Within 6 months	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Treatment Evaluation (Continued) - Final Page in Questionnaire

19. Response to Chinese herbs is slower in:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Overweight patients	☐	☐	☐	☐	☐	☐	☐	☐
Blood stasis conditions	☐	☐	☐	☐	☐	☐	☐	☐
Phlegm Damp accumulation conditions	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Chinese Herbal Medicine in the treatment of Polycystic Ovary Syndrome

20. When regulating menstruation in PCOS, a regular menstrual cycle is the observation of:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
3 consecutive menstrual cycles	☐	☐	☐	☐	☐	☐	☐	☐
Menstrual cycles, each 35 days or less in length	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

21. When prescribing Chinese herbs for delayed periods in PCOS (cycles longer than 35 days), a regular menstrual cycle is observed:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Within 6 months	☐	☐	☐	☐	☐	☐	☐	☐
Within 9 months	☐	☐	☐	☐	☐	☐	☐	☐
Within 12 months	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

22. When prescribing Chinese herbs for absent periods in PCOS (no period for 6 months or more), a regular menstrual cycle is observed:

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Within 6 months	☐	☐	☐	☐	☐	☐	☐	☐
Within 9 months	☐	☐	☐	☐	☐	☐	☐	☐
Within 12 months	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Thank you

You have now reached the end of the questionnaire - thank you for your help in answering these questions.

The responses you have given will now be analysed together with the responses given by other herbalists participating in this study. I will be in touch with feedback on your responses, which may also involve a further short questionnaire.

Thank you in the meantime for your continued participation. I look forward to being in touch with you again in the New Year.

With kind regards,

Appendix 20: Example Of Personalised Questionnaire Distributed To One Participant In Delphi Round Three

H08 Questionnaire 2: Chinese Herbal Medicine in the treatment of

An interview and questionnaire study with Chinese medical herbalists

Thank you for your responses to the initial online questionnaire.

Your responses as a group have now been collected and I am pleased to report that consensus was reached on most questionnaire items. A brief summary of these will follow shortly.

A small number of items did not reach agreement. In this questionnaire, I will present you with these items again and invite you to re-consider your original rating.

Your participation in this questionnaire is important to the research study which should take no more than 10 minutes of your time.

I appreciate your help so far on this project and hope to receive your responses soon.

Summary of Responses for Initial Questionnaire

As a group, there was strong consensus that patients with PCOS present in the clinic with the following symptoms:

- Delayed and absent periods
- Infertility
- Acne
- Hirsutism
- Issues with weight and emotions.

There was also a strong consensus about various aspects of decision-making on treatment provision and treatment evaluation. The following items are examples of items that reached strong agreement:

- Chinese medicine treatment should be based on pattern differentiation
- Knowledge of a patient's biomedical status informs Chinese medicine treatment
- Response to herbs is slower in patients who are overweight and in those with Phlegm dampness conditions
- In PCOS, a treatment duration of 6 months is suitable for regulating menses.

Item 1: Invitation to reconsider rating

1. I would now like to invite you to reconsider the following item:

'In PCOS, treatments initially prioritise clearing excess patterns.'

The combined group rating was 'Neither agree nor disagree'. This means that, as a group, there was equal strength in agreement and disagreement in this statement.

You rated this 'Neither agree nor disagree'.

Would you like to amend your answer?

☐ Yes

☐ No

H08 Questionnaire 2: Chinese Herbal Medicine in the treatment of

Item 1: New rating

2. For your reference, the combined group rating for this item was 'Neither agree nor disagree'.

You rated this 'Neither agree nor disagree'.

Please provide your new rating below.

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
In PCOS, treatments initially prioritise clearing excess patterns	☐	☐	☐	☐	☐	☐	☐	☐

Item 2: Invitation to reconsider rating

3. Please reconsider the following item:

'Response to Chinese herbs is slower in Blood stasis conditions.'

The combined group rating was 'Neither agree nor disagree'. This means that, as a group, there was equal strength in agreement and disagreement in this statement.

You rated this 'Disagree'.

Would you like to amend your answer?

- ☐ Yes
- ☐ No

Item 2: New rating

4. For your reference, the combined group rating for this item was 'Neither agree nor disagree'.

You rated this 'Disagree'.

Please provide your new rating below.

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Response to Chinese herbs is slower in Blood stasis conditions	☐	☐	☐	☐	☐	☐	☐	☐

H08 Questionnaire 2: Chinese Herbal Medicine in the treatment of

New items: Final page of questionnaire

5. Please reconsider the following item:

‘Whilst patients are actively trying to conceive, Blood stasis removing herbs are not prescribed after CYCLE DAY 14.’

This statement has now been amended to two items - please rate how much you agree or disagree with these items below.

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
Whilst patients are actively trying to conceive, Blood stasis removing herbs are not prescribed after OVULATION	☐	☐	☐	☐	☐	☐	☐	☐
Whilst patients are actively trying to conceive AND if they have a Blood stasis condition, it is suitable to prescribe Blood stasis removing herbs after ovulation	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

6. After careful consideration of group feedback, the following items have been added. Please rate your answer to these items below.

	Strongly disagree	Disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Agree	Strongly agree	N/A
PCOS is diagnosed as a result of fertility investigations	☐	☐	☐	☐	☐	☐	☐	☐
In PCOS, CHM only ie. without acupuncture is effective	☐	☐	☐	☐	☐	☐	☐	☐
In PCOS, acupuncture only ie. without CHM is effective	☐	☐	☐	☐	☐	☐	☐	☐
In PCOS, both acupuncture and CHM are necessary to provide effective treatment	☐	☐	☐	☐	☐	☐	☐	☐

If you would like to make any further comments about these items, please use the box below

Thank you

You have now reached the end of the questionnaire - thank you for your help in answering these questions. Your continued participation is important to this study and I am grateful for your time and your help so far.

Your responses will be analysed alongside the responses given by other herbalists participating in this study. I will be in touch as soon as all the responses have been collected to provide an update and which may involve a third and final short questionnaire.

H08 Questionnaire 2: Chinese Herbal Medicine in the treatment of

Thank you again in the meantime for your continued participation. I look forward to providing you with an update soon.

With kind regards,

Lily

Appendix 21: Good Clinical Practice Guidelines For The Treatment Of Polycystic Ovary Syndrome With Chinese Herbal Medicine

Version 3 Last Updated 18/12/2012

Good Clinical Practice Guidelines for the Treatment of Polycystic Ovary Syndrome with Chinese Herbal Medicine

This clinical guideline has been developed by researchers at the University of Southampton using a practitioner-consultation exercise following the Delphi method. This guideline describes key features of good clinical practice that were developed with a panel of 11 herbalists practicing in the UK on the topic of Chinese herbal medicine (CHM) prescribing for polycystic ovary syndrome (PCOS).

For clinical practice items where consensus has been sought, these have been graded as follows:

A = Strong consensus; B = Good consensus; C = Weak consensus; D = No consensus

For clinical practice items where formal consensus was not sought and which describe a range of opinions, these have been summarised and graded 'NA'.

Chinese medicine (CM) here includes acupuncture, Chinese herbal medicine, moxibustion and tuina.

Clinical Practice Items	Consensus
1. Clinical Presentation	
1.1. In the clinic, patients with PCOS present with one or more of the following signs and symptoms:	
1.1.1. Delayed periods (cycles longer than 35 days)	A
1.1.2. Absent periods (no period for 6 months or more)	A
1.1.3. Infertility	A
1.1.4. Acne	A
1.1.5. Hirsutism (excessive facial and body hair)	A
1.1.6. Pre-menstrual syndrome (PMS)	A
1.1.7. Emotional issues	A
1.1.8. Weight management issues	A
1.1.9. Heavy periods	B
1.1.10. Painful periods	C
1.2. PCOS is diagnosed as a result of fertility investigations	C
2. Chinese Medicine Diagnosis	
2.1. Treatments in Chinese medicine are based on pattern differentiation	A
2.2. In PCOS, combined excess and deficiency patterns are found	A
2.3. In PCOS, knowledge of a patient's biomedical status, such as status of ovaries or testosterone levels, informs the Chinese medicine treatment	A
2.4. The following excess patterns are found in PCOS:	
2.4.1. Phlegm Damp accumulation	A
2.4.2. Blood stasis	A
2.4.3. Liver Qi stagnation	A
2.4.4. Excess Cold in the Uterus	A
2.4.5. Stagnated Liver Heat	A
2.5. The following deficiency patterns are found in PCOS:	

2.5.1. Kidney Yang deficiency	A
2.5.2. Spleen Qi deficiency	A
2.5.3. Spleen Yang deficiency	A
2.5.4. Blood deficiency	B
2.5.5. Kidney Yin deficiency	C

3. Chinese Medicine Treatment Strategy

3.1. Chinese medicine is an integrated system of interventions and self-care measures tailored to the individual	A
3.2. With combined excess and deficiency patterns in PCOS, Chinese medicine treatments should address both simultaneously	A
3.3. In PCOS, when excess patterns start to clear, treatments should prioritise nourishing deficiencies	A
3.4. In PCOS, treatments should initially prioritise clearing excess patterns	D

4. Chinese Medicine Interventions Planning

4.1. When providing Chinese medicine treatment for PCOS, one or more of the following are recommended:	
4.1.1. Chinese herbs	A
4.1.2. Acupuncture	A
4.1.3. Stress management techniques	A
4.1.4. Dietary changes	A
4.1.5. Appropriate work-life balance	A
4.1.6. Advice on exercise	A
4.2. Chinese herbs have the following advantages over acupuncture:	
4.2.1. More effective for chronic conditions	A
4.2.2. More effective for severe patterns of deficiency	A
4.2.3. Have a longer-lasting effect	A
4.2.4. More effective for hormonal conditions	A
4.2.5. More effective for severe patterns of excess	A
4.2.6. Can be administered more readily on a daily basis	A
4.3. Acupuncture has the following advantages over Chinese herbs:	
4.3.1. Provides rapid relief of pain	A
4.3.2. Moves Qi rapidly	A
4.3.3. More effective for emotional issues	B
4.3.4. Provides direction for Qi	B
4.4. In PCOS, CHM only i.e. without acupuncture is effective	A
4.5. In PCOS, both acupuncture and CHM are necessary to provide effective treatment	B
4.6. In PCOS, acupuncture only i.e. without CHM is effective	D

5. Chinese Herbal Intervention Planning		
5.1. Decoctions are more effective than concentrated powders		A
5.2. Concentrated powders are suitably effective for PCOS		A
5.3. Individualised herbs are more effective than standardised herbs		A
5.4. Individualisation is important:		
5.4.1. To adapt to the specific needs of the patient		A
5.4.2. To prevent resistance to a herbal prescription		C
5.5. In Blood stasis, herbs for removing Blood stasis should be prescribed for use during menses		A
5.6. Whilst patients are actively trying to conceive:		
5.6.1. Blood stasis removing herbs should not be prescribed after ovulation		B
5.6.2. It is suitable to prescribe Blood stasis removing herbs after ovulation, IF patients also present with a Blood stasis condition		A
5.7. The prescribed daily dosage range of concentrated powders is 5g to 25g		NA
5.8. The most frequently prescribed daily dosage range of concentrated powders is 5g to 15g.		NA
6. Treatment Assessment and Evaluation		
6.1. Chinese herbs are effective for the following PCOS-related symptoms:		
6.1.1. Delayed periods (cycles longer than 35 days)		A
6.1.2. Infertility		A
6.1.3. Absent periods (no period for 6 months or more)		A
6.1.4. Heavy periods		A
6.1.5. Pre-menstrual syndrome (PMS)		A
6.1.6. Acne		A
6.1.7. Hirsutism (excessive facial and body hair)		A
6.1.8. Painful periods		A
6.1.9. Emotional issues		A
6.1.10. Weight management issues		B
6.2. In PCOS, initial response to Chinese herbs is determined by assessing one or more of the following:		
6.2.1. Cycle lengths		A
6.2.2. Heaviness of menstrual flow		A
6.2.3. Duration of menstrual bleeding		A
6.2.4. Menstrual clotting		A
6.2.5. Period pain		A
6.2.6. Colour of menstrual blood		A
6.2.7. Pulse palpation		A
6.2.8. Basal body temperature chart		A

Version 3 Last Updated 18/12/2012

6.2.9. Emotional wellbeing	B
6.2.10. Abdominal palpation	B
6.2.11. Tongue appearance	B
6.3. Response to Chinese herbs is slower in:	
6.3.1. Phlegm Damp accumulation conditions	A
6.3.2. Overweight patients	B
6.3.3. Blood stasis conditions	D
6.4. When regulating menstruation in PCOS, a regular menstrual cycle is the observation of 3 consecutive menstrual cycles, each 35 days or less in length	A
6.5. In PCOS, an initial response to Chinese herbs is observed within 3 months	A
6.6. When prescribing Chinese herbs for delayed periods in PCOS (cycles longer than 35 days), a regular menstrual cycle is observed within 6 months	A
6.7. When prescribing Chinese herbs for absent periods in PCOS (no period for 6 months or more), a regular menstrual cycle is observed within 9 months	A

Appendix 22: Revised Protocol For ORCHID Study

The ORCHID study: Polycystic Ovary Syndrome: A Randomised feasibility and pilot study using Chinese Herbal medicine to explore Impact on Dysfunction

Protocol Title Page and Contact List

Protocol Description

The ORCHID study: A feasibility and pilot, randomised study comparing the effects of standardised Chinese herbal medicine and individualised Chinese herbal medicine for polycystic ovary syndrome in England.

Protocol Reference: Version 4

Date Last Updated: 5th November 2012

Study Sponsor and Monitor

Name: Emma Farrant

Company Name: Register of Chinese Herbal Medicine

Address: 1 Exeter Street
Norwich
NR2 4QB

Email: emma.farrant@virgin.net

Telephone: 01603 623 994

Fax: 01603 667 557

Funding

The principal investigator's position is supported by a research training fellowship awarded by the National Institute for Health Research as part of the National School for Primary Care Research. Otherwise, this study has received no other funding.

Support

The Chinese herbal medicinal (CHM) products for this study have been provided at a discounted rate by a UK distributor, Phoenix Medical Direct Limited, who is a registered supplier on the Register of Chinese Herbal Medicine's Approved Suppliers List.

Conflicts of Interest

Lily Lai is a registered CHM practitioner in the UK and declares no other potential conflicts of interest. Dr. Andrew Flower is a registered CHM practitioner in the UK, currently holds a research fellowship position with the National Institute for Health Research to investigate the use of CHM in primary care and declares no other potential conflicts of interest. Professor George Lewith and Dr. Michael Moore declare no conflicts of interest.

Names of Investigators

Principal Investigator	Miss Lily Lai	LYWL1G10@soton.ac.uk
Co-Investigators	Professor George Lewith	GL3@soton.ac.uk
	Dr Michael Moore	mvm198@soton.ac.uk
	Dr Andrew Flower	flower.power@which.net

Study Sites

Type of study site	Address
Study clinic (Hertfordshire)	The Treatment Rooms Berkhamsted Sports Centre Lagley Meadow Douglas Gardens Berkhamsted Hertfordshire HP4 3PE
Study clinic (Hertfordshire)	Revive Sports Rehabilitation & Acupuncture Clinic 106a London Road Apsley Hemel Hempstead Hertfordshire HP3 9EW
Study clinic (London)	The White Crane Clinic 13 St George's Mews Primrose Hill London NW1 8XE
Study clinic (London)	The Women's Health Natural Practice The Glasshouse River Lane Richmond Surrey TW10 7AG

Study clinic on standby (Essex)	Phoenix Acupuncture and Herbal Clinic Phoenix House 41 Beehive Lane Chelmsford Essex CM2 9TQ
Study dispensary	Phoenix Medical Direct Phoenix House 41 Beehive Lane Chelmsford Essex CM2 9TQ

Study medical representatives

Name: Professor George Lewith
 Title: Medical doctor and professor of health research
 Role: Primary medical representative
 Address: Complementary and Integrated Medicine Research Unit
 Primary Care and Population Sciences
 University of Southampton
 Aldermoor Health Centre
 Aldermoor Close
 SO16 5ST
 Email: GL3@soton.ac.uk
 Telephone: +44 (0) 23 8024 1073

Name: Dr. Michael Moore
 Title: Medical doctor and reader in health research
 Role: Secondary medical representative
 Address: Primary Care and Population Sciences
 University of Southampton
 Aldermoor Health Centre
 Aldermoor Close
 SO16 5ST
 Email: mvm198@soton.ac.uk
 Telephone: +44 (0) 23 8024 1056

Other medical, technical departments or institutions involved

Name: George He
 Title: Director of UK distributing company for Chinese herbal medicine
 Company: Phoenix Medical Direct
 Role: Chinese herbal medicine dispensing and storage site
 Address: Phoenix House
 41 Beehive Lane
 Chelmsford

Essex

CM2 9TQ

Email: george.he@phoenixmd.co.uk

Telephone: +44 (0) 1245 350 822

0800 6128 188

Fax : +44 (0) 1245 267 001

Name: Philip Prescott

Title: Medical statistician

Company: University of Southampton

Role: Design and conduct the randomisation procedures and statistical analysis

Address: Complementary and Integrated Medicine Research Unit

Primary Care and Population Sciences

University of Southampton

Alder Moor Health Centre

Alder Moor Close

SO16 5ST

Email: P.Prescott@soton.ac.uk

Name: Ms JieHua (Jessica) Zhang

Title: Business supporting manager, marketing department

Company: Jiangyin Tianjiang Pharmaceutical Company Limited

Role: Contact for manufacturer in case of queries relating to product manufacture

Address: No. 8, Qin Wang Shan Road, Economic Development Zone, Jiang Yin

City, Wu Xi, Jiang Su Province, China 214434

Website: www.tianjiang.com

Email: zhangjh@tianjiang.com

Telephone: +86 (0) 510 8640 8692

Fax: +86 (0) 510 8640 0199

Name: Dr. Martina Prude

Title: Head of Research Governance

Company: University of Southampton

Role: Oversees university insurance issues

Address: Research Governance Office
George Thomas Building 37
Room 4055
University of Southampton
Highfield
Southampton
SO17 1BJ

Email: M.A.Prude@soton.ac.uk

Telephone: 023 8059 8848

Fax: 023 8059 5781

Name: Dr. Trevor Wing

Title: Practitioner of Chinese herbal medicine and acupuncture

Company : The Women's Natural Health Practice

Role: Study practitioner

Address: The Glasshouse
River Lane
Richmond
Surrey
TW10 7AG

Email: trevor@naturalgynae.com

Telephone: 0845 688 5270

Website: www.naturalgynae.com

Name: Bruno Miguel

Title: Practitioner of Chinese herbal medicine and acupuncture

Company : Phoenix Acupuncture and Herbal Clinic

Role: Study practitioner on standby

Address: Phoenix House
41 Beehive Lane
Chelmsford
Essex
CM2 9TQ

Email: bruno@phoenixmd.co.uk

Telephone: 01245 350 822

Website: phoenixchinesemedicalcentre.com

Name: Andrew Flower

Title: Practitioner of Chinese herbal medicine and acupuncture

Company : White Crane Clinic

Role: Study practitioner on standby

Address: The White Crane Clinic

13 St George's Mews

Primrose Hill

London

NW1 8XE

Email: flower.power@which.net

Telephone: 0207 586 6639

Website: www.whitecraneclinic.co.uk

Peer reviewers

We are grateful for the feedback and comments provided by our peer reviewers:

Name: Dr. Beth Stuart

Title: Medical statistician specializing in Primary Medical Care statistics

Name: Dr. Caroline Eyles

Title: Postdoctoral researcher with expertise in qualitative research methods, complex interventions and feasibility study design

Name: Mr Martin Logue

Title: Lecturer and practitioner of Chinese herbal medicine and acupuncture, research supervisor of herbal medicine

List of Abbreviations and Definitions

Adverse Reaction (AR)

All noxious and unintended responses to a medicinal product related to any dose where a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Blinding

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Chinese Herbal Medicine (CHM)

Herbs prescribed for medicinal purposes, identified within the Chinese pharmacopoeia and that includes crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts. CHM may be entire, fragmented, powdered or granulated.

Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality

Prevention of disclosure, to other than authorised individuals, of a sponsor's proprietary information or of a subject's identity.

Co-Investigator (Co-I)

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multi-centre trial.

Consent Form

A written record of the study participant's decision to take part in the research study.

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Finished herbal products

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished

products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team.

Multi-centre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Participant

An individual who participates in a clinical trial as a recipient of any trial intervention administered.

Participant Identification Number

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Participant Information Sheet

A form appropriate for the study population, explaining what the research involves and how the research study will affect the participant.

Principal Investigator (PI)

An individual who has primary responsibility for the design, execution, and management of a research project and who will be involved in the project in a significant manner.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Research Ethics Committee (REC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Research Ethics Committees may differ among countries, but should allow the Research Ethics Committee to act in agreement with GCP as described in this guideline.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor

An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Study Site

The location(s) where study-related activities are conducted. In this protocol, this includes the clinics where consultations and assessments will take place and the herbal dispensary where herbal prescriptions will be compiled.

Study Site Team

In this protocol, this is the group of individuals at each study site who are delegated study-related duties.

Study Team

This is defined in this protocol to include the investigators and named individuals who are delegated study-related duties.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the product information.

The above list of abbreviations and definitions have been adapted from the European Medicines Agency's ICH Topic E6 (R1) Guideline for Good Clinical Practice (July 2002) and the World Health Organisation's General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine (2000).

1. Introduction

1.1. Background

Polycystic ovary syndrome (PCOS) is recognised as the most common female endocrine disorder, affecting an estimated 6-18% of women of reproductive age (Asuncion et al., 2000, March et al., 2010). PCOS is a heterogeneous disorder characterised by menstrual irregularities, polycystic ovaries, infertility, hirsutism and abdominal obesity (Ehrmann, 2005).

PCOS accounts for 73% of women presenting with oligomenorrhoea or amenorrhoea and is the leading cause of anovulatory infertility (Hull, 1987). Women with PCOS presenting with menstrual irregularities have been associated with an increased risk of developing type II diabetes and metabolic disorder compared with women with PCOS without menstrual irregularities (Moran and Teede, 2009). In addition, these women may be more likely to require assisted reproductive treatments (ARTs), are more likely to demonstrate a reduced response rate to such ARTs and may be at risk of developing endometrial carcinoma (Imani et al., 2002, Balen, 2001). Regulating menstruation at an early stage is therefore an important strategy in PCOS to improve both metabolic and reproductive outcomes as well as to reduce potential cancer risk.

Whilst the precise cause of PCOS is unknown, it is believed to involve a complex interaction between excessive levels of androgens and of insulin (Barbieri et al., 1986, Dunaif, 1997). As a result, mainstream care typically addresses these pathological processes to regulate menses and features a variety of pharmaceutical and self-care measures such as combined oral contraceptives and insulin-sensitising agents. However, combined oral contraceptives have been linked with increased cardiovascular and metabolic risks, raising concerns regarding its suitability for use amongst a population already at risk (Nader et al., 1997, Dahlgren et al., 1998, Wild et al., 2000, Morin-Papunen et al., 2000). Several studies have suggested that metformin, the most frequently prescribed insulin-sensitising agent for PCOS, is associated with increased gastrointestinal side-effects and that adherence rates to

metformin are poor, raising questions regarding its overall effectiveness (Fleming et al., 2002, Donnan et al., 2002, Grant et al., 2003, Legro et al., 2007). Furthermore negative feelings of frustration and anxiety are frequently associated with diagnosis of PCOS and usual management of PCOS with pharmacological interventions such as oral contraceptives are deemed unsatisfactory by patients (Sills et al., 2001). This highlights a number of issues and barriers that women can experience as part of mainstream management of their condition and a subsequent need to explore other treatments that may be more acceptable and more effective for women with PCOS.

Interest has emerged regarding the use of Chinese herbal medicines (CHM) for PCOS which has been historically effective for menstrual irregularities such as those found in PCOS (Raja-Khan et al., 2011). A recent Cochrane review on CHM and subfertility in PCOS concluded that there is evidence to suggest an added benefit of using CHM alongside clomiphene for improving clinical pregnancy rates when compared with monotherapy, i.e. CHM alone or clomiphene alone (Zhang et al., 2010a). Basic science studies also suggest that Chinese herbs can be effective against PCOS by improving insulin sensitivity, reducing testosterone levels and correcting hypothalamic-pituitary-ovarian axis (Wang et al., 2009, Hui et al., 2009, Wu et al., 2007, Geng et al., 2010). Furthermore, women with PCOS are reportedly supportive of seeking safe and effective alternative treatments to birth control pills and fertility drugs (Sills et al., 2001). Further rigorous research in CHM using designs such as randomised controlled trials (RCTs) is thus warranted in order that we can further investigate the potential CHM has for PCOS and to close such evidence gaps by providing a stronger evidence-base to inform clinical decision-making.

This study team initially proposed to conduct an RCT to investigate the effects of the following three parallel groups on PCOS-related oligomenorrhoea and amenorrhoea – CHM plus usual care, placebo plus usual care and usual care only. This design would have enabled a comparison be made of specific effects (CHM vs placebo), contextual effects (placebo vs usual care) and real-world effects (CHM vs usual care). This protocol was initially developed by the study team and had involved extensive consultation with the regulatory authorities and with CHM manufacturers and UK distributors. However, this project had proved extremely difficult to set up due to the information that

was legally required for clinical trials approval to be granted by the Medicines and Healthcare Products Regulatory Agency (MHRA), and the amount of information that was subsequently required of the CHM supplier. This helped the study team to identify a number of key issues when conducting CHM research in the UK and it is for these reasons that the study team now propose instead to conduct a feasibility and pilot study to investigate the effects of CHM on oligomenorrhoea and amenorrhoea in PCOS.

Feasibility and pilot studies are recognised as important research designs as part of the MRC complex interventions research framework and are typically adopted to gather valuable information for planning resources and reducing uncertainties for a full-scale trial (MRC, 2000, Lancaster et al., 2004, Craig et al., 2008, Arain et al., 2010, Thabane et al., 2010). This is especially relevant when conducting a CHM trial in England for a number of reasons. Whilst prevalence of herbal medicine use remains high, CHM has suffered a tarnished public image in recent years owing to adverse media reports on its safety and it is unclear how this may affect the acceptability of the intervention to patients (Hunt et al., 2010). Whilst a small number of CHM RCTs have been conducted in England (Sheehan et al., 1995, Flower et al., 2009), none have recruited specifically from a PCOS population and it is unclear how successful recruitment to such a trial would be. Furthermore, and as the study team has already experienced, trials of complimentary medical interventions and in particular trials conducted in NHS settings such as primary care require specific practical considerations (van der Windt et al., 2000, Fransen et al., 2007, Bell-Syer et al., 2008). Owing to these uncertainties involved in planning a definitive trial and the difficulties experienced by the study team of setting up such a study, initial investigation using a feasibility pilot study design is warranted. This will enable important preliminary data be gathered regarding the study's feasibility and will enable the study team to pilot the study techniques.

1.2. Feasibility and Main Study Research Questions

1.2.1. Main study research question

It is important to provide context as to what this study team plans to investigate in a definitive main study in order to justify subsequent feasibility research questions in this present study.

In the main study, the primary research question will be:

- 5) Is CHM plus usual care more effective than usual care alone for oligomenorrhoea and amenorrhoea in PCOS?

The main study secondary research questions will be:

- 6) Does CHM reduce obesity or hirsutism in PCOS?
- 7) Does CHM improve quality of life in PCOS?
- 8) Is CHM safe?

1.2.2. Feasibility study research question

For this present study and in order to provide further information for the main study, the primary feasibility question:

- 1) Is oligomenorrhoea and amenorrhoea appropriate as the primary outcome measure for the main study?

Secondary feasibility questions:

- 2) Are other measures more appropriate for investigation as the primary outcome measure for the main study?
- 3) What is the safety profile of CHM?
- 4) How should the CHM intervention in the main study be delivered?
- 5) Can a double-blind, randomised trial with CHM for PCOS be conducted?

1.3. Study Design and Rationale

To answer the above feasibility questions, it is proposed that a prospective service evaluation is conducted with nested randomised, parallel-group and double-blind components.

This study will be conducted in UK private practices whereby participants will be randomised to one of two treatment groups: individualised CHM plus usual care and standardised CHM plus usual care. Usual care is defined here as usual conventional medical and pharmacological treatments typically prescribed for regulating menstruation in PCOS. This includes interventions such as oral contraceptives e.g.. Diane 35, insulin-sensitising agents e.g. Metformin, anti-androgens e.g. Spironolactone and weight loss interventions featuring exercise and dietary regimens. These usual care interventions for regulating menstruation will be accepted during this study provided they have

been used for 6 months or longer prior to the study. This will be checked at baseline and throughout the study during assessments to ensure that effects at the end of the study can be attributed to the prescribed CHM interventions. Further information regarding permitted and prohibited medications and interventions can be found in sections 5.10.1 Permitted medications and interventions and 5.10.2 Prohibited medications and interventions.

Both individualised CHM and standardised CHM in this study are prescribed in PCOS, though individualised CHM is typically regarded as ‘gold-standard’ practice. This study team wishes to explore effects of both for PCOS and this study will therefore involve comparing two types of CHM interventions used alongside usual care.

This study will be recording the effects and details of CHM treatments that are prescribed as part of routine practice in the UK and will therefore act in part as a service evaluation of routine CHM practice. Importantly and as part of this service evaluation, safety data will be gathered prospectively and which will contribute towards the preliminary body of safety data that has emerged from other CHM RCTs conducted in recent years (Bensoussan et al., 1998, Flower et al., 2009, Lechner et al., 2011). Whilst it is acknowledged that this feasibility study will not be appropriately powered to detect clinically meaningful differences that could exist between these two groups, the purpose of this study is to obtain preliminary scientific and process data to inform the design of the CHM intervention(s) for a definitive main study. The service evaluation aspect of this study design will therefore help provide information to satisfy the above-specified feasibility questions 1-4.

Feasibility question 5 relates to piloting and evaluating the conduct of elements and collaborators of a CHM RCT. To meet this purpose, the study will be a multi-centre, parallel-group, randomised, patient-blind and practitioner-blind design. This will enable an evaluation be made of certain components of the usual RCT design such as recruitment and consent rates, acceptability of the randomisation process, of study assessments and recording outcome measures. Patient and practitioner blinding will enable the study team to control for participant expectation effects and of practitioner attention effects and an evaluation of the security of blinding will be conducted

(Paterson and Dieppe, 2005). Study processes such as the study visits, data collection and the involvement of collaborators as study practitioners and CHM dispensaries will also be piloted. These components within the study design will therefore help assess whether and how an RCT involving CHM can be conducted within the targeted population in the UK.

The following sections will provide in detail the specific methods that will be used in the study and with full justification where appropriate.

2. Study Objectives and Endpoints

Following recently published recommendations for the reporting of pilot studies, study objectives and endpoints where relevant will now be detailed with clear rationale provided in terms of how this data will inform a definitive study (Thabane et al., 2010).

It is acknowledged that definitive feasibility ‘criteria’ can be useful and which has been recommended in some publications (Thabane et al., 2010). However, it would be difficult to make a truly relevant assessment of feasibility when the resources at this study team’s disposal for the main study have not yet been defined and when feasibility could be improved upon with relatively minor amendments to study procedures. For this reason, feasibility criteria have not been presented in this protocol. The end-of-study report(s) will instead document information gathered from the primary and secondary objectives outlined below and, where applicable, present comments and suggestions for changes could be made to improve feasibility.

2.1. Feasibility study objectives and endpoints

A table summarising the below primary and secondary objectives and endpoints can be seen in Appendix 24.

2.1.1. Primary Objective and Endpoints

The primary objective of this feasibility study is to assess the suitability of oligomenorrhoea and amenorrhoea as the primary outcome measure for the

main study and to provide scientific data to enable a sample size calculation to be made. This objective will be met by obtaining the following scientific and process data:

- Is CHM effective for regulating periods in PCOS?
 - Treatment effects in menstrual frequency and variability of cycle length, calculated from recording the mean and standard deviation of the number of days between menses during the 6-month treatment period and during the final 3 months of the treatment period. This is because some herbalists in our earlier consensus study expressed views that menstruation may not improve until after 3 months of treatment whilst others felt an improvement within the first month was possible. By analysing menstrual cycle data collected during the 6-month treatment period and that collected during the final 3 months, we will be able to conduct an exploratory analysis and choose an appropriate measurement for the main study. An improvement due to treatment in this study is determined as a reduction from baseline in standard deviation to reflect stability in the variability of cycle length, and a reduction from baseline in the mean number of days between menses towards a 21-35 days interval which is clinically accepted as a regular cycle length. This analysis will be conducted for between-group and within-patient comparisons before and after treatment.
- Can menstrual data be obtained?
 - Percentage of missing menstrual data, which is aimed to be collected at baseline as recall data for at least 6 months, and at the end of the treatment period at 6 months.
- Is regulating menses important to women with PCOS?
 - Ranking of oligomenorrhoea and amenorrhoea amongst self-reported symptoms that are important to women with PCOS recorded in the questionnaire Measure Yourself Medical Outcome Profile (MYMOP) (Paterson, 1996), a copy of which is found in Appendix 50. Where available, relevant data will be extracted from end-of-study participant feedback questionnaires which can be viewed in Appendix 54.

2.1.2. Secondary Objectives and Endpoints

The secondary objectives of this feasibility pilot study are:

- 3 To explore other measures that may be more appropriate for investigation by looking at:
 - Frequency and rank order of self-reported symptoms regarded as being of importance to women with PCOS which will be recorded in MYMOP;
 - Relevant data provided from end-of-study participant feedback questionnaires;
 - Treatment effects at 6 months by obtaining point estimates and variance in the following:

- Body mass index (BMI) and classified according to WHO cut-off points for normal range (18.50 – 24.99), overweight (25 – 29.99) and obese (≥ 30);
- Weight (kg) where a clinically significant loss in weight for overweight and obese patients is determined as a loss of $\geq 5\%$ of initial weight (Moran et al., 2010);
- Waist circumference, classified following WHO cut-off points for increased risk of metabolic complications ($>80\text{cm}$), or substantially increased risk of metabolic complications ($>88\text{cm}$) (2008);
- Waist hip ratio, classified following WHO cut-off points for substantially increased risk of metabolic complications (≥ 0.85) (2008);
- Hirsutism using modified Ferriman-Gallwey (mFG) score, where a score of ≥ 6 signifies hirsutism (Yildiz et al., 2010). This questionnaire can be found in Appendix 51;
- Polycystic ovary syndrome questionnaire (PCOSQ) for health-related quality of life, where a minimally important difference in the score of 0.5 on the 1 to 7 scale represents the smallest change in score that women feel is important in their daily lives (Cronin et al., 1998);
- Dermatology Life Quality Index (DLQI), a dermatology-specific quality of life measure owing to dermatological complaints such as acne that are frequently found in PCOS but the impact of which are not covered in PCOSQ. This questionnaire is available in Appendix 49. The minimal important difference for general skin conditions is a change in DLQI score of ≥ 3.2 points (Finlay and Khan, 1994, Basra et al., 2008). An observer-assessment of acne will not be conducted since there is currently no agreed standard or reliable method of acne assessment;
- Measure Your Medical Outcome Profile (MYMOP) where the minimal important difference for the change in score is 1.0 (Paterson, 1996, Guyatt et al., 1998).

4 To evaluate the safety and tolerance of CHM:

- Number, nature, severity, seriousness and expectedness of adverse and serious adverse events arising which have been assessed as being possibly related to CHM use for all participants in the study and by treatment group;
- Exploration of Chinese medical diagnoses as a covariate when examining frequency and seriousness of adverse events;
- Relevant data from end-of-study participant feedback questionnaires.

