UNIVERSITY OF SOUTHAMPTON

FACULTY OF HEALTH SCIENCES

The Epidemiology and Clinical Importance of Forefoot Bursae in Patients with Rheumatoid Arthritis

by

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ABSTRACT

THE EPIDEMIOLOGY AND CLINICAL IMPORTANCE OF FOREFOOT BURSAE IN PATIENTS WITH RHEUMATOID ARTHRITIS

By Lindsey Hooper

The epidemiology of foot complications in patients with rheumatoid arthritis (RA) is poorly understood. A number of patients report ongoing foot-related pain, impairment, footwear restriction and activity limitation, despite developments in pharmacological disease management. Forefoot bursae (fluid filled sacks, FFB) have been previously shown to be highly prevalent and related to foot complications in patients with RA. However, the longitudinal epidemiology and clinical importance of FFB in this patient population remains unclear.

It is anticipated that an improved understanding of the mechanisms by which FFB are responsive to, or contribute to, fluctuations in RA disease activity will inform future evaluation of foot health and novel therapeutic targets.

Through a series of four experimental studies this work has shown that ultrasound (US) detectable FFB are highly prevalent in patients with RA compared to healthy volunteers (HV) and are clinically relevant. The natural history of FFB remains consistent longitudinally in a cohort of patients with established RA disease at baseline. US-detectable FFB were determined to be significant prognostic indicators of foot-related disability after three years. Furthermore, the distribution of US-detected FFB across forefoot sites was identified as significantly different between HV and patients with predominantly inflammatory or degenerative arthritis; uniquely patients with RA have a number of FFB within the central forefoot region, in addition to those located laterally, which were frequently present in all comparative groups. Thus, in patients with RA ~50% of US-detected FFB may be of greatest clinical relevance, due to their positioning within the central forefoot region.

Detection of FFB using MRI defined a series of FFB characteristics of clinical relevance in patients with RA. The presence of plantar forefoot fluid lesions or intermetatarsal soft tissue lesions was significantly related to RA disease activity. The presence of plantar soft tissue lesions was significantly related to increased biomechanical impairment. However, a high proportion of plantar predominantly soft tissue FFB was also noted to be actively inflamed whilst other MRI-based markers of disease activity within the forefoot were minimal.

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List of publications, presentations & awards

The following publications, presentations and awards have resulted from the work completed as part of this candidature for Doctor of Philosophy:

Awards:

- NIHR/CNO Clinical Doctoral Research Fellowship
- Research Grant; Pfizer UK
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- **Hooper, L**, Bowen, CJ, Gates, L, Culliford, DJ, Ball, C, Edwards, CJ and Arden, NK 2012. Prognostic indicators of foot related disability in patients with rheumatoid arthritis: results of a prospective three-year study. *Arthritis Care and Research.* doi: 10.1002/acr.21672. [Epub ahead of print]
- **Hooper, L**, Bowen, CJ, Edwards, CJ and Arden, NK 2011. Bursae as a cause of forefoot pain in a patient with rheumatoid arthritis: a case report. *Podiatry Now*. 14**(1)**:30-33.

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- **Hooper, L**, Bowen, CJ, Gates, L, Culliford, DJ, Ball, C, Edwards, CJ and Arden, NK 2012. Prognostic indicators of foot related disability in patients with rheumatoid arthritis. Oral presentation. *British Society for Rheumatology 2012 Annual conference*.
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- **Hooper, L** 2012. Accessing clinical academic careers. Oral presentation. *Department of Health conference for clinical academic practice.*
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- **Hooper, L** and Backhouse, M 2011. Integrating and furthering AHP doctoral research within rheumatology; speaker and session chair. BHPR research forum. *British Society for Rheumatology 2011 Annual conference*.

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- **Hooper, L** 2010. Integrating NIHR research into clinical practice. *Early Arthritis Clinic Launch event*.
- **Hooper, L** and Bowen, CJ 2009. NIHR clinical academic training pathways: experiential notes. *NIHR CAT launch event*.
- **Hooper, L** 2009. Principles of biomechanics and Vicon use. *Osteoarthritis Research Syndicate meeting, University of Oxford*.