5 To evaluate the feasibility of conducting a double-blind, randomised trial with CHM for PCOS;

- Eligibility rate from those responding to recruitment methods, and to assess reasons for ineligibility which will help evaluate the restrictiveness of eligibility criteria;

- Percentage of participants requiring further assessment in order to confirm diagnosis of PCOS and breakdown of type of assessment required e.g. ultrasound scan, assessment of hyperandrogenism. This will help evaluate the number of diagnosed and undiagnosed women who are recruited;
- Overall and monthly consent rate by study site and by recruitment method. This will provide useful data in terms of variation in rates based on geographical location of study sites, cost-effectiveness of recruitment methods and time lag between initiation of recruitment method to participant enrolment;
- Overall and monthly consent rate from those eligible, and assess reasons for ineligibility and those declining participation. This will help in ascertaining the overall recruitment for the duration of the study, and the initial acceptability of the study to participants after being provided information regarding the intervention and of the study procedures;
- Randomisation rate from those consenting and assess reasons for refusing randomisation. This will enable exploration of the acceptability to participants of being randomised;
- Retention rate, and withdrawal rate and numbers lost to follow-up and assess reasons for withdrawal and loss-to-follow up. This will enable an evaluation be made regarding acceptability to participants of the intervention and of the study procedures;
- Percentage of missing data by data collection method, which will enable a comparison be made of the efficiency of different methods of data collection;
- Security of practitioner-blinding by assessing Bang Blinding indices over time and between groups, which will assess the value of attempting to blind in this study design (Bang et al., 2004);
- Security of the randomisation and allocation procedures, by comparing the allocation of participants at end-of-study with the allocation list initially generated by the statistician;
- Adherence to CHM administration using observer-reported methods and self-reported measures such as the Morisky Medication Adherence Scale (MMAS-8), available in Appendix 46 (Morisky et al., 1986, Morisky et al., 2008). Reasons affecting CHM adherence will also be recorded and will provide an initial exploration of the acceptability of the CHM and of the dosing regimen;
- Adherence to the study protocol by measuring study assessment rates and compulsory and non-compulsory study visit rates, and reporting on reasons affecting assessment rates. This will allow an initial assessment be made of the feasibility of study participants being seen as would be expected in routine practice;
- Number and percentage of participants unable to continue with full and minimum study doses. Details are provided in sections 5.6 Dosing regimen and 5.7.1 Changes to CHM dosage;
- Impact on study outcomes of covariates such as baseline BMI, severity of menstrual irregularity, rationale credibility and expectancy score at baseline using the Credibility/Expectancy

Questionnaire (CEQ) which can be viewed in Appendix 53 (Deville and Borkovec, 2000);

- Number and percentage of participants providing menstrual data and assessment of self-reported accuracy;
 - Time taken for study processes such as study visits to provide data for resource planning and costing for the main study;
 - Data relevant to feasibility from end-of-study participant feedback questionnaires.
- 6 To pilot and evaluate the management of the following study components:
- Piloting of recruitment methods;
 - Piloting of eligibility screening methods;
 - Piloting of data collection methods;
 - Piloting of statistical analysis;
 - Piloting of involvement of CHM dispensary;
 - Piloting of involvement of study practitioners;
 - Evaluation of study experiences by study personnel by administering an end-of-study feedback questionnaire. This can be viewed in Appendix 55.
- 7 To determine the CHM intervention for the main study:
- Doses prescribed of individual herbs to enable a preliminary exploration of dose-response and of safe-dosing parameters. A definitive evaluation of this will not be attempted since different doses of CHM will not be prospectively prescribed as part of this feasibility study;
 - Frequency and rank order of individual CHM prescribed in individualised prescriptions, to enable a list of individual herbs and CHM combinations be collated;
 - Frequency and rank order of diagnoses of participants in the study, to enable a list of the most frequently observed diagnoses be collated;
 - Content of additional lifestyle and dietary advice that is typically offered within a CHM consultation for PCOS;
 - Data relevant to the choice of CHM intervention from end-of-study participant feedback questionnaires.

3. Study Population

3.1. Number of Participants

In order to obtain sufficient data to provide an estimate of treatment effect and variance of this estimate of treatment effect, this feasibility study requires a sample size of 40. Further information can be found in the later section 7.1

Sample Size Calculation

3.2. Inclusion criteria

Participants will be eligible for the study if they satisfy the following criteria:

4. Female aged 18-44, considered reproductive age during which menstrual cycles are sufficiently stable following onset of menarche and prior to menopause;
5. Present with oligomenorrhoea, defined as intervals between periods of > 35 days and <200 days, or with amenorrhoea, defined as intervals between periods $\geq$ 200 days, following recently published ESHRE/ASRM guidance (Fauser et al., 2012);
6. Diagnosed with PCOS consistent with the Rotterdam criteria which can be viewed in Appendix 25 (2004).

3.3. Exclusion criteria

Participants will be excluded if they:

13. Suffer from other causes of hyperandrogenism and menstrual irregularities such as acromegaly, congenital adrenal hyperplasia, androgen-secreting tumours of the ovary or adrenal gland, Cushing's syndrome, exogenous androgens, genetic defects in insulin action, primary hypothalamic amenorrhoea, primary ovarian failure, prolactin disorders and thyroid disease (2004);
14. Are pregnant, or suspected to be pregnant since the safety of CHM during pregnancy has not been confirmed;
15. Are breastfeeding within 6 months of study start date since this could influence study outcome measures;
16. Are receiving treatment that is prohibited for use within 6 months of the study start date as detailed in 5.10.2 Prohibited medications and interventions, that could influence the study outcome measures;
17. Are receiving prohibited medications, CHM and Western herbal medicines that could influence the study outcome measures or interact with the study medications as detailed in 5.10.2 Prohibited medications and interventions;
18. Have a history of liver or kidney pathologies such as cirrhosis, glomerulonephritis, pyelonephritis as a precautionary safety measure;
19. Have a history of psychotic illness, by asking potential participants whether they have ever had a psychotic illness such as schizophrenia, have ever seen a psychiatrist, or have ever been diagnosed with an eating disorder or hospitalised for a mental-health related incident. This is important owing to questionnaires being used as part of outcomes assessments which rely on the participant being emotionally and mentally stable in order for results to remain valid.
20. Have major depression, by asking potential participants whether they are currently depressed. If participants answer yes to this question, they will then be screened with the Patient Health Questionnaire (PHQ-9), where a score of 15 is indicative of moderately severe major depression. This is also important to ensure participants are emotionally and mentally stable for questionnaire results to remain valid;

21. Have a current history of harmful and hazardous drinking. This will be determined firstly by screening using the Fast Alcohol Screening Test (FAST) where a score of 3 or more suggests a greater risk of harmful and hazardous drinking (Babor et al., 2001). If FAST screening is positive, an assessment will then be made using the Alcohol Use Disorders Identification Test (AUDIT) where a total score of 8 or more suggests hazardous and harmful alcohol use. FAST and AUDIT questionnaires can be viewed in Appendix 26 and Appendix 27 respectively. These will be used as a precautionary measure to minimise potential interactions between alcohol and the CHM product;
22. Have allergies to any one of the following common herbal ingredients that are contained within the standardised CHM product: nuts, citrus fruit peel, goji berry, licorice or cinnamon;
23. Do not have the spoken or written language skills necessary to take part. This is important since study assessments will be conducted in English and materials such as participant information sheets and questionnaires will only be available in English. This is owing to funding and other issues relating to limited resources at the study team's disposal;
24. Present with abnormal liver and/or kidney function at screening, defined as whole blood alanine aminotransferase (ALT) > 60 IU/l and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² as a precautionary safety measure.

4. Participant Selection and Enrolment

4.1. Identifying Participants

As this study will be conducted in private practice, advertising for recruitment onto this study will use a variety of methods to seek both practitioner-referrals and patient self-referrals. These methods include, but not limited to, those listed below.

1. Recruitment methods direct to patients from study practitioners:
 - General email shot to current patient database, where permission has been obtained to contact such patients;
 - Study invitations direct to patients registered on clinical databases, where permission has been obtained to contact such patients;
 - Recruitment posters and plasma television advertising in the study sites and local area;
 - Social networking sites such as Facebook and Twitter;
 - Adverts and RSS feed on practice websites.
2. Recruitment methods direct to CHM practitioners to seek referrals:

- Email circulars and articles or adverts using professional organisations such as the RCHM and ATCM and their journals;
 - Advertisements from CHM suppliers using methods such as e-newsletters, email circulars and automated email responses sent to practitioners upon receiving CHM orders;
 - Advertisements on practitioner website forums;
 - Email shots to CHM practitioners known to study practitioners;
 - Presentations at conferences and other events attended by CHM practitioners.
3. Recruitment methods direct to associate practitioners to seek referrals:
- Adverts on websites and other promotional material belonging to associated colleagues;
 - Email circulars to associated practitioner regulatory bodies such as the British Acupuncture Council and the National Institute of Medical Herbalists;
 - Email shots to associate practitioners known to study practitioners and the study team.
4. Recruitment methods to the general public:
- Search engine optimised research study website containing study-related information and by using it as a platform for web-casts, blogs, RSS feeds and social networking links such as Twitter and Facebook;
 - Recruitment posters in public areas such as sports centres and community centres and local businesses;
 - Posts on discussion forums and social networking sites owned by charity organisations and patient support groups such as Verity;
 - Advertisements in newsletters of charity organisations and patient support groups such as Verity;
 - Press releases with newspapers and magazines distributed in relevant areas;
 - Presentations and web-casts to the general public, charity organisations and patient support groups.

An example of a recruitment flyer directly aimed at participants can be viewed in Appendix 28. An example of a request for practitioner referrals for potential participants can be viewed in Appendix 29. An example of the study website can be viewed in Appendix 30.

4.2. Recruitment Plan

4.2.1. Initial recruitment targets

It is estimated that a consent rate of 15% of all initial enquiries will be achieved and which has been calculated based on consent rates in a recent Swedish acupuncture RCT recruiting from a PCOS population (Jedel et al., 2011). In

order to recruit a total of 40 participants, it is therefore estimated that 270 enquiries will need to be generated from the above recruitment methods.

Recruitment will be phased to ensure study personnel are not unduly burdened at the beginning of the study and to correct for any issues in the study processes that may be identified in the initial phase of the study. For this reason, recruitment targets will be calculated according to the forecast below and according to when approvals for the study have been obtained to enable recruitment to begin.

For Month 1, recruitment target will be 3-5. Following on from this and taking into consideration seasonal availability of participants and study personnel, the recruitment targets for subsequent months will be calculated as follows:

November	December	January	February	March	April	May
5	5	5	8	10	10	10

Recruitment targets will be reviewed each month. Where targets are not met for two consecutive months, the study team will review progress of recruitment to decide upon contingency measures that may be required.

4.2.2. Contingency measures

Measures to boost recruitment will be attempted in a number of ways such as, but not limited to, the following:

1. Increasing frequency of advertisements and communications to referral groups outlined in section 4.1 Identifying Participants;
2. Adopting new study sites for current study practitioners which could be more convenient for participants, some of which are already named in the protocol as a standby study clinic;
3. Adopting new study practitioners which would enable the study to recruit from a number of geographical locations and which could also be more convenient for participants and increase the study capacity. Some of these study practitioners have already provided their consent to be named as a standby study practitioner in this protocol.

Where the above measures are adopted that include new study sites or study practitioners such as those outlined in measures 2 and 3 above, the study team will be responsible for ensuring all processes are adhered to that are outlined in this protocol. In these circumstances, the sponsor should be

notified of such changes, although permission will be not be formally required by the sponsor prior to implementation.

Consistent with procedures outlined in 12.1 Protocol amendments and where amendments to recruitment may be considered major or not adherent to the protocol, the study team will check with the sponsor to determine the requirement of submission of any protocol amendments for committee approval prior to implementation.

4.3. Screening

Screening of potential participants will be conducted in three phases to minimise demand on study resources: firstly an initial web-based screening, secondly a telephone screening interview and thirdly remaining screening criteria will be checked for at the baseline study visit.

4. Web-based screening

Women who are initially interested in the study will firstly complete a web-based screening questionnaire that will be developed specifically for this study. A copy of this questionnaire has been provided in Appendix 32.

A link to this questionnaire will be publicised to invite self-referred screening.

After women have completed and submitted the screening questionnaire, an assessment of eligibility will be made based on the information provided. Women who are not eligible will be informed of this by email. For women who remain eligible, an appropriate time for the second stage of screening via a telephone interview will be arranged.

Prior to the telephone interview, women will be provided further information regarding the study and will be emailed a study invitation letter Appendix 33, participant information sheet (PIS) (Appendix 31) and consent form (CF) (Appendix 34). The PIS and CF have both been developed in consultation with 2 patient and public involvement (PPI) representatives, further details of which can be found in section 11.4 Patient and Public Involvement (PPI).

The study invitation letter, PIS and CF that will be provided to women at this stage will be for information purposes only, and women will not be expected to return the consent form to the study team at this point. Women will be

provided with at least 24 hours between receiving information regarding the study and their telephone interview. This will provide women with sufficient time to consider what will be required of them for this study. If women are disinterested having received study information, they may opt out of the study prior to telephone screening. Women who opt out at this stage will be sent an email acknowledging their decision to decline participation and invite them to state a brief reason. Women who remain interested and who have further questions will be given the opportunity to raise these with a member of the study team during the telephone screening interview.

5. Telephone screening interview

The telephone screening interview will be conducted to reduce unnecessary visits for those clearly ineligible and to promote participant commitment to the study. This interview will ensure women meet further eligibility criteria before arranging a study visit, and to provide women with further information regarding study procedures. All reasons for ineligibility or for women declining to take part following telephone screening will be noted. Those who are found to be ineligible will be informed so during this interview.

Where a diagnosis of PCOS is not clear, women will be informed of this by the end of the screening interview and will be asked to visit a suitable healthcare professional such as a GP or gynaecologist for further assessments.

Women who remain eligible and who are otherwise satisfied with the study procedures will be invited to attend a baseline visit at the clinic of one of the study practitioners.

6. Baseline study visit

At the initial baseline visit, eligibility assessments will be completed. This will include a liver and kidney function test to check for normal baseline levels. It may also be necessary for assessments to be conducted to obtain a PCOS diagnosis as outlined above.

Following these checks, women found to be ineligible will be informed so during this visit. Those eligible will during the same visit be consented according to procedures described in the subsequent section.

An overview of the eligibility criteria that will be checked at each screening phase are presented in Table 1.

Table 1: Eligibility criteria checked at each screening phase

	Web	Telephone	Baseline visit
Inclusion criteria			
Female aged 18-44	✓	-	-
Present with oligomenorrhoea or amenorrhoea	✓	-	-
Diagnostic criteria consistent with the Rotterdam criteria	✓	✓*	✓*
Exclusion criteria			
Other causes of hyperandrogenism/menstrual irregularities	-	✓	-
Pregnant, or possibly pregnant	✓	✓*	✓*
Breastfeeding in last 6 months	✓	-	-
Checked for permitted medications and interventions	✓	✓	✓*
Checked for prohibited medications and interventions	✓	✓	✓*
History of liver/kidney pathologies	-	✓	-
History of psychotic illness	-	✓	-
Current history of major depression	-	✓	-
Current history of hazardous drinking	-	✓	-
Known allergies to standardised CHM product ingredients	-	✓	-
Not fluent in English	✓	✓	-
Abnormal liver and kidney function	-	-	✓
Study-specific criteria			
Able to visit study centre	✓	✓	✓*
Interest in taking CHM daily for up to 6 months	✓	✓	✓*
Able to make scheduled study visits	-	✓	✓*

*as necessary

4.4. Consenting Participants

Consenting procedures will comply with the definition of informed consent stated in paragraph 3(1) of Part 1 of Schedule to the regulations, implementing

Article 2(j) of the EU Directive 2001/20/EC. Conditions applying to giving of informed consent by a capable adult as per Part 3 of Schedule 1 to the Regulations implementing Article 3(2) to the EU Directive will also be adhered to. The consent form must be signed by the participant in the presence of the researcher.

4.4.1. Methods

Prior to telephone screening, women will have received study information by email. During telephone screening, an overview of the study processes will have been explained.

Following the final stages of eligibility assessment during the baseline study visit, study processes will be described in detail such as the randomisation procedure, directions for CHM administration, frequency of study assessments and visits, and completing questionnaires. By this point, women will have been informed of the nature, significance, implications and risks of the trial. They will also have been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. Women will then be offered the opportunity to ask further questions. Finally, they will be asked to provide written informed consent during this visit.

Where women are uncertain about taking part in the study, respect will be maintained at all times and they will be permitted to leave the visit to take time to consider participation further. Women will be asked to contact the study team if they choose to consent to taking part. Where the study team do not hear from women who have attended a baseline visit and not yet consented, reasonable attempts will be made to follow these women up.

4.4.2. Following consent procedure

After obtaining consent, women will be considered recruited onto the study as participants and assigned a participant ID number.

After consenting to the study, participants will be asked to consent to the study team notifying the participant's GP of study participation. Where consent is obtained, a letter will be sent to the GP providing notice of their patient

being part of a clinical study with a brief description of the nature of the study. Contact details of the study team will also be provided where enquiries can be directed. A template of this letter is provided in Appendix 35. Where consent is not obtained from the participant for GP notification, this will be documented and their GP will not be contacted. These participants will continue to remain eligible for inclusion onto the study.

4.4.3. Other consent issues

During the study where participants withdraw following process outlined in section 4.8 Withdrawal Procedures, it is possible to withdraw from the interventional aspect of the study and to permit the study team to monitor them during the remainder of the study. In these cases, consent will be asked for this limited participation.

4.5. Ineligible and Non-Recruited Participants

A record will be kept of the number of women who:

- initially express an interest in the study;
- complete web-based screening, and those who are either eligible, ineligible with reasons or decline participation with reasons;
- are sent out a study invitation letter, PIS and CF and those who choose to attend the telephone interview, or decline participation after receiving this information with reasons;
- complete telephone screening interview, and those who are either eligible, ineligible with reasons or decline participation with reasons;
- complete their baseline visit screening and those who are either eligible, ineligible with reasons or decline participation with reasons.

Following web-based screening, women who are not eligible will be informed by email. For women who are found to be ineligible during the telephone interview or at the initial baseline visit will be informed of this immediately during the interview or visit.

4.6. Randomisation

4.6.1. Sequence generation

An independent statistician will use a computer-generated random numbers table to provide an irregular block allocation sequence prior to the study. Block randomisation to either of the two groups, individualised or standardised CHM treatment, will be performed with random block sizes of 4, 6 or 8 participants to ensure equal numbers in groups and to prevent the study team

and the dispensary team from being able to predict a pattern to the randomisation. A treatment allocation ratio of 1:1 will be used with equal chance of participants being randomised to either of the two groups.

Prior to and during the study, study practitioners and members of the study team will have no knowledge of the randomisation sequence generated or of treatment allocation for each participant.

4.6.2. Allocation concealment

Allocation codes describing group allocation will be transferred to sealed opaque envelopes by the statistician and sent on to the study dispensary. The study dispensary will be asked to keep the envelopes in the order in which it was sent to them.

During the baseline visit, screening will be completed baseline outcome measures obtained. The CHM consultation will be conducted as part of the baseline visit, at the end of which an individualised CHM prescription will be written for the participant as would be expected in routine practice. This prescription and corresponding participant ID number will be forwarded onto the study dispensary.

Upon receiving the ID number of a new participant, a member of the dispensary team will open the envelope at the top, or at the front, of the pile of envelopes containing the allocation codes. Inside the envelope, information will be found regarding whether this new participant is to be allocated to individualised or standardised treatment. A note of the participant's ID number and allocated treatment group will be made, stored in a password-protected secure and centralised document and the randomisation envelope and its contents discarded. The corresponding CHM prescription will then be compiled for this participant.

For individualised treatment, the prescription provided by the study practitioner will be compiled. For the standardised group, the prescription provided by the study practitioner will be ignored by the dispensing team and instead, the pre-determined standardised prescription will be compiled. The dispensing team will be asked not to communicate any information to the

study practitioner that could allude to the treatment allocation of the participant, unless in emergency situations. In emergency situations and where appropriate, one of the study CIs should be contacted by the dispensing team for further advice.

For the remainder of the study, the named participant will stay within this allocated group and subsequent CHM prescriptions dispensed accordingly. When the study practitioner provides the CHM dispensary with the prescription for a new participant, the next envelope in the pile will be opened to determine allocation for this participant and the above procedure is then repeated.

The dispensing team will be responsible for updating the centralised document that will contain information of treatment allocation for each participant recruited onto the study. In case of emergency unblinding procedures, the study team and the dispensing team should be allowed access at all times to an updated list of participant allocation throughout the study. The final list of allocation will be downloaded at the end of the study to assist in data analysis. This final list will be checked against the original list of allocation codes to ensure allocation was performed as intended.

4.7. Temporary Discontinuation

A participant is permitted to stop the CHM treatment temporarily for reasons such as experiencing side-effects, whilst on holidays or where the study practitioner feels it clinically appropriate for the participant as per routine practice. Attempts will be made to discuss the reasons with the participant for temporary discontinuation and measures to reduce the dosage to the minimum acceptable dosage can be taken as detailed in section 5.7.1 Changes to CHM dosage

Should it be deemed necessary to stop CHM temporarily, this should be for a maximum period of 7 days each time which is considered acceptable as part of routine practice. Participants must re-enter the study at the end of this discontinuation period either on the full or reduced dosage of CHM. Study assessments should continue as initially scheduled despite temporary discontinuation.

If participants refuse to continue taking CHM following temporary discontinuation and where processes detailed in section 5.7.1 Changes to CHM dosage have been unsuccessfully conducted, participants will be considered for withdrawal from the study as outlined in the section below 4.8 Withdrawal Procedures.

4.8. Withdrawal Procedures

Participants will be withdrawn from the study either at their own request for personal reasons, or for other reasons without their consent such as:

- The participant develops serious intercurrent illness and continuing participation in the study could be harmful to the participant's health;
- The participant develops symptoms or side effects relating to the CHM product that could be harmful to the participant's health or unacceptable to the participant;
- The participant becomes pregnant during the study since the safety of administering the CHM product during pregnancy is unknown;
- The participant requires or is administered treatment that is not permitted in the study and continuing participation in the study could be harmful to the participant's health;
- The participant is found to be ineligible following enrolment, for example due to false information or misinterpretation of eligibility criteria and continuing participation in the study could be harmful to the participant's health;
- The study is terminated prematurely by the study team.

Before involuntary withdrawal, reasonable attempts will be made to address the issue(s) affecting the participant's continued participation. Study practitioners will be asked to notify the study team of any withdrawals as soon as possible.

Where the study team deem it appropriate to continue to monitor the participant for safety and other outcome measures, the participant will be asked to withdraw from the interventional aspect and to provide informed consent for this limited participation in the study. Participants who consent to being monitored for the remainder of the study will be assessed at scheduled study assessment time points where possible. Where this is not possible or not appropriate, an assessment at study close at Week 24 will be made.

Where the participant's consent for continued monitoring is not obtained, the participant will be considered withdrawn from the study.

Once the decision has been made to withdraw a participant from the study, participants will be informed that the participation in the study is being terminated and the reason(s) provided. They will be asked to attend a withdrawal visit which will involve a withdrawal discussion, collecting unused study medication and completing paperwork. It will also involve completing necessary assessments which are detailed in section 5.14 Study Assessments.

The study team will aim to record information regarding withdrawal such as:

- Specific reason for withdrawal (for voluntary withdrawals, participants will be asked for a reason but are not obligated to provide one under the ICH Good Clinical Practice guideline);
- Last day of study adherence;
- Recent adverse events and other changes in health;
- Concomitant medications and any recent changes to these;
- Amount of study medication remaining;
- Whether the blind was broken for the patient or the study practitioner at the time of withdrawal.

Where a withdrawal visit is not possible, reasonable attempts will be made to conduct the withdrawal discussion and to obtain the above information by other means such as by video-conferencing, telephone or by email.

As this is a feasibility study, participants withdrawn from this study will not be replaced. Withdrawal from the study alone does not provide sufficient grounds for unblinding. All data collected prior to the participant's withdrawal from the study will be retained and analysed as part of the study data, unless the participant specifically requests their data to be withdrawn.

4.9. Emergency Unblinding Procedures

A member of the study team, in consultation with at least one other member of the team, will assess the need for unblinding in situations such as, though not limited to, the following:

- A compelling medical need as assessed by the treating medical doctor e.g. a serious adverse event (SAE) has occurred and the treatment allocation is required to inform subsequent clinical care. Further information regarding SAEs are provided in section 8 Adverse Events and Serious Adverse Events.
- Ingestion of study products by a child;
- Ingestion of excessive amounts of study products either by the participant, or by an adult not participating in this study. Further information can be seen in section 5.9 Excessive dosing.

In case of unblinding, a member of the study team not conducting study assessments will use the participant ID number and check allocation by accessing the centralised allocation list. Upon unblinding, participant allocation and withdrawal from the study will be noted in the participant's clinical and study notes.

If possible, the sponsor will be notified before unblinding takes place. If this is not possible, the sponsor will be notified as soon as possible after this has taken place.

4.10. Lost to Follow Up

Participants will be considered lost to follow up if they:

- Fail to respond to multiple attempts by the study team to contact them regarding study assessments and visits;
- Fail to complete the formal withdrawal process as outlined in 4.8 Withdrawal Procedures.

Participants will not continue to be dispensed CHM as part of the study. The study team will continue to attempt to collect data following the processes outlined in section 6.8 Procedures for Participants Lost to Follow Up.

All data provided up to the point where participants have been lost to follow up will be retained and analysed as part of study data.

4.11. Indemnity

In the unlikely event that participants experience harm as a result of taking part in the study, all practitioners in the study possess professional indemnity insurance, which will be checked by the sponsor prior to insurance being granted for the study.

5. Study Interventions

This section will describe in detail the CHM interventions that will be involved in this study. All information presented fulfils the information required of the CONSORT statement extension to the reporting of RCTs of herbal interventions. A copy of this statement can be viewed in Appendix 37.

5.1. Duration of Study Interventions

Both the individualised and the standardised groups will be prescribed CHM for 24 weeks (6 months). This has been regarded an appropriate length of treatment to obtain sufficient information to meet this study's primary objective of examining clinical effects on regulating menstruation in PCOS. This has also been supported by CHM clinical practice guidelines that have been produced by a Delphi consensus study conducted by this research team and which sought the views of a group of experienced Chinese medical herbalists who were consulted about their views on treating PCOS with CHM. The concluding set of clinical practice guidelines can be seen in Appendix 21.

5.2. Study Assessments, Study Visits and Protocol Adherence

To be considered adherent to the protocol, participants must undergo study assessments at Weeks 0, 2, 4, 8, 12, 16, 20 and 24, totalling 8 assessments in all.

Of these study assessments, it is compulsory for the participant to physically attend a study visit at Weeks 0, 4, 8 and 12 as part of safety assessments and to check suitability of the prescription for the participant as per routine CHM practice. At Weeks 2, 16 and 20, it will be at the discretion of the study practitioner as to whether assessments take place as study visits or as remote assessments via methods such as video-conferencing, telephone or email. This is considered routine practice that adheres to RCHM Codes of Conduct.

For Week 24, attempts will be made to arrange for the participant to physically attend a study visit in order to collect end-of-study data.

These requirements are summarised in Table 2.

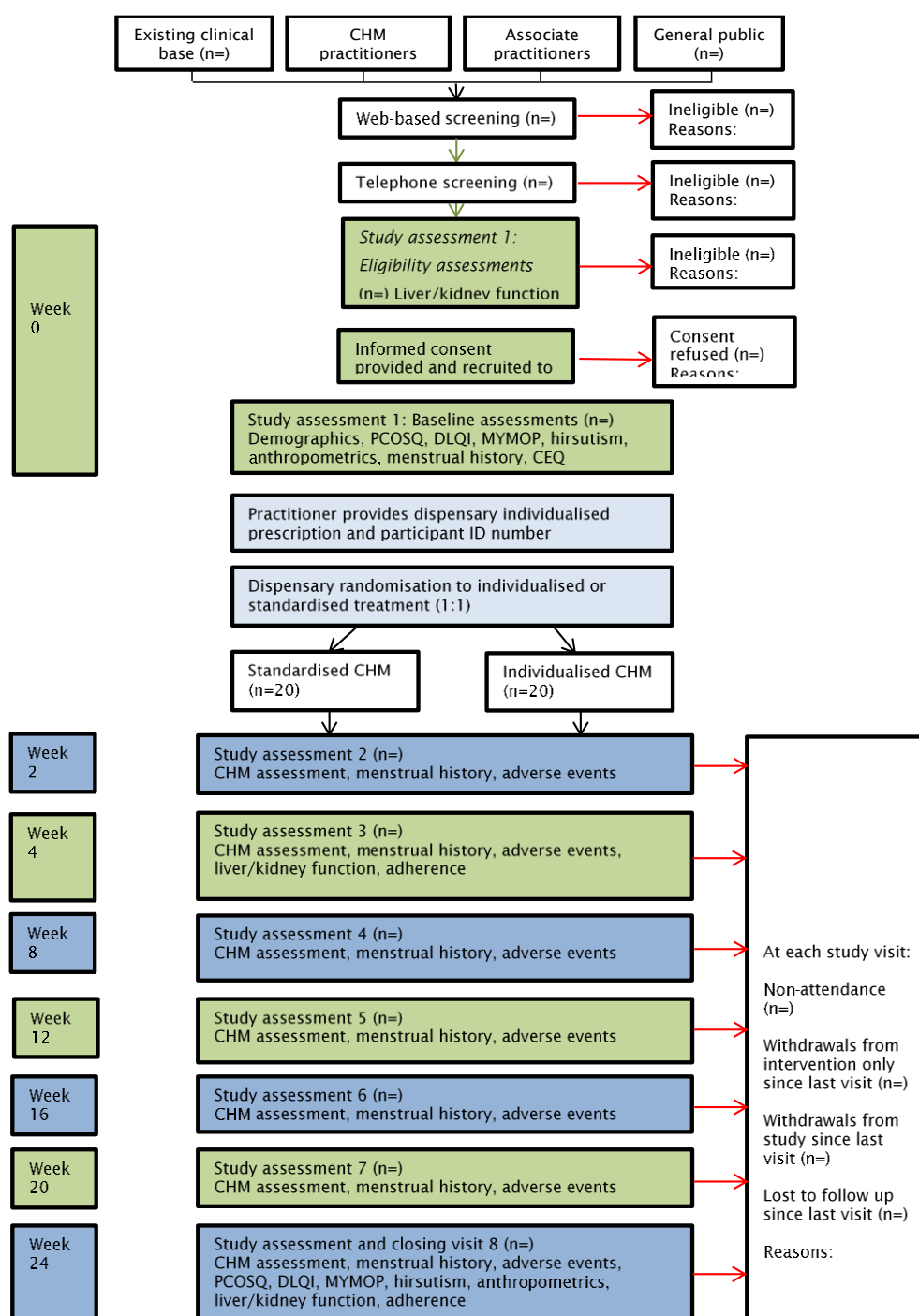
Table 2: Format of compulsory study assessments by visit or remotely

Study Assessment number	1	2	3	4	5	6	7	8	Withdrawal
Study week	0	2	4	8	12	16	20	24	
Visit/Remote	V	V/R	V	V	V	V/R	V/R	V/R	V/R

Where participants are unable to demonstrate adherence to the protocol in this manner, they will be withdrawn from the interventional aspect of the study and invited for monitoring as per procedures outlined in section 4.8 Withdrawal Procedures.

The frequency and timing of the proposed study assessments can be seen in Figure 1.

Figure 1: Overview of study procedures



5.3. Study Practitioners and Study Sites

A minimum of 5 years' of clinical experience is required of study practitioners in order to be deemed suitably experienced. All study practitioners will be registered with the RCHM and hold a valid certificate for CHM professional indemnity and public liability insurance which have been provided as supporting documentation.

It is planned for recruitment to take place from study sites in Hertfordshire and in London and which have been named in the protocol. As part of contingency recruitment measures, new study sites and new practitioners may need to be included onto the study at a later date to aid recruitment. The study team will ensure that the above requirements for study practitioners and study sites are met and that the relevant documentation is in place prior to recruitment.

5.4. Study Medications

As specified in earlier sections of the protocol, a placebo group will not be used in this study due to the information legally required for clinical trials approval to be granted by the MHRA, and the amount of information subsequently required of the CHM supplier in a timely manner as part of this study team's initial research protocol. The intervention groups in this study will therefore involve comparing two CHM interventions that are currently available in routine practice.

5.4.1. Contents of Study Medications

All herbs dispensed in this study will be compliant with the UK professional regulatory guidance for CHM offered by the Register of Chinese Herbal Medicine (RCHM) and the European Directive on Traditional Herbal Medicinal Products (THMPD) 2004/24/EC. As such, no animal or mineral products will be dispensed and only plant materials will be used.

5.4.2. Individualised CHM

The contents and dosages of the individualised CHM will be provided in a prescription written by the study practitioner following a consultation with the study participant. Since each prescription will be individualised to each participant, it is not possible to pre-determine the complete list of CHM that will be dispensed in the study. However, a list of CHM that are commonly

prescribed in PCOS has been collated from a systematic review of RCTs investigating the use of CHM for PCOS. This list is available in Appendix 6.

During the course of the study, data from individualised prescriptions will be collected. At the end of the study, a list of all single herbs used in the study, dosages and CHM prescriptions will be available.

5.4.3. Standardised CHM

The standardised CHM product that will be dispensed in this study consists of a pre-defined formula of 14 single herbal granules which were chosen using an evidence-informed approach. This consisted of extrapolating frequently found Chinese medicine presentations and treatment strategies from CHM practice guidelines provided in Appendix 23, and from extracting the methods used within Chinese-language RCTs as part of a systematic review process conducted by this study team. These documents have enabled the study team to reach a standardised formula of 14 herbs that are commonly prescribed in PCOS and that have been chosen for the CHM management of typical symptoms and signs in PCOS. The list, dried herbal and corresponding granulated dosages of the 14 herbs are provided in Table 2.

APPENDICES

Table 2: Contents of standardised CHM

	Chinese Pinyin Name	Common name	Family name	Part used	Botanical Name	Dried herbal daily dosage (g)	Percentage (%)
1	Bai Shao (Chao)	peony (dry fried)	Paeoniaceae	root	<i>Paeonia lactiflora</i> Pall.	15	10.64
2	Chai Hu	bupleurum	Umbelliferae	root	<i>Bupleurum chinense</i> DC.	9	6.38
3	Chen Pi	tangerine peel	Rutaceae	peel	<i>Citrus reticulata</i> Blanco	9	6.38
4	Chuan Xiong	Szechwan lovage rhizome	Umbelliferae	rhizome	<i>Ligusticum chuanxiong</i> Hort.	9	6.38
5	Dang Gui Wei	angelica extremities	Umbelliferae	root tail	<i>Angelica sinensis</i> (Oliv.) Diels	9	6.38
6	Gan Cao (Mi Zhi)	liquorice root (honey-fried)	Fabaceae	root	<i>Glycyrrhiza uralensis</i> Fisch.	6	4.26
7	Gou Qi Zi	goji berry	Solanaceae	fruit	<i>Lycium barbarum</i> L.	9	6.38
8	Gui Zhi	cinnamon twig	Lauraceae	twig	<i>Cinnamomum cassia</i> Presl.	9	6.38
9	Hong Hua	safflower	Asteraceae	flower	<i>Carthamus tinctorius</i> L.	9	6.38
10	Tao Ren	peach kernel	Rosaceae	seed	<i>Prunus persica</i> (L.) Batsch.	9	6.38
11	Tu Si Zi	Chinese dodder seed	Convolvulaceae	seed	<i>Cuscuta chinensis</i> Lam.	12	8.52*
12	Xiang Fu (Cu Zhi)	purple nutsedge (vinegar-fried)	Cyperaceae	rhizome	<i>Cyperus rotundus</i> L.	12	8.52*
13	Yi Mu Cao	motherwort	Lamiaceae	top	<i>Leonurus japonicus</i> Houtt.	15	10.64
14	Zhi Ke	bitter orange	Rutaceae	mature fruit	<i>Citrus aurantium</i> L.	9	6.38

APPENDICES

Total daily prescription weight	141

5.4.4. Summary of CHM Product Characteristics

For the list of CHM provided in Appendix 6 and Table 2 details of common practice indications, contraindications and expected side-effects for each are provided in Appendix 39.

5.4.5. CHM Side-effects

CHM may be associated with adverse effects that include diarrhoea, nausea, loss of appetite and headaches. These effects are not expected to last longer than 48 hours of initial administration. CHM can also be associated with a temporary aggravation of existing symptoms and which will be handled by the study practitioner according to their clinical judgment. Participants will be informed of potential temporary side-effects and will be asked to contact a member of the study team for advice should they be concerned about their symptoms or should their symptoms persist for longer than 48 hours.

In rare instances, adverse effects associated with CHM intake relate to impaired liver and kidney function (Patel et al., 2012). In cases of impaired liver functioning, symptoms can include extreme and unexplained tiredness, malaise, fever, diarrhoea, yellowing of the skin, urine and white of the eyes and muscle and joint aches. Possible symptoms relating to impaired kidney functioning include muscle and joint aches, weight loss, shortness of breath, fluid retention, decreased urinary output, confusion and chest pain. Symptoms and signs of impaired liver and kidney functioning will be checked for as part of the AE/SAE assessments with non-leading questions as discussed in section 8.2. Where it is suspected that there may be an AE or SAE, participants will be asked to stop taking the CHM immediately and will undergo AE/SAE procedures as outlined in section 8 Adverse Events and Serious Adverse Events.

5.4.6. CHM identification

5.4.6.1. Individualised CHM

The individualised CHM will consist of a number of single herbs mixed together at the dispensary. These single herbs will consist of coarse granules that are white, yellow, beige and brown in colour and the resulting prescription

of mixed granules will therefore consist overall of a beige or brown colour. The resulting prescription can have a moderate to strong aroma and may have combined flavours of being sweet, sour or bitter.

5.4.6.2. Standardised CHM

The standardised formula will consist of 14 single herbs and the resulting standardised prescription consists of coarse brown granules. This has a moderately strong aroma and a sweet and bitter flavour.

5.4.7. CHM Manufacturer

The manufacturer of the individual CHM single granules is Jiang Yin Tian Jiang Pharmaceutical Company Limited, located in mainland China. The company address is:

Jiang Yin Tian Jiang Pharmaceutical Company Limited
No. 8 Qin Wang Shan Road
Economic Development Zone
Jiang Yin City
Jiang Yin
Jiang Su Province, 214434
China

5.4.8. Marketing Authorisation Holder

The CHM products as prescribed in their finished form are not available on the market and as such do not possess a marketing authorisation.

5.4.9. Quality assurance

As a measure of quality assurance, the manufacturer possesses a certificate of Good Manufacturing Practice (GMP) for pharmaceutical products. This certificate has been granted by regulatory authorities from the People's Republic of China and a copy of this certificate can be viewed in Appendix 42. This ensures that the manufacturer conforms to pre-determined standards in manufacturing processes to maintain consistency in quality of CHM and enables a systematic audit of CHM source, CHM identification, traceability and accountability of all procedures.

Certificates of analysis (C of As) are also available for each batch of single CHM granules that are produced at this manufacturer. These analyses are typically performed within 7 days of manufacture and include details such as date of

production and of analysis, batch number, expiry date, description of appearance, and conformity assessments for thin layer chromatography (TLC) identification of herb, moisture $\leq 6.0\%$ (%), solubility in water, heavy metal content i.e. Lead (Pb), cadmium (Cd), arsenic (As), mercury (Hg), microbiological ($<1000\text{cfu/g}$), fungal account ($<100\text{cfu/g}$) and Escherichia coli (absent in 1g). An example of a C of A of a CHM typically prescribed in PCOS is provided in Appendix 43. C of As for the list of commonly prescribed CHM in PCOS presented in Appendix 6 are provided as supporting documentation separate from this protocol.

At the end of the study, a compilation of C of As for all batches of single CHM granules that are dispensed in this study will be made.

5.4.10. Stability data

Since the CHM products have not been pre-manufactured and are not available on the market as finished herbal products, no formal stability data for the finished products is available. Stability data for the products in this study will not be collected due to limited resources available to the study team for analysis but is planned to be conducted for the main study.

5.4.11. CHM Distributor and Dispensary

All CHM products provided in both treatment groups will be dispensed by a UK distributor and dispensary that has been approved by the RCHM and is registered on the RCHM Approved Suppliers Scheme. A copy of the Approved Suppliers certificate can be viewed in Appendix 40. A copy of the Dispensary and Pharmacognosy training certificate that a member of the dispensary team has completed can be found in Appendix 41.

The address of the UK distributor is:

Phoenix Medical Direct
Phoenix House
41 Beehive Lane
Chelmsford
Essex
CM2 9TQ
UK

5.4.12. Labelling and Packaging

Both the individualised and standardised CHM will be packaged by the CHM dispensary in white pharmaceutical grade plastic bottle containers with a tamper-evident seal as in routine practice. Each container will be labelled with the following information:

- Statement of 'For Clinical Trials Use Only: Study reference code XXXX'
- Statement of total weight of contents. '100g of Chinese herbal medicine granules'
- Directions for use 'For ORAL use as directed by study practitioner, or in participant information sheet'
- Details of storage instructions 'Do not store above 30°C. Keep in a dry place away from strong odours and bright light. Do not refrigerate or freeze. Keep out of reach of children.'
- Expiry date in MM/YYYY form
- Reference number 'ABCD1111'
- Date of dispatch and study week number 'DD/MM/YYYY, Week X'
- Participant identification number '012345'
- Statement of 'Please hand this bottle and any unused herbs to your herbalist at end of study'
- Name and telephone number for member of study team.

An example of the formatting of the label is provided in Appendix 44.

To preserve patient and practitioner blinding, there will be no information provided on the label regarding the ingredients prescribed in either the standardised or in the individualised CHM. The prescription will instead be assigned a different prescription reference number by the dispensary each time a prescription is compiled and distributed, regardless of whether the CHM is standardised or individualised.

5.4.13. Storage

The single herbal granules and manufacturing of the CHM prescriptions will take place within the CHM dispensary at the following address:

Phoenix Medical Direct
Phoenix House
41 Beehive Lane
Chelmsford
Essex
CM2 9TQ
UK

A voucher specimen will be retained for each batch of single herbs that are used for the standardised and the individualised group. Samples are kept as

part of routine dispensary practice in a storage area separate from the dispensary room at the dispensary site.

It is the manufacturer's recommendation that the CHM products for this study is not stored above 30°C and that it should be kept away from bright light and moisture, for which written confirmation has been provided and can be seen in Appendix 45.

5.4.14. Justification for expiry dates

An expiry date of 3 months from date of dispatch will be assigned by the study dispensary to each prescription. Single CHM granules manufactured at Jiangyin Tianjiang Pharmaceutical Company possess expiry dates 5 years from production, as supported by C of As provided with each batch of single CHM granules that is produced. Owing to the manufacture that takes place at the UK dispensary and mixing together the single CHM granules to form each prescription for this study, the manufacturer and dispensary deem it appropriate that a 3 month use-by date is assigned to these prescriptions, as can be seen by the letter provided in Appendix 45.

5.4.15. Accountability Procedures

The study sponsor will remain accountable for professional conduct of study practitioners during this study. In order to fulfil this requirement, the study sponsor will ensure that each practitioner is being adequately supervised by one or more named CHM practitioners during the course of the study.

The CHM dispensary will be held accountable for issues relating to the dispensing of the prescriptions. Where issues arise that may relate to source raw materials and overseas processing of single herbs into granules, the CHM dispensary will be the main point of contact for the overseas manufacturer regarding such issues.

5.5. Study Medication Distribution and Disposal

Participants will receive CHM products after each consultation with the study practitioner. CHM will be distributed as per usual practice following processes that adhere to RCHM guidance.

The prescription weight and frequency of CHM products to be sent will be identical regardless of the treatment allocation.

Participants will be asked to return any unused CHM at Week 12 and at their final study visit, or at a withdrawal visit. After the study team have calculated weights of unused CHM, CHM will be disposed of responsibly as per RCHM codes of practice.

5.6. Dosing regimen

CHM treatments in both arms will be prescribed by the study practitioner for participants to self-administer orally at a dosage of 8g of CHM granules per dosage, two dosages daily. Each participant will therefore take 16g per day for the study duration of 24 weeks.

Participants will be instructed to prepare the CHM as in usual practice. This involves using a plastic measuring spoon provided by the dispensary to measure the correct dosage of CHM granules and putting this into an empty mug. A tablespoon of cold water is then added to the granules and stirred to make a paste. Boiled water should then be added to the paste to make a tea. This tea should be taken whilst warm and approximately 30-60 minutes after meals. Administration prior to a meal is permitted, but participants should be informed that this could increase the likelihood of developing temporary digestive side effects detailed in section 5.4.5 CHM Side-effects.

Participants will be advised to leave at least one hour either side of taking the CHM when administering other medications or supplements permitted on this study, and to take CHM approximately 3 hours either side of having alcohol. This recommendation follows usual practice in order to reduce the likelihood of possible interactions.

5.7. Changes to interventions

5.7.1. Changes to CHM dosage

Where participants are finding it difficult to take the recommended dose of CHM because of taste, participants will be permitted to make the prescription

more palatable as is usual practice. Advice that study practitioners offer as per routine practice will be accepted. This includes, though is not limited to, adding up to a tablespoon of honey or sugar, or making a mixture consisting of 25% fruit juice such as apple juice and 75% water.

Where participants continue to experience difficulty in taking the recommended dose of CHM, or if the study practitioner feels it clinically appropriate, participants will initially be permitted to reduce the dosage of CHM up to a minimum of 5g per day, considered in CHM clinical practice guidelines as the minimum standard dosage for prescribing in PCOS (see Appendix 21). Adjusting the dosage according to individual circumstances in this manner is considered part of usual practice. Such adjustments to dosages and reasons for adjustments will be noted in study records to inform feasibility of the intervention as prescribed and to explore potential dose-responses.

Dose adjustments will be monitored by the study practitioner for the remainder of the study and, where appropriate, return to the recommended dose attempted.

Where participants continue to experience problems at this minimal dosage, they will be permitted to discontinue the CHM temporarily as per procedures detailed in section 4.7 Temporary Discontinuation before attempting to return to the minimal dosage.

Where participants continue to find it difficult to take the minimum dosage of 5g per day, they will be permitted to continue taking the CHM as they find suitable. These participants will continue to be dispensed CHM prescriptions provided they can attend study assessments as required of them to be considered adherent to the protocol as per section 5.2 Study Assessments, Study Visits and Protocol Adherence. Where participants are fail to take the CHM as prescribed as well as attend study assessments as scheduled, withdrawal processes should be followed as outlined in section 4.8 Withdrawal Procedures.

5.7.2. Changes to CHM prescription

Changes to the CHM prescription contents between scheduled study assessments are not permitted as part of this study protocol. Where participants report experiencing problems with taking a prescription as prescribed, changes to CHM dosage as specified above should be followed.

5.7.3. Changes in study practitioner

Post-randomisation changes in study practitioner will not be permitted as part of this study protocol.

5.7.4. Changes in location

Where a study practitioner offers study consultations at more than one location, it is permissible for a participant to change the location at which she receives this consultation.

5.8. Participant Adherence

Adherence to the protocol in terms of attending study visits has already been discussed in section 5.2 Study Assessments, Study Visits and Protocol Adherence and which describes the minimum compulsory requirements for attendance that each participant needs to demonstrate. This section will discuss participant adherence to the CHM intervention which will not be a compulsory requirement since the statistical analysis for the main study will be based on an intention-to-treat approach. However, adherence to the intervention will be assessed in this study as part of the feasibility criteria and to provide further information to aid the design of the main study. Participant adherence to the CHM interventions will be assessed using both self-reported means and observer-reported means.

Participants will be administered the 8-item Morisky Medication Adherence Scale (MMAS-8) at Weeks 4 and 24 and at withdrawal assessments to assess for self-reported medication adherence. This is a validated questionnaire where a total score of 0 to <6 suggests low adherence, 6 to <8 medium adherence and 8 high adherence (Morisky et al., 1986, Morisky et al., 2008). The questionnaire can be viewed in Appendix 46.

For observer-reported measures, participants will be asked at each study assessment non-leading questions regarding whether or not they have been experiencing problems taking the CHM. The frequency and size of CHM orders and re-orders will also be recorded. At Week 12 and at the end of the study, participants will be asked to return all unused study medication to enable the study team to calculate total CHM usage during the study. This will be clearly stated at the baseline visit and placed on the labels of the CHM.

To be considered adherent to the CHM as prescribed, participants must take CHM at the minimum recommended dosage of 5g per day, for a minimum of 18 of the 24 weeks of the study and with a break from CHM administration of no more than 7 days at a time.

Non-adherence to the CHM intervention alone will be insufficient grounds alone for withdrawing a participant provided they demonstrate adherence to the study protocol. This means that participants may continue to be prescribed CHM if they are able to complete each study assessment as required by the protocol.

Where relevant, non-adherence should firstly follow procedures outlined in sections 5.7.1 Changes to CHM dosage and 5.7.2 Changes to CHM prescription. The study team will attempt to maximise adherence to the intervention and will discuss ways to remember taking the CHM with each participant prior to their enrolment. Where participants request reminder aids, prompts and reminders may be used such as text or email reminders.

5.9. Excessive dosing

Where participants report taking a higher than prescribed dose, participants will be asked to contact a member of the study team or a medical doctor immediately for further advice. Excessive dosing has been defined in this study as taking more than twice the standard daily dosage for this study i.e. more than 32g per day. This has been determined by taking into consideration the routine practice dosage range of 5g to 25g reported in the CHM guidelines provided in Appendix 21.

As a precautionary measure, participants who report excessive dosing will be instructed to immediately stop taking study CHMs. Where necessary, an assessment will be made of the participant's liver and kidney function and the participant will be checked against adverse events (AEs) and serious adverse events (SAEs). Where necessary, referral to a medical doctor will be made. AEs/SAEs are described in further detail in section 8 Adverse Events and Serious Adverse Events.

Re-entry onto the study will be permitted providing the participant is willing and is considered to be in adequate health and after all necessary medical tests have been performed, as determined by the study's medical representative and by the study team.

Where it is inappropriate for the participant to continue in the study, withdrawal procedures will be followed as detailed in section 4.8 Withdrawal Procedures.

5.10. Prior and concomitant medications and interventions

This study permits some usual care interventions and medications alongside the CHM interventions. For some of these interventions and medications, constraints have been imposed as part of this study's protocol. These permitted and prohibited medications and interventions are detailed below and with full justification where appropriate.

During screening, participants will be asked for information regarding prescribed medications and supplements and how long they have taken these for. At the start of the study, participants will be reminded to provide details of any medications, supplements and other interventions that are newly prescribed or administered during the course of the study, and where possible to check with the study team regarding taking newly prescribed medications, supplements and other interventions.

For participants who report starting new interventions at study assessments, an assessment will be made against the permitted and prohibited medications and interventions on this study to determine further action. In cases where an

intervention has not been listed in the sections below, the study team will evaluate this individually to determine the suitability of a participant to continue with the study, or to be withdrawn, with a record of these decisions made accordingly.

5.10.1. Permitted medications and interventions

5.10.1.1. Permitted medications and interventions at all times

The following medications, supplements and interventions are permitted for use prior to, and at any point during, this study:

- Analgesics e.g. Aspirin, paracetamol;
- Antidepressants such as amitriptyline or SSRIs;
- Vitamin, mineral and selected natural supplements e.g. Coenzyme Q10, Evening Primrose Oil, B vitamins, Zinc, magnesium, milk thistle, mint;
- Weight loss interventions e.g. Exercise, diet.

Whilst it is recognised that the administration of these medications, supplements or interventions could potentially have an effect on the outcome measures in this study, these are used commonly amongst women with PCOS and the study team, after careful consideration, regard these as acceptable for use within this study.

5.10.1.2. Permitted medications and interventions if used for 6 months or longer

The following medications are permitted in this study, provided they have been administered for 6 months or longer at the start of the study:

- Insulin-sensitising agents e.g. Metformin;
- Oral contraceptives e.g. Diane-35;
- Anti-androgens e.g. Spironolactone;
- Acupuncture.

The above interventions are permitted since 6 months is deemed a sufficient period of time to have lapsed in order for clinical improvements from such treatments to have stabilised prior to administering CHM. These medications and interventions have been used safely and without record of serious adverse events from previous RCTs involving CHM for PCOS.

During the study, participants may start taking the above medications and interventions or be found to have been taking these within 6 months of

starting the study. Since these participants will have been randomised and are likely to have been receiving study CHMs for a period of time, these participants will not be withdrawn from the study, but will be considered separately in the analysis.

5.10.2. Prohibited medications and interventions

The following is a list of medications and interventions that are prohibited from use during the study at all times. Where a participant needs to be prescribed such medication or where a participant begins to administer this during the study without the study team's prior knowledge, the participant will be considered for withdrawal. However, the decision whether to withdraw the participant, or whether to withdraw from certain aspects of the study will be considered on an individual basis by the study team. More details regarding withdrawal procedures are outlined in section 4.8 Withdrawal Procedures.

5.10.2.1. Prohibited medications and interventions at all times

The following medications and interventions are not permitted during this study due to potential interaction with study medication or due to potential effects on the study outcome measures:

- Anticoagulants such as heparin and warfarin;
- Anti-hypertensives;
- Diuretics;
- Cardiac glycosides (Digoxin);
- Ciprofloxacin;
- Corticosteroids;
- Lithium;
- CHM and other herbal supplements that have a potential action on symptoms of PCOS or could interact with the study medication e.g. St Johns Wort, black cohosh, vitex agnus castus, saw palmetto;
- Ovulation-inducing agents e.g. Clomiphene citrate, letrozole, tamoxifen;
- Fertility procedures e.g. In vitro fertilization, intrauterine insemination;
- Laparoscopic ovarian cauterization.

5.10.3. Concomitant advice

Aside from CHM administration, study practitioners will be permitted to provide participants with additional advice according to Chinese medicine theory as appropriate. This includes advice on lifestyle, stress-management or general wellbeing which is commonplace in routine CHM practice and which will be recorded within the clinical notes. It is acknowledged that offering

additional advice could be a potential confounder of this study. However, concomitant advice will be offered to both treatment groups as part of pragmatic routine practice and is considered by this study team as an acceptable co-intervention.

Study practitioners will be asked to not offer additional advice outside that which is given in a typical CHM consultation. Where study practitioners are uncertain whether advice is acceptable for this study protocol, the study team should be contacted for further clarification.

5.11. Study Restrictions

As there is no available safety data of CHM use during pregnancy, participants will be strongly advised against trying to conceive whilst being administered CHM in this study. However, after study CHM ceases to be administered, it is deemed safe for participants to conceive. This will be stated clearly in the PIS, CF and at the baseline study visit.

Participants will be asked not to change their diet or activity level during the study other than what the study practitioners have recommended. There will be no other study restrictions.

5.12. Safety Assessments

5.12.1. Liver and kidney function

Whilst the herbs contained within this prescription are widely prescribed by CHM practitioners, the safety profile of this CHM product is unknown. Liver and kidney function will therefore be monitored during this study by monitoring alanine aminotransferase (ALT) and creatinine to determine estimated glomerular filtration rate (eGFR). This will be performed using serum blood tests or the Reflotron Desktop Analyzer, a validated point-of-care test device involving finger prick blood (Thue and Sandberg, 1993). These tests will be conducted as part of the eligibility criteria at baseline and to monitor safety during the study at Week 4, Week 24 and at withdrawal visits. As stated in section 5.2 Study Assessments, attendance at study visit Week 4 is considered a compulsory requirement in order that study practitioners can check for safety prior to sending out further CHM prescriptions.

5.12.2. Adverse Events and Serious Adverse Events

During all study assessments and withdrawal assessments, participants will be checked for adverse events (AEs) and serious adverse events (SAEs) as part of safety monitoring. Details of AEs and SAEs are provided in section 8 Adverse Events and Serious Adverse Events.

5.13. Chinese medicine clinical assessment

All participants will undergo CHM assessments at each study assessment and during the withdrawal assessment. This will involve a brief clinical overview of symptoms and signs, providing an appropriate Chinese medicine diagnosis for the participant's current presentation, treatment principle(s) of the CHM and details of other associated assessments by the study practitioner such as tongue and pulse observations. At the baseline CHM assessment, participants will be asked for known allergies to any products, and specifically checked for allergies to the following group of common CHM ingredients: seeds, peppermint, ginger and dandelion. These CHMs are not contained in the standardised CHM product and as such, it is possible for participants with allergies to this group of CHM to be recruited into the study but for the study practitioner to write individualised CHM prescriptions with these allergies in mind.

The data record form for this assessment has been developed for this study and piloted and a copy can be seen in Appendix 47.

5.14. Study Assessments

This following section will now describe the content and timing of study-related assessments and when each will be taken. Permission has been checked for use of and amendments to questionnaires used in this study and obtained where required.

5.14.1. Screening criteria

As part of the inclusion and exclusion criteria, participants will undergo assessment for hazardous drinking through the FAST questionnaire and a blood test to confirm normal baseline liver and kidney function. Where FAST score is positive, the AUDIT questionnaire will also be used. Copies of the

FAST and AUDIT questionnaire can be viewed in Appendix 26 and Appendix 27 respectively. Where diagnosis of PCOS is unclear for a participant, further assessments may be required to confirm diagnosis. This will be conducted using ultrasound scans, or assessments for hyperandrogenism, for example by using the modified Ferriman-Gallwey questionnaire, available in Appendix 51. A demographics questionnaire will also be administered at baseline (see Appendix 48).

5.14.2. Menstrual history

As there will be no run-in period in this study, participants will be asked to recall a minimum of 3-month menstrual frequency data at baseline and to score on a Likert scale of how confident they are of this data's accuracy. During the study they will be asked to keep a menstrual diary to note the first day of each menstruation they experience and which will be recorded by the study practitioner at each study assessment and at withdrawal assessments.

5.14.3. Anthropometric measurements

Measurements for height, weight, waist and hip measurements will be taken at Week 0, Week 24 and for withdrawal assessments. These will follow Standard Operating Procedures (SOPs) to ensure consistency in measuring of outcome data.

5.14.4. Quality of life

This will be assessed using standardised questionnaires, the polycystic ovary syndrome questionnaire (PCOSQ), Dermatology Life Quality Index (DLQI) and measure yourself medical outcome profile questionnaire (MYMOP). Quality of life will be measured at Week 0, Week 24 and during withdrawal assessments. Copies of the DLQI and MYMOP are provided in Appendix 49 and Appendix 50 respectively.

5.14.5. Modified Ferriman-Gallwey questionnaire

The modified Ferriman-Gallwey (mFG) questionnaire is a standardised and validated questionnaire that involves observer-assessment of hirsutism where 9 body areas are scored between 1 and 4.

This assessment will be carried out at Week 0, Week 24 and during withdrawal assessments. This may also be used as part of the inclusion criteria in order for participants to be diagnosed with PCOS where an FG score of ≥ 6 is indicative of hirsutism (Yildiz et al., 2010).

5.14.6. Practitioner blinding questionnaire

This will be checked by asking study practitioners to fill out a set of simple questions regarding which group assignment they feel has been given for each participant under their care.

Study practitioners will be asked 'Do you feel this participant was assigned to standardised, or to individualised CHM?' and will be asked to provide a statement of group assignment. They will then be asked for their certainty in these statements with the question 'How sure are you of your answer'.

Practitioners will be able to use one of three answers 'Not sure at all, just guessed', 'Fairly sure' or 'Entirely sure'.

Finally practitioners will be asked to provide a reason for their answer regarding group assignment.

This set of simple questions has been recommended for use to assess success of blinding in controlled trials and has previously been used in acupuncture studies (Bang et al., 2004, Kolahi et al., 2009, Enblom et al., 2011). These assessments will be conducted via questionnaire at Week 4, Week 12 and Week 24 and during withdrawal assessments. A copy of the questionnaire can be viewed in Appendix 52.

Patient blinding will not be monitored as participants will be unaware of the difference in group assignments.

5.14.7. Chinese medicine treatment details

Details of the treatment provided by each study practitioner will also be collated and will involve recording individualised prescription data and additional Chinese medicine advice offered.

5.14.8. Credibility/Expectancy Questionnaire

In order to obtain a measure of treatments expectancy and rationale credibility, participants will be administered at baseline a short 6-item credibility/expectancy questionnaire (CEQ) provided in Appendix 53. As instructed by the questionnaire developers, this questionnaire has been modified for this study by substituting the word in the original questionnaire of ‘therapy’ for ‘treatment’, and the word of ‘trauma’ with the word ‘PCOS’. Study site teams will be kept blind from the answers provided to protect against potential subsequent care effects from the site team.

5.14.9. Morisky Medication Adherence Scale (MMAS-8)

To record self-reported medication adherence, the Morisky Medication Adherence Scale (MMAS-8) will be used at Weeks 4, 24 and withdrawal visits. This is a validated questionnaire where a total score of 0 to <6 suggests low adherence, 6 to <8 medium adherence and 8 high adherence (Morisky et al., 1986, Morisky et al., 2008). A copy of the questionnaire can be viewed in Appendix 46. This questionnaire has been adapted for this study by substituting the word in the original questionnaire of ‘medicine’ with ‘herbs’, and the word ‘patient’ with ‘participant’. Table 3 provides a summary of all study assessments and method of assessment.

Table 3: Summary of study assessments

Study Assessment number	1	2	3	4	5	6	7	8	Withdrawal
Study week	0	2	4	8	12	16	20	24	
Visit/Remote	V	V/R	V	V	V	V/R	V/R	V	V/R
Demographics	✓	-	-	-	-	-	-	-	-
FAST	✓	-	-	-	-	-	-	-	-
CEQ	✓	-	-	-	-	-	-	-	-
PCOSQ	✓	-	-	-	-	-	-	✓	✓
DLQI	✓	-	-	-	-	-	-	✓	✓
MYMOP	✓	-	-	-	-	-	-	✓	✓
Blinding	-	-	✓	-	✓	-	-	✓	✓
Hirsutism	✓	-	-	-	-	-	-	✓	✓
Anthropometric measurements	✓	-	-	-	-	-	-	✓	✓
Liver and kidney function	✓	-	✓	-	-	-	-	✓	✓
Adherence	-	-	✓	-	-	-	-	✓	✓
CHM assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
Menstrual history	✓*	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	-	✓	✓	✓	✓	✓	✓	✓	✓

*in last 12 months

FAST=Fast Alcohol Screening Test, CEQ=Credibility/Expectancy Questionnaire, PCOSQ=Polycystic Ovary Syndrome Questionnaire, DLQI=Dermatology Life Quality Index, MYMOP=Measure Yourself Medical Outcome Profile

5.15. End-of-study evaluation

5.15.1. Participants

An end-of- study evaluation will be conducted to explore participants' experiences of taking part in this study. This will be conducted after participation in the study has ceased after Week 24 or following a withdrawal visit by administering a semi-structured questionnaire specifically designed for this study and which is provided in Appendix 54.

5.15.2. Study personnel

A semi-structured questionnaire will also be distributed to study personnel including the study team, study practitioners and CHM dispensary to invite their feedback and comments as part of piloting the methods of the study. This questionnaire has been designed specifically for the study and asks for feedback in terms of recruitment methods, eligibility screening methods, data collection methods and study involvement. A copy has been provided in Appendix 55.

6. Data Collection

The methods of data collection and measures to maximise completeness of data collection will now be discussed.

Outcome measures data will come from self-assessments and observer-assessments. CHM treatments data will be recorded directly into clinical notes.

6.1. Self-assessments

Self-assessments will be required of both participants and study practitioners. For participants, self-assessed data will be collected for demographics, FAST alcohol screening, PCOSQ, DLQI, baseline menstrual history, CEQ and MMAS-8. MYMOP will be self-assessed at the baseline visit with the guidance of the study practitioner, and then administered for self-assessment at the end of the

study. For study practitioners, self-assessed data will be collected for practitioner blinding questionnaire.

For self-assessments, data collection will initially be attempted electronically by using web-based questionnaires and electronic questionnaires. Participants and study practitioners will be given the option of completing paper-based questionnaires if they state this method of data collection is preferable.

Web-based questionnaires will be hosted on an online survey management tool. Electronic data capture can maximise the consistency in data collection and provides an initial screening for accuracy of data entry by displaying error messages instantly where data is missing or inputted in the incorrect format by participants prior to submission of the questionnaire. The data from completed web-based questionnaires will be accessible to the study team in the survey-management interface and can be downloaded directly into a spreadsheet format in Microsoft Excel 2010 or SPSS.

Electronic questionnaires will be presented in Word 2010, Excel 2010 or Pages for Macintosh users. These can be completed by computer and returned as an email attachment to a member of the study team.

Paper-based questionnaires can either be printed from an electronic PDF that has been emailed, posted direct or provided in person during study visits. A stamped and self-addressed envelope will also be offered to participants who opt for paper-based questionnaires.

This study will require participants to record menstrual cycle data throughout. Advice and information on how to record this data will be offered to all participants prior to enrolment onto the study e.g. using mobile phone applications, using a diary.

As the data collection methods will be piloted and an assessment of feasibility made as part of the feasibility criteria in this study, issues arising from these proposed methods of data collection will be evaluated and reasonable attempts made to respond flexibly to maximise completeness of data collection.

6.2. Observer-assessments

Observer-assessments will be made with scheduled study assessments which will be undertaken at study visits or remotely. Attendance of study visits will attempt to be maximised by sending appointment reminders.

Observer-assessments involve recording data such as anthropometric measurements and hirsutism; liver and kidney functions as per methods outlined in section 5.12 Safety Assessments; and clinical data such as Chinese medicine assessments, menstrual history from Week 2 and checking for adverse events.

This data may be collected using paper-based, electronic or online data forms. SOPs for completing data forms will be provided to study sites and investigators to ensure accuracy and consistency in data recording.

A table displaying a summary of the data collection methods for study assessments ordered by study week can be seen in Table 4.

Table 4: Summary of data collection methods for study assessments

Study Assessment number	1	2	3	4	5	6	7	8	Withdrawal
Study week	0	2	4	8	12	16	20	24	
Visit/Remote	V	V/R	V	V	V	V/R	V/R	V	V/R
Demographic	S	-	-	-	-	-	-	-	-
FAST	S	-	-	-	-	-	-	-	-
PCOSQ	S	-	-	-	-	-	-	S	S
CEQ	S	-	-	-	-	-	-	-	-
DLQI	S	-	-	-	-	-	-	S	S
MYMOP	S	-	-	-	-	-	-	S	S
Blinding	-	-	S	-	S	-	-	S	S
Hirsutism	O	-	-	-	-	-	-	O	O
Anthropometric measurements	O	-	-	-	-	-	-	O	O
Liver and kidney function	O	-	O	-	-	-	-	O	O

Adherence	-	-	S	-	-	-	-	S	S
CHM assessment	O	O	O	O	O	O	O	O	O
Menstrual history	S*	O	O	O	O	O	O	O	O
Adverse events	-	O	O	O	O	O	O	O	O

*in last 12 months

FAST=Fast Alcohol Screening Test, CEQ=Credibility/Expectancy Questionnaire, PCOSQ=Polycystic Ovary Syndrome Questionnaire, DLQI=Dermatology Life Quality Index, MYMOP=Measure Yourself Medical Outcome Profile

S=Self-assessment, O=Observer-assessment

6.3. CHM assessments data

Data regarding CHM diagnoses, prescriptions and concomitant advice provided by study practitioners will be recorded directly into participants' clinical notes.

6.4. End-of-study evaluation data

6.4.1. Participants

Participants' experiences of taking part in this study will be captured with a semi-structured questionnaire. These will be provided as web-based questionnaires, electronic questionnaires or paper-based questionnaires and can be returned to a member of the study team following completion following the same procedures outlined in section 6.1 Self-assessments.

6.4.2. Study personnel

Experiences and feedback from study personnel regarding involvement in the study will be captured on web-based, electronic or paper-based questionnaires distributed to study personnel at the end of the study. These will be returned to a member of the study team following completion as per procedures in section 6.1 Self-assessments.

6.5. Source data

Source data for this study will be considered to be:

1. spreadsheets downloaded from the survey management tool for web-based data;
2. questionnaires or data forms returned to the study team;
3. clinical notes;
4. Case Report Forms (CRFs) designed by the study team for collection of study-specific data.

Relevant data from source data types 1-3 will be inputted into Case Report Forms (CRFs) according to SOPs for completing CRFs to maximise consistency in data recording and collection. Some data may be inputted directly into CRFs and for this data, the CRF may be considered the source data.

6.6. Timing of data collection

For self-assessments, participants will be sent questionnaires prior to each study visit up to a maximum of 7 days before the visit. This may take the form of emails containing links to web-based questionnaires or electronic/paper-based questionnaires where web-based completion is not possible. 7 days before the visit is considered an acceptable timeframe in which to start collecting data for each time point. Participants will be asked to complete these questionnaires prior to their study visit.

Email or text reminders to complete questionnaires will be sent to participants before the study visit. Where questionnaires have not yet been completed by the study visit, participants will be asked to complete questionnaires during the study visit, or shortly after the study visit. Where appropriate, participants will continue to be sent reminders to complete these questionnaires following the study visit.

Where participants fail to return questionnaires despite repeated reminders, attempts will be made to contact participants in order to complete questionnaires with them.

For observer-assessments, data will be collecting during study assessments. CRFs for each study assessment should be completed within 24 hours of the study assessment to maximise accuracy and minimise recall bias.

End-of-study evaluations will be made after participation in the study has ceased by administering questionnaires and which will be offered to participants and study personnel. This will be sent after they have ceased participation in the study to minimise recall bias.

6.7. Procedures for Withdrawn Participants

Participants who are withdrawn will follow procedures outlined in section 4.8 Withdrawal Procedures.

Where it is appropriate to withdraw the participant from the interventional aspect of the study and to continue monitoring the participant for safety and other outcome measures, informed consent for this limited participation in the study will be sought. Relevant procedures outlined in section 4.8 Withdrawal Procedures should then be followed.

Participants who are withdrawn from all aspects of the study, both interventional and monitoring, will undergo a withdrawal assessment and data attempted to be collected as outlined in section 4.8 Withdrawal Procedures. Following the withdrawal visit, no further requests for collecting data will be formally required by the study team.

6.8. Procedures for Participants Lost to Follow Up

Participants will be considered lost to follow up if they do not attend study visits, despite reminders being sent out by the study team and who have not undergone formal withdrawal procedures. These participants will continue to be sent invitations to complete questionnaires at each scheduled data collection time point but will not be dispensed any further CHM. These questionnaires will involve self-assessments and, for observer-assessed data, participants will be asked to provide self-reported data only on anthropometric measurements, menstrual history and adverse events. Other data that is usually observer-assessed such as Chinese medicine assessment and hirsutism cannot be reliably self-reported and follow up on these measures will therefore not be attempted.

6.9. Procedures for unscheduled contact

Participants may make unscheduled contact such as visits, telephone calls, texts or emails. Where such contact is considered potentially relevant for evaluation of study processes and management, or has clinical relevance, then the content and nature of the contact will be recorded using a standardised form.

7. Statistics and Data Analysis

7.1. Sample Size Calculation

In order to obtain sufficient data to compute a sample size for a larger main study, this feasibility study will require a sample size of 40. This sample size has been calculated based on requiring approximately 15 participants per arm in order that sufficient data is provided to calculate an estimate of the treatment effect and associated variability of the treatment effect (Thabane et al., 2010). Accounting for a 25% dropout rate each treatment group based on data from similar studies (Flower et al., 2011b, Yasmin et al., 2011), 20 participants will be required from each group, totalling 40 participants.

7.2. Proposed Analyses

Primary analysis will consist of a descriptive analysis of the feasibility criteria that have been outlined earlier in section 2.1 Feasibility study objectives and endpoints.

For statistical analysis, principles of intention-to-treat will be adopted by keeping participants within their allocated treatment for analysis. Formal data imputation will however not be conducted, although an exploration of the suitability of data imputation for the main study will be made. The main statistical analysis in this study will therefore be an available-case analysis which analyses the data for every participant for whom the outcome was obtained.

Statistical analysis will be piloted in this feasibility study to check its suitability for the main study and will be conducted by a statistician independent of the study team named in the protocol. This analysis will test for within-patient and between-group differences at Week 0 and at Week 24 and which will be analysed for clinical treatment effects outlined in section 2.1 Feasibility study objectives and endpoints. Continuous variable comparisons can be assessed at Week 24 adjusted for baseline assessments for the two groups using analysis of variance, or an analysis of covariance to include the effects of BMI, WHR, severity of menstrual disorder, demographic variables, CEQ score and adherence.

Menstrual data will be analysed from the first menses since randomisation onto the study.

Investigating the effects of these variables is important to initially explore whether groups of participants are likely to experience different treatment effects. Since these statistical analyses will be piloted in this feasibility study and as no formal power calculations have been carried out, results from the statistical analysis that are presented as part of the feasibility study findings should be considered preliminary and must be interpreted cautiously (Lancaster et al., 2004). Statistical analysis will be conducted by a statistician independent of the study.

Clinical notes detailing lifestyle and dietary advice given by study practitioners will be analysed using content analysis.

Study-evaluation questionnaire data will be analysed using content analysis for text-responses and descriptive summaries for Likert scales.

7.3. Other statistical considerations

This study will aid in exploring the methods most suitable for handling missing data in the main study.

Data collection has been specified in terms of study weeks within this protocol so far. However, it is difficult for data to be collected specifically within the study weeks. Therefore, for this study, the acceptable timeframe for data collection by study assessment has been considered and are presented in Table 5.

Table 5: Permissible timeframes for data collection by assessment number

Assessment number	Study week	Data to be collected	Data collection permissible timeframes	
			Earliest	Latest
1	0	Demographic, FAST, PCOSQ, DLQI, MYMOP, hirsutism, anthropometric, liver and kidney function, Chinese medicine treatment, menstrual history	14 days prior to Week 0	Prior to taking CHM

2	2	Chinese medicine assessment/treatment, menstrual history, adverse events	≥ Week 1	< Week 3
3	4	Liver and kidney function, Chinese medicine treatment, menstrual history, adverse events	≥ Week 3	< Week 7
4	8	Chinese medicine treatment, menstrual history, adverse events	≥ Week 7	< Week 11
5	12	Chinese medicine treatment, menstrual history, adverse events	≥ Week 11	< Week 15
6	16	Chinese medicine treatment, menstrual history, adverse events	≥ Week 15	< Week 19
7	20	Chinese medicine treatment, menstrual history, adverse events	≥ Week 19	< Week 23
8	24	PCOSQ, DLQI, MYMOP, hirsutism, anthropometric, liver and kidney function, Chinese medicine treatment, menstrual history	≥ Week 23	None imposed
Withdrawal	-	PCOSQ, DLQI, MYMOP, hirsutism, anthropometric, liver and kidney function, Chinese medicine treatment, menstrual history	From notification of withdrawal	None imposed

8. Adverse Events and Serious Adverse Events

8.1. Definitions

Adverse Events (AEs) as defined by the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) include ‘any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An...(AE)...can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.’ Following the same guidelines, Serious Adverse Events (SAEs) are ‘any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect.’

Hospitalisations for treatment planned prior to randomisation and for elective treatment of a pre-existing condition will not be considered as an AE.

8.2. Detection

All AEs and SAEs will be recorded from consent until the last study assessment or withdrawal assessment.

At each study assessment, participants will be monitored for AEs and SAEs. This will be done by asking non-leading questions in an effort to detect these, for example:

‘How are you feeling?’

Or

‘Since you were last asked, have you felt unwell or different from usual?’

At each study assessment, participants will also be asked if they have been admitted to hospital, had any accidents, used any new medications or changed concomitant medication regimens since the last assessment.

Participants will be informed at their baseline visit that if they feel any unusual symptoms or signs, they should to contact a member of the study site team or PI about this at any time during the study.