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- **Hooper, L**, Bowen, CJ, Culliford, CJ, Ball, C, Costello, P, Edwards, CJ and Arden, NK 2011. The prevalence of forefoot bursae in RA and OA. *Ann Rheum Dis* 2011;70(Suppl3).
- Goulston, L, Warner, M, **Hooper, L**, Gates, L, Metcalf, C, Bowen, C, Culliford, D, Maskell, J, White, K, Burridge, JH, Stokes, MJ and Arden, NK 2011. A pilot study to compare static and dynamic knee alignment measurements in knee osteoarthritis. *Ann Rheum Dis* 2011;70(suppl13).
- **Hooper, L**, Bowen, CJ, Culliford, CJ, Ball, C, Costello, P, Edwards, CJ and Arden, NK 2011. The prevalence of forefoot bursae in patients with primary inflammatory or mechanical arthritis. *The Faculty of Health Sciences, University of Southampton Post-Graduate Annual Research Conference*.
- **Hooper, L**, Warner, M, Gates, L, Goulston, L, Bowen, CJ, Edwards, CJ and Arden, NK 2010. Within subject foot motion variability in patients with rheumatoid arthritis. *The Society of Chiropodists & Podiatrists Annual conference*.

Other associated publications:

- **Hooper, L**, Edwards, CJ and Taylor, P 2012. Measuring Movement & Gait. In *Oxford Textbook of Rheumatology* (3rd Edition). Oxford University Press.
- **Hooper, L** 2011. NIHR/CNO Clinical academic doctoral research fellowships. Department of Health. [Online]. Available from: http:www.doh.gov/nihr-cdrf
- **Hooper, L**, Edwards, CJ, Bowen, CJ and Arden, NK 2010. 'Best foot forward': New research at Southampton focuses on foot pain. *National Rheumatoid Arthritis Society, Quarterly publication*. Available online from: http://nras.org.uk/about_rheumatoid_arthritis/newly_diagnosed/who_will_be_involved_in_my_care/best_foot_forward.aspx
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- Bowen, CJ, **Hooper, L**, Culliford, DJ, Dewbury, K, Sampson, M, Burridge, JH, Edwards, CJ and Arden, NK 2010. Assessment of the natural history of forefoot bursae using ultrasonography in patients with rheumatoid arthritis: a twelve month investigation. *Arthritis Care and Research*. 62**(12)**:1756-1762.
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Declaration of authorship

I, Lindsey Hooper, declare that the thesis entitled:

'The epidemiology and clinical importance of forefoot bursae in patients with rheumatoid arthritis'

and the work presented in this thesis, is both my own and has been generated by me as a 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 quotation, 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*;

Parts of this work have been published as listed previously.

Signed: .....

Date: .....

**The baseline and year-one follow-up data used within this thesis to allow longitudinal data analysis was completed by previous researchers and should not be considered as part of the authors own or original work.*