8.3. Recording

Relevant documentation (e.g. hospital notes, laboratory reports) relating to the AE/SAE should be reviewed by the study practitioner. All information relevant to these events will be recorded in standardised forms.

Information to be collected includes dose, type of event, onset date, assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

8.4. Evaluation

Each initial AE will be considered for seriousness, causality, severity and expectedness. Serious cases that are considered at least possibly related to

the CHM are likely to temporarily withdrawn from the interventional aspect of the study as further assessment may be required. Depending on circumstances, it is possible for initial AEs to be reclassified as a SAE and likewise for an SAE to be reclassified to an AE.

8.4.1. Assessment of Seriousness

This should differentiate between an AE and an SAE according to the definitions provided in section 8 Adverse Events and Serious Adverse Events.

8.4.2. Assessment of Severity

A record of the severity of the AE/SAE should be noted according to the following descriptions:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities

Severe: An event that prevents normal everyday activities

Please note that the term 'severe' used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria.

8.4.3. Assessment of Causality

The study practitioner should make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

Unrelated: Where an event is not considered to be related to the study medications.

Possibly: Although a relationship to the study medications cannot be ruled out, other explanations are possible for reasons such as the nature of the event, the underlying disease and concomitant medication.

Probably: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study medications.

Definitely: The known effects of the study medications suggest that it is the most likely cause.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the CHM, or interactions between the CHM and another drug or intervention will be considered as Adverse Reactions/Serious Adverse Reactions (ARs/SARs). All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the CHM and another drug or intervention will also be considered to be ARs/SARs.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered. The blind should not be broken for the sole purpose of making this assessment of causality.

8.4.4. Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented as an expected side-effect, detailed earlier in section 5.4.5 CHM Side-effects.

Expected: An AR, the nature or severity of which is considered against information provided in section 5.4.5 CHM Side-effects.

Unexpected: An AR, the nature or severity of which is not consistent with information in section 5.4.5 CHM Side-effects.

8.4.5. Reporting

8.4.5.1. AEs

As AEs are not classified as being serious, then it is not required that they be reported to the study sponsor. Instead, they will be evaluated and recorded following the procedures specified in the above sections 8.4.1 Assessment of Seriousness, 8.4.2 Assessment of Severity, 8.4.3 Assessment of Causality and 8.4.4 Assessment of Expectedness.

8.4.5.2. SAEs

All SAEs should be reported immediately by telephone or by email to the study sponsor within 24 hours of learning of the event.

An SAE form must then be provided to the study sponsor and which should be:

- completed as thoroughly as possible with all available details of the event;
- signed by the study practitioner or member of the study team;
- faxed or scanned and emailed to the study sponsor within 24 hours of becoming aware of the event.

The SAE form must provide an assessment of causality and expectedness at the time of the initial report to the study sponsor according to sections 8.4.3 Assessment of Causality and 8.4.4 Assessment of Expectedness. If all required information is not available at the time of reporting, the study practitioner must ensure that any missing information is provided as soon as it becomes available. It should be indicated on the form that this information is follow-up information of a previously reported event.

In light of follow-up information, opinions regarding causality can be changed and recorded on the SAE form accordingly.

Assessment of the need for supplementary investigations of SAEs should be made based on clinical judgement of the likely causative factors. Where a need has been determined and is feasible within the timeframes and resources available to the study team, supplementary investigations may be conducted such as seeking specialist opinion or performing additional tests. These investigations may require information to be provided from the study team for example regarding the CHM products or from clinical notes. Blinding will be maintained where possible but where information is urgently required to aid diagnosis or in the provision of medical treatment, unblinding of the study treatment will be required and will follow unblinding procedures as specified in section 4.9 Emergency Unblinding Procedures.

No medical help, diagnosis or advice should be withheld from the participant due to an inability to contact the study sponsor.

8.4.6. Follow Up Procedures

After recording an AE, or recording and reporting an SAE, the study team is required to follow each participant until resolution. Follow up information on an SAE should be reported to the study sponsor as appropriate.

9. Pregnancy

In case of suspected or confirmed pregnancy, participants will be immediately advised to stop taking the CHM and to inform a member of the study team for further advice. If pregnancy is confirmed, the participant will be asked to withdraw from the intervention in the study and asked for their consent to remain for safety monitoring purposes.

Information should be recorded in a Pregnancy Notification Form. The notification form should be submitted to the study sponsor within 14 days of being made aware of the pregnancy.

Attempts should be made by the study team to follow-up on any pregnancy that occurs in a participant during the study until birth.

10. Monitoring and Quality Assurance

10.1. Project Management Group

The project management group will consist of the investigators named in this study protocol.

10.2. Trial Management

The PI will act as trial manager for this study and be held accountable for trial management procedures and checking CRFs for completeness. Any queries will be resolved by consultation between the PI and at least two CIs.

A Delegation Log will be prepared for each study site and for the CHM dispensary, detailing the responsibilities of each member of staff working on the study. A site-investigator will be assigned to each site and who will be responsible for all tasks and duties to be carried out at their site.

10.3. Risk Assessment

Issues relating to risk such as participant reimbursement, confidentiality and data protection are discussed in later sections 11.7, 11.12 and 11.13 respectively. Other issues and risks arising from the study will be discussed below.

Participants may experience anxiety since sensitive information such as weight will be measured during this study. Data will be collected in a sensitive manner for example using questionnaires instead of face-to-face assessments where possible, and providing participants with adequate privacy during study assessments to minimise any potential discomfort.

This research study will involve participants discussing in some detail about their medical history as part of the usual CHM consultation and which could cause anxiety as a result of these discussions. Participants will however have prior knowledge of this and will be fully informed through the provision of a participant information sheet which will detail these processes and the purposes of collecting this information during the study.

Where participants feel they have cause for complaint or wish to raise concerns relating to the conduct of the study, they may approach the PI directly, or the Research Governance Office at any point of the study. Contact details for all parties will be provided in the participant information sheet, in the Participant Emergency Contact card and on the study website.

In the case where a participant is distressed regarding medical issues and where it is relevant, the study team will recommend participants to speak with their GP for further advice or provide participants with details of NHS organisations to contact for further advice.

The study will involve travelling to a number of clinics to conduct study visits. In the case when these study visits occur in the evening and for personal safety, study practitioners will ensure that two colleagues have their contact telephone number, the allocated appointment times and duration, and details of the clinic location. Study practitioners will make arrangements beforehand to contact one of these two colleagues by telephone or email at the end of the last study visit of the day to confirm safety.

11. Good Clinical Practice Module

11.1. Ethical conduct of the study

This study will be conducted according to the Declaration of Helsinki, the ICH-GCP guidelines and the RCHM codes of professional conduct.

The protocol and related documents will be submitted for review by the RCHM Research Ethics Committee (REC) and written approval received before the study can commence.

11.2. Regulatory compliance of the study

This feasibility study is being conducted as part of routine UK CHM practice since both CHM interventions are available for prescription following a consultation by a member of the public with a registered practitioner. According to the Research Governance Framework, this study is considered to be a service evaluation of routine CHM practice and will not be considered as research that is undertaken within the NHS. It therefore does not fall under the governance of the EU Directive 2001/20/EC or the Medicines for Human Use (Clinical Trials) Regulations 2004 according to the Medicines and Healthcare Regulatory Agency (MHRA). The study team has received written confirmation for this by the MHRA Clinical Trials Unit Manager, a copy of which is provided in Appendix 36. All herbs dispensed in this study will be compliant with the UK professional regulatory guidance for CHM offered by the RCHM and the European Directive on Traditional Herbal Medicinal Products (THMPD) 2004/24/EC.

This study will not commence until ethical approval from the RCHM REC and insurance approval from the University of Southampton has been obtained.

11.3. Study audit

The study team will permit monitoring and audits by the sponsor during the study and will provide direct access to source data and documents for auditing purposes.

11.4. Patient and Public Involvement (PPI)

As per NIHR requirements for public and patient involvement in research, two PPI representatives were involved in the development of the PIS for this study. The PPI panel consisted of one patient with PCOS and one male representative who had taken CHM for digestive issues. These representatives were invited for feedback on the study's PIS including clarity of what was being asked of participants in our study and suggestions of what other information they may wish to see if they were study participants.

All comments and suggestions that were made have been taken into consideration whilst developing the PIS. The comments that were made by the panel and subsequent action points are summarised in a PPI report presented in Appendix 36.

11.5. Investigator responsibilities

The PI is responsible for the overall conduct of the study, compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, responsibilities that are listed later in this section also belong to the PI. Responsibilities may be delegated to the site-investigator and members of the study site team. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

The PI has received training for the GCP module to ensure that this study conforms to expected requirements of the RCHM REC. A copy of this training certificate can be viewed in Appendix 38.

11.6. Informed consent

Written informed consent from each participant will be obtained prior to participation in the study in accordance with ICH GCP guidelines, Declaration of Helsinki 2000 and RCHM requirements.

The decision to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants will receive adequate oral and written information through the provision of the PIS and CF, which can be seen in Appendix 31 and Appendix 34 respectively.

Oral explanation will be given to the participant and will cover all the elements specified in the PIS or CF.

The participant will be provided sufficient time to consider the information provided. The participant may withdraw their consent to participate at any time of the study without loss of benefits to which they would otherwise be entitled.

The participant should be informed and agree to their medical records being inspected by regulatory authorities and will be informed that their name will not be disclosed outside of the study team and study practitioners.

The participant will sign and date the CF to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed with study documents.

11.7. Participant reimbursement

Participants will not be reimbursed for out of pocket expenses such as travel expenses, inconvenience and time involved for routine study procedures. This will be clearly described in the web-based screening, Participant Information Sheet and with a further reminder during the baseline visit prior to obtaining consent.

If the study is terminated prior to completion, or a participant withdraws or is withdrawn from the study before completion, no reimbursement will be available for inconvenience and time involved.

11.8. Emergency contact with investigators

All participants will be provided with a Participant Emergency Contact Card with contact details of whom to contact in case of an emergency. In case of complaint, all participants will also be provided with contact details of the PI,

another member of the study team, and a representative of the University's research governance office.

11.9. Notification of GP

With consent from each participant, the participant's GP will be notified of participation in the study at the beginning of the study. A letter will be sent to the GP providing notice of their patient being part of a clinical study with a brief description of the nature of the study. Contact details of the study team will also be provided where enquiries can be directed. An example of the letter can be seen in Appendix 35.

Where consent is refused by the participant, this will be documented by the study team and their GP will not be contacted but they will remain eligible for inclusion onto the study.

11.10. Study site staff

The PI must ensure that the site-investigators and study site staff involved are familiar with the CHM interventions, the protocol and the study requirements. It is the PI's responsibility to ensure that all assisting with the study are adequately informed about their related duties throughout the study process.

11.11. Data recording

Site-investigators will be responsible for checking the quality of the data recorded in the CRF. The PI is responsible for checking the quality of all CRF data upon receipt.

11.12. Confidentiality

All point-of-care test specimens, evaluation forms, reports and other records will be identified in a manner to maintain participant confidentiality and in accordance with the Data Protection Act 1998. All records will be kept in a secure storage area on site with access restricted only to staff delegated duties on the study. Clinical information will not be released without the written permission of the participant, except in cases of emergency or as necessary for

monitoring and auditing by the study sponsor. The three sites where data will be stored are:

- Revive Sports Rehabilitation & Acupuncture Clinic (satellite data storage site for Berkhamsted, Hemel Hempstead and Primrose Hill clinics)
- The Women's Health Natural Practice (data storage site for Richmond clinic)
- Phoenix Medical Direct (data storage site for Chinese herbal prescription data)

Data, clinical records and any other confidential information cannot be disclosed during the study for any purpose other than for recording the performance of the study. Where disclosure of this information is required during the study for other purposes it may be appropriate to consult the study sponsor.

Secure disposal of participant-identifiable information will be ensured using methods such as paper shredding.

Where possible, contact with the participant will not immediately allude to their participation in a clinical study for a medical condition. For example, study information will not be contained within email subject headings and will have general subject headings such as 'Information required' or 'Appointment confirmation'. Voicemail messages left for the participant will likewise be general and follow scripts such as 'Hello, this is a message for Ms X. It's Lily here, calling regarding some further information we need from you to complete our paperwork. Could you give me a call back at your earliest convenience on the phone number XXX, many thanks.' Whilst access to personal voicemail messages and email could be considered the responsibility of the participant, the study team feels it appropriate to provide an additional layer of protection in this manner.

11.13. Data protection

All study staff must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via usernames and passwords. Information will be kept on an encrypted drive and

backed up on a daily basis. Should the password-protected computer be stolen or mislaid, data from the study will remain available via backups made and access to this data protected from external parties by placing the data on an encrypted drive.

Should secure access to data from the questionnaire software be compromised, a member of the study team will download available data from the website and immediately remove the survey and data.

Disseminated results will not contain any personal identifiable data of individual participants.

The web-based questionnaire software and the study website platform will use secure encryption in the form of Secure Sockets Layer (SSL) which ensures that data sent by participants cannot be obtained by third parties. Access to administrative interfaces is also secured using SSL.

12. Study Administrative Procedures

12.1. Protocol amendments

Any changes in research activity must be reviewed and approved by the PI, unless it is necessary to remove an apparent immediate hazard to the participant. Where such changes to the protocol are not thought to increase the risk of the safety of the participants or the scientific integrity of the study, these will be considered minor amendments that can be approved by the PI with notification of these to the study sponsor.

Where major amendments are proposed, these must be submitted to the study sponsor for approval prior to participants being enrolled into an amended protocol.

12.2. Protocol Violations and Deviations

Any deviations from the protocol should not be implemented without prior agreement from the PI. Where appropriate, it may be necessary to consult remaining members of the study team and the study sponsor.

In the event that the investigator needs to deviate from the protocol, the nature of and reasons for the deviation should be recorded in the CRF. If this necessitates a subsequent protocol amendment, this should be submitted to the study sponsor for review and approval if appropriate.

12.3. Study record retention

Study documentation should be retained for 15 years as per the University of Southampton Faculty of Medicine research guidelines. Participant files and other essential documents must be kept for this period of time in accordance with these requirements.

Should the study documentation be assigned to another party or moved to another location, the study sponsor should be notified.

12.4. Retention of other study specific samples

Retention of voucher specimens of each batch of single herbal granules used on this study will be stored by the CHM dispensary.

12.5. End of study

The end of study is defined as the last participant's last visit. After the last visit, the study team will send out a card to thank participants for their help on this study.

The study team have the right at any time to terminate the study for clinical or administrative reasons.

A summary report of the study will be provided to the sponsor at the end of the study. Study close-out procedures will be conducted to ensure all study data has been checked and submitted from each study site.

12.6. Stopping rules, discontinuation criteria and early termination of the study

For individual patients, temporary discontinuation and withdrawal procedures are outlined in sections 4.7 and 4.8 respectively.

The study may be terminated prematurely by the PI and by the sponsor for reasons including, though not limited to, the following:

- The number and/or severity of AEs justify discontinuation of the study;
- New data become available which raise concern about the safety of the study medications such that continuation might cause unacceptable risks for subjects;
- The study team regard the study no longer feasible to continue due to low recruitment rates or high dropout rates.

The sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects only on grounds for valid scientific or administrative reasons.

Following a decision to terminate a study prematurely, the PI must contact all participants and ensure that the appropriate follow up is arranged for participants. Written notification will also be provided to the study sponsor.

12.7. Continuation of CHM following the end of the study

Study close-out procedures will assess each participant's suitability to continue with CHM administration. Should participants wish to continue with CHM administration, participants will be provided with information for UK CHM regulatory bodies such as the RCHM for them to search for a suitably qualified practitioner. In some cases, participants may be advised to refrain from taking CHM for a period of time, after which point they are permitted to receive CHM.

Study practitioners may continue to treat participants as patients as part of their usual clinical practice and will be permitted to retain copies of the study clinical notes as part of continued clinical care outside of the study.

Participants will be eligible for one free telephone consultation at the end of the study with a herbalist to discuss further treatment options. This will be offered at the final study visit and will be valid for 4 weeks after this final study visit, and has been specified clearly in the PIS.

13. Reporting, publications and notification of results

13.1. Authorship policy

Ownership of the data arising from this study belongs to the study team. On completion of the study, the study data will be analysed and the findings will be prepared in a clinical study report.

13.2. Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. All publications will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement as seen in Appendix 37.

The study team aims to report the results of this study in a peer-reviewed and topically-relevant journal. This will be regardless of the final results of the study and whether the publication suggests that CHM are helpful or not for symptoms of PCOS.

13.3. Summaries of results

Summaries of results will be made available to study personnel involved in the study for dissemination, and to participants of the study.

Appendix 23: Letter Of Confirmation From Medicines Healthcare Regulatory Agency

From: Lewith G. [mailto:gl3@soton.ac.uk]

Sent: 03 April 2012 09:12

To: Godfrey, Dr Elaine

Subject:

Dear Elaine

As I mentioned to you on the phone, we're having very major problems with our suppliers for Lily's polycystic ovary syndrome trial. Sun Ten in Taiwan are clearly not playing ball and our contacts in Australia will have trouble organising things I think and we've probably left it a bit too late in terms of the timing to fly out to Taiwan or China and go through a whole process of meetings to design a placebo controlled trial. This issue has nothing to do with the products. All the products we're planning to use are freely available in the United Kingdom and prescribable by herbalists as a normal part of routine care well as having already existing Australian GMP for each individual herb. Therefore what we're planning to do must be seen as looking at reasonable and normal treatment options within usual clinical practice that would realistically be used by Chinese herbal practitioners in the UK offering treatment to women with PCOS.

We would plan to run the trial in Lily Lai's practice and she's a registered herbalist. There would be two processes of randomisation: the first would be to randomise patients to a waiting list control or immediate treatment because we don't think we could cope with the flow of patients if we did it any other way, and the second would be to randomise the patients who are receiving treatment to receive either a standardised remedy prescribed by Lily Lai or an individualised remedy also prescribed by Lily Lai. Both these remedies would be made up into powders and given to the patients to make as a tea morning and evening with clear instructions about dose.

There would be a variety of research questions that we wish to ask. These would include:

- Can we recruit to a clinical trial like this?
- Is taking Chinese herbal medicines for a period of 6 months (all patients would receive 6 months' treatment) acceptable and are the patients treatment compliant?
- The primary clinical outcome will be regularising the patient's menstrual cycle and we will be providing patients with some simple diaries and outcome measures to assess their quality of life with PCOS as well as their menstrual regularity just prior to and during

treatment.

- We will be using a standard quality of life PCOS questionnaire and we will be evaluating their clinical status at entry and at completion (BMI and waist/hip ratio).
- We will during this study be monitoring safety very carefully and looking at renal and hepatic function.

Effectively we will be monitoring very carefully routine clinical practice and looking at the effects of using Chinese herbs and whether there is any difference between a standardised and individualised remedy in a relatively small sample of patients. We will seek ethics approval from the ethics committee at the RCHM for this study

With best wishes

George

Professor George Lewith

Prof George Lewith

www.cam-research-group.co.uk

www.collegeofmedicine.org.uk

From: Godfrey, Dr Elaine [mailto:Elaine.Godfrey@mhra.gsi.gov.uk]

Sent: 03 April 2012 18:15

To: Lewith G.

Subject: RE:

Dear George

Thank you for this summary. I can confirm that a protocol developed from the outline provided would not constitute a CTIMP trial provided that it was clearly written to show that the comparison is between individualised remedies versus standardised remedies rather than being a study into the efficacy of Chinese herbs for the treatment of PCOS. The bullet points are fine, it is only the sentence in the final paragraph that would need clarification (whether there is any clinical benefit in using Chinese herbs).

Hope this helps.

Elaine

From: Lewith G.

Sent: 03 April 2012 19:17

To: 'Godfrey, Dr Elaine'

Cc: lilylai@acupunctureandherbs.co.uk; 'Andrew Flower'; 'glewith@scmrt.org.uk'; Moore M.V.

Subject: RE: RE:

Thank you Elaine. This is very clear. The issue around CHM having any clinical benefit is solely related to this being a simple clinical outcome study NOT a study of specific efficacy. We do not plan to use a placebo but simply to monitor patients' perceptions of the outcome of treatment and we would *not* be in a position to make any specific claims about the treatment. This will simply improve our systematic understanding of these treatments and the processes involved in any future study (recruitment, adherence, cost etc). This data will allow us to progress to a placebo controlled RCT if the outcomes indicate this is reasonable.

Does this clarify our position and is this acceptable to the MHRA? Bw George
Prof George Lewith

www.cam-research-group.co.uk

www.collegeofmedicine.org.uk

From: Lewith G. [mailto:gl3@soton.ac.uk]

Sent: 24 April 2012 17:39

To: Godfrey, Dr Elaine

Cc: George Lewith

Subject: FW: RE:

Importance: High

Dear Elaine,

As we just discussed this afternoon on the phone we will change the last paragraph so that it is clear that this trial is within the context of routine clinical practice.

The last para did read;

Effectively we will be monitoring very carefully routine clinical practice and looking to see whether there is any clinical benefit in using Chinese herbs and whether there is any difference between a standardised and individualised remedy in a relatively small sample of

patients within the context of a pilot trial. We will seek ethics approval from the ethics committee at the RCHM or EHTPA for this study.

The last para will now read;

Effectively we will be monitoring very carefully routine clinical practice and looking at the effects of using Chinese herbs and whether there is any difference between a standardised and individualised remedy in a relatively small sample of patients. We will seek ethics approval from the ethics committee at the RCHM for this study.

Is this now acceptable? Other small changes from the original email are highlighted in yellow

Many thanks for talking to me this evening and for your good wishes

Bw George

Prof George Lewith

www.cam-research-group.co.uk

www.collegeofmedicine.org.uk

From: Godfrey, Dr Elaine [mailto:Elaine.Godfrey@mhra.gsi.gov.uk]

Sent: 24 April 2012 17:41

To: Lewith G.

Subject: RE: RE:

Dear George

This looks fine now.

Best wishes

Elaine

From: Lewith G.

Sent: 24 April 2012 17:50

To: 'Godfrey, Dr Elaine'

Subject: RE: RE:

Thanks very much Elaine

Prof George Lewith

www.cam-research-group.co.uk

www.collegeofmedicine.org.uk

Appendix 24: Table To Show Feasibility And Study Objectives With Justifications

Objectives in feasibility and pilot study	Justification in the context of the main study
Scientific	
To obtain data on treatment effects at 6 months in menstrual frequency and variability of cycle length	To provide scientific data to support sample size calculations for a main study
To obtain data on treatment effects at 6 months on obesity, quality of life, hirsutism	To explore whether worthy of further investigation as an outcome measure in the main study
To assess liver and kidney functions, and adverse effects of CHM	To determine safety and acceptability of CHM for main study
To explore impact of covariates on study outcomes	To inform statistical analysis, the design and recruitment for main study
To exploring between-group and within-group treatment effects on menstruation when using menstrual data recorded after the study intervention has been administered for 3 months	To assess differences in treatment effects when using post 3 month menstrual data
Process	
To estimate percentage of missing menstrual data at baseline and at 6 months and an assessment of reliability	To evaluate usefulness of measuring menstrual data as outcome measure, and to inform design of main study
To determine eligibility rate from those responding to our recruitment methods	To examine restrictiveness of our eligibility criteria
To estimate percentage of diagnosed and undiagnosed women with PCOS who are recruited	To enable planning of study resources and to inform recruitment plan
To pilot recruitment, eligibility screening, data collection, statistical analysis methods	To examine overall efficiency and highlight problems in study methods
To pilot involvement of CHM dispensary and study practitioners and evaluate study experiences of study personnel	To examine overall efficiency and highlight problems experienced
To determine the overall and monthly consent rate by study site	To determine variation in recruitment based on geographical location of study sites
To determine the overall and monthly consent rate by recruitment method	To determine the most cost-effective recruitment methods for use in the main study To determine time lag between initiation of recruitment method to participant recruitment to aid recruitment planning in the main study

To determine the overall and monthly consent rate from those eligible	To determine patterns in overall recruitment for the duration of the study To explore the initial acceptability to participants after being provided information regarding the intervention and of the study procedures
To determine the randomisation rate from those consenting and assess reasons for refusing randomisation	To explore the acceptability to participants of being randomised
To determine the retention rate, withdrawal rate and loss to follow up and assess reasons for withdrawal and loss to follow up	To explore acceptability to participants of the intervention and of the study procedures
To determine security of blinding	To inform us of the value of attempting to blind in this study design
To determine security of randomisation and allocation procedures	To check procedures were conducted as planned
To determine adherence to CHM administration and assess reasons affecting adherence	To examine acceptability of the CHM and of the dosing regimens to participants and conduct a preliminary exploration of dose-response and safe-dosing parameters
To determine adherence to protocol and assessing CHM consultation rates and reasons affecting consultation rates	To assess feasibility of participants being seen as expected in routine practice
To determine number and percentage of participants unable to continue with full and minimum study doses.	To assess acceptability of the routine and minimal prescribed dosages of CHM
To collect contents of individualised CHM prescriptions	To provide a list of single herbs prescribed and examine patterns of use
To collate a list of Chinese medical diagnoses	To determine most common presentations in PCOS for this study
To record content of lifestyle and dietary advice offered as part of consultations	To provide a list of advice offered routinely as part of CHM prescribing
To pilot data collection methods	To highlight any issues arising from collection data on proposed outcome measures
To determine percentage of missing data by data collection method	To compare efficiency of different methods and investigate ways of improving efficiency
To pilot statistical analysis	To ensure that proposed statistical analysis for the main study can be performed on the data collected
To obtain feedback from participants and study sites	To inform design and conduct of main study
To collate data on symptoms and signs most important to women with PCOS	To inform choice of primary and secondary outcome measures
Resources	

To determine time required per patient for study processes e.g. telephone screening, baseline and study visits	To provide data for resource management of main trial
To determine capacity and management issues from multiple study sites	To highlight particular problems that could require revision to study management

Appendix 25: Rotterdam Diagnostic Criteria For Polycystic Ovary Syndrome

Revised Rotterdam 2003 criteria

1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries

And exclusion of other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumours, Cushing's syndrome).

Reference:

2004. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*, 19, 41-7.

Appendix 26: Fast Alcohol Screening Test (FAST) Questionnaire

Fast Alcohol Screening Test (FAST)

For the following questions please circle the answer which best applies.

1 drink = 1/2 pint of beer or 1 glass of wine or 1 single spirits

- 1 MEN: How often do you have EIGHT or more drinks on one occasion?
WOMEN: How often do you have SIX or more drinks on one occasion?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily

- 2 How often during the last year have you been unable to remember what happened the night before because you had been drinking?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily

- 3 How often during the last year have you failed to do what was normally expected of you because of drinking?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily

- 4 In the last year has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

No	Yes, on one occasion	Yes, on more than one occasion

Reference:

HODGSON, R., ALWYN, T., JOHN, B., THOM, B. & SMITH, A. 2002. The FAST Alcohol Screening Test. *Alcohol Alcohol*, 37, 61-6.

Appendix 27: Alcohol Use Disorders Identification Test (AUDIT)

Box 10

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest.

Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

Reference

BABOR, T., HIGGINS-BIDDLE, J., SAUNDERS, J. & MONTEIRO, M. 2001. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. *In*: DEPENDENCE, D. O. M. H. A. S. (ed.). World Health Organisation.

Appendix 28: Example of Participant Recruitment Flyer

Do you have polycystic ovary syndrome (PCOS)? Are you interested in using herbs to help?

Chinese herbs can be used to help women with PCOS in a number of ways such as:

- Regulating your **periods**
- **Preparing** your body for conception
- Managing your **weight**
- Help with skin problems such as **acne** and **hirsutism**
- Improving **emotional wellbeing** and **stress**.

You could be eligible for up to **6 months'** worth of Chinese herbal treatment **free of charge** as part of an **NHS-funded** research study led by the University of Southampton.

For more information about this study, please contact Lily quoting 'Orchid' on:

07815 885 947
info@ChineseMedicineResearch.co.uk

or visit the **ORCHID** study website:
www.ChineseMedicineResearch.co.uk






**National Institute for
Health Research**

Appendix 29: Example Of Request For Practitioner Referrals

Do you have patients with polycystic ovary syndrome? Could you support us in our herbal research project?



As part an **NHS-funded** research study led by the University of Southampton, we are looking for women who could join our study and who have polycystic ovary syndrome (PCOS).

We are asking if **medical professionals** and **complementary health practitioners** like you could help us by:

- Referring existing PCOS patients to the study
- Directing new PCOS patients to the study
- Helping us to publicise this study amongst your colleagues and patients.

Women would be eligible for up to **6 months'** worth of Chinese herbal treatment **free of charge** and would be closely monitored throughout the study by the study team consisting of two Chinese medical herbalists and two GPs. All herbs used in the trial are **GMP-certified** and have been approved for use in this study by an **ethics committee**.

For more information about this study, please contact the principal investigator Lily quoting 'Orchid' by telephone on 07815885947, or by email on info@ChineseMedicineResearch.co.uk.

For more details, you can also visit the **Orchid** study website:

www.ChineseMedicineResearch.co.uk

UNIVERSITY OF
Southampton

NHS
**National Institute for
Health Research**

Appendix 30: ORCHID Study Website Screenshots

The Orchid Study

RESEARCHING CHINESE HERBAL MEDICINE FOR POLYCYSTIC OVARY SYNDROME



[HOME](#)
[ABOUT THE STUDY](#)
[ABOUT US](#)
[REGISTER](#)
[ENQUIRY](#)
[USEFUL INFORMATION](#)
[LOGIN](#)

Welcome

Thank you for your interest in the Orchid study.

The Orchid study involves using Chinese herbal medicines for symptoms and problems experienced by women with polycystic ovary syndrome (PCOS). This study has been funded by an NHS research organisation and is led by a team of GPs and researchers from the University of Southampton.

The purpose of this website is to provide patients, healthcare providers and associated organisations with further information about the Orchid study.

After you have read this information...

Do you have PCOS?

If so and you are interested in receiving more information about the study, register to receive updates [here](#).

If you are interested in taking part in the study, register to join [here](#).

Do you know somebody with PCOS?

Whether they are a family member, a friend or a patient, if you think they may be interested in finding out more information about the study, please feel free to forward them the link to this website. You may also wish to find out more information about the study before speak with them, so please feel free to register to receive more information [here](#).

This Research is Supported By




National Institute for Health Research
School for Primary Care Research

Join The Study

Search

Contact Us

[Register for more information](#)

[Make an enquiry](#)

[Join the study](#)

Study Updates

This will feature an RSS feed of the study blog.

Copyright © 2012, University of Southampton. All rights reserved.



The Orchid Study

RESEARCHING CHINESE HERBAL MEDICINE FOR POLYCYSTIC OVARY SYNDROME



HOME ABOUT THE STUDY ABOUT US REGISTER ENQUIRY USEFUL INFORMATION LOGIN

About the study

Background to the study (5 entries)

- What is polycystic ovary syndrome?
- Why is this research being done?
- What is the Orchid study?
- What is a feasibility and pilot study?
- Why is it called the Orchid study?

During the study (11 entries)

- Who can take part in the study?
- What will the study involve?
- Where will the study take place?
- What benefits could there be if I take part?
- What disadvantages or risks could be involved if I take part?
- Can I try for a baby whilst taking these herbs?
- Will my expenses be covered?
- After I have joined the study, can I withdraw if I change my mind?
- What happens if I have a question?
- What happens if I want to make a complaint?
- Will my taking part in this study be kept confidential?

About your herbs (4 entries)

- Are the herbs safe?
- Will I have to spend a long time boiling herbs every day?
- How do I take the herbs?
- Are there any side-effects with herbs?

Management of the study (3 entries)

- Who has approved this study?
- Who is funding this research?
- Who is organising this research?

Joining the Study (2 entries)

- How do I join the study?
- What do your pre-study checks involve?

After the study (2 entries)

- Can I carry on with my herbs after the study has finished?
- Will I have access to the research findings?



Join The Study

Search

Contact Us

Register for more information

Make an enquiry

Join the study

Study Updates

This will feature an RSS feed of the study blog.

The Orchid Study

RESEARCHING CHINESE HERBAL MEDICINE FOR POLYCYSTIC OVARY SYNDROME



[HOME](#)
[ABOUT THE STUDY](#)
[ABOUT US](#)
[REGISTER](#)
[ENQUIRY](#)
[USEFUL INFORMATION](#)
[LOGIN](#)

About the study > Background to the study (5 entries)

- What is polycystic ovary syndrome?

What is polycystic ovary syndrome? Polycystic ovary syndrome (PCOS) is a common condition that affects many women in the UK. Some of the symptoms ...
- Why is this research being done?

There are a number of treatments that are available to women with PCOS. However, not all treatments are suitable and some women with PCOS end up looking for other treatment ...
- What is the Orchid study?

The Orchid study is a feasibility and pilot study. This kind of study will not be able to tell us with certainty whether one treatment is more effective ...
- What is a feasibility and pilot study?

Before we can conduct a larger effectiveness study, important information can be collected by firstly doing a feasibility and pilot study. The feasibility part of the study will help ...
- Why is it called the Orchid study?

'ORCHID' is the acronym that is made up of the underlined letters in the full study title that is shown below:
Polycystic O vary Syndrome: A R andomised Feasibility ...

This Research is Supported By



Join The Study

Search

Contact Us

Register for more information
Make an enquiry
Join the study

Study Updates

This will feature an RSS feed of the study blog.

Copyright © 2012, University of Southampton. All rights reserved.



Appendix 31: Participant Information Sheet For ORCHID Study

UNIVERSITY OF
Southampton

Medicine

NHS
National Institute for
Health Research



Participant Information Sheet

The **ORCHID** Study:

**Polycystic Ovary Syndrome: Randomised feasibility pilot study using
Chinese Herbal medicine to explore impact on Dysfunction**

Principal Investigator: Lily Lai

Ethics Number: <Insert after approvals>

We are writing to invite you to take part in a research study involving Chinese herbs for polycystic ovary syndrome (PCOS). Before you decide whether or not to take part in the study, it is important for you to understand why the research is being done and what it will involve. This information sheet provides further details about the study - please take some time to read it carefully. If you are happy to participate, you will be asked to sign a consent form stating that you have read this information.

What is the purpose of the study?

Chinese herbs have long been used and researched in China and other countries in the Far East for symptoms of polycystic ovary syndrome (PCOS). It is one of the main traditional Chinese medical treatments and is often used instead of, or alongside, acupuncture for PCOS.

We would like to investigate the use of herbs for PCOS by carrying out a feasibility and pilot study. The feasibility part of the study will help us see if it is possible, or feasible, to carry out a full-scale clinical trial on the NHS. For example, we will be able to see if women with PCOS are interested in using herbs for their symptoms. The pilot part of the study will enable us to do a practice-run of study procedures such as arranging appointments and filling out forms so that we can plan our processes better for a full-scale trial.

Why have I been approached?

We are inviting women aged 18-44 with PCOS to take part in this study. You may have expressed an interest about the study and asked for more information. Your healthcare provider or complementary therapist may also have provided you with this information because they felt that you may be interested.

Are Chinese herbs safe?

Chinese herbs are usually very safe when prescribed by a qualified herbalist. The herbs in this study are routinely prescribed in the UK for symptoms of PCOS and are manufactured according to Good Manufacturing Practice (GMP). This is a recognised quality assurance standard that is required by the Register of Chinese Herbal Medicine, the UK's main herbal regulatory body.

Herbs are sometimes associated with side-effects such as diarrhoea, loss of appetite and headaches in the first 48 hours and will usually subside after this time. However, you will be closely monitored throughout the study by fully qualified and experienced herbalists and any medical issues that do arise will be escalated to a registered medical doctor on our study team.

Do I have to take part?

Taking part in this study is entirely voluntary.

What should I expect if I take part in this study?

You will be prescribed one of two types of Chinese herbs for 6 months. You will have a 50/50 chance of receiving either type of herbs which will be decided randomly by a computer. During the study, neither you nor your herbalist will know which type of Chinese herbs you are taking. Over the 6 months, we will ask you to fill out some questionnaires, undergo some assessments and attend clinic visits to see a herbalist for consultations. Further details are provided overleaf in Table 1.

Table 1: Outline of study tasks

Timeline	Location	What you will be asked to do	Duration
Pre-study	Telephone (study team)	Answer some questions about your medical history.	20-30 minutes
	Online/paper	Fill out questionnaires about your symptoms, how you feel about PCOS and general wellbeing.	20 minutes
Week 0	Study clinic (herbalist)	Opportunity for you to ask further questions about the study. If you agree to participate, your herbalist will ask you to complete and sign a consent form. 10-15 minute Chinese herbal medicine consultation to ask about your symptoms and general wellbeing. Other checks: blood test (finger prick or from arm), some measurements (weight, height, waist, hip), a brief assessment of hair growth on your back, thighs and face.	45-60 minutes
	Online/paper	Fill out questionnaire to see how you feel about the study so far.	5 minutes
Week 2	Study clinic (herbalist)	Follow-up Chinese herbal medicine consultation to check your symptoms and general wellbeing.	10-15 minutes
Week 4	Study clinic (herbalist)	Follow-up Chinese herbal medicine consultation to check your symptoms and general wellbeing. Blood test (finger prick or from arm).	10-15 minutes
	Online/paper	Fill out questionnaire to see how you feel about taking the herbs.	5 minutes
Weeks 8 and 12	Study clinic (herbalist)	Follow-up Chinese herbal medicine consultation to check your symptoms and general wellbeing. Week 12: Bring any unused herbs to this visit.	10-15 minutes
Weeks 16 and 20	Study clinic or telephone (herbalist)	Follow-up Chinese herbal medicine consultation to check your symptoms and general wellbeing.	10-15 minutes
Week 24	Online/paper	Fill out questionnaires about your symptoms, how you feel about PCOS and general wellbeing.	20 minutes
	Study clinic (herbalist)	Follow-up Chinese herbal medicine consultation to check your symptoms and general wellbeing. Other checks: blood test (finger prick or from arm), some measurements (weight, height, waist, hip), a brief assessment of hair growth on your back, thighs and face. Bring any unused herbs to this visit.	30 minutes
	Online/paper	Invitation to provide study feedback by questionnaire.	15-30 minutes

Who has approved this study?

This study has received ethical approval from the Register of Chinese Herbal Medicine, the UK's main herbal regulatory body. This ethics committee ensures that the study is conducted according to internationally recognised ethical principles as described in the Declaration of Helsinki.

The University of Southampton Research Governance Office has also checked that the expected requirements for insurance purposes are met.

Who is funding or organising this research?

This research study is being funded by the National Institute for Health Research, a Department of Health organisation that funds research relevant to the NHS. It is organised by a study team consisting of GPs and researchers within the University of Southampton's Faculty of Medicine division of Primary Medical Care.

Where will the clinic visits be held?

Visits will be in Berkhamsted/Hemel Hempstead (Hertfordshire), and in Primrose Hill/Richmond (London). Depending on the clinic, daytime and evening appointments will be available on some weekdays and on weekends. We will endeavour to arrange for your visits to be at a location and time convenient to you.

How do I take the herbs?

Your herbs will be sent to you after each consultation with the herbalist and you will receive powdered herbs in plastic bottles. A plastic measuring spoon will be provided for you to measure the correct dose of herbs. You will place your dosage of herbs into an empty mug and mix with hot water to make into an 'instant' tea that can be taken straight away. You will initially be asked to take this twice a day - morning and evening. If you are finding it difficult to take the herbs or if you are going away on holiday, please ask your herbalist who will be able to offer you further suggestions and advice, or organise a temporary break from taking the herbs.

Can I continue with my usual medications or treatments during the study?

In most cases, this will not be a problem. However, the use of some medications and treatments is restricted for safety reasons. A member of the study team will go through these with you in the pre-study check.

What benefits could there be if I take part?

The Chinese herbs and consultations with experienced herbalists that you will be entitled to during this study would typically cost £800-1000. The herbs used in this study are prescribed for symptoms of PCOS and you could experience relief from symptoms and an increase in your general wellbeing. You will also be benefiting from careful monitoring throughout the study by experienced herbalists. Your participation in this study will also be helpful in supporting further research into other potential treatments for women with PCOS.

What disadvantages or risks could be involved if I take part?

As mentioned earlier, herbs are occasionally associated with side-effects such as diarrhoea, loss of appetite and headaches in the first 48 hours. These usually subside after 48 hours and will be monitored closely by your herbalist. Herbs can sometimes aggravate symptoms but this is usually temporary and will be closely monitored by your herbalist. You may experience minor discomfort or bruising following the blood test.

Are the herbs suitable for use whilst trying for a baby?

The Chinese herbs that will be prescribed in this study may be helpful for preparing your body for conception. However, the safety of the herbs in this study has not been formally tested during pregnancy and we strongly discourage participants from actively trying for a baby whilst taking these herbs during the study. It will be safe for you to try for a baby immediately after stopping the herbs.

Will my taking part in this study be kept confidential?

Yes, all data collection and storage procedures will adhere to the Data Protection Act 1998 and will only be accessed by authorised persons who are study personnel or competent authorities who need to audit the study processes. Any information you give that is collected during this study will be anonymised, treated as strictly confidential and only used for medical research. Study data may be used by other research institutions but confidence and anonymity will be strictly maintained. Study data will be stored securely for a minimum of 15 years as per University of Southampton guidelines.

Can I withdraw if I change my mind after I have joined the study?

Yes, you are free to withdraw from the study at any point and for any reason. The study team will invite you to attend a withdrawal visit and will ask you to complete some further information, though you are not obliged to attend this visit nor provide any further information if you do not wish to. The information that you have provided up until the point that you withdraw will contribute to the final analysis of the study. After you have attended the withdrawal visit, you will not be contacted by the study team for any further information.

What expenses will be covered?

All participants taking part in this trial will receive all Chinese herbs and consultations free of charge. We will however be unable to reimburse you for expenses that may be incurred such as travel costs.

Can I continue with my Chinese herbal treatment after the study has finished?

At the end of the study, we will ask you to return any unused herbs that were sent out to you during the study. After this end-of-study visit, you may continue to see your herbalist privately. If you would like to visit another herbalist, we can provide you with details of herbalists who are members of professional herbal regulatory bodies such as the Register of Chinese Herbal Medicine.

Will I have access to the research findings?

Yes, all participants will be entitled to receive a summary report of the study findings following data analysis.

What happens if I want to make a complaint?

All complaints and concerns relating to this study will be taken seriously and can be directed at any time to:

Principal Investigator (PI): Lily Lai, Primary Medical Care, Faculty of Medicine, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, Hampshire, SO16 5ST
<insert telephone after approvals> info@ChineseMedicineResearch.co.uk

Research Governance Office (RGO): Dr. Martina Prude, Head of Research Governance, Research Governance Office, Corporate Services, George Thomas Building 37, Room 4055, University of Southampton, University Road, Highfield, Southampton, SO17 1BJ
[023 8059 28848, M.A.Prude@southampton.ac.uk](mailto:M.A.Prude@southampton.ac.uk)

Where can I get more information?

More information can be found on the study website at: www.ChineseMedicineResearch.com.

You can also contact the principal investigator Lily Lai at any time for further information by email on info@ChineseMedicineResearch.co.uk, or by telephone on <insert after approvals>.

How can I register to participate?

You can register your participation using one of the three ways:

1. By visiting our study website: www.ChineseMedicineResearch.com and following the link to the questionnaire to register.
2. By emailing Lily on info@ChineseMedicineResearch.co.uk, requesting further information.
3. By calling Lily on <insert after approvals>.

Thank you for taking the time to read this information sheet and for considering taking part in this study.

With kind regards,

Lily Lai and the ORCHID study team

Appendix 32: Web-Based Screening Questionnaire For ORCHID Study

Chinese herbal medicine for polycystic ovary syndrome: Initial assessment (Copy)

 Response data will not be saved in this preview mode. This will affect any section logic you have applied as previous response data cannot be viewed and verified.

Thank you for your interest in this Chinese herbal medicine study.

This study is supported by the National Institute for Health Research, a UK government body that funds research for the National Health Service (NHS).

It is being co-ordinated by a team of researchers at the University of Southampton and has received ethical approval from the Register of Chinese Herbal Medicine.

In this study, we will be asking women to take Chinese herbal medicines for up to 6 months and to provide some information about their symptoms during the course of the study. All Chinese herbal medicines and consultations to the value of £800-1000 will be provided at no cost to participants in this study.

As part of the study procedures, it is important for us to check a few things to ensure that you are able to take part.

Please complete the following questions. We will be in touch again by email after we have received your information.

☐ Please tick (check) this box to indicate that you consent to taking part in this survey

[Click here to start this survey](#)



Chinese herbal medicine for polycystic ovary syndrome: Initial assessment (Copy)

1. Basic information

Question 1.

So that we can get in touch with you after you have completed this questionnaire, please provide your contact details here.

We will never forward your details to third parties, marketing companies or research institutions. If we contact you, it will be in relation to your enquiry about this study.

First name	
Last name	
City/town of residence	
Address Line 1	
Address Line 2	
Address Line 3	
Town/City	
County	
Postcode	
Email address	
Please re-enter your email address	
Telephone number	

Question 2.

When is the best time to contact you by telephone:

On weekdays?

On weekends?

Question 3.

How did you hear about this study? (please tick all that apply)

- ☐ My doctor
- ☐ Chinese medicine practitioner
- ☐ Other practitioner
- ☐ Study website
- ☐ Charity group
- ☐ Poster/flyer
- ☐ Friend
- ☐ Family member
- ☐ Facebook
- ☐ Twitter
- ☐ Email circular
- ☐ Newsletter
- ☐ Newspaper/Magazine
- ☐ Search engine results eg. Google/Yahoo
- ☐ Scanned QR code
- ☐ LinkedIn
- ☐ Other

Question 4.

What is your date of birth?

/ /

Survey Progress

Start ☐ ☐ ☐ Finish

[Save and Continue](#)

Chinese herbal medicine for polycystic ovary syndrome: Initial assessment (Copy)

2. Study processes information

Question 1.

For this study, we will be seeing participants from more than one location. Please indicate below how convenient each location is for you.

Primrose Hill, London	Please select
Richmond, London	Please select
Berkhamsted, Hertfordshire	Please select
Hemel Hempstead, Hertfordshire	Please select

Survey Progress

Start ☐ ☒ ☐ Finish[Back a page](#)[Save and Continue](#)

Chinese herbal medicine for polycystic ovary syndrome: Initial assessment (Copy)

3. Overview of medical history

This section will ask you about some aspects of your medical history.

Question 1.

Which of the following best describes the pattern of your periods in the last 12 months?

- ☐ I get my period every 21-35 days
- ☐ My periods are more than 35 days apart
- ☐ I can go 6 months without a period
- ☐ Other

Question 2.

Have you ever had an ultrasound scan of your ovaries?

- ☐ Yes
- ☐ No

Question 3.

Have you ever had a blood test for the hormone testosterone?

- ☐ Yes
- ☐ No

Question 4.

Do you have excessive hair growth in any of the following areas: face, chest, thighs, buttocks, lower back, lower abdomen?

- ☐ Yes
- ☐ No
- ☐ I'm not sure

Question 5.

Do you have acne?

- ☐ Yes
- ☐ No
- ☐ I'm not sure

Question 6.

Are you currently pregnant?

- ☐ Yes definitely
- ☐ No definitely not
- ☐ I'm not sure

Question 7.

Have you ever breastfed?

- ☐ Yes
☐ No

Question 8.

Have you ever taken Western or pharmaceutical medications for symptoms of PCOS?

- ☐ Yes
☐ No
☐ I'm not sure

Question 9.

Are you currently taking Chinese herbal medicines?

- ☐ Yes
☐ No
☐ I'm not sure

Survey Progress

Start ☐ ☐ ☒ Finish

 **Back a page**

Save and Finish

Once this button is pressed you will not be able edit your

Appendix 33: Study Invitation Letter For ORCHID Study

UNIVERSITY OF
Southampton

Medicine

NHS
National Institute for
Health Research



Research Study Invitation letter

The **ORCHID** Study:

**Polycystic Ovary Syndrome: Randomised feasibility pilot study using
Chinese Herbal medicine to explore impact on Dysfunction**

Principal Investigator: Lily Lai

Ethics Number: <Insert after approvals>

<insert date>

Dear <insert name of potential participant>,

You recently expressed an interest to be contacted about this research project and we are writing to invite you to take part in this study involving Chinese herbs for polycystic ovary syndrome (PCOS).

What is the research about?

Chinese herbs have long been used and researched in China and other countries in the Far East for symptoms of polycystic ovary syndrome (PCOS). It is one of the main traditional Chinese medical treatments and is often used instead of, or alongside, acupuncture for PCOS.

This research is being funded by the NHS and is led by a research team at the University of Southampton.

What should I do next?

We have enclosed a Participant Information Sheet and Consent Form with this letter which we would like you to read through carefully. This will help provide you with more information about why the research is being done and what it will involve and which is important for you to consider before you decide whether or not to take part in the study. Please feel free to discuss with family members and friends if you wish.

I would like some more information:

More information can be found on the study website at: www.ChineseMedicineResearch.co.uk.

You can also contact the principal investigator Lily Lai at any time for further information by email on info@ChineseMedicineResearch.co.uk, or by telephone on <insert after approvals>.

I am interested in joining this study:

You can register your participation using one of three ways:

1. By visiting our study website: www.ChineseMedicineResearch.co.uk and following the link to the questionnaire to register.
2. By emailing Lily on info@ChineseMedicineResearch.co.uk, who will provide you with further information.
3. By calling Lily on <insert after approvals>.

Thank you for taking the time to read this letter, and for considering taking part in this study.

With kind regards,

Lily Lai and the **ORCHID** study team

Primary Medical Care, Faculty of Medicine, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, Hampshire, SO16 5ST

<insert telephone after approvals> info@ChineseMedicineResearch.co.uk

ORCHID Study Invitation Letter, Version 2, Last updated 10/09/2012

1

Appendix 34: Consent Form For ORCHID Study

UNIVERSITY OF
Southampton

Medicine

NHS
National Institute for
Health Research



Consent Form

The **ORCHID** Study:

**Polycystic Ovary Syndrome: Randomised feasibility pilot study using
Chinese Herbal medicine to explore Impact on Dysfunction**

Principal Investigator: Lily Lai

Ethics Number: <Insert after approvals>

In order to show that you have been informed of the study procedures, please **initial** on the dotted lines beside each statement below:

1. I have read and understood the participant information sheet provided to me about this study (Version 3, dated 10/09/2012). I have had the opportunity to consider the information, to ask questions with a member of the study team and have had these questions answered satisfactorily.

.....
Please initial

2. I understand that my participation is voluntary and I am free to withdraw at any time without giving any reason.

.....
Please initial

3. I understand that the information I provide may be used in reporting the study but that these will be anonymised.

.....
Please initial

4. I understand that my identifying information will be stored securely and access to this information restricted to authorised persons.

.....
Please initial

5. I agree to take part in the above study.

.....
Please initial

Signature:

Print name:

Date:

Please give your consent form to your herbalist, or send it back to the study team:

- By email to info@ChineseMedicineResearch.co.uk, attaching a digital copy, or
- By fax to 02380 701 125, or
- By post. A stamped self-addressed envelope is available on request.

With many thanks,

Lily Lai

On behalf of the **ORCHID** study team

Primary Medical Care, Faculty of Medicine, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, Hampshire, SO16 5ST
info@ChineseMedicineResearch.co.uk
<Insert telephone number here after approvals>

Appendix 35: Notification Of Study Participation Letter To GP

Professor George Lewith
University of Southampton
Primary Care and Population Sciences
Aldermoor Health Centre
Aldermoor Close
Southampton
Hampshire
SO16 5ST

<insert GP address>

<insert date>

Dear *<insert GP name>*,

Re: Participation of a patient registered at your practice named *<insert participant's name>* of *<insert address>* in a clinical study led by the University of Southampton.

I am writing to inform you that the above patient has recently self-referred and consented to joining a clinical study. This study involves taking herbal medicines for up to 6 months for symptoms of polycystic ovary syndrome (PCOS). This research is funded by the National Institute for Health Research (NIHR) and has received full ethical approval prior to its commencement. All herbal medicines used in this study are GMP-certified and are prescribed during the study by qualified herbalists who are fully insured and registered with the Register of Chinese Herbal Medicine (RCHM).

Please find attached a copy of the participant information sheet and completed study consent form for your practice records. If you would like further information about this research project, or about the herbs used in this study, please do not hesitate to contact me by telephone on 023 8024 1073 or by email on GL3@southampton.ac.uk. I would be more than happy to discuss any details and answer any queries for you.

With very kind regards,

Professor George Lewith
Professor of Health Research

University of Southampton

Primary Care and Population Sciences, Aldermoor Health Centre, Aldermoor Close, Southampton, Hampshire,
SO16 5ST

Appendix 36: Summary Report Of Comments By Patient And Public Involvement Representatives

Action point	PPI 1	PPI 2
General comments	Mostly succinct and concise, some minor points.	Overall I found it clear and easy to understand.
Clarity regarding what a feasibility study is	Some clarity regarding what a feasibility study is, and clarity with wording	Could a sentence or two be added explaining (briefly) what a randomised feasibility pilot study is, for anyone who doesn't know/ is interested.
More information about Chinese herbs, preparation and administration	NA	Will participants already be using chinese herbs? If not, is it worth adding a couple of lines explaining a bit more about them, for example how they are administered (from my perspective, I've not ever used them so not sure how you actually take them, and how time consuming preparation is).
Clarity regarding safety and potential side-effects	NA	On page 1 'Are chinese herbs safe' it says chinese herbs are usually very safe. Is it worth here referring people to the point on page 3 where you outline potential side effects?
Amend accordingly	NA	In the same paragraph - this is a very tiny point! - I'd expect it to say that herbalists are 'fully qualified and experienced', as I'd see 'fully qualified' as being the bare minimum required, with the experience coming after qualification?
Clarify permitted medications usage	Can I take medications alongside the herbs?	On page 3 - 'Can I continue with my..' - should this say 'usual' medications or treatments - just for clarification?
Clarify permission to try to conceive	Can I try to conceive whilst taking herbs?	NA
Clarify participation duties and how the two interventions will be administered to participants	'What should I expect if I take part' text in this section - Don't fully understand what is involved to take part - key points are Section is a bit tricky to understand. Key points - 6 months of herbs, randomised allocation to two types of herbs, will need to fill questionnaires and consultations over 6 months. Could say that details are provided in the following table. Really like the table/timeline -Weeks 8-20 could be one line as this is repetitive and could make people think there's more work to do than is actually being asked of them.	On page 1 'What should I expect...' I think a word might be missed out of the first sentence as the meaning isn't completely clear at the moment. The word 'offered' suggests to me that I might be able to choose one of the two - this is clarified later but I wonder whether 'used' or something similar would be clearer.

APPENDICES

Provide more information regarding clinic visits	NA	On page 3 'Where will the clinic visits...' - could this be expanded to when and where will the clinics be held, with a bit of information about whether appointments will all be in working hours, or available out of working hours as I imagine this will have implications for some on whether they can participate.
Adding potential saving costs	Cost of herbs? Can you indicate how much free herbs they are getting?	On page 3 - can you add in here the approximate value of the herbs and consultations each participant will be receiving, as I imagine it's quite substantial and might motivate participation from some?
Provide information regarding access to research findings	NA	Will participants be able to have access to the research findings?
Amend accordingly	RCHM - explain abbreviation	NA
Add details regarding anonymisation	Anonymisation of information?	NA
Amend accordingly	Is there a standard procedure and safeguard e.g. insurance if something goes wrong?	NA
Add phone number, consider having email address as: orchid@ChineseMedicineResearch.com	Add phone number to contact PI Email could be a bit difficult to type 'LYWL1G10@southampton.ac.uk' - could you simplify this?	NA
Consider uploading NHS/NIHR logo and Orchid study logo to documentation	Can you make the sheet more interesting / colourful to read?	NA

Appendix 37: Reporting Randomized, Controlled Trials Of Herbal Interventions: An Elaborated CONSORT Statement

*Appendix Table. Proposed Elaborations of CONSORT Items for Randomized, Controlled Trials of Herbal Medicine Interventions**

Paper Section and Topic	Item Number	Descriptor	Reported on Page Number
Title and Abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized" or "randomly assigned"). <i>Either the title or abstract, or both, should state the herbal medicinal product's Latin binomial, the part of the plant used, and the type of preparation.</i>	
Introduction Background	2	Scientific background and explanation of rationale. <i>Including a brief statement of reasons for the trial with reference to the specific herbal medicinal product being tested and, if applicable, whether new or traditional indications are being investigated.</i>	
Methods Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected. <i>If a traditional indication is being tested, a description of how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication.</i>	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
	4A: Herbal medicinal product name	1. The Latin binomial name and the botanical authority and family name for each herbal ingredient; common name(s) should also be included. 2. The proprietary product name (i.e., brand name) or the extract name (e.g., EGb-761) and the name of the manufacturer of the product. 3. Whether the product used is authorized (licensed, registered) in the country in which the study was conducted.	
	4B: Characteristics of the herbal product	1. The part(s) of plant used to produce the product or extract. 2. The type of product used (e.g., raw [fresh or dry], extract). 3. The type and concentration of extraction solvent used (e.g., 80% ethanol, 100% H ₂ O, 90% glycerine, etc.) and the ratio of herbal drug to extract (e.g., 2 to 1). 4. The method of authentication of raw material (i.e., how done and by whom) and the lot number of the raw material. State if a voucher specimen (i.e., retention sample) was retained and, if so, where it is kept or deposited, and the reference number.	
	4C: Dosage regimen and quantitative description	1. The dosage of the product, the duration of administration, and how these were determined. 2. The content (e.g., as weight, concentration; may be given as range where appropriate) of all quantified herbal product constituents, both native and added, per dosage unit form. Added materials, such as binders, fillers, and other excipients (e.g., 17% maltodextrin, 3% silicon dioxide per capsule), should also be listed. 3. For standardized products, the quantity of active/marker constituents per dosage unit form.	
	4D: Qualitative testing	1. Product's chemical fingerprint and methods used (equipment and chemical reference standards) and who performed the chemical analysis (e.g., the name of the laboratory used). Whether a sample of the product (i.e., retention sample) was retained and if so, where it is kept or deposited. 2. Description of any special testing/purity testing (e.g., heavy metal or other contaminant testing) undertaken; which unwanted components were removed and how (i.e., methods). 3. Standardization: what to standardize (e.g., which chemical components of the product) and how (e.g., chemical processes, or biological/functional measures of activity).	
	4E: Placebo/control group	The rationale for the type of control or placebo used.	
	4F: Practitioner	A description of the practitioners (e.g., training and practice experience) who are a part of the intervention.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). <i>Outcome measures should reflect the intervention and indications tested considering, where applicable, underlying theories and concepts.</i>	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization Sequence allocation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	

Continued on following page

Appendix Table—Continued

Paper Section and Topic	Item Number	Descriptor	Reported on Page Number
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group. <i>Including concomitant medications, herbal and complementary medicine use.</i>	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat." State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes. <i>Interpretation of the results in light of the product and dosage regimen used.</i>	
Generalizability	21	Generalizability (external validity) of the trial findings. <i>Where possible, discuss how the herbal product and dosage regimen used relate to what is used in self-care and/or practice.</i>	
Overall evidence	22	General interpretation of the results in the context of current evidence. <i>Discussion of the trial results in relation to trials of other available products.</i>	

* CONSORT items (1, 17) are listed in normal text. Proposed recommendations for reports of herbal medicine and randomized, controlled trials are listed in italicized text. CONSORT = Consolidated Standards of Reporting Trials.

Reference

- GAGNIER, J., BOON, H., ROCHON, P., BARNES, J., MOHER, D. & BOMBARDIER, C. 2006.
Improving the quality of reporting of randomized controlled trials evaluating herbal interventions: implementing the CONSORT statement [corrected]. *Explore (NY)*, 2, 143-9.

Appendix 38: Good Clinical Practice Training Certificate


**National Institute for
Health Research**
Clinical Research Network

Certificate of Attendance

Lily Lai

attended

Introduction to Good Clinical Practice (GCP):
A practical guide to ethical and scientific
quality standards in clinical research

on 12/08/2011

Sessions include:

1. The Value of Clinical Research and the role of the NIHR CRN
2. GCP: the standards and why we have them
3. Study set up: responsibilities, approvals and essential documents
4. The process of informed consent
5. Case report form, source data and data entry completion
6. Safety reporting in clinical trials



Paul Maher
NIHR CRN GCP Training Manager



Appendix 39: Summary Of Pharmacological Product Characteristics For Chinese Herbal Medicines Commonly Used In Polycystic Ovary Syndrome

Chinese pinyin name	Botanical name	Typical daily raw herbal dosage range (g)	Pharmacology	Cautions, contra-indications, toxicity and side-effects
Ba Ji Tian	<i>Morinda officinalis</i> How	6-15	Crude preparations shows no androgen-like effect with oral administration (rat)	NA
Bai Jie Zi	<i>Brassica alba</i> (L.) Boiss.	3-9	Antifungal effect – inhibitory effect in vitro against many dermatomycoses	NA
Bai Shao	<i>Paeonia lactiflora</i> Pall	6-15	Anti-spasmodic – on intestinal specimens and counteracts effect of oxytocin on uterus (animal) Anti-inflammatory effect – protective function against stress ulcers, slightly raised acidity of stomach secretions and improved appetite (rat) Lowers temperature in artificially-induced fevers and in normal temperature (rat)	LD ₅₀ for intravenous injection of paeoniflorin into white mice is 3550mg/kg
Bai Zhu	<i>Atractylodes macrocephala</i> Koidz.	4.5-9	Significant and prolonged diuretic effect (animal) Increases assimilation of glucose and lowered plasma glucose levels (animal) Hematologic effect - Mildly elevates prothrombin time (rat) Increases weight and endurance (rat)	LD ₅₀ for peritoneal injection is 13.3g/kg. When rats fed decoctions of herb in doses of 0.5g/kg for two months, no toxic symptoms developed although mild lymphopaenia and anaemia developed without any signs of damage to brain, heart or liver.
Bu Gu Zhi	<i>Psoralea corylifolia</i> L.	3-9	Cardiovascular effect – selectively dilates coronary blood vessels, positive inotropic effect on hearts (animal) Antibiotic effect – <i>in vitro</i> inhibitory effect against <i>Staphylococcus aureus</i> Smooth muscle effect – stimulates intestines (animal), and relaxing effect on uterus (rat)	Extremely large doses has some teratogenic effect (animal)

APPENDICES

			Stops menorrhagia	
Cang Zhu	<i>Atractylodes lancea</i> (Thunb.) DC.	4.5-9	Endocrine effect – lowers blood sugar in artificially-induced diabetes mellitus (animal) Genitourinary effect – decoctions showed no diuretic effect but increased excretion of salts (rat)	NA
Chen Pi	<i>Citrus reticulata</i> Blanco	3-9	Smooth muscle effect – exhibits inhibitory effect on smooth muscle (animal) Cardiovascular effect – small doses exert positive inotropic effect and increases cardiac output in hearts without affecting heart rate (animal); large doses have inhibitory effect; causes dilation of coronary arteries in rabbit heart specimens but constriction of renal arteries when injected intravenously into dogs Use in mastitis treatment (human)	NA
Chai Hu	<i>Bupleurum chinense</i> D.C. or <i>B. scorzoneraefolium</i> Wild.	3-12	Temperature regulation – large dosage has antipyretic effect on artificially-induced fever (animal); lowers fever secondary to upper respiratory tract infections Immune system – oral preparations inhibit increase in capillary permeability caused by histamine and 5-hydroxy-tryptamine Bacteriostatic effect against <i>Mycobacterium tuberculosis</i> and strong <i>in vitro</i> inhibitory effect against influenza and poliomyelitis viruses Tranquilising effect (animal) Lowers blood pressure and has a negative inotropic effect on the heart (animal)	NA
Chuan Niu Xi	<i>Cyathula officinalis</i> Kuan	4.5-9	Uterine effects – contractions and relaxations in uteri (animal) Inhibits motility of mice intestinal specimens and	NA

			increases contractions in guinea pig intestine Reduction in blood pressure due to inhibition of the heart and peripheral vasodilation (animal) Analgesic effect – peritoneal injection exerts analgesic effect (mice)	
Chuan Xiong	<i>Ligusticum chuanxiong</i> Hort.	3-6	Central nervous system effect – oral decoctions at dosage of 25/50g/kg exerts sedative effect (rats/mice) Cardiovascular effect – weak antihypertensive effect (oral administration), significant reduction in blood pressure in anaesthetized animals (intravenous and intramuscular injection) (animal); decoctions in doses of 4g/kg per day lowers blood pressure in renal hypertensives by 20mmHg with no effect on experimental essential hypertensives (animal) Smooth muscle – small amounts of 10% solution stimulates pregnant rabbit uterus specimens, large amounts stop contractile effects; small amounts of decoction inhibits contraction of small intestine specimens, whilst large amounts stopped all contractions (animal) Antibiotic effect – in vitro inhibitory effect against many pathogenic bacteria such as <i>Shigella sonnei</i>, <i>Pseudomonas aeruginosa</i>, <i>Salmonella typhi</i> and <i>Vibrio cholera</i> <i>In vitro</i> inhibitory effect against many dermatomycoses	NA
Da Zao	<i>Ziziphus jujube</i> Mill. Var. <i>inermis</i> (Bge.) Rehd.	10-30	Increase in weight and endurance (mice) Promotes recovery from carbon tetrachloride exposure (animal) Significantly reduces high serum transaminase in hepatitis or cirrhosis (human)	NA

APPENDICES

Dan Shen	<i>Salvia miltiorrhiza</i> Bge.	6-15	Cardiovascular effect – decoctions have marked vasodilatory effect on coronary arteries, though negative chronotropic effect (animal); no β - blocker effect; mild peripheral vasodilation and short-lived reduction in blood pressure (animal) Marked improvements in ECG readings in angina pectoris (human) Lowers serum cholesterol levels (human) Significant sedative effect and prolonged hypnotic effect of barbiturates (mice) <i>In vitro</i> inhibitory effect against <i>mycobacterium tuberculosis</i> and some pathogenic dermatomycoses Injection of decoctions at 0.5g/kg exerts hypoglycaemic effect lasting up to 5 hours	LD ₅₀ for peritoneal injection in mice is 36.7g/kg; intravenous injection into anaesthetized animals of doses 40-80 times standard clinical dose produced no toxic reactions; intravenous injection of 20-30 times standard clinical dose for 14 days produced no side effects of adverse changes in blood or in tests of liver and kidney function; tincture administrations can lead to pruritus, stomach ache or reduced appetite
Dang Gui	<i>Angelica sinensis</i> (Oliv.) Diels	3-15	Uterine effects – causes contractions in situ and relaxation in uterus specimens (animal); more regular contractions of uterus (animal) Hepato-protective effect – on livers exposed to carbon tetrachloride; increases oxygen consumption of liver without affecting amount of nucleic acids, potentially due to generalised increase in metabolism (mice) Cardiovascular effect – inhibitory effect on heart specimen (animal); lowers blood pressure in anaesthetised animals; in artificial atherosclerosis causes less plaque formation (animal) Inhibitory effect in vitro against many bacteria including hemolytic <i>Streptococcus</i> and <i>Shigella</i> Mild sedative effect Injection for treatment of various chronic pain conditions such as neuralgias, ischaemic pain and arthritis	NA

			Inhibits motility both <i>in situ</i> intestines and intestinal specimens (animal)	
Dang Shen	<i>Codonopsis pilosula</i> (Franch.) Nannf.	9-30	Haemologic effect – oral and intravenous use increases red blood cell count and haemoglobin, decrease in leucocyte number and increased percentage of neutrophils (animal) Endocrine effect – raises serum glucose when injected subcutaneously (animal) Cardiovascular effect – lowers blood pressure in anaesthetised dogs, speculated to have been derived from a vasodilatory effect on terminal blood vessels Effect on fatigue – prolonged swimming time in a dose-related manner (mice) Immunologic effect – inhibited febrile reaction to toxins such as turpentine (mice/rats); inhibits leukocytosis in rats already injected with toxins Central nervous system effect – preparations in doses of 6-7mcg/kg caused general stimulatory response e.g. reduction in sleep time (mice)	NA
Fa Ban Xia	<i>Pinellia ternata</i> (Thunb.) Breit (prepared)	4.5-12	Antiemetic effect – oral administration can have a significant antiemetic effect Antidotal effect against strychnine and acetylcholine toxicity Improvement in acute suppurative otitis media (tincture in human)	LD ₅₀ of unprepared form injected intraperitoneally into mice is approximately 13g/kg; overdosage can lead to burning and numbness in throat and lips, queasy stomach and nausea and feeling of pressure in the chest, cure with oral administration of raw ginger
Fu Ling	<i>Poria cocos</i> (Schw.) Wolf	9-15	Central nervous system effect – tranquilising effect (mice) Smooth muscle effect – direct relaxing effect on intestine specimens (animal) Endocrine effect – reduced plasma glucose	

APPENDICES

			Urinary effect with intraperitoneal injections – increased excretion of sodium (animal); no diuretic effect when given in normal dosage as decoctions to rabbits, rats or humans, or intravenously to dogs	
Gan Cao	<i>Glycyrrhiza uralensis</i> Fischer	2-12	Treatment of diabetes insipidus (human) Anti-inflammatory effect (rat) Anti-allergic effect – markedly reduced anaphylactoid and skin reaction to albumen (animal) Gastro-intestinal effect – relaxed stomach and intestinal specimens and relieved spasms caused by acetylcholine, histamine and barium (rat) Lipid metabolism – lowered cholesterol levels and stopped progression of lesions of experimentally-induced atherosclerosis (rat), and lowered cholesterol levels and blood pressure in hypertension (human) Effect on jaundice – lowered serum bilirubin and increased urinary excretion of urobilinogen with ligated bile ducts (animal) Reduces toxicity of many substances e.g. cocaine, arsenobenzol, urethane, caffeine, acetylcholine, pilocarpine, nicotine (animal)	Very low toxicity Taken long-term can cause hypertension and/or oedema
Gou Qi Zi	<i>Lycium barbarum</i> L. or <i>L. chinense</i> Mill.	6-18	Hepatoprotective – water extractions reduced damage to hepatic cells secondary to exposure to carbon tetrachloride and hastened recovery as measured by liver function studies and histological examination (mice) Reduces blood pressure with and stimulates intestinal specimens with intravenous administration (animal)	May cause loose stools
Gui Zhi	<i>Cinnamomum cassia</i> Blume	3-9	Antibiotic effect – strong inhibitory effect against <i>Staphylococcus aureus</i> and <i>Salmonella typhi</i> , and an inhibiting effect <i>in</i>	NA

			<i>vitro</i> against Asian flu virus A and ECHO virus Mild antipyretic effect primarily by vasodilation Potent diuretic	
Han Lian Cao	<i>Eclipta prostrata</i> L.	9-15	Used with supportive treatment for diphtheria	NA
Hong Hua	<i>Carthamus tinctorius</i> L.	3-9	Cardiovascular effect – weak inhibitory effect on the heart and lowered blood pressure in anaesthetised animals; vasoconstriction of peripheral blood vessels in the ear; decoctions increase coronary blood flow and no significant effect on blood pressure (animal) Decoctions result in marked improvement in ECG readings in coronary heart disease (human) Decoctions stimulate uterus (animal) Oral administration lowers elevated serum cholesterol (animal) Tinctures reduce swelling and subcutaneous haemorrhage due to acute sprains (human)	Meal containing 6% of herb showed no changes, at 8-10% experienced weight loss (animal)
Nu Zhen Zi	<i>Ligustrum lucidum</i> Ait	4.5-15	Cardiotonic and diuretic effects	Extremely safe – 75g given as one dosage without toxic effect (animal)
Shan Zhu Yu	<i>Cornus officinalis</i> Sieb.et.Zucc.	3-12	Antibiotic effect – decoctions have <i>in vitro</i> inhibitory effect against <i>Staphylococcus aureus</i> Decoctions have diuretic effect and lowers blood pressure with little effect on serum glucose on anaesthetised dogs	Very low toxicity when administered to different animals, except increased congestion of the gastric mucosa; very low incidence of side effects and is a mild parasympathomimetic
Shu Di Huang	<i>Rehmannia glutinosa</i> (Gaertn.) Libosch. or <i>R. glutinosa</i> Libosch. f. <i>hueichingensis</i> (Chao et Schih) Hsiao	9-30	Decreases mean blood pressure and serum cholesterol levels in hypertension and improves cerebral blood flow and ECG readings (human)	Mild side effects including diarrhoea, abdominal pain, dizziness, lack of energy, palpitations which usually disappear with continued administration
Su Mu	<i>Caesalpinia sappan</i> L.	3-9	Decoctions causes vasoconstriction and showed a positive inotropic effect on heart specimens (animal) Hypnotic effect which in extremely large dosages can lead to coma and death (animal);	NA

APPENDICES

			counteracts stimulatory effect of strychnine and cocaine Very strong <i>in vitro</i> inhibitory effect against <i>Staphylococcus aureus</i> and <i>Salmonella typhi</i>; some inhibitory effect against other pathogenic bacteria	
Tao Ren	<i>Prunus persica</i> (L.) Batsch. or <i>P. davidana</i> (Carr.) Franch.	4.5-9	Alcohol extractions have a weak anticoagulant effect Antitubercular effect (mice)	Oral administration of 4g of the herb daily for 1 week led to no observed effects on serum glucose, serum albumin, liver function studies or histology of the major organs (rat)
Tu Si Zi	<i>Cuscuta chinensis</i> Lam.	9-15	Positive inotropic effect on frog heart specimens and lowers blood pressure in anaesthetised dogs	Oral administration of 30-40g/kg of the herb resulted in no signs of toxicity (animal); LD ₅₀ for subcutaneous injection of preparations is 2.5g/kg
Xian Mao	<i>Curculigo orchioidea</i> Gaertn.	3-9	NA	Toxic reaction includes swelling of the tongue
Xiang Fu	<i>Cyperus rotundus</i> L.	4.5-12	Inhibitory effect in pregnant and nonpregnant uteri (animal) Volatile oils contain an oestrogen-like substance Subcutaneous injection significantly raises pain threshold (mice)	NA
Yi Mu Cao	<i>Leonurus heterophyllus</i> Sweet	9-60	Directly stimulates uterine specimens similar to oxytocin (animal) Effective in causing uterus to contract after delivery Intravenous injection of water extractions lowers blood pressure for a short duration (animal) Stimulates respiratory centre in the brain and inhibits central nervous system (animal) Treatment of acute glomerulonephritis (human)	Oral administration in pregnant rabbits resulted in miscarriages and no other side effects; Daily subcutaneous injection in rabbits in doses of 30mg/kg for two weeks resulted in no side effects; LD ₅₀ for intravenous injection in mice was 572mg/kg
Zhi Ke	<i>Citrus aurantium</i> L. (Rutaceae)	3-9	NA	NA

**Appendix 40: Certificate Of Study Dispensary As A Supplier
Approved By The Register Of Chinese Herbal Medicine**

This is to certify that Phoenix Medical Direct Has been audited by CMBarnett Pharma Services Ltd against the standards of the Register of Chinese Herbal Medicine's Approved Suppliers Scheme and having met those standards is entitled to use the title RCHM Approved Supplier Dated <u>16th February 2012</u> Signed <u>Emma Farrant</u> Emma Farrant (RCHM CEO)	
 RCHM	Approved Supplier RCHM Register of Chinese Herbal Medicine 中醫藥協會

**Appendix 41: Certificate Of Dispensary And Pharmacognosy
Training For A Member Of The Dispensing Team**

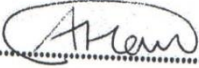

RCHM
THE REGISTER OF CHINESE
HERBAL MEDICINE
中医药会

This is to certify that

Bruno Miguel Pires
.....

has successfully completed the
Register of Chinese
Herbal Medicine's

Dispensary &
Pharmacognosy training

Signed.......... A.Harrison

16th April 2011
.....Date



Appendix 42: Certificate Of Good Manufacturing Practice By The Study Manufacturer

中 华 人 民 共 和 国	
药品GMP证书	
CERTIFICATE OF GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS PEOPLE'S REPUBLIC OF CHINA	
证书编号: 苏 J0677 Certificate No. : 苏 J0677	
企业名称:	江阴天江药业有限公司
Manufacturer:	Jiang Yin Tian Jiang Pharmaceutical Co., Ltd.
地 址:	江阴市经济开发区秦望山路 8 号
Address:	NO.8, Qin Wang Shan Road, Economy Development Zone, Jiang Yin City, Jiang Su Province
认证范围:	颗粒剂(中药配方颗粒)
Scope of Inspection:	Granules (Concentrated Granule For Prescription)
经审查,符合中华人民共和国《药品生产质量管理规范》要求。 特发此证。 <i>This is to certify that the above-mentioned manufacturer complies with the requirements of Chinese Good Manufacturing Practices for Pharmaceutical Products.</i>	
有效期至	2013 年 12 月 30 日
<i>This certificate remains valid until 30/12/2013</i>	
发证机关: 江苏省食品药品监督管理局	
Issued By JIANGSU FOOD AND DRUG ADMINISTRATION	
Date for Issuing	31/12/2008 2008 年 12 月 31 日
国家食品药品监督管理局制	
PRINTED BY STATE FOOD AND DRUG ADMINISTRATION	

Appendix 43: Certificate Of Analysis For A Single Chinese Herbal Medicine

CERTIFICATE OF ANALYSIS

品名 PRODUCT NAME : ATRACTYLODIS RHIZOMA PRAEP./cang zhu (fu chao)

生产厂家 PRODUCER: TIANJIANG PHARMACEUTICAL CO. , LTD.