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List of abbreviations

ACR…….. American College of Rheumatology
ALARA……..... As Low As Reasonably Acceptable
AIR..... Adjusted Incidence Ratio
BHPR..... British Health Professions in Rheumatology
BSR.....……. British Society for Rheumatologists
CRP……..…….. C-Reactive Protein
CVR……..…… Content Validity Ratio
DAS……..……..…… Disease Activity Score
DMARD…….. Disease Modifying Anti-Rheumatic Drug
DTML……..…… Deep Transverse interMetatarsal Ligament
EULAR……..……. European League Against Rheumatism
ER…….....……...……..ERosion
ESR…….....…… Erythrocyte Sedimentation Rate
FeeTURA……..…….... Foot and ankle sTUdies in Rheumatoid Arthritis
FFB……..……..... ForeFoot Bursae
FoV……..……... Field of View
FPI……..…… Foot Posture Index
GH……..……..... General Heath
ICF……..……... International Classification for Functioning
IM……..…….. InterMetatarsal
QALYs……..……. Quality Adjusted Life Years
FIS……..……..…… Foot Impact Score
MCP ……..……..……..… MetataCarpoPhalangeal
MDA……..……..……..… Minimal Disease Activity
MFPDQ……..……..…… Manchester Foot Pain and Disability Questionnaire
MRI……..……..…… Magnetic Resonance Imaging
MSK……..…….. MusculoSKeletal
MTP……..……..…… MetaTarsoPhalangeal
NAO……...……National Audit Office
NHS……..……..…… National Health Service
NOAR…….....……..…… NOrfolk Arthritis Register
NVB……..……..…… NeuroVascular Bundle
OA……..……..……... Osteoarthritis
OMERACT……..…… Outcome MEasures in Rheumatoid Arthritis Clinical Trials
OR……..……..…… Odds Ratio
PCC……..…… Pearson's Correlation Coefficient
PD……..…… Power Doppler
PIPJ……..……..…… Proximal InterPhalangeal Joint

PROMs…….....…… Patient Reported Outcome Measures
R & D…….....…… Research and Development
RA……...…….. Rheumatoid Arthritis
RADAI-5……..……..… Rheumatoid Arthritis Disease Activity Index- 5
RAMRIS ……Rheumatoid Arthritis Magnetic Resonance Imaging Score
RF ……..……..…… Radio Frequency
RR……..…… Risk Ratio
SD……..……..……..… Standard Deviation
SH...……..……..……..…… Synovial Hypertrophy
SJC……..……..… Swollen Joint Count
SPSS……..……..……..… Statistical Package for Social Sciences
STIR……..……..……...… Short Tau Inversion Rate
SUHT……..……..……..… Southampton University Hospitals' Trust
TJC……..……..……...… Tender Joint Count
TNFα..... Tumour Necrosis Factor-alpha
UIA……..……..……Undifferentiated Inflammatory Arthritis
UK……..……..……..…… United Kingdom
UoS……..……..……...… University of Southampton
US……..……..……..… musculoskeletal UltraSound
VAS……..……..…… Visual Analogue Scale
VIDEO……..……..……..… VItamin D dEficiency in Osteoarthritis
WHO……..……..…… World Health Organisation
WTCRF…….....…… Wellcome Trust Clinical Research Facility

Chapter one

Introduction

1.0 Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory polyarthritis affecting multiple tissues and organs (Elliott and O'Dell 2002). The disease is typified by symmetrical, diarthrodial joint damage that particularly affects the peripheral joints of the hands and feet (Elliott and O'Dell 2002). Historically pharmacological intervention sought to slow RA disease progression while total remission was uncommon (Shaver *et al.* 2008, van Tuyl *et al.* 2009). This is exemplified by radiographical works of the time which document progressive cortical bone erosion at the metacarpophalangeal or metatarsophalangeal joints (Lawrence 1965, Wittenborg and Creutzig 1973, Fischer 1976, Limido *et al.* 1985, Akerman *et al.* 1991). However, advances in the pharmacological treatment of RA disease have heralded a new era in disease management (Singh *et al.* 2009, Edwards *et al.* 2005, Edwards 2005). Remission is the current target for all healthcare practitioners and their patients (Aletaha and Smolen 2011). Accordingly, new ways of assessing disease activity or its progression are sought and evaluation of bone erosion or joint destruction considered too slow an indication (Shaver *et al.* 2008, Aletaha *et al.* 2011, Aletaha and Smolen 2011). Recent research has utilised alternate imaging methods, such as musculoskeletal ultrasound (US) or magnetic resonance imaging (MRI), in order to identify earlier manifestations of disease activity in both bone and soft tissue structures (Wakefield 2006, Wakefield 2007, Wakefield *et al.* 2008, Ostergaard 2008, Ostergaard *et al.* 2011, Cohen *et al.* 2011, Conaghan *et al.* 2003). The use of these modalities has raised the concept of minimal disease activity, where it is increasingly apparent that systemic serological or composite indicators may be insensitive to ongoing subtle activity within the peripheral joints of the hands and feet (van der Heijde *et al.* 1992, van der Leeden *et al.* 2007, van der Leeden *et al.* 2008). As such localised investigation of disease activity within both the bone and of tissue structures in the peripheral joints is warranted (Haraoui *et al.* 2011, Aletaha *et al.* 2011, Aletaha *et al.* 2010).