生产日期 DATE OF PRODUCTION : 2011-7-4 批号 BATCH NO. : 1107024

检验日期 DATE OF ANALYSIS : 2011-7-9 有效期 Expiry date: 201606

检验依据 : CORRESPONDING TO CHINESE PH. AND TIANJIANG PHARM. SPECIFICATION

检验项目 DETERMINATION	标准 SPECIFICATION	结果 RESULT
外观 Appearance :	浅黄颗粒 Light yellow particle .	Conform
薄层层析鉴别 TLC :	应检出苍术 ATRACTYLODIS RHIZOMA	Conform
水分 Moisture :	≤ 6. 0%	2.7 %
溶化性 Solubility :	Soluble in water	Conform
重金属 Heavy metals:		
Pb :	(Less than 5mg/kg)	Negative mg/kg
Cd :	(Less than 1.0mg/kg)	0.02mg/kg
As :	(Less than 2mg/kg)	0.17mg/kg
Hg :	(Less than 0.1mg/kg)	Negative mg/kg

细菌 Microbiological : (Less than 1000 cfu /g) 140cfu /g

霉菌 Fungal account : (Less than 100 cfu /g) <10cfu /g

大肠埃氏菌 Escherichia coli : (absent in 1g) Negative

检验结果 Final result: 符合规定 Conform

化验员 ANALYST:

梅王 廖王
印亚 芳

复核人 COLLATOR:

仁单
江

质保部经理 MANAGER:

荣朱
印文

Appendix 44: Label For Dispensed ORCHID Study Chinese Herbal Medicines

For Clinical Trials Use Only: Trial Reference <u>RCHM 0123456</u>	
Participant ID: <u>1234567</u>	
<u>100g</u> Chinese herbal medicine	Batch no: <u>ABCD1111</u>
granules	
Dispatched: <u>01/10/2012</u>	Expiry date: <u>01/2013</u>
Do not store above 30°C	
Keep in a dry place	
Keep away from strong odours and bright light	
Keep out of reach of children	
Please hand this bottle and any unused herbs to your herbalist at end of study	
In case of emergency, contact Lily Lai on 01234 567 8910	

Underlined information to be edited following approvals and according to each dispensed item.

Appendix 45: Letter To Confirm Manufacturer Recommendations



16th August 2012

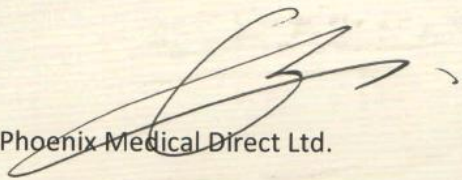
To whom it may concern,

This is to clarify storage conditions for TianJiang concentrated herbal granule products as follows,

Temperature: from -10°C to $+30^{\circ}\text{C}$

Humidity: below 75% (the products must be air proofed)

Any prescriptions retained and stored in accordance with the above outlined conditions; in relation to Temperature, Humidity and air proofing then a 3-month quality consistency can be guaranteed.



Phoenix Medical Direct Ltd.

鳳凰醫藥，致力於高品質中醫藥的推广

Phoenix, a professional team, is passionate about promoting premier quality natural health products.

Customer Care: 0800 612 8188 www.phoenixmd.co.uk 41 Beehive Lane, Chelmsford CM2 9TQ, United Kingdom

Appendix 46: Morisky Medication Adherence Scale (MMAS8)

This questionnaire has been adapted by substituting 'medicine' with 'herbs' and 'patient' with 'participant'.

Morisky 8-Item Medication Adherence Questionnaire

Question	Participant answer Yes/No
Do you sometimes forget to take your herbs?	
People sometimes miss taking their herbs for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?	
Have you ever cut back or stopped taking your herbs without telling your doctor because you felt worse when you took it?	
When you travel or leave home, do you sometimes forget to bring along your herbs?	
Did you take all your herbs yesterday?	
When you feel like your symptoms are under control, do you sometimes stop taking your herbs?	
Taking herbs every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	
How often do you have difficulty remembering to take all your herbs?	Never/rarely Once in a while Sometimes Usually All the time

Adapted from:

MORISKY, D. E., GREEN, L. W. & LEVINE, D. M. 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*, 24, 67-74.

Appendix 47: Record Of Chinese Herbal Medicine Assessment Data

Participant ID number:

Study assessment number: Week

Date of assessment:

Study practitioner:

Study site:

Assessment by visit / teleconference call / telephone / email / Other

Clinical signs and symptoms:

Clinical observations or physical assessments:

Chinese medicine advice given:

Appendix 48: Demographics Questionnaire

Please note some relevant demographics data will be recorded in screening questionnaire and from telephone interviewing. This demographics questionnaire will collect remaining data such as the following:

Demographics Questionnaire

We would like to ask for some background information about you – please complete the questions below.

1. Which of the following best describes your marital status?
 - a. Single
 - b. Co-habiting
 - c. Married
 - d. Separated
 - e. Divorced
 - f. Widowed
2. Do you have any children?
 - a. Yes. Please state number of children:
 - b. No.
3. Please indicate below the highest level of education that you have completed:
 - a. None completed
 - b. GCSE, O-level and other secondary school equivalent
 - c. A-levels, college and other equivalent
 - d. Bachelor's degree
 - e. Master's degree
 - f. Doctoral degree
4. Which of the following best describes your employment status?
 - a. Full-time employment
 - b. Part-time employment
 - c. Self-employed
 - d. Out-of-work looking for work
 - e. Out-of-work not currently looking for work
 - f. Homemaker
 - g. Student
 - h. Retired
 - i. Unable to work
5. Please provide details of complementary and alternative treatments you have received for PCOS-related problems:

6. How would you describe your ethnicity?
 - a. Caucasian (e.g. British, Irish)
 - b. Black (e.g. Caribbean, African)
 - c. South Asian (e.g. East Indian, Pakistani, Sri Lankan)
 - d. Chinese
 - e. Japanese
 - f. Korean
 - g. Filipino
 - h. South East Asian (e.g. Singaporean, Vietnamese, Cambodian)
 - i. West Asian (e.g. Iranian, Afghan)
 - j. Other
 - k. Prefer not to say
7. Do you smoke?
 - a. Yes, currently. Please state number of cigarettes per day:
 - b. Not now, I used to smoke. Please state number of cigarettes per day:
 - c. Never smoked.
8. How many hours of exercise do you manage in a typical week?
 - a. Please state number of hours per week:
 - b. Never exercised regularly.
9. How many of the following caffeinated drinks do you have per day?
 - a. Tea: ___ cups
 - b. Coffee: ___ cups
 - c. Cola: ___ cups
10. Have you ever taken Chinese herbal medicines before:
 - a. for any condition?
 - b. for a problem relating to PCOS?
11. Please provide brief reason(s) for participating in this study:

Appendix 49: Dermatology Life Quality Index (DLQI) Questionnaire

DERMATOLOGY LIFE QUALITY INDEX

Hospital No:

Date:

DLQI

Name:

Score:

Address:

Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☐ one box for each question.

1. Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?

Very much	☐
A lot	☐
A little	☐
Not at all	☐
2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?

Very much	☐
A lot	☐
A little	☐
Not at all	☐
3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?

Very much	☐
A lot	☐
A little	☐
Not at all	☐

 Not relevant ☐
4. Over the last week, how much has your skin influenced the **clothes** you wear?

Very much	☐
A lot	☐
A little	☐
Not at all	☐

 Not relevant ☐
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?

Very much	☐
A lot	☐
A little	☐
Not at all	☐

 Not relevant ☐
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?

Very much	☐
A lot	☐
A little	☐
Not at all	☐

 Not relevant ☐
7. Over the last week, has your skin prevented you from **working** or **studying**?

Yes	☐
No	☐

 Not relevant ☐

If "No", over the last week how much has your skin been a problem at **work** or **studying**?

A lot	☐
A little	☐
Not at all	☐
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?

Very much	☐
A lot	☐
A little	☐
Not at all	☐

 Not relevant ☐
9. Over the last week, how much has your skin caused any **sexual difficulties**?

Very much	☐
A lot	☐
A little	☐
Not at all	☐

 Not relevant ☐
10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?

Very much	☐
A lot	☐
A little	☐
Not at all	☐

 Not relevant ☐

Please check you have answered EVERY question. Thank you.

©AY Finlay, GK Khan, April 1992 www.dermatology.org.uk, this must not be copied without the permission of the authors.

Reference

FINLAY, A. Y. & KHAN, G. K. 1994. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. *Clin Exp Dermatol*, 19, 210-6.

Appendix 50: Measure Yourself Medical Outcome Profile (MYMOP) Questionnaire

* MYMOP2 *

Full name Date of birth

Address and postcode.....

Today's date Practitioner seen

Choose one or two symptoms (physical or mental) which bother you the most. Write them on the lines.
Now consider how bad each symptom is, over the last week, and score it by circling your chosen number.

SYMPTOM 1: 0 1 2 3 4 5 6
..... As good as it As bad as it
..... could be could be

SYMPTOM 2: 0 1 2 3 4 5 6
..... As good as it As bad as it
..... could be could be

Now choose one activity (physical, social or mental) that is important to you, and that your problem makes difficult or prevents you doing. Score how bad it has been in the last week.

ACTIVITY: 0 1 2 3 4 5 6
..... As good as it As bad as it
..... could be could be

Lastly how would you rate your general feeling of wellbeing during the last week?

0 1 2 3 4 5 6
As good as it As bad as it
could be could be

How long have you had Symptom 1, either all the time or on and off? Please circle:

0 - 4 weeks 4 - 12 weeks 3 months - 1 year 1 - 5 years over 5 years

Are you taking any medication FOR THIS PROBLEM? Please circle: YES/NO

IF YES:

1. Please write in name of medication, and how much a day/week

.....

2. Is cutting down this medication: Please circle:

Not important a bit important very important not applicable

IF NO:

Is avoiding medication for this problem:

Not important a bit important very important not applicable

MYMOP. Measure Yourself Medical Outcome Profile

Reference

PATERSON, C. 1996. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. *BMJ*, 312, 1016-20.

Appendix 51: Modified Ferriman-Gallwey (mFG) Questionnaire

Please score each of the nine body areas on your patient by rating each area from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth). The ratings from each area are then added to obtain a total score.

1. Upper lip
2. Chin
3. Chest
4. Upper abdomen
5. Lower abdomen
6. Upper arms
7. Inner thighs
8. Upper back
9. Lower back

Adapted from:

FERRIMAN, D. & GALLWEY, J. D. 1961. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab*, 21, 1440-7.

Appendix 52: Practitioner Blinding Questionnaire

Participant ID:

Date of questionnaire completion:

Thank you for your continued participation in this study so far as a practitioner.

As part of our study evaluation, we would like to ask you some questions about the participant referred to above who you are currently treating, and your thoughts about the herbs they are taking.

Please complete the following questions:

1. Given the information that you have received about the participant to this date, which treatment group do you feel this participant was assigned to?
 - a. Standardised CHM
 - b. Individualised CHM
2. How certain are you of your answer?
 - a. Not sure at all, just guessed
 - b. Fairly sure
 - c. Entirely sure
3. Why do you think this participant was assigned to this treatment group?
Please provide as much information as you would like.

Thank you for completing this questionnaire.

Appendix 53: Credibility/Expectancy Questionnaire (CEQ)

The Credibility/Expectancy Questionnaire (CEQ) has been modified for this study by substituting 'therapy' for 'treatment' and 'trauma' with 'PCOS'.

Set I

1. At this point, how logical does the treatment offered to you seem?

1	2	3	4	5	6	7	8	9
Not at all logical			Somewhat logical			Very logical		

2. At this point, how successfully do you think this treatment will be in reducing your PCOS symptoms?

1	2	3	4	5	6	7	8	9
Not at all useful			Somewhat useful			Very useful		

3. How confident would you be in recommending this treatment to a friend who experiences similar problems?

1	2	3	4	5	6	7	8	9
Not at all confident			Somewhat confident			Very confident		

4. By the end of the treatment period, how much improvement in your PCOS symptoms do you think will occur?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Set II

For this set, close your eyes for a few moments, and try to identify how what you really *feel* about the treatment and its likely success. Then answer the following questions:

1. At this point, how much do you really *feel* that treatment will help you to reduce your PCOS symptoms?

1	2	3	4	5	6	7	8	9
Not at all			Somewhat			Very much		

2. By the end of the treatment period, how much improvement in your PCOS symptoms do you really *feel* will occur?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Reference

DEVILLY, G. J. & BORKOVEC, T. D. 2000. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry*, 31, 73-86.

Appendix 54: End-Of-Study Questionnaire For Study Participant

Thank you for participating in this study.

As part of our study evaluation, we would like to ask you some questions about your experiences and thoughts about taking part in this study. Any comments and suggestions that you might have will be able to help us see how we can improve the experience of taking part in herbal research so please answer as honestly as you would like.

Please complete the following questions:

1. Would you agree to participate in a study like ORCHID again?

- Definitely
- Probably
- Probably not
- Definitely not
- Not sure

Please provide reasons for your answer:

2. What do you think could have been done better about the ORCHID study?

3. What did you particularly like about taking part in the ORCHID study?

4. What did you think of the herbs offered in the ORCHID study?

Thank you for completing this questionnaire.

Appendix 55: End-Of-Study Questionnaire For Study Personnel

Thank you for your assistance during this study. You have had an invaluable role in helping to see this project through and your help and co-operation has been much appreciated by the study team.

In order to see how we could improve on our study processes, we would be interested in obtaining feedback from you. Any comments and suggestions that you might have will be able to help us see how we can improve the experience of taking part in research from your perspective. This will help inform the design and management of future research projects and which we hope to share with other research groups in presentations or in formal publications.

1. Would you agree to participate in a study like ORCHID again?

- Definitely
- Probably
- Probably not
- Definitely not
- Not sure

Please provide reasons for your answer:

2. What do you think could have been done better about the ORCHID study?

3. What did you particularly like about taking part in the ORCHID study?

Thank you for completing this questionnaire.

Appendix 56: ORCHID Study Protocol Publication

+Model
EUJIM-315; No. of Pages 8

ARTICLE IN PRESS



ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

European Journal of Integrative Medicine xxx (2014) xxx.e1–xxx.e8

European Journal of
**INTEGRATIVE
MEDICINE**www.elsevier.com/eujim

Original article

Polycystic Ovary syndrome: A Randomised feasibility and pilot study using Chinese Herbal medicine to explore Impact on Dysfunction (ORCHID)—Study protocol

Lily Lai^{a,*}, Andrew Flower^a, Michael Moore^a, Philip Prescott^b, George Lewith^a

^a University of Southampton, Primary Care and Population Sciences, Aldermoor Health Centre, Aldermoor Close, Southampton, Hampshire SO16 5ST, United Kingdom

^b University of Southampton, Mathematical Sciences, Highfield, Southampton, Hampshire SO17 1BJ, United Kingdom

Received 10 December 2013; received in revised form 26 February 2014; accepted 3 March 2014

Abstract

Introduction: We aim to evaluate the feasibility of, and pilot procedures for, a randomised study in the UK administering Chinese herbal medicine (CHM) to women with polycystic ovary syndrome (PCOS) related oligo- and/or amenorrhoea. Our primary aim of this feasibility study is to evaluate how appropriate oligo- and amenorrhoea is as the primary outcome of the main study.

Methods: A prospective, multi-centre, randomised, patient- and practitioner-blind, feasibility and pilot study will be conducted. 40 women with PCOS-related oligo- and/or amenorrhoea will be randomised to one of two parallel arms comparing standardised CHM treatment against individualised CHM treatment as usual for 6 months. Participants will be prescribed 8 g of CHM granulated extracts twice daily, totalling 16 g per day. Feasibility will be determined by collecting data on menstrual regularity, body mass index, waist hip ratio, weight, Polycystic Ovary Syndrome Questionnaire, Measure Yourself Medical Outcome Profile, Dermatology Life Quality Index, Morisky Medication Adherence Scale, modified Ferriman–Gallwey scale, liver and kidney function, practitioner-blinding questionnaire and participant feedback forms. Process data will also inform feasibility such as recruitment rate, completion rate and reasons for dropout. Statistical analysis will be piloted in this study. We will present descriptive statistics for primary and secondary variables and use analysis of variance and Chi-squared tests where appropriate.

Results and conclusion: This study received ethical approval in December 2012. 40 participants were recruited between January 2013 and August 2013 and the study is expected to complete in March 2014.

© 2014 Elsevier GmbH. All rights reserved.

Keywords: Chinese herbal medicine; Polycystic ovary syndrome; Feasibility study; Pilot; Menstrual disorders; Randomised controlled trial

Introduction

Polycystic ovary syndrome (PCOS) affects an estimated 6–18% of women of reproductive age and is a heterogeneous condition characterised by endocrine and metabolic disturbances [1–3]. Oligomenorrhoea and amenorrhoea are cardinal symptoms of PCOS and primary care management typically involves oral contraceptives and insulin-sensitising agents.

However, there is evidence of dissatisfaction with such treatments which has been associated with intolerable side-effects, poor adherence rates and a potential increase in cardiovascular and metabolic risk [4–8]. This highlights a number of issues and barriers with current management and thus warrants exploration of other potentially more effective treatments that could be offered in primary care.

There is anecdotal evidence and emerging evidence from randomised controlled trials (RCTs) suggesting Chinese herbal medicine (CHM) could play an important role in the treatment of oligo- and amenorrhoea [9]. However, such studies are conducted in China, limiting the generalisability of findings to Western populations and which necessitates further exploration with a fully powered RCT in a UK setting. Prior to such a study

* Corresponding author. Tel.: +44 02380 241073; fax: +44 02380 701 125.

E-mail addresses: LYWL1G10@southampton.ac.uk, lilylai888@gmail.com (L. Lai), flower.power@which.net (A. Flower), mvm198@southampton.ac.uk (M. Moore), p.prescott@southampton.ac.uk (P. Prescott), GL3@southampton.ac.uk (G. Lewith).

<http://dx.doi.org/10.1016/j.eujim.2014.03.001>
1876-3820/© 2014 Elsevier GmbH. All rights reserved.

and given the novel nature of offering CHM in primary care, it is important to first conduct a feasibility and pilot study to plan resources and reduce uncertainties [10–14]. The aims of this study are to determine the feasibility of conducting a randomised study in the UK administering CHM to women with PCOS-related oligo- and/or amenorrhoea, and to pilot and evaluate the study procedures.

Our primary feasibility question is:

1. Is oligomenorrhoea and amenorrhoea appropriate as the primary outcome measure for the main study?
Our secondary feasibility questions are:
2. Are other measures more appropriate for investigation as the primary outcome measure for the main study?
3. What is the safety profile of CHM?
4. How should the CHM intervention in the main study be delivered?
5. Can a double-blind, randomised trial with CHM for PCOS be conducted?

Methods

Design

A prospective, multi-centre, randomised, patient- and practitioner-blind, feasibility and pilot study will be conducted. This is a pragmatic study with two parallel arms comparing standardised CHM treatment against individualised CHM treatment as usual for PCOS-related oligo- or/and amenorrhoea. Although both standardised and individualised CHM are routinely available in the UK, individualised CHM is typically regarded as 'gold standard' practice, a view that is supported in the clinical literature [15] as well as an earlier Delphi study conducted by this research team (unpublished results). However, we are interested in exploring differences that may exist between the two interventions and preliminary scientific data gathered from this present study will inform the CHM intervention for the main study.

This study received ethical approval in December 2012 from the Register of Chinese Herbal Medicine (RCHM) and University of Southampton ethics committees (Approvals ID 3977) and is registered with Current Controlled Trials. It is conducted in accordance with the Declaration of Helsinki (1964) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) (1996).

Eligibility criteria

Participants will be included if they: (1) are females aged 18–44, (2) present with oligo- and/or amenorrhoea with oligomenorrhoea defined as intervals between periods of >35 days and <200 days and amenorrhoea as intervals between periods of ≥200 days, (3) have received a diagnosis of PCOS consistent with the Rotterdam criteria [16].

Participants will be excluded if they: (1) present with other causes of hyperandrogenism or menstrual irregularities, (2) are

currently pregnant, suspected to be pregnant, or actively trying to conceive, (3) are breastfeeding within 6 months of joining the study, (4) are receiving prohibited treatments such as hormonal contraceptives, (5) have a history of liver or kidney pathologies such as cirrhosis, glomerulonephritis, pyelonephritis, (6) have a history of psychotic illness or have been diagnosed with an eating disorder, (7) have currently active major depression, (8) are currently at risk of harmful and hazardous drinking, (9) have allergies to any of the following common herbal ingredients that are contained within the standardised CHM treatment: nuts, citrus fruit peel, goji berry, licorice or cinnamon, (10) do not have the spoken or written language skills necessary to take part, (11) are unable to attend the proposed study visits, (12) present with abnormal liver and/or kidney function at screening.

Recruitment and setting

Recruitment will take place in the community inviting self-referrals and using a study website, posters and flyers, online forums, social media and press releases and which have been used in similar studies [17–20]. Recruitment methods and literature were ethically approved prior to study commencement.

Eligibility will be initially assessed via a self-completed screening questionnaire or telephone interview with a member of the study team. Final eligibility criteria will be checked at the screening visit by the study practitioner who will explain in full the study procedures before asking for written informed consent.

Study visits will take place in UK-based CHM clinics and conducted by CHM practitioners who will be required to have a minimum 5 years in practice, be registered with a professional CHM organisation, be fully insured, have access to liver and kidney function testing and agree to carry out the study procedures as stated in the protocol. A list of active study sites can be obtained from the lead author.

This feasibility study requires a sample size of 40, based on requiring data from 15 participants per arm to calculate an estimate of the treatment effect and associated variability of the treatment effect to inform the power calculation for a main study [14]. Accounting for a 25% dropout rate based on similar studies [21,22], 20 participants will be required from each group, totalling 40 participants. A feasibility search conducted at a Wiltshire general practice surgery suggested a 10% eligibility rate and 400 enquiries will therefore be required to meet our recruitment target.

Study visits and assessments

Participants will undergo 8 study assessments in total at weeks 0, 2, 4, 8, 12, 16, 20 and 24. Of these assessments, the participant will be asked to physically attend visits at weeks 0, 4, 8, 12 and 24 whilst other assessments may be conducted by telephone or email at the practitioner's discretion. A participant flow diagram can be seen in Fig. 1.

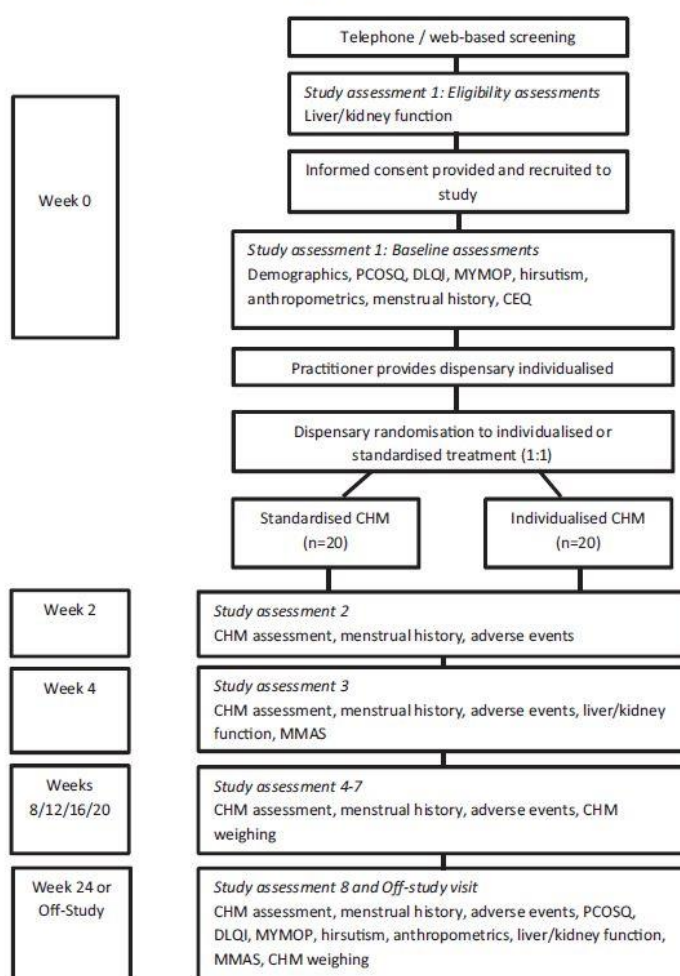


Fig. 1. Participant flow diagram.

Abbreviations: CHM = Chinese herbal medicine; PCOSQ = Polycystic Ovary Syndrome Questionnaire; DLQI = Dermatology Life Quality Index; MYMOP = Measure Yourself Medical Outcome Profile; CEQ = Credibility/Expectancy Questionnaire; MMAS = Morisky Medication Adherence Scale.

Randomisation, allocation concealment and blinding

Prior to the study, an independent statistician (PP) will use computer-generated random numbers with allocation ratio 1:1 to provide an irregular block allocation sequence. Allocation codes describing group allocation will be transferred to sealed opaque envelopes and sent to the dispensary prior to recruitment. Prior to and during the study, practitioners and members of the study team will have no knowledge of the randomisation sequence generated or of treatment allocation.

Participants and practitioners will be blinded throughout this study. Participants will be informed they will be randomised to one of two active CHM treatments but will remain blind to the difference between treatments during the study. At the

final visit, this information will be revealed to the participants although their allocation will not be disclosed until the study is complete.

Practitioners will be informed of the difference between the two interventions but will remain blind to allocation to minimise performance bias. As practitioners will also be conducting assessments during the study, practitioner-blinding will be required to minimise measurement bias. Following each assessment, the practitioner will write an individualised prescription and send this to the dispensary. Upon receipt of an individualised prescription for a new participant, a member of the dispensary team will open the next randomisation envelope containing the allocation codes, note the participant's allocation and dispense the corresponding prescription. Where

Table 1
Contents of standardised Chinese herbal medicine prescription.

Chinese Pinyin name	Common name	Family name	Part used	Botanical name	Dried herbal daily dosage (g)	Percentage (%)
Bai Shao (Chao)	Peony (dry fried)	Paeoniaceae	Root	<i>Paeonia lactiflora</i> Pall.	15	10.64
Chai Hu	Bupleurum	Umbelliferae	Root	<i>Bupleurum chinense</i> DC.	9	6.38
Chen Pi	Tangerine peel	Rutaceae	Peel	<i>Citrus reticulata</i> Blanco	9	6.38
Chuan Xiong	Szechwan lovage rhizome	Umbelliferae	Rhizome	<i>Ligusticum chuanxiong</i> Hort.	9	6.38
Dang Gui Wei	Angelica extremities	Umbelliferae	Root tail	<i>Angelica sinensis</i> (Oliv.) Diels	9	6.38
Gan Cao (Mi Zhi)	Liquorice root (honey-fried)	Fabaceae	Root	<i>Glycyrrhiza uralensis</i> Fisch.	6	4.26
Gou Qi Zi	Goji berry	Solanaceae	Fruit	<i>Lycium barbarum</i> L.	9	6.38
Gui Zhi	Cinnamon twig	Lauraceae	Twig	<i>Cinnamomum cassia</i> Presl.	9	6.38
Hong Hua	Safflower	Asteraceae	Flower	<i>Carthamus tinctorius</i> L.	9	6.38
Tao Ren	Peach kernel	Rosaceae	Seed	<i>Prunus persica</i> (L.) Batsch.	9	6.38
Tu Si Zi	Chinese dodder seed	Convolvulaceae	Seed	<i>Cuscuta chinensis</i> Lam.	12	8.52 ^a
Xiang Fu (Cu Zhi)	Purple nutsedge (vinegar-fried)	Cyperaceae	Rhizome	<i>Cyperus rotundus</i> L.	12	8.52 ^a
Yi Mu Cao	Motherwort	Lamiaceae	Top	<i>Leonurus japonicus</i> Houtt.	15	10.64
Zhi Ke	Bitter orange	Rutaceae	Mature fruit	<i>Citrus aurantium</i> L.	9	6.38
Total prescription weight					141	

^a Rounded up for column total to equal 100%.

a participant is allocated to standardised CHM, all future individualised prescriptions provided by the practitioner for that participant will be ignored by the dispensary.

Unblinding is permissible when a compelling medical need arises such as a serious adverse event. Unblinding will be conducted by a member of the research team not involved in data collection or analysis.

Interventions

All information presented fulfils the requirements of the elaborated CONSORT statement for reporting RCTs of herbal interventions [23].

Usual CHM practice combines a number of single herbs to produce a CHM prescription that is individualised to the patient. In this pragmatic comparative study, standardised treatment will be compared against individualised treatment as usual. Although a placebo-controlled study in primary care was initially planned, the time required by the herbal manufacturer to collect the required information for clinical trials approval was inconsistent with project deadline commitments and which necessitated a revision of the initial study design to our present protocol. The reason for our present choice of interventions is that we are interested in exploring potential differences between these two groups in clinical and safety effects and, should this study progress to a main study, to inform the design of a CHM intervention in primary care.

Standardised treatment consists of a pre-defined prescription of 14 single CHM granulated extracts, the contents of which can be seen in Table 1. This prescription is based on frequently occurring Chinese medicine presentations and treatment strategies extrapolated from a Delphi study, and on herbs used in RCTs for PCOS-related menstrual irregularities from a systematic review conducted by this study team (unpublished results). This prescription is not licensed for purchase over the counter and is available in the UK through registered CHM practitioners following a one-to-one consultation.

Individualised treatment will follow usual practice whereby the study practitioner will write an individualised prescription following an assessment with a participant, containing details of the base formulae if relevant, and details of the single herbs and dosages.

Both CHM treatments will be offered as granulated extracts for 6 months (24 weeks). Following good practice guidelines developed from our Delphi study, granulated extracts have been regarded by our panel of UK CHM practitioners as suitably effective in the treatment of PCOS, and 6 months deemed an appropriate length of treatment to observe improvements in oligo- and amenorrhoea (unpublished results).

Following each assessment, participants will receive a bottled container containing sufficient CHM until the next scheduled assessment. Participants will be instructed to use a measuring spoon provided to mix five level spoons (8 g) of granules with hot water and to take morning and evening after meals, totalling 16 g per day.

CHM dispensary and manufacturer

Phoenix Medical Direct Limited will dispense all CHM granulated extracts which are manufactured in China by Jiangyin Tianjiang Pharmaceutical Company Limited, a certified Good Manufacturing Practice (GMP) company. The solvent used for extraction is purified water to generate an 8:1 source to product extraction ratio. Authentication of raw materials and of the finished product is conducted using macroscopic and microscopic examination, and chemical methods such as thin layer chromatography for product identity and high-pressure liquid chromatography for potency which are checked for conformity to specifications in the Chinese Pharmacopoeia. Heavy metal testing and microbiological testing is conducted to confirm absence of microorganisms and pesticide residue. For each batch of single CHM granulated extract used, certificates of analysis and voucher specimens will be retained.

Dispensing procedures and quality assurance measures follow the standards set by the RCHM and are compliant with and the European Directive on Traditional Herbal Medicinal Products (THMPD) 2004/24/EC. No animal or mineral products will be dispensed and only plant materials will be used.

Concomitant care

Permitted medications and interventions prior to, and at any point during, the study include analgesics, antidepressants, vitamin and mineral supplements, weight loss interventions and selected natural supplements such as evening primrose oil, milk thistle and mint.

Medications and interventions that are permitted only after 6 months' use include insulin-sensitising agents, anti-androgens and acupuncture. 6 months is deemed a sufficient period of time to have lapsed in order for clinical improvements from such treatments to have stabilised prior to administering CHM.

Medications and interventions that are not permitted at any time during the study due to potential interactions with study medication or potential effects on the study outcome measures include: hormonal contraceptives, anticoagulants such as heparin and warfarin, anti-hypertensives, diuretics, cardiac glycosides, ciprofloxacin, corticosteroids, lithium, ovulation-inducing agents, laparoscopic ovarian cauterization and fertility procedures. CHM and other herbal supplements that have a potential action on symptoms of PCOS or could interact with the study medication will also not be permitted and include St. Johns wort, black cohosh, vitex agnus castus and saw palmetto.

Practitioners will be permitted to provide participants with additional advice such as lifestyle, stress-management or general wellbeing according to Chinese medicine theory. It is acknowledged that offering such advice could be a potential confounder but since it will be offered to both treatment groups as part of pragmatic practice, we consider this to be an acceptable co-intervention. Practitioners will be asked not to offer advice outside of routine CHM practice.

Study restrictions

There is no available safety data regarding CHM use during pregnancy and participants will be strongly advised against trying to conceive whilst participating in this study. Participants will be asked not to change their diet or activity level during the study other than what their practitioner has recommended. To maintain participant-blinding, practitioners will be asked not to disclose information to participants regarding individualising prescriptions during the study.

Modifications, discontinuation and post-trial care

Modification to the standard 16 g daily dosage is permitted in response to adverse effects or at the participant's request and a daily dose range of 5–25 g is considered adherent to the protocol. Temporary discontinuation of CHM treatment is permitted for reasons such as experiencing side-effects or whilst on holidays and should be for a maximum period of 7 days each time to

be considered adherent to the protocol. Changes in study practitioner and to the prescription between scheduled assessments are not permitted owing to resource constraints.

Should a compelling medical need arise for any participant, subsequent medical treatment will take precedent. Since this study has been approved by our sponsor and study interventions are routinely available and provided by fully qualified practitioners, study participants are insured both in terms of treatments provided as well as for research-related activities.

Participants will be withdrawn from the study either at their own request for personal reasons, or for other reasons without their consent, including situations in which continuing the study could be harmful to the participant's health, becoming pregnant or requiring treatment that is prohibited during the study. Participants will be invited to attend an end of study visit to collect final outcome data. Where appropriate, participants may be withdrawn from the interventional aspect but invited for monitoring of safety and other outcomes for the remainder of the study. Participants withdrawn from this study will not be replaced.

Upon study completion, participants will be offered a final telephone consultation with their practitioner within 4 weeks of their final visit.

Data management

Standardised online questionnaires will be used where possible to maximise completeness of data collection, and standardised electronic or paper-based forms where this is not possible. All source data will be transferred to standardised case report forms (CRFs) which will be anonymised.

Access to, and handling of, data will be restricted to delegated study staff who must comply with the requirements of the Data Protection Act 1998. Disclosure of confidential information can only be made during routine procedures such as monitoring and auditing by the study sponsor or in emergency situations such as when a compelling medical need arises.

Outcome measures

The clinical outcome of primary interest is regularity of menses measured as the number of days between menses. As there will be no run-in period, participants will be asked to recall data for a minimum of 3 menstrual cycles preceding the baseline visit. These will be used to calculate a baseline mean cycle length and standard deviation which will be compared with menstrual data obtained during the 6-month study period. An improvement is determined as a reduction from baseline in standard deviation to reflect stability in the variability of cycle length, and a reduction from baseline in the mean number of days between menses towards a 21–35 days interval which is clinically accepted as a regular cycle length. On-study menstrual data will be analysed from the first menses since randomisation onto the study. Self-reported confidence in the accuracy of baseline menstrual data using a 4-point Likert scale will be recorded.

Secondary outcomes of interest will be measured at baseline and at end of study. These include anthropometric measurements such as body mass index [24]; weight (kg) where a clinically

significant loss in weight for overweight and obese patients is determined as a loss of $\geq 5\%$ of initial weight [25]; waist circumference (WC) where risk of metabolic complications is increased with a WC >80 cm and substantially increased with a WC >88 cm [26]; and waist hip ratio (WHR) where WHR ≥ 0.85 is considered to substantially increase risk of metabolic complications [26]. Clinically validated instruments will be used for anthropometric measurements such as a constant-tension stretch-resistant measuring tapes and weighing scales that are minimum class III. Quality of life questionnaires administered include Polycystic Ovary Syndrome Questionnaire (PCOSQ), where a minimally important difference in the score of 0.5 on the 1–7 scale represents the smallest change in score that is important to women [27]; Measure Yourself Medical Outcome Profile (MYMOP), where the minimal important difference for change in score is 1.0 [28,29]; and Dermatology Life Quality Index (DLQI) where the minimal important difference for general skin conditions is a change in DLQI score of ≥ 3.2 points [30,31]. Hirsutism will be assessed by the practitioner using the validated modified Ferriman–Gallwey Questionnaire (mFG), that scores 9 body areas between 1 and 4 and where an mFG score of >6 is indicative of hirsutism [32].

Safety will be assessed by monitoring liver and kidney function at week 4 and end of study using serum blood tests or the validated point-of-care device Reflotron Desktop Analyzer [21,33]. We will also examine frequency and type of adverse events (AEs) and serious adverse events (SAEs) which will be captured at each study assessment from time of consent until the last study assessment. Monitoring will be conducted by asking non-leading questions such as ‘How are you feeling?’ or ‘Since you were last asked, have you felt unwell or different from usual?’. Such events will be recorded in clinical notes and using a standardised adverse event form. Relevant documentation such as laboratory reports relating to the event will be collected and will include an assessment of type of event, onset date, severity and causality, expectedness, date of resolution as well as treatment required and outcome. AEs will be evaluated as routine study data and will not need to be reported to the study sponsor. SAEs should be reported immediately by telephone or by email to the study sponsor within 24 hours of learning of the event and an SAE form completed providing all available details of the event. After recording an AE, or recording and reporting an SAE, the study team will make all attempts to follow up each participant until resolution.

Practitioner-blinding will be assessed at weeks 4, 12 and at end of study by administering a 3-item standardised questionnaire that asks practitioners: ‘(1). Given the information that you have received about the participant to date, which treatment group do you feel this participant was assigned to? (Response: Standardised/Individualised), (2). How certain are you of your answer? (Response: Not at all sure, just guessed/Fairly sure/Entirely sure), (3). Why do you think this participant was assigned to this treatment group? Please provide as much information as you would like (Response: Free text)’ [34].

Adherence will be monitored using the Morisky Medication Adherence Scale (MMAS-8) administered at week 4 and at end of study, where a score of >2 is indicative of low adherence, 1–2

medium adherence and 0 high adherence [35]. Adherence will also be measured by calculating total CHM usage by weighing prescription containers during the study.

Baseline comparisons will be checked for characteristics such as age, history of conventional medication and complementary and alternative medicine use, time since diagnosis, education level and smoking status. Baseline comparisons will also be made for treatment expectations using the Credibility/Expectancy Questionnaire [36] (CEQ) administered once via online questionnaire after the baseline visit but prior to CHM administration.

Clinical treatment data will be collected including CHM diagnoses, individualised prescription details and concomitant advice. Practitioners will be asked to provide an assessment at baseline on expected effectiveness of the standardised prescription for each participant based on a 7-point Likert score. This data will inform the CHM intervention for the main study by, for example, assessing frequency and rank order of individual CHM prescribed, frequency and rank order of diagnoses of study participants and doses prescribed. Comparison of treatment effects and of safety between individualised and standardised CHM will also provide further information regarding the choice of CHM intervention for the main study. Other process data such as recruitment rate, dropout rate, reasons for dropout, resource usage will be collected. Evaluation of study participation will be collected via feedback questionnaires administered to participants, practitioners and dispensary at study close.

Analysis

Descriptive statistics will be calculated for primary and secondary variables. Principles of intention-to-treat will be adopted by analysing available data from all randomised participants, regardless of completion and compliance rates. Owing to the feasibility nature of this study, formal data imputation will not be conducted.

Statistical analysis will be piloted in this feasibility study to check suitability of statistical methods for the main study based on the proposed outcomes. The analysis will test for within-patient and between-group differences in measurements taken at baseline and at end of study. Continuous variable comparisons will be assessed at end of study adjusted for baseline assessments for the two groups using analysis of variance, or an analysis of covariance to include the effects of body mass index, waist hip ratio, severity of menstrual disorder, demographic variables, CEQ score and adherence. Categorical data will be analysed using Chi-squared tests. Where assumptions of normality are not met nonparametric methods will be used.

As no formal power calculations have been carried out, results from the statistical analysis should be considered preliminary and must be interpreted cautiously [11].

Textual data that is collected from sources such as clinical notes and evaluation questionnaires will be analysed using content analysis.

Dissemination and discussion

The recruitment period lasted from January 2013 until August 2013. The final study visit is expected in March 2014.

Disseminated findings shall contain no participant-identifiable data. On completion of the study and regardless of the findings, a clinical study report will be prepared for presentation at scientific meetings and for publication in a peer-reviewed and topically relevant journal. Publications will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.

At the end of this study, we will examine the feasibility of conducting such a study in the UK, discuss piloting the procedures, and provide comment as to whether or not progression to a main study is recommended.

Conflict of interest

None.

Acknowledgements

The ORCHID study is supported by a PhD research training fellowship awarded to the main author by the National Institute for Health Research (NIHR) School for Primary Care Research, a partnership between the Universities of Birmingham, Bristol, Keele, Manchester, Nottingham, Oxford, Southampton and University College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

We are grateful to the University of Southampton Department of Primary Care and Population Sciences for providing financial support towards the cost of clinical equipment and medical tests. We would like to acknowledge Phoenix Medical Direct Limited for supplying discounted herbs and Dr. Trevor Wing for advice on the study design and for medical imaging and phlebotomy services. Other than the role stated, those named have had no other contribution to the study design, analysis or writing of the protocol and of this report.

References

- [1] Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 2000;85(7):2434–8.
- [2] March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod* 2010;25(2):544–51.
- [3] Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005;352(12):1223–36.
- [4] Sills ES, Perloe M, Tucker MJ, Kaplan CR, Genton MG, Schattman GL. Diagnostic and treatment characteristics of polycystic ovary syndrome: descriptive measurements of patient perception and awareness from 657 confidential self-reports. *BMC Womens Health* 2001;1(1):3.
- [5] Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab* 2002;87(2):569–74.
- [6] Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabet Med* 2002;19(4):279–84.
- [7] Grant RW, Devita NG, Singer DE, Meigs JB. Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care* 2003;26(5):1408–12.
- [8] Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;356(6):551–66.
- [9] Raja-Khan N, Stener-Victorin E, Wu X, Legro RS. The physiological basis of complementary and alternative medicines for polycystic ovary syndrome. *Am J Physiol Endocrinol Metab* 2011;301(1):E1–10.
- [10] MRC. A framework for development and evaluation of RCTs for complex interventions to improve health. Medical Research Council; 2000.
- [11] Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004;10(2):307–12.
- [12] Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;337:a1655.
- [13] Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Med Res Methodol* 2010;10:67.
- [14] Thabane L, Ma J, Chu R, Cheng J, Ismail A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010;10:1.
- [15] Maciocia M. The foundations of Chinese medicine: a comprehensive text for acupuncturists and herbalists. Edinburgh: Elsevier Churchill Livingstone; 1997.
- [16] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Fertil Steril* 2004;81(1):19–25.
- [17] Ward E, Bower P, Collier D, Delaney B, Graffy J, Kinmonth A-L, et al. Primary care research recruitment: a practical guide. National Institute for Health Research; 2010.
- [18] Jedel E, Labrie F, Oden A, Holm G, Nilsson L, Janson PO, et al. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. *Am J Physiol Endocrinol Metab* 2011;300(1):E37–45.
- [19] Bell-Syer SE, Thorpe LN, Thomas K, Macpherson H. GP participation and recruitment of patients to RCTs: lessons from trials of acupuncture and exercise for low back pain in primary care. *Evid Based Complement Alternat Med* 2011;2011:687349.
- [20] Johansson J, Redman L, Veldhuis PP, Sazonova A, Labrie F, Holm G, et al. Acupuncture for ovulation induction in polycystic ovary syndrome: a randomized controlled trial. *Am J Physiol Endocrinol Metab* 2013;304(9):E934–43.
- [21] Flower A, Lewith GT, Little P. A feasibility study exploring the role of Chinese herbal medicine in the treatment of endometriosis. *J Altern Complement Med* 2011;17(8):691–9.
- [22] Yasmin E, Glanville J, Barth J, Balen AH. Effect of dose escalation of metformin on clinical features, insulin sensitivity and androgen profile in polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2011;156(1):67–71.
- [23] Gagnier J, Boon H, Rochon P, Barnes J, Moher D, Bombardier C. Improving the quality of reporting of randomized controlled trials evaluating herbal interventions: implementing the CONSORT statement [corrected]. *Explore (NY)* 2006;2(2):143–9.
- [24] NICE. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London, UK: National Institute for Health and Clinical Excellence; 2006.
- [25] Moran LJ, Lombard CB, Lim S, Noakes M, Teede HJ. Polycystic ovary syndrome and weight management. *Womens Health (Lond Engl)* 2010;6(2):271–83.
- [26] WHO. Waist circumference and waist-hip ratio: report of a WHO expert consultation; 2008.

- [27] Cronin L, Guyatt G, Griffith L, Wong E, Azziz R, Futterweit W, et al. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). *J Clin Endocrinol Metab* 1998;83(6):1976–87.
- [28] Paterson C. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. *BMJ* 1996;312(7037):1016–20.
- [29] Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ* 1998;316(7132):690–3.
- [30] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19(3):210–6.
- [31] Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008;159(5):997–1035.
- [32] Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. *Hum Reprod Update* 2010;16(1):51–64.
- [33] Thue G, Sandberg S. Performance of the Reflotron and the Seralyzer in primary health care. *Scand J Clin Lab Invest* 1993;53(3):253–61.
- [34] Kolahi J, Bang H, Park J. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. *Community Dent Oral Epidemiol* 2009;37(6):477–84.
- [35] Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;24(1):67–74.
- [36] Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry* 2000;31(2):73–86.

References

2000. Sixth Report. *In: TECHNOLOGY*, S. C. O. S. A. (ed.).
2004. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*, 19, 41-7.
2008. Public Perceptions of Herbal Medicines. Ipsos MORI.
2009. National Institute for Health and Clinical Excellence: The guidelines manual.
2013. Clinical trials: Third report of session 2013-14. *In: COMMITTEE*, H. O. C. S. A. T. (ed.). London: The Stationery Office Limited.
- ABBOTT, D. H., BARNETT, D. K., BRUNS, C. M. & DUMESIC, D. A. 2005. Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome? *Hum Reprod Update*, 11, 357-74.
- ABBOTT, D. H., DUMESIC, D. A. & FRANKS, S. 2002. Developmental origin of polycystic ovary syndrome - a hypothesis. *J Endocrinol*, 174, 1-5.
- ALRAEK, T., BORUD, E. & WHITE, A. 2011. Selecting acupuncture treatment for hot flashes: a delphi consensus compared with a clinical trial. *J Altern Complement Med*, 17, 33-8.
- ARAIN, M., CAMPBELL, M. J., COOPER, C. L. & LANCASTER, G. A. 2010. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Med Res Methodol*, 10, 67.
- ASUNCION, M., CALVO, R. M., SAN MILLAN, J. L., SANCHO, J., AVILA, S. & ESCOBAR-MORREALE, H. F. 2000. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab*, 85, 2434-8.
- ATTIA, G. R., RAINEY, W. E. & CARR, B. R. 2001. Metformin directly inhibits androgen production in human thecal cells. *Fertil Steril*, 76, 517-24.
- AZZIZ, R., CARMINA, E., DEWAILLY, D., DIAMANTI-KANDARAKIS, E., ESCOBAR-MORREALE, H. F., FUTTERWEIT, W., JANSSEN, O. E., LEGRO, R. S., NORMAN, R. J., TAYLOR, A. E. & WITCHEL, S. F. 2006. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*, 91, 4237-45.
- AZZIZ, R. & KASHAR-MILLER, M. D. 2000. Family history as a risk factor for the polycystic ovary syndrome. *J Pediatr Endocrinol Metab*, 13 Suppl 5, 1303-6.
- AZZIZ, R., MARIN, C., HOQ, L., BADAMGARAV, E. & SONG, P. 2005. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. *J Clin Endocrinol Metab*, 90, 4650-8.
- AZZIZ, R., WOODS, K. S., REYNA, R., KEY, T. J., KNOCHENHAUER, E. S. & YILDIZ, B. O. 2004. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*, 89, 2745-9.
- BABOR, T., HIGGINS-BIDDLE, J., SAUNDERS, J. & MONTEIRO, M. 2001. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. *In: DEPENDENCE*, D. O. M. H. A. S. (ed.). World Health Organisation.
- BALEN, A. 2001. Polycystic ovary syndrome and cancer. *Hum Reprod Update*, 7, 522-5.
- BALEN, A. H., CONWAY, G. S., KALTSAS, G., TECHATRASAK, K., MANNING, P. J., WEST, C. & JACOBS, H. S. 1995. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. *Hum Reprod*, 10, 2107-11.
- BANG, H., NI, L. & DAVIS, C. E. 2004. Assessment of blinding in clinical trials. *Control Clin Trials*, 25, 143-56.
- BAO, W. Y. 2009. Treatment of polycystic ovary syndrome with nourishing kidney and resolving phlegm combined with blood-activating. *Tianjin Journal of Traditional Chinese Medicine [Tian Jin Zhong Yi Yao]*, 26, 375-376.
- BARBIERI, R. L., MAKRI, A., RANDALL, R. W., DANIELS, G., KISTNER, R. W. & RYAN, K. J. 1986. Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. *J Clin Endocrinol Metab*, 62, 904-10.

REFERENCES

- BASRA, M. K., FENECH, R., GATT, R. M., SALEK, M. S. & FINLAY, A. Y. 2008. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*, 159, 997-1035.
- BEKX, M. T., CONNOR, E. C. & ALLEN, D. B. 2010. Characteristics of adolescents presenting to a multidisciplinary clinic for polycystic ovarian syndrome. *J Pediatr Adolesc Gynecol*, 23, 7-10.
- BELL-SYER, S. E., THORPE, L. N., THOMAS, K. & MACPHERSON, H. 2008. GP Participation and Recruitment of Patients to RCTs: Lessons from Trials of Acupuncture and Exercise for Low Back Pain in Primary Care. *Evid Based Complement Alternat Med*, 687349.
- BENSKY, D. & BAROLET, R. 1990. *Chinese herbal medicine: Formulas & strategies*, Seattle, Eastland Press.
- BENSON, S., HAHN, S., TAN, S., MANN, K., JANSSEN, O. E., SCHEDLOWSKI, M. & ELSENBURCH, S. 2009. Prevalence and implications of anxiety in polycystic ovary syndrome: results of an internet-based survey in Germany. *Hum Reprod*, 24, 1446-51.
- BENSOUSSAN, A., TALLEY, N. J., HING, M., MENZIES, R., GUO, A. & NGU, M. 1998. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *JAMA*, 280, 1585-9.
- BOCCUZZI, S. J., WOGEN, J., FOX, J., SUNG, J. C., SHAH, A. B. & KIM, J. 2001. Utilization of oral hypoglycemic agents in a drug-insured U.S. population. *Diabetes Care*, 24, 1411-5.
- BOYATZIS, R. E. 1998. *Transforming qualitative information: Thematic analysis and code development*, California, SAGE Publications.
- BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3, 77-101.
- BROWN, A. J., SETJI, T. L., SANDERS, L. L., LOWRY, K. P., OTVOS, J. D., KRAUS, W. E. & SVETKEY, P. L. 2009. Effects of exercise on lipoprotein particles in women with polycystic ovary syndrome. *Med Sci Sports Exerc*, 41, 497-504.
- BUSHNELL, D. M., MARTIN, M. L., MOORE, K. A., RICHTER, H. E., RUBIN, A. & PATRICK, D. L. 2010. Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life. *Curr Med Res Opin*, 26, 2745-55.
- CAIN, J., LOWELL, J., THORNDYKE, L. & LOCALIO, A. R. 2000. Contraceptive requirements for clinical research. *Obstet Gynecol*, 95, 861-6.
- CALDEIRA, D., VAZ-CARNEIRO, A. & COSTA, J. 2014. The impact of dosing frequency on medication adherence in chronic cardiovascular disease: Systematic review and meta-analysis. *Rev Port Cardiol*.
- CAO, H., POLANSKY, M. M. & ANDERSON, R. A. 2007. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. *Arch Biochem Biophys*, 459, 214-22.
- CARMINA, E., BUCCHIERI, S., ESPOSITO, A., DEL PUENTE, A., MANSUETO, P., ORIO, F., DI FEDE, G. & RINI, G. 2007. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. *J Clin Endocrinol Metab*, 92, 2500-5.
- CHAO, J., NAU, D. P., AIKENS, J. E. & TAYLOR, S. D. 2005. The mediating role of health beliefs in the relationship between depressive symptoms and medication adherence in persons with diabetes. *Res Social Adm Pharm*, 1, 508-25.
- CHEN, H. Y., LIN, Y. H., WU, J. C., CHEN, Y. C., YANG, S. H., CHEN, J. L. & CHEN, T. J. 2011. Prescription patterns of Chinese herbal products for menopausal syndrome: analysis of a nationwide prescription database. *J Ethnopharmacol*, 137, 1261-6.
- CHEN, L., XU, W. M. & ZHANG, D. 2014. The association of abdominal obesity, insulin resistance, and oxidative stress in adipose tissue in women with polycystic ovary syndrome. *Fertil Steril*.
- CHESHIRE, A., POLLEY, M., PETERS, D. & RIDGE, D. 2013. Patient outcomes and experiences of an acupuncture and self-care service for persistent low back

- pain in the NHS: a mixed methods approach. *BMC Complement Altern Med*, 13, 300.
- CHEUNG, A. P. 2001. Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. *Obstet Gynecol*, 98, 325-31.
- CHITTENDEN, B. G., FULLERTON, G., MAHESHWARI, A. & BHATTACHARYA, S. 2009. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. *Reprod Biomed Online*, 19, 398-405.
- CHOI, H. K., WON, E. K., JANG, Y. P. & CHOUNG, S. Y. 2013. Antiobesity Effect of *Codonopsis lanceolata* in High-Calorie/High-Fat-Diet-Induced Obese Rats. *Evid Based Complement Alternat Med*, 2013, 210297.
- COCHRANE, S., SMITH, C. A. & POSSAMAI-INESEDY, A. 2011. Development of a fertility acupuncture protocol: defining an acupuncture treatment protocol to support and treat women experiencing conception delays. *J Altern Complement Med*, 17, 329-37.
- COLOMBO, G. L., ROSSI, E., DE ROSA, M., BENEDETTO, D. & GADDI, A. V. 2012. Antidiabetic therapy in real practice: indicators for adherence and treatment cost. *Patient Prefer Adherence*, 6, 653-61.
- COSTELLO, M., SHRESTHA, B., EDEN, J., SJOBLUM, P. & JOHNSON, N. 2007a. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. *Cochrane Database Syst Rev*, CD005552.
- COSTELLO, M. F., SHRESTHA, B., EDEN, J., JOHNSON, N. P. & SJOBLUM, P. 2007b. Metformin versus oral contraceptive pill in polycystic ovary syndrome: a Cochrane review. *Hum Reprod*, 22, 1200-9.
- COSYNS, J. P., JADOUL, M., SQUIFFLET, J. P., WESE, F. X. & VAN YPERSELE DE STRIHOU, C. 1999. Urothelial lesions in Chinese-herb nephropathy. *Am J Kidney Dis*, 33, 1011-7.
- CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I. & PETTICREW, M. 2008. Developing and evaluating complex interventions: The new Medical Research Council guidance. *BMJ*, 337, a1655.
- CRONIN, L., GUYATT, G., GRIFFITH, L., WONG, E., AZZIZ, R., FUTTERWEIT, W., COOK, D. & DUNAIF, A. 1998. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). *J Clin Endocrinol Metab*, 83, 1976-87.
- DAHLGREN, E., JANSON, P. O., JOHANSSON, S., LAPIDUS, L. & ODEN, A. 1992. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet Gynecol Scand*, 71, 599-604.
- DAHLGREN, E., LANDIN, K., KROTKIEWSKI, M., HOLM, G. & JANSON, P. O. 1998. Effects of two antiandrogen treatments on hirsutism and insulin sensitivity in women with polycystic ovary syndrome. *Hum Reprod*, 13, 2706-11.
- DAILEY, G., KIM, M. S. & LIAN, J. F. 2002. Patient compliance and persistence with anti-hyperglycemic therapy: evaluation of a population of type 2 diabetic patients. *J Int Med Res*, 30, 71-9.
- DALKEY, N. C. 1968. The Delphi method: An experimental study of group opinion.
- DAVIS, E. L., OH, B., BUTOW, P. N., MULLAN, B. A. & CLARKE, S. 2012. Cancer patient disclosure and patient-doctor communication of complementary and alternative medicine use: a systematic review. *Oncologist*, 17, 1475-81.
- DE NIET, J. E., DE KONING, C. M., PASTOOR, H., DUIVENVOORDEN, H. J., VALKENBURG, O., RAMAKERS, M. J., PASSCHIER, J., DE KLERK, C. & LAVEN, J. S. 2010. Psychological well-being and sexarche in women with polycystic ovary syndrome. *Hum Reprod*, 25, 1497-503.
- DEEKS, J. J., HIGGINS, J. P. T. & ALTMAN, D. G. 2011. Chapter 9: Analysing data and undertaking meta-analysis. In: HIGGINS, J. P. T. & GREEN, S. (eds.) *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration.
- DELBECQ, A. L., VAN DE VAN, A. H. & GUSTAFSON, D. H. 1975. *Group techniques for program planning: A guide to nominal group technique and Delphi processes*, Glenview, IL, Scott, Foresman & Company.

- DEVILLY, G. J. & BORKOVEC, T. D. 2000. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry*, 31, 73-86.
- DI FEDE, G., MANSUETO, P., LONGO, R. A., RINI, G. & CARMINA, E. 2009. Influence of sociocultural factors on the ovulatory status of polycystic ovary syndrome. *Fertil Steril*, 91, 1853-6.
- DIAMANTI-KANDARAKIS, E., MITRAKOU, A., HENNES, M. M., PLATANISSIOTIS, D., KAKLAS, N., SPINA, J., GEORGIADOU, E., HOFFMANN, R. G., KISSEBAH, A. H. & RAPTIS, S. 1995. Insulin sensitivity and antiandrogenic therapy in women with polycystic ovary syndrome. *Metabolism*, 44, 525-31.
- DONG, C. Y. & TIAN, Y. M. 2010. Clinical observation of rising liver-energy in treating Polycystic Ovary Syndrome (PCOS) in 30 cases. *Hebei Journal of Traditional Chinese Medicine [Hei Bei Zhong Yi]*, 32, 38-39.
- DONNAN, P. T., MACDONALD, T. M. & MORRIS, A. D. 2002. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabet Med*, 19, 279-84.
- DUNAIF, A. 1997. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev*, 18, 774-800.
- DUNAIF, A., CHANG, R. J., FRANKS, S. & LEGRO, R. S. 2008. *Polycystic ovary syndrome: Current controversies, from the Ovary to the Pancreas*, New Jersey, USA, Springer Science & Business Media.
- DUNAIF, A. & GRAF, M. 1989. Insulin administration alters gonadal steroid metabolism independent of changes in gonadotropin secretion in insulin-resistant women with the polycystic ovary syndrome. *J Clin Invest*, 83, 23-9.
- DURANT, R. H., JAY, M. S., LINDER, C. W., SHOFFITT, T. & LITT, I. 1984. Influence of psychosocial factors on adolescent compliance with oral contraceptives. *J Adolesc Health Care*, 5, 1-6.
- EARDLEY, S., BISHOP, F. L., PRESCOTT, P., CARDINI, F., BRINKHAUS, B., SANTOS-REY, K., VAS, J., VON AMMON, K., HEGYI, G., DRAGAN, S., UEHLEKE, B., FØNNEBØ, V. & LEWITH, G. 2012. CAM use in Europe – The patients' perspective. Part I: A systematic literature review of CAM prevalence in the EU. In: LEWITH, G. (ed.) *Final Report of CAMbrella Work Package 4*.
- EDWARDS, J. E., THOMAS, M. D., ROSENFELD, P. & BOOTH-KEWLEY, S. 1997. *How to conduct organizational surveys: A step-by-step guide*, Thousand Oaks, CA, SAGE Publications.
- EGGER, M., DAVEY SMITH, G., SCHNEIDER, M. & MINDER, C. 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 315, 629-34.
- EHRMANN, D. A. 2005. Polycystic ovary syndrome. *N Engl J Med*, 352, 1223-36.
- EHRMANN, D. A., BARNES, R. B., ROSENFELD, R. L., CAVAGHAN, M. K. & IMPERIAL, J. 1999. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care*, 22, 141-6.
- EHRMANN, D. A., ROSENFELD, R. L., BARNES, R. B., BRIGELL, D. F. & SHEIKH, Z. 1992. Detection of functional ovarian hyperandrogenism in women with androgen excess. *N Engl J Med*, 327, 157-62.
- ENBLUM, A., JOHNSON, A., HAMMAR, M., STEINECK, G. & BORJESON, S. 2011. The nonpenetrating telescopic sham needle may blind patients with different characteristics and experiences when treated by several therapists. *Evid Based Complement Alternat Med*, 2011, 185034.
- ESCOBAR-MORREALE, H. F., LUQUE-RAMIREZ, M. & SAN MILLAN, J. L. 2005. The molecular-genetic basis of functional hyperandrogenism and the polycystic ovary syndrome. *Endocr Rev*, 26, 251-82.
- ESSAH, P. A., APRIDONIDZE, T., IUORNO, M. J. & NESTLER, J. E. 2006. Effects of short-term and long-term metformin treatment on menstrual cyclicity in women with polycystic ovary syndrome. *Fertil Steril*, 86, 230-2.
- EVANS, D. J., HOFFMANN, R. G., KALKHOFF, R. K. & KISSEBAH, A. H. 1983. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. *J Clin Endocrinol Metab*, 57, 304-10.

- FALSETTI, L. & PASINETTI, E. 1995. Effects of long-term administration of an oral contraceptive containing ethinylestradiol and cyproterone acetate on lipid metabolism in women with polycystic ovary syndrome. *Acta Obstet Gynecol Scand*, 74, 56-60.
- FAUSER, B. C., TARLATZIS, B. C., REBAR, R. W., LEGRO, R. S., BALEN, A. H., LOBO, R., CARMINA, E., CHANG, J., YILDIZ, B. O., LAVEN, J. S., BOIVIN, J., PETRAGLIA, F., WIJEYERATNE, C. N., NORMAN, R. J., DUNAIF, A., FRANKS, S., WILD, R. A., DUMESIC, D. & BARNHART, K. 2012. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril*, 97, 28-38 e25.
- FEI, Y. T. & LIU, J. P. 2008. [Herbal CONSORT statement and standardization of reporting traditional Chinese drug trials]. *Zhongguo Zhong Yao Za Zhi*, 33, 89-94.
- FERRIMAN, D. & GALLWEY, J. D. 1961. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab*, 21, 1440-7.
- FINLAY, A. Y. & KHAN, G. K. 1994. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. *Clin Exp Dermatol*, 19, 210-6.
- FISCHER, F. H., LEWITH, G., WITT, C. M., LINDE, K., VON AMMON, K., CARDINI, F., FALKENBERG, T., FONNEBO, V., JOHANNESSEN, H., REITER, B., UEHLEKE, B., WEIDENHAMMER, W. & BRINKHAUS, B. 2014. High prevalence but limited evidence in complementary and alternative medicine: guidelines for future research. *BMC Complement Altern Med*, 14, 46.
- FIXLER, M., OGDEN, C., MOIR, F. & POLLEY, M. J. 2012. Patient experience of acupuncture provision in a GP practice. *Complement Ther Clin Pract*, 18, 140-4.
- FLAWS, B. 2005. *A compendium of Chinese medical menstrual diseases*, Colorado, Blue Poppy Press.
- FLEMING, R., HOPKINSON, Z. E., WALLACE, A. M., GREER, I. A. & SATTAR, N. 2002. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab*, 87, 569-74.
- FLOWER, A., LEWITH, G. & LITTLE, P. 2011a. Combining rigour with relevance: a novel methodology for testing Chinese herbal medicine. *J Ethnopharmacol*, 134, 373-8.
- FLOWER, A., LEWITH, G. T. & LITTLE, P. 2007. Seeking an oracle: using the Delphi process to develop practice guidelines for the treatment of endometriosis with Chinese herbal medicine. *J Altern Complement Med*, 13, 969-76.
- FLOWER, A., LEWITH, G. T. & LITTLE, P. 2011b. A feasibility study exploring the role of Chinese herbal medicine in the treatment of endometriosis. *J Altern Complement Med*, 17, 691-9.
- FLOWER, A., LIU, J. P., CHEN, S., LEWITH, G. & LITTLE, P. 2009. Chinese herbal medicine for endometriosis. *Cochrane Database Syst Rev*, CD006568.
- FRANKS, S. 1995. Polycystic ovary syndrome. *N Engl J Med*, 333, 853-61.
- FRANKS, S. 2002. Adult polycystic ovary syndrome begins in childhood. *Best Pract Res Clin Endocrinol Metab*, 16, 263-72.
- FRANKS, S., GHARANI, N., WATERWORTH, D., BATTY, S., WHITE, D., WILLIAMSON, R. & MCCARTHY, M. 1997. The genetic basis of polycystic ovary syndrome. *Hum Reprod*, 12, 2641-8.
- FRANKS, S., STARK, J. & HARDY, K. 2008. Follicle dynamics and anovulation in polycystic ovary syndrome. *Hum Reprod Update*, 14, 367-78.
- FRANSEN, G. A., VAN MARREWIJK, C. J., MUJAKOVIC, S., MURIS, J. W., LAHEIJ, R. J., NUMANS, M. E., DE WIT, N. J., SAMSOM, M., JANSEN, J. B. & KNOTTNERUS, J. A. 2007. Pragmatic trials in primary care. Methodological challenges and solutions demonstrated by the DIAMOND-study. *BMC Med Res Methodol*, 7, 16.
- GAGNIER, J., BOON, H., ROCHON, P., BARNES, J., MOHER, D. & BOMBARDIER, C. 2006. Improving the quality of reporting of randomized controlled trials evaluating herbal interventions: implementing the CONSORT statement [corrected]. *Explore (NY)*, 2, 143-9.

- GALLETLY, C., CLARK, A., TOMLINSON, L. & BLANEY, F. 1996. A group program for obese, infertile women: weight loss and improved psychological health. *J Psychosom Obstet Gynaecol*, 17, 125-8.
- GARCIA-RUDAZ, M. C., ROPELATO, M. G., ESCOBAR, M. E., VELDHUIS, J. D. & BARONTINI, M. 1998. Augmented frequency and mass of LH discharged per burst are accompanied by marked disorderliness of LH secretion in adolescents with polycystic ovary syndrome. *Eur J Endocrinol*, 139, 621-30.
- GENG, S. S., LI, H. Z., WU, X. K., DANG, J. M., TONG, H., ZHAO, C. Y., LIU, Y. & CAI, Y. Q. 2010. Effect of Wujijing Oral Liquid on menstrual disturbance of women. *J Ethnopharmacol*, 128, 649-53.
- GERVASIO, C. G., BERNUCI, M. P., SILVA-DE-SA, M. F. & ROSA, E. S. A. C. 2014. The role of androgen hormones in early follicular development. *ISRN Obstet Gynecol*, 2014, 818010.
- GILLING-SMITH, C., WILLIS, D. S., BEARD, R. W. & FRANKS, S. 1994. Hypersecretion of androstenedione by isolated thecal cells from polycystic ovaries. *J Clin Endocrinol Metab*, 79, 1158-65.
- GLINTBORG, D. & ANDERSEN, M. 2010. An update on the pathogenesis, inflammation, and metabolism in hirsutism and polycystic ovary syndrome. *Gynecol Endocrinol*, 26, 281-96.
- GRANT, R. W., DEVITA, N. G., SINGER, D. E. & MEIGS, J. B. 2003. Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care*, 26, 1408-12.
- GRANT, S. J., BENSOUSSAN, A., CHANG, D., KIAT, H., KLUPP, N. L., LIU, J. P. & LI, X. 2009. Chinese herbal medicines for people with impaired glucose tolerance or impaired fasting blood glucose. *Cochrane Database Syst Rev*, CD006690.
- GRANT, S. J., CHANG, D. H., LIU, J., WONG, V., KIAT, H. & BENSOUSSAN, A. 2013. Chinese herbal medicine for impaired glucose tolerance: a randomized placebo controlled trial. *BMC Complement Altern Med*, 13, 104.
- GUO, A. J., CHOI, R. C., CHEUNG, A. W., LI, J., CHEN, I. X., DONG, T. T., TSIM, K. W. & LAU, B. W. 2009. Stimulation of Apolipoprotein A-IV expression in Caco-2/TC7 enterocytes and reduction of triglyceride formation in 3T3-L1 adipocytes by potential anti-obesity Chinese herbal medicines. *Chin Med*, 4, 5.
- GUYATT, G. H., JUNIPER, E. F., WALTER, S. D., GRIFFITH, L. E. & GOLDSTEIN, R. S. 1998. Interpreting treatment effects in randomised trials. *BMJ*, 316, 690-3.
- HAM, C., DIXON, A. & BROOKE, B. 2012. Transforming the delivery of health and social care: The case for fundamental change.
- HAN, Y., JUNG, H. W., BAE, H. S., KANG, J. S. & PARK, Y. K. 2013. The extract of Cinnamomum cassia twigs inhibits adipocyte differentiation via activation of the insulin signaling pathway in 3T3-L1 preadipocytes. *Pharm Biol*, 51, 961-7.
- HAO, H. N. 2010. Combined treatment of Huatan Bushen Tang and Diane-35 in 30 cases of polycystic ovary syndrome-related infertility. *Henan Traditional Chinese Medicine*, 30, 783-784.
- HAOULA, Z., SALMAN, M. & ATIOMO, W. 2012. Evaluating the association between endometrial cancer and polycystic ovary syndrome. *Hum Reprod*, 27, 1327-31.
- HARBORNE, L., FLEMING, R., LYALL, H., SATTAR, N. & NORMAN, J. 2003. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. *J Clin Endocrinol Metab*, 88, 4116-23.
- HARRIGAN, J. T. 2011. Patient disclosure of the use of complementary and alternative medicine to their obstetrician/gynaecologist. *J Obstet Gynaecol*, 31, 59-61.
- HASSON, F., KEENEY, S. & MCKENNA, H. 2000. Research guidelines for the Delphi survey technique. *J Adv Nurs*, 32, 1008-15.
- HAUBER, A. B., MOHAMED, A. F., JOHNSON, F. R. & FALVEY, H. 2009. Treatment preferences and medication adherence of people with Type 2 diabetes using oral glucose-lowering agents. *Diabet Med*, 26, 416-24.
- HEIBASHY, M. I. A., MAZEN, G. M. A. & SHAHIN, M. I. 2013. Metabolic changes and hormonal disturbances in polycystic ovarian syndrome rats and the amelioration effects of metformin and/or cinnamon extraction. *Journal of American Science*, 9, 54-62.