Disease progression within the foot may be compounded by its' functional role during daily weight bearing activity (Turner *et al.* 2008, van der Leeden *et al.* 2008, van der Leeden *et al.* 2006). The biomechanical or inflammatory stresses arising within the anatomical structures of the foot in patients with RA are unclear (Turner *et al.* 2008, Helliwell *et al.* 2000). However, it is known that patient-reported foot-related disability is high in this population (Grondal *et al.* 2008, Rojas-Villarraga *et al.* 2009, Turner *et al.* 2006). Additionally, foot complications and foot-related disability have been shown to persist despite the current advances in pharmacological disease management (Nagasawa *et al.* 2010, Otter *et al.* 2009, Grondal *et al.* 2008). Thus, the patient and clinician goal of disease remission is not always met. There is a need to identify factors contributing to the propagation of foot-related disability in this patient group and to better target

intervention. Previous cross-sectional studies have suggested that forefoot bursae (fluid filled sacks: FFB) are associated with RA disease activity and patient-reported foot-related disability (Bowen *et al.* 2009, Bowen *et al.* 2010c). However, it is unclear whether these are spurious relationships, confounding effects or true physiological responses. None the less, FFB arguably represent a much needed potential indicator of localised disease activity or therapeutic target. The determination of the natural history and clinical importance of FFB in patients with RA will potentially facilitate improved disease management or disability prevention.

1.1 Main thesis aim

This thesis, therefore aims to utilise novel US and MRI imaging techniques for the determination of the epidemiology and clinical importance of FFB in patients with RA. It is intended that the findings of the four experimental studies completed as part of this thesis will: 1) contribute to the current understanding of the clinical importance of US-detectable FFB, 2) contribute to the current understanding of the biological mechanisms by which US-detectable FFB are clinically relevant, 3) provide a robust tool for the identification and characterisation of FFB and 4) contribute to the current understanding of which FFB are pathological and why, providing an evidence-based framework for future clinical intervention. The research hypothesis central to this thesis, and underpinning the basis of study, is therefore:

H_1: 'FFB are clinically relevant in patients with RA'
H_0: 'FFB are not clinically relevant in patients with RA'

The thesis has been structured thus:

Chapter 2: 'Background & literature review'. This chapter details the background literature informing the research topic. An overview of current concepts within rheumatology regarding the aetiology, diagnosis, prevalence, monitoring and management of RA are discussed. An overview of foot specific complications reported in patients with RA is given and differentiation between articular and extra-articular manifestations of disease made. In particular the epidemiology, characterisation, diagnosis and clinical importance of FFB are discussed.

Chapter 3: 'Methodology'. This chapter presents and justifies the overall philosophical approach and methodological design employed in this thesis. An overview of the aim and objectives for each experimental chapter is given. The ethical considerations related to this body of work are presented and discussed. A summary of the studied populations, outcome measures and analysis techniques used throughout the body of work are also presented and justified.

Chapter 4: 'The epidemiology & clinical importance of US-detectable forefoot bursae in patients with rheumatoid arthritis'. This chapter draws upon previously reported cross-sectional data and data collected as part of this research project in order to uniquely determine the natural history

of US-detectable FFB in patients with RA. Potential associations between FFB and disease activity or patient-reported foot-related disability are explored. The clinical importance of FFB, both cross-sectionally and longitudinally is considered. Differences in the US-characteristics of observed FFB are discussed and the potential relevance of these considered. The hypothesis that FFB presence is related to both biomechanical impairment and inflammation is proposed.