- HIGGINS, J. P. & THOMPSON, S. G. 2002. Quantifying heterogeneity in a meta-analysis. *Stat Med*, 21, 1539-58.
- HIGGINS, J. P., THOMPSON, S. G., DEEKS, J. J. & ALTMAN, D. G. 2003. Measuring inconsistency in meta-analyses. *BMJ*, 327, 557-60.
- HIGGINS, J. P. T., ALTMAN, D. G. & STERNE, J. A. C. 2011a. Cochrane Handbook for Systematic Reviews of Interventions. In: HIGGINS JPT, G. S. (ed.) Version 5.1.0 (updated March 2011) ed.: The Cochrane Collaboration.
- HIGGINS, J. P. T., DEEKS, J. J. & ALTMAN, D. G. 2011b. Chapter 16: Special topics in statistics. In: HIGGINS, J. P. T. & GREEN, S. (eds.) *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration.
- HIMELEIN, M. J. & THATCHER, S. S. 2006. Depression and body image among women with polycystic ovary syndrome. *J Health Psychol*, 11, 613-25.
- HO, S. G. Y., YEUNG, C. K. & CHAN, H. H. L. 2009. Methotrexate versus traditional Chinese medicine in psoriasis: a randomized, placebo-controlled trial to determine efficacy, safety and quality of life. *Clinical and Experimental Dermatology*, 35, 717-722.
- HODGSON, R., ALWYN, T., JOHN, B., THOM, B. & SMITH, A. 2002. The FAST Alcohol Screening Test. *Alcohol Alcohol*, 37, 61-6.
- HOLLMANN, M., RUNNEBAUM, B. & GERHARD, I. 1996. Effects of weight loss on the hormonal profile in obese, infertile women. *Hum Reprod*, 11, 1884-91.
- HSCIC 2011. Prescriptions dispensed in the community: England statistics for 2001 to 2011. In: HEALTH AND SOCIAL CARE INFORMATION CENTRE, P. A. P. C. S. (ed.).
- HSCIC 2012. Prescribing for diabetes in England: 2005/6 to 2011/12. In: HEALTH AND SOCIAL CARE INFORMATION CENTRE, P. A. P. C. S. (ed.).
- HUBER-BUCHHOLZ, M. M., CAREY, D. G. & NORMAN, R. J. 1999. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab*, 84, 1470-4.
- HUI, H., TANG, G. & GO, V. L. 2009. Hypoglycemic herbs and their action mechanisms. *Chin Med*, 4, 11.
- HULL, M. G. 1987. Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. *Gynecol Endocrinol*, 1, 235-45.
- HUNT, K. J., COELHO, H. F., WIDER, B., PERRY, R., HUNG, S. K., TERRY, R. & ERNST, E. 2010. Complementary and alternative medicine use in England: results from a national survey. *Int J Clin Pract*, 64, 1496-502.
- IBISWORLD 2013. Traditional Chinese medicine hospitals in China: Market research report.
- ICH 2004. E2E: ICH Harmonised tripartite guideline: Pharmacovigilance Planning. 4 ed.: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
- IMANI, B., EIJKEMANS, M. J., TE VELDE, E. R., HABBEMA, J. D. & FAUSER, B. C. 2002. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *Fertil Steril*, 77, 91-7.
- JACKSON, C. J. & FURNHAM, A. 2000. *Designing and analysing questionnaires and surveys: A manual for health professionals and administrators*, London, Whurr.
- JEDEL, E., LABRIE, F., ODEN, A., HOLM, G., NILSSON, L., JANSON, P. O., LIND, A. K., OHLSSON, C. & STENER-VICTORIN, E. 2011. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. *Am J Physiol Endocrinol Metab*, 300, E37-45.
- JIN, J., SKLAR, G. E., MIN SEN OH, V. & CHUEN LI, S. 2008. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag*, 4, 269-86.
- JOHANSSON, J., REDMAN, L., VELDHIJS, P. P., SAZONOVA, A., LABRIE, F., HOLM, G., JOHANSSON, G. & STENER-VICTORIN, E. 2013. Acupuncture for ovulation induction in polycystic ovary syndrome: a randomized controlled trial. *Am J Physiol Endocrinol Metab*, 304, E934-43.

REFERENCES

- JONES, G. L., HALL, J. M., LASHEN, H. L., BALEN, A. H. & LEDGER, W. L. 2011. Health-related quality of life among adolescents with polycystic ovary syndrome. *J Obstet Gynecol Neonatal Nurs*, 40, 577-88.
- JONES, J. & HUNTER, D. 1995. Consensus methods for medical and health services research. *BMJ*, 311, 376-80.
- KAPTCHUK, T. J. 2000. *The Web That Has No Weaver: Understanding Chinese Medicine*, Chicago, Contemporary Books.
- KARIMZADEH, M. A. & JAVEDANI, M. 2010. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. *Fertil Steril*, 94, 216-20.
- KASIM-KARAKAS, S. E., ALMARIO, R. U. & CUNNINGHAM, W. 2009. Effects of protein versus simple sugar intake on weight loss in polycystic ovary syndrome (according to the National Institutes of Health criteria). *Fertil Steril*, 92, 262-70.
- KAUFFMAN, R. P., BAKER, V. M., DIMARINO, P., GIMPEL, T. & CASTRACANE, V. D. 2002. Polycystic ovarian syndrome and insulin resistance in white and Mexican American women: a comparison of two distinct populations. *Am J Obstet Gynecol*, 187, 1362-9.
- KAWADZKI, J. & DUNAIF, A. 1992. Diagnostic criteria for polycystic ovary syndrome: a rational approach. In: DUNAIF, A., GIVENS, J., HASELTINE, F. & GR., M. (eds.) *Polycystic Ovary Syndrome*. Cambridge, MA: Blackwell Scientific.
- KEANE, F. M., MUNN, S. E., DU VIVIER, A. W., TAYLOR, N. F. & HIGGINS, E. M. 1999. Analysis of Chinese herbal creams prescribed for dermatological conditions. *BMJ*, 318, 563-4.
- KEENEY, S., HASSON, F. & MCKENNA, H. 2006. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. *J Adv Nurs*, 53, 205-12.
- KERSHAW, E. E. & FLIER, J. S. 2004. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*, 89, 2548-56.
- KIDDY, D. S., HAMILTON-FAIRLEY, D., BUSH, A., SHORT, F., ANYAOKU, V., REED, M. J. & FRANKS, S. 1992. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)*, 36, 105-11.
- KIDDY, D. S., SHARP, P. S., WHITE, D. M., SCANLON, M. F., MASON, H. D., BRAY, C. S., POLSON, D. W., REED, M. J. & FRANKS, S. 1990. Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. *Clin Endocrinol (Oxf)*, 32, 213-20.
- KING-FAI, C., PING-CHUNG, L., LAI-YI, W. & YUET-SHIM, F. 2008. Patient recruitment for clinical trials on traditional Chinese medicine: Challenges, barriers, and strategies. *Patient Prefer Adherence*, 2, 207-14.
- KITZINGER, C. & WILLMOTT, J. 2002. 'The thief of womanhood': women's experience of polycystic ovarian syndrome. *Soc Sci Med*, 54, 349-61.
- KNOCHENHAUER, E. S., KEY, T. J., KAHSAR-MILLER, M., WAGGONER, W., BOOTS, L. R. & AZZIZ, R. 1998. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab*, 83, 3078-82.
- KOLAH, J., BANG, H. & PARK, J. 2009. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. *Community Dent Oral Epidemiol*, 37, 477-84.
- LAI, L. Y. W., FLOWER, A., MOORE, M., PRESCOTT, P. & LEWITH, G. 2014. Polycystic Ovary syndrome: A Randomised feasibility and pilot study using Chinese Herbal medicine to explore Impact on Dysfunction (ORCHID) - Study protocol. *European Journal of Integrative Medicine*, 6, 392-399.
- LAKATOS, P. L., CZEGLÉDI, Z., DAVID, G., KISPAL, Z., KISS, L. S., PALATKA, K., KRISTOF, T., NAGY, F., SALAMON, A., DEMETER, P., MIHELLER, P., SZAMOSI, T., BANAI, J., PAPP, M., BENE, L., KOVACS, A., RACZ, I. & LAKATOS, L. 2010. Association of adherence to therapy and complementary and alternative medicine use with

- demographic factors and disease phenotype in patients with inflammatory bowel disease. *J Crohns Colitis*, 4, 283-90.
- LAMBERT, T. D., MORRISON, K. E., EDWARDS, J. & CLARKE, C. E. 2010. The use of complementary and alternative medicine by patients attending a UK headache clinic. *Complement Ther Med*, 18, 128-34.
- LANCASTER, G. A., DODD, S. & WILLIAMSON, P. R. 2004. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*, 10, 307-12.
- LECHNER, M., STEIRER, I., BRINKHAUS, B., CHEN, Y., KRIST-DUNGL, C., KOSCHIER, A., GANTSCHACHER, M., NEUMANN, K. & ZAUNER-DUNGL, A. 2011. Efficacy of individualized Chinese herbal medication in osteoarthritis of hip and knee: a double-blind, randomized-controlled clinical study. *J Altern Complement Med*, 17, 539-47.
- LEGRO, R. S., ARSLANIAN, S. A., EHRMANN, D. A., HOEGER, K. M., MURAD, M. H., PASQUALI, R. & WELT, C. K. 2013. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 98, 4565-92.
- LEGRO, R. S., BARNHART, H. X., SCHLAFF, W. D., CARR, B. R., DIAMOND, M. P., CARSON, S. A., STEINKAMPF, M. P., COUTIFARIS, C., MCGOVERN, P. G., CATALDO, N. A., GOSMAN, G. G., NESTLER, J. E., GIUDICE, L. C., LEPPERT, P. C. & MYERS, E. R. 2007. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med*, 356, 551-66.
- LEGRO, R. S., DRISCOLL, D., STRAUSS, J. F., 3RD, FOX, J. & DUNAIF, A. 1998. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. *Proc Natl Acad Sci U S A*, 95, 14956-60.
- LI, X. B., LI, L. Y., FU, F. & HU, X. D. 2007. Clinical study on Ling Zhu Granule and Shen Qi Capsule for PCOS. *Journal of Traditional Chinese Medicine*.
- LI, X. B., ZHAI, J. L., LI, L. Y. & HU, X. D. 2011a. Influence of Lingzhu Granules on endocrine and lipid metabolism of polycystic ovary syndrome patients. *Journal of Traditional Chinese Medicine*, 52, 32-34.
- LI, X. P., YE, S., LIN, S. & S., Z. C. 2011b. Effects of modified Zi Kui prescription on polycystic ovary syndrome-related hyperandrogenism in Liver and Kidney yin deficiency syndrome. *Guangming Traditional Chinese Medicine*, 26, 242-244.
- LIN, Y. H., CHEN, K. K. & CHIU, J. H. 2012. Coprescription of Chinese Herbal Medicine and Western Medications among Prostate Cancer Patients: A Population-Based Study in Taiwan. *Evid Based Complement Alternat Med*, 2012, 147015.
- LINSTONE, H. A. & TUROFF, M. 2002. The Delphi Method: Techniques and Applications. *In*: LINSTONE, H. A. & TUROFF, M. (eds.).
- LOMBARD, C. B., DEEKS, A. A., BALL, K., JOLLEY, D. & TEEDE, H. J. 2009. Weight, physical activity and dietary behavior change in young mothers: short term results of the HeLP-her cluster randomized controlled trial. *Nutr J*, 8, 17.
- LORD, J. M., FLIGHT, I. H. & NORMAN, R. J. 2003a. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev*, CD003053.
- LORD, J. M., FLIGHT, I. H. & NORMAN, R. J. 2003b. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ*, 327, 951-3.
- LUDWIG, E. 1977. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol*, 97, 247-54.
- LUO, H., LI, Q., FLOWER, A., LEWITH, G. & LIU, J. 2012. Comparison of effectiveness and safety between granules and decoction of Chinese herbal medicine: a systematic review of randomized clinical trials. *J Ethnopharmacol*, 140, 555-67.
- LUO, S. W. 2003. *Bencao Gangmu: Compendium of Materia Medica*, Foreign Languages Press.
- LYTTLETON, J. 2013. *The treatment of infertility with Chinese medicine*, Churchill Livingstone: Elsevier.
- MACIOCIA, M. 2011. *Obstetrics and Gynecology in Chinese Medicine*, London, Churchill Livingstone: Elsevier.

- MACPHERSON, H. & SCHROER, S. 2007. Acupuncture as a complex intervention for depression: a consensus method to develop a standardised treatment protocol for a randomised controlled trial. *Complement Ther Med*, 15, 92-100.
- MANHEIMER, E., WIELAND, S., KIMBROUGH, E., CHENG, K. & BERMAN, B. M. 2009. Evidence from the Cochrane Collaboration for Traditional Chinese Medicine therapies. *J Altern Complement Med*, 15, 1001-14.
- MANI, H., LEVY, M. J., DAVIES, M. J., MORRIS, D. H., GRAY, L. J., BANKART, J., BLACKLEDGE, H., KHUNTI, K. & HOWLETT, T. A. 2012. Diabetes and cardiovascular events in women with polycystic ovary syndrome; a 20 years retrospective cohort study. *Clin Endocrinol (Oxf)*.
- MANSFIELD, R., GALEA, R., BRINCAT, M., HOLE, D. & MASON, H. 2003. Metformin has direct effects on human ovarian steroidogenesis. *Fertil Steril*, 79, 956-62.
- MARCH, W. A., MOORE, V. M., WILLSON, K. J., PHILLIPS, D. I., NORMAN, R. J. & DAVIES, M. J. 2010. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod*, 25, 544-51.
- MCKENNA, H. P. 1994. The Delphi technique: a worthwhile research approach for nursing? *J Adv Nurs*, 19, 1221-5.
- MCPHERSON, M. L., SMITH, S. W., POWERS, A. & ZUCKERMAN, I. H. 2008. Association between diabetes patients' knowledge about medications and their blood glucose control. *Res Social Adm Pharm*, 4, 37-45.
- MERKIN, S. S., AZZIZ, R., SEEMAN, T., CALDERON-MARGALIT, R., DAVIGLUS, M., KIEFE, C., MATTHEWS, K., STERNFELD, B. & SISCOVICK, D. 2011. Socioeconomic status and polycystic ovary syndrome. *J Womens Health (Larchmt)*, 20, 413-9.
- MEYER, C., MCGRATH, B. P. & TEEDE, H. J. 2007. Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. *Diabetes Care*, 30, 471-8.
- MHRA. 2010. Clarification of contraceptive wording in clinical trials conducted in the UK. Available: <http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033037.pdf>.
- MICHELMORE, K. F., BALEN, A. H., DUNGER, D. B. & VESSEY, M. P. 1999. Polycystic ovaries and associated clinical and biochemical features in young women. *Clin Endocrinol (Oxf)*, 51, 779-86.
- MOGHETTI, P., CASTELLO, R., NEGRI, C., TOSI, F., PERRONE, F., CAPUTO, M., ZANOLIN, E. & MUGGIO, M. 2000. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab*, 85, 139-46.
- MOLL, E., BOSSUYT, P. M., KOREVAAR, J. C., LAMBALK, C. B. & VAN DER VEEN, F. 2006. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *BMJ*, 332, 1485.
- MOLL, E., KOREVAAR, J. C., BOSSUYT, P. M. & VAN DER VEEN, F. 2008. Does adding metformin to clomifene citrate lead to higher pregnancy rates in a subset of women with polycystic ovary syndrome? *Hum Reprod*, 23, 1830-4.
- MORAN, L. & TEEDE, H. 2009. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. *Hum Reprod Update*, 15, 477-88.
- MORAN, L. J., LOMBARD, C. B., LIM, S., NOAKES, M. & TEEDE, H. J. 2010. Polycystic ovary syndrome and weight management. *Womens Health (Lond Engl)*, 6, 271-83.
- MORAN, L. J., NOAKES, M., CLIFTON, P. M., TOMLINSON, L., GALLETLY, C. & NORMAN, R. J. 2003. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab*, 88, 812-9.
- MORAN, L. J., PASQUALI, R., TEEDE, H. J., HOEGER, K. M. & NORMAN, R. J. 2009. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril*, 92, 1966-82.

- MORIN-PAPUNEN, L. C., KOIVUNEN, R. M., RUOKONEN, A. & MARTIKAINEN, H. K. 1998. Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. *Fertil Steril*, 69, 691-6.
- MORIN-PAPUNEN, L. C., VAUHKONEN, I., KOIVUNEN, R. M., RUOKONEN, A., MARTIKAINEN, H. K. & TAPANAINEN, J. S. 2000. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab*, 85, 3161-8.
- MORISKY, D. E., ANG, A., KROUSEL-WOOD, M. & WARD, H. J. 2008. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)*, 10, 348-54.
- MORISKY, D. E., GREEN, L. W. & LEVINE, D. M. 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*, 24, 67-74.
- MOROZ, A., FREED, B., TIEDEMANN, L., BANG, H., HOWELL, M. & PARK, J. J. 2013. Blinding measured: a systematic review of randomized controlled trials of acupuncture. *Evid Based Complement Alternat Med*, 2013, 708251.
- MRC. 2000. A framework for development and evaluation of RCTs for complex interventions to improve health. Available: <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003372> [Accessed 20/08/2012].
- NADER, S., RIAD-GABRIEL, M. G. & SAAD, M. F. 1997. The effect of a desogestrel-containing oral contraceptive on glucose tolerance and leptin concentrations in hyperandrogenic women. *J Clin Endocrinol Metab*, 82, 3074-7.
- NESTLER, J. E. & JAKUBOWICZ, D. J. 1996. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med*, 335, 617-23.
- NORMAN, R. J., MASTERS, L., MILNER, C. R., WANG, J. X. & DAVIES, M. J. 2001. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. *Hum Reprod*, 16, 1995-8.
- ORIO, F., GIALLAURIA, F., PALOMBA, S., MANGUSO, F., ORIO, M., TAFURI, D., LOMBARDI, G., CARMINA, E., COLAO, A. & VIGORITO, C. 2008. Metabolic and cardiopulmonary effects of detraining after a structured exercise training programme in young PCOS women. *Clin Endocrinol (Oxf)*, 68, 976-81.
- PALOMBA, S., GIALLAURIA, F., FALBO, A., RUSSO, T., OPPEDISANO, R., TOLINO, A., COLAO, A., VIGORITO, C., ZULLO, F. & ORIO, F. 2008. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. *Hum Reprod*, 23, 642-50.
- PANIDIS, D., MACUT, D., TZIOMALOS, K., PAPADAKIS, E., MIKHAILIDIS, K., KANDARAKI, E. A., TSOURDI, E. A., TANTANASIS, T., MAVROMATIDIS, G. & KATSIKIS, I. 2013. Prevalence of metabolic syndrome in women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)*, 78, 586-92.
- PANIDIS, D., TZIOMALOS, K., CHATZIS, P., PAPADAKIS, E., DELKOS, D., TSOURDI, E. A., KANDARAKI, E. A. & KATSIKIS, I. 2012. Association between menstrual cycle irregularities and endocrine and metabolic characteristics of the polycystic ovary syndrome. *Eur J Endocrinol*.
- PATEL, D. N., LOW, W. L., TAN, L. L., TAN, M. M., ZHANG, Q., LOW, M. Y., CHAN, C. L. & KOH, H. L. 2012. Adverse events associated with the use of complementary medicine and health supplements: An analysis of reports in the Singapore Pharmacovigilance database from 1998 to 2009. *Clin Toxicol (Phila)*, 50, 481-9.
- PATERSON, C. 1996. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. *BMJ*, 312, 1016-20.
- PATERSON, C. & DIEPPE, P. 2005. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *BMJ*, 330, 1202-5.
- PEIRIS, A. N., MUELLER, R. A., STRUVE, M. F., SMITH, G. A. & KISSEBAH, A. H. 1987. Relationship of androgenic activity to splanchnic insulin metabolism and

- peripheral glucose utilization in premenopausal women. *J Clin Endocrinol Metab*, 64, 162-9.
- PETERS, D., PINTO, G. J. & HARRIS, G. 2000. Using a computer-based clinical management system to improve effectiveness of a homeopathic service in a fundholding general practice. *Br Homeopath J*, 89 Suppl 1, S14-9.
- PILKINGTON, K. & BOSHNAKOVA, A. 2012. Complementary medicine and safety: a systematic investigation of design and reporting of systematic reviews. *Complement Ther Med*, 20, 73-82.
- POSADZKI, P., WATSON, L. & ERNST, E. 2013a. Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews. *Eur J Clin Pharmacol*, 69, 295-307.
- POSADZKI, P., WATSON, L. K., ALOTAIBI, A. & ERNST, E. 2013b. Prevalence of use of complementary and alternative medicine (CAM) by patients/consumers in the UK: systematic review of surveys. *Clin Med*, 13, 126-31.
- RAJA-KHAN, N., STENER-VICTORIN, E., WU, X. & LEGRO, R. S. 2011. The physiological basis of complementary and alternative medicines for polycystic ovary syndrome. *Am J Physiol Endocrinol Metab*, 301, E1-E10.
- RANDEVA, H. S., LEWANDOWSKI, K. C., DRZEWSKI, J., BROOKE-WAVELL, K., O'CALLAGHAN, C., CZUPRYNIAK, L., HILLHOUSE, E. W. & PRELEVIC, G. M. 2002. Exercise decreases plasma total homocysteine in overweight young women with polycystic ovary syndrome. *J Clin Endocrinol Metab*, 87, 4496-501.
- RAUDRANT, D. & RABE, T. 2003. Progestogens with antiandrogenic properties. *Drugs*, 63, 463-92.
- RAUTIO, K., TAPANAINEN, J. S., RUOKONEN, A. & MORIN-PAPUNEN, L. C. 2005. Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome. *Eur J Endocrinol*, 152, 269-75.
- REEVES, B., DEEKS, J., HIGGINS, J. & WELLS, G. 2011. Chapter 13: Including non-randomized studies. In: HIGGINS JPT, G. S. (ed.) *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011.
- RESTON, J. 1971. Now, Let Me Tell You About My Appendectomy in Peking... *New York Times*, Monday 26 July 1971.
- RITCHIE, J. & SPENCER, L. 1994. Qualitative data analysis for applied policy research. In: BRYMAN, A. B. & BURGESS, R. G. (eds.) *Analyzing qualitative data*. Abingdon: Routledge.
- ROSEN, M. P., BREITKOPF, D. M. & NAGAMANI, M. 2003. A randomized controlled trial of second- versus third-generation oral contraceptives in the treatment of acne vulgaris. *Am J Obstet Gynecol*, 188, 1158-60.
- ROSENBERG, M. J. & WAUGH, M. S. 1998. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. *Am J Obstet Gynecol*, 179, 577-82.
- ROSENBERG, M. J., WAUGH, M. S. & MEEHAN, T. E. 1995. Use and misuse of oral contraceptives: risk indicators for poor pill taking and discontinuation. *Contraception*, 51, 283-8.
- SAVIN, R. C. 1994. *Evaluating androgenetic alopecia in male and female patients*, Kalamazoo, MI, The Upjohn Company.
- SCHEID, V. 2002. *Chinese medicine in contemporary China: Plurality and synthesis*, Durham & London, Duke University Press.
- SCHNYER, R. N., CONBOY, L. A., JACOBSON, E., MCKNIGHT, P., GODDARD, T., MOSCATELLI, F., LEGEDZA, A. T., KERR, C., KAPTCHUK, T. J. & WAYNE, P. M. 2005. Development of a Chinese medicine assessment measure: an interdisciplinary approach using the delphi method. *J Altern Complement Med*, 11, 1005-13.
- SCHULZ, K. F., ALTMAN, D. G. & MOHER, D. 2010a. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*, 340, c332.

- SCHULZ, K. F., ALTMAN, D. G. & MOHER, D. 2010b. [CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials (Chinese version)]. *Zhong Xi Yi Jie He Xue Bao*, 8, 604-12.
- SHANG, A., HUWILER, K., NARTEY, L., JUNI, P. & EGGER, M. 2007. Placebo-controlled trials of Chinese herbal medicine and conventional medicine comparative study. *Int J Epidemiol*, 36, 1086-92.
- SHEEHAN, M. P., STEVENS, H., OSTLER, L. S., ATHERTON, D. J., BROSTOFF, J. & RUSTIN, M. H. 1995. Follow-up of adult patients with atopic eczema treated with Chinese herbal therapy for 1 year. *Clin Exp Dermatol*, 20, 136-40.
- SHEEHAN, M. T. 2004. Polycystic ovarian syndrome: diagnosis and management. *Clin Med Res*, 2, 13-27.
- SILLS, E. S., PERLOE, M., TUCKER, M. J., KAPLAN, C. R., GENTON, M. G. & SCHATTMAN, G. L. 2001. Diagnostic and treatment characteristics of polycystic ovary syndrome: descriptive measurements of patient perception and awareness from 657 confidential self-reports. *BMC Womens Health*, 1, 3.
- SINGH, D., GUPTA, R. & SARAF, S. A. 2012. Herbs-are they safe enough? an overview. *Crit Rev Food Sci Nutr*, 52, 876-98.
- SMALLWOOD, C. 2005. The role of complementary and alternative medicine in the NHS. FreshMinds.
- SMITH, C. A. & BETTS, D. 2014. The practice of acupuncture and moxibustion to promote cephalic version for women with a breech presentation: implications for clinical practice and research. *Complement Ther Med*, 22, 75-80.
- SMITH, C. A., GRANT, S., LYTTLETON, J. & COCHRANE, S. 2012. Using a Delphi consensus process to develop an acupuncture treatment protocol by consensus for women undergoing Assisted Reproductive Technology (ART) treatment. *BMC Complement Altern Med*, 12, 88.
- SOLIMAN, P. T., OH, J. C., SCHMELER, K. M., SUN, C. C., SLOMOVITZ, B. M., GERSHENSON, D. M., BURKE, T. W. & LU, K. H. 2005. Risk factors for young premenopausal women with endometrial cancer. *Obstet Gynecol*, 105, 575-80.
- SPIZZER, R. L., KROENKE, K. & WILLIAMS, J. B. 1999. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*, 282, 1737-44.
- STAMETS, K., TAYLOR, D. S., KUNSELMAN, A., DEMERS, L. M., PELKMAN, C. L. & LEGRO, R. S. 2004. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertil Steril*, 81, 630-7.
- STEIN, I. F. & LEVENTHAL, M. L. 1934. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol*, 29, 181-191.
- STENER-VICTORIN, E., JEDEL, E. & MANNERAS, L. 2008. Acupuncture in polycystic ovary syndrome: current experimental and clinical evidence. *J Neuroendocrinol*, 20, 290-8.
- STROWITZKI, T., CAPP, E. & VON EYE CORLETA, H. 2010. The degree of cycle irregularity correlates with the grade of endocrine and metabolic disorders in PCOS patients. *Eur J Obstet Gynecol Reprod Biol*, 149, 178-81.
- STUNKARD, A. J. & MESSICK, S. 1985. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res*, 29, 71-83.
- TAPONEN, S., MARTIKAINEN, H., JARVELIN, M. R., LAITINEN, J., POUTA, A., HARTIKAINEN, A. L., SOVIO, U., MCCARTHY, M. I., FRANKS, S. & RUOKONEN, A. 2003. Hormonal profile of women with self-reported symptoms of oligomenorrhea and/or hirsutism: Northern Finland birth cohort 1966 study. *J Clin Endocrinol Metab*, 88, 141-7.
- TAYLOR, K. 2005. *Chinese Medicine in Early Communist China, 1945-1963: A Medicine of Revolution*, Oxon, RoutledgeCurzon.
- TEEDE, H., DEEKS, A. & MORAN, L. 2010. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med*, 8, 41.

REFERENCES

- TEIXEIRA, P. J., GOING, S. B., HOUTKOOPER, L. B., CUSSLER, E. C., METCALFE, L. L., BLEW, R. M., SARDINHA, L. B. & LOHMAN, T. G. 2004. Pretreatment predictors of attrition and successful weight management in women. *Int J Obes Relat Metab Disord*, 28, 1124-33.
- THABANE, L., MA, J., CHU, R., CHENG, J., ISMAILA, A., RIOS, L. P., ROBSON, R., THABANE, M., GIANGREGORIO, L. & GOLDSMITH, C. H. 2010. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol*, 10, 1.
- THOMAS, K. J., NICHOLL, J. P. & COLEMAN, P. 2001. Use and expenditure on complementary medicine in England: a population based survey. *Complement Ther Med*, 9, 2-11.
- THOMSON, P., JONES, J., EVANS, J. M. & LESLIE, S. L. 2012. Factors influencing the use of complementary and alternative medicine and whether patients inform their primary care physician. *Complement Ther Med*, 20, 45-53.
- THOMSON, R. L., BUCKLEY, J. D., NOAKES, M., CLIFTON, P. M., NORMAN, R. J. & BRINKWORTH, G. D. 2008. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab*, 93, 3373-80.
- THUE, G. & SANDBERG, S. 1993. Performance of the Reflotron and the Seralyzer in primary health care. *Scand J Clin Lab Invest*, 53, 253-61.
- TORCHEN, L. C., FOGEL, N. R., BRICKMAN, W. J., PAPARODIS, R. & DUNAIF, A. 2014. Persistent Apparent Pancreatic beta-Cell Defects in Premenarchal PCOS Relatives. *J Clin Endocrinol Metab*, jc20141474.
- TRUSSELL, J. 2011. Contraceptive failure in the United States. *Contraception*, 83, 397-404.
- TURNER-MCGRIEVEY, G. M., DAVIDSON, C. R., WINGARD, E. E. & BILLINGS, D. L. 2014. Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study. *Nutr Res*, 34, 552-8.
- TWEEDALE, J. 1823. Case of Anasarca successfully treated by Acupuncture. *Lancet*, 1, 19-20.
- UNSCHULD, P. U. 2010. *Medicine in China: A history of ideas*, Berkeley, University of California Press.
- VAN DER WINDT, D. A., KOES, B. W., VAN AARST, M., HEEMSKERK, M. A. & BOUTER, L. M. 2000. Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. *Br J Gen Pract*, 50, 371-4.
- VAN SANTBRINK, E. J., HOP, W. C. & FAUSER, B. C. 1997. Classification of normogonadotropic infertility: polycystic ovaries diagnosed by ultrasound versus endocrine characteristics of polycystic ovary syndrome. *Fertil Steril*, 67, 452-8.
- VRBIKOVA, J., STANICKA, S., DVORAKOVA, K., HILL, M., VONDRA, K., BENDLOVA, B. & STARKA, L. 2004. Metabolic and endocrine effects of treatment with peroral or transdermal oestrogens in conjunction with peroral cyproterone acetate in women with polycystic ovary syndrome. *Eur J Endocrinol*, 150, 215-23.
- VUTYAVANICH, T., KHANIYAO, V., WONGTRA-NGAN, S., SRESHTHAPUTRA, O., SRESHTHAPUTRA, R. & PIROMLERTAMORN, W. 2007. Clinical, endocrine and ultrasonographic features of polycystic ovary syndrome in Thai women. *J Obstet Gynaecol Res*, 33, 677-80.
- WALDSTREICHER, J., SANTORO, N. F., HALL, J. E., FILICORI, M. & CROWLEY, W. F., JR. 1988. Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian disease: indirect evidence for partial gonadotroph desensitization. *J Clin Endocrinol Metab*, 66, 165-72.
- WALLEN, G. R. & BROOKS, A. T. 2012. To Tell or Not to Tell: Shared Decision Making, CAM Use and Disclosure Among Underserved Patients with Rheumatic Diseases. *Integr Med Insights*, 7, 15-22.
- WANG, G., MAO, B., XIONG, Z. Y., FAN, T., CHEN, X. D., WANG, L., LIU, G. J., LIU, J., GUO, J., CHANG, J., WU, T. X. & LI, T. Q. 2007. The quality of reporting of

- randomized controlled trials of traditional Chinese medicine: a survey of 13 randomly selected journals from mainland China. *Clin Ther*, 29, 1456-67.
- WANG, H., PENG, D. & XIE, J. 2009. Ginseng leaf-stem: bioactive constituents and pharmacological functions. *Chin Med*, 4, 20.
- WANG, S. & XIE, J. 2010. Clinical observation of traditional Chinese medicine combined with diane-35 in treating infertility induced by Polycystic Ovary Syndrome (PCOS). *Hubei Journal of Traditional Chinese Medicine [Hu Bei Zhong Yi Za Zhi]*, 32, 14-16.
- WEBBER, L. J., STUBBS, S., STARK, J., TREW, G. H., MARGARA, R., HARDY, K. & FRANKS, S. 2003. Formation and early development of follicles in the polycystic ovary. *Lancet*, 362, 1017-21.
- WEI, L. N., HUANG, R., LI, L. L., FANG, C., LI, Y. & LIANG, X. Y. 2014. Reduced and delayed expression of GDF9 and BMP15 in ovarian tissues from women with polycystic ovary syndrome. *J Assist Reprod Genet*.
- WEST, S., LASHEN, H., BLOIGU, A., FRANKS, S., PUUKKA, K., RUOKONEN, A., JARVELIN, M. R., TAPANAINEN, J. S. & MORIN-PAPUNEN, L. 2014. Irregular menstruation and hyperandrogenaemia in adolescence are associated with polycystic ovary syndrome and infertility in later life: Northern Finland Birth Cohort 1986 study. *Hum Reprod*.
- WESTHOFF, C. L., TORGAL, A. T., MAYEDA, E. R., SHIMONI, N., STANCZYK, F. Z. & PIKE, M. C. 2012. Predictors of noncompliance in an oral contraceptive clinical trial. *Contraception*, 85, 465-9.
- WESTON, M. & GRABOWSKA, C. 2013. Complementary therapy for induction of labour. *Pract Midwife*, 16, S16-8.
- WHO 2002. WHO Traditional medicine strategy 2002-2005.
- WHO 2008. Waist circumference and waist-hip ratio: report of a WHO expert consultation.
- WHO 2012. The regional strategy for traditional medicine in the Western Pacific (2011-2020).
- WILD, S., PIERPOINT, T., MCKEIGUE, P. & JACOBS, H. 2000. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol (Oxf)*, 52, 595-600.
- WILLIAMSON, E. M. 2001. Synergy and other interactions in phytomedicines. *Phytomedicine*, 8, 401-9.
- WITT, C. M., AICKIN, M., CHERKIN, D., CHE, C. T., ELDER, C., FLOWER, A., HAMMERSCHLAG, R., LIU, J. P., LAO, L., PHURROUGH, S., RITENBAUGH, C., RUBIN, L. H., SCHNYER, R., WAYNE, P. M., WITHERS, S. R., ZHAO-XIANG, B., YOUNG, J. & BERMAN, B. M. 2014. Effectiveness guidance document (EGD) for Chinese medicine trials: a consensus document. *Trials*, 15, 169.
- WU, J. H., YU, C. Q. & ZHOU, Q. L. 2007. [Clinical study on effect of Bushen Huayu Qutan Recipe in treating polycystic ovarian syndrome]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, 27, 883-6.
- WU, N. 2008. Clinical Study on Bushen Huayu Qutan Treatment for PCOS. *Chinese Journal of Modern Application of Pharmacy [Zhong Guo Xian Dai Ying Yong Yao Xue Za Zhi]*, 25, 167-170.
- WU, T., GAO, X., CHEN, M. & VAN DAM, R. M. 2009a. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. *Obes Rev*, 10, 313-23.
- WU, T., LI, Y., BIAN, Z., LIU, G. & MOHER, D. 2009b. Randomized trials published in some Chinese journals: how many are randomized? *Trials*, 10, 46.
- YASMIN, E., GLANVILLE, J., BARTH, J. & BALEN, A. H. 2011. Effect of dose escalation of metformin on clinical features, insulin sensitivity and androgen profile in polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol*, 156, 67-71.
- YILDIZ, B. O., BOLOUR, S., WOODS, K., MOORE, A. & AZZIZ, R. 2010. Visually scoring hirsutism. *Hum Reprod Update*, 16, 51-64.
- YILDIZ, B. O., BOZDAG, G., YAPICI, Z., ESINLER, I. & YARALI, H. 2012. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. *Hum Reprod*, 27, 3067-73.

REFERENCES

- YIP, Y. & SINCLAIR, R. D. 2006. Antiandrogen therapy for androgenetic alopecia. *Expert Review of Dermatology*, 1, 261-9.
- ZASLAWSKI, C. 2010. Ethical Considerations for Acupuncture and Chinese Herbal Medicine Clinical Trials: A Cross-cultural Perspective. *Evid Based Complement Alternat Med*, 7, 295-301.
- ZHANG, J., LI, T., ZHOU, L., TANG, L., XU, L., WU, T. & LIM, D. C. 2010a. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. *Cochrane Database Syst Rev*, 9, CD007535.
- ZHANG, J., LI, T., ZHOU, L., TANG, L., XU, L., WU, T. & LIM, D. C. 2010b. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. *Cochrane Database Syst Rev*, CD007535.
- ZHENG, J. Q., LV, S. G. & LI, H. 2008. Chinese herbal medicine artificial cycle therapy for PCOS in 45 cases. *China Journal of Traditional Chinese Medicine [Zhong Hua Zhong Yi Yao Za Zhi]*, 23, 458-9.
- ZHENG, Y., GU, R. & WU, T. 2009. Chinese medicinal herbs for measles. *Cochrane Database Syst Rev*, CD005531.
- ZHOU, Y. H., HUANG, Y. J., LIU, W. & YU, H. 2010. Clinical research on combined therapy of traditional Chinese and Western medicine on polycystic ovarian syndrome. *Liaoning Journal of Traditional Chinese Medicine*, 37, 1328-1330.
- ZHOU YH, T. Y. 2010. Clinical study of laparoscopic surgery combined with traditional Chinese Medicine in treating Polycystic Ovary Syndrome (PCOS). *Jiangsu Journal of Traditional Chinese Medicine [Jiang Su Zhong Yi Yao]*, 42, 27-28.