Chapter 5: 'The relationship between FFB & inflammation or biomechanical impairment'. This chapter seeks to further explore the potential relationship between US-detectable FFB and biomechanical impairment of the lower limb or disease mediated inflammation. This is achieved via comparative investigation of FFB epidemiology between healthy volunteers, patients with medial knee OA (considered as a surrogate primarily degenerative non-inflammatory cohort) and patients with RA (considered as a primarily inflammatory cohort). Potential associations between FFB presence and markers of inflammation or biomechanical impairment are determined. Differences in the distribution of FFB across forefoot sites between participant groups are reported and their potential clinical importance explored. The findings of this study provide additional evidence to support the hypothesis that FFB are related to both inflammation and biomechanical impairment in patients with RA. The need for a reliable, user-independent method of identifying and characterising FFB is proposed.

Chapter 6: 'Detecting forefoot bursae in patients with rheumatoid arthritis using MRI: Development of the '*FFB-Score''*. This chapter presents the rationale, justification for, and process of MRI-based score development for the identification and characterisation of FFB in patients with RA. The collaborative process of score design, implemented by a team of rheumatologists, radiologists, and a podiatrist from centres within the UK and Germany, is presented. The reliability and validity of the proposed score is reported.

Chapter 7: 'The epidemiology & clinical importance of MRI-detectable forefoot bursae in patients with rheumatoid arthritis'. This chapter documents the observed presence, distribution and characteristics of MRI-detected FFB in patients with rheumatoid arthritis. The relationship between FFB MRI characteristics and inflammation or biomechanical impairment is explored. The clinical importance of the presence of MRI-detectable FFB, and the characteristics thereof, in patients with rheumatoid arthritis, is considered.

Chapter 8: 'Discussion, conclusions & future research'. This chapter draws together the findings of the four previous experimental studies, discussing the findings in the context of an integrated programme of research. The advancement in knowledge and contribution towards clinical practice made by this research programme is considered. The conclusion is made that 'FFB are clinically relevant in patients with rheumatoid arthritis' and the alternate thesis hypothesis is accepted. Limitations within the reported studies are acknowledged and recommendations for future research proposed.

1.2 Scope of the thesis

The four experimental studies that form this thesis were conducted over a 27 month period from October 2009 to January 2012. All data collection was completed within either the Southampton Biomedical Research Centre, within University Hospital Southampton NHS Foundation Trust or the MRI suite at the Spire Hospital, Southampton. Please note, the baseline and one-year follow-up data used for the longitudinal evaluation of FFB, presented in Chapter four, has been previously reported and is not presented as the author's own work (Bowen *et al.* 2009, Bowen *et al.* 2010b).

Chapter two

Background & literature review

2.0 Introduction

This chapter provides a critical overview of the academic literature pertinent to the diagnosis, classification, evaluation and treatment of rheumatoid arthritis (section 2.1). The complications associated with RA are discussed with particular reference to those which are related to the foot (section 2.2). Forefoot bursae (FFB) are highlighted as a key soft tissue complication present in patients with RA (section 2.3). The clinical importance, epidemiology, characterisation and identification of FFB are subsequently reviewed and need for future research in this area is highlighted (summary).

2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory polyarthritis that affects multiple body tissues and organs, although is typified by symmetrical, peripheral, diarthrodial joint damage (figure one), (Elliott and O'Dell 2002). Those joints frequently affected include the metacarpophalangeal joints of the hand and metatarsophalangeal joints of the feet (40-50%, 30-50% of initial presentation respectively) (van der Leeden *et al.* 2008, Otter *et al.* 2009, Woodburn and Helliwell 1997, Silman and Hochberg 2001). At the point of diagnosis, these joints present clinically with swelling, redness and tenderness (Silman and Hochberg 2001). Joint subluxation, tissue degradation and fixed deformity can occur latterly (figure one: c-d, f-g), leading to difficulties in walking or manual dexterity tasks (Silman and Hochberg 2001, Otter *et al.* 2009, Helliwell *et al.* 2007).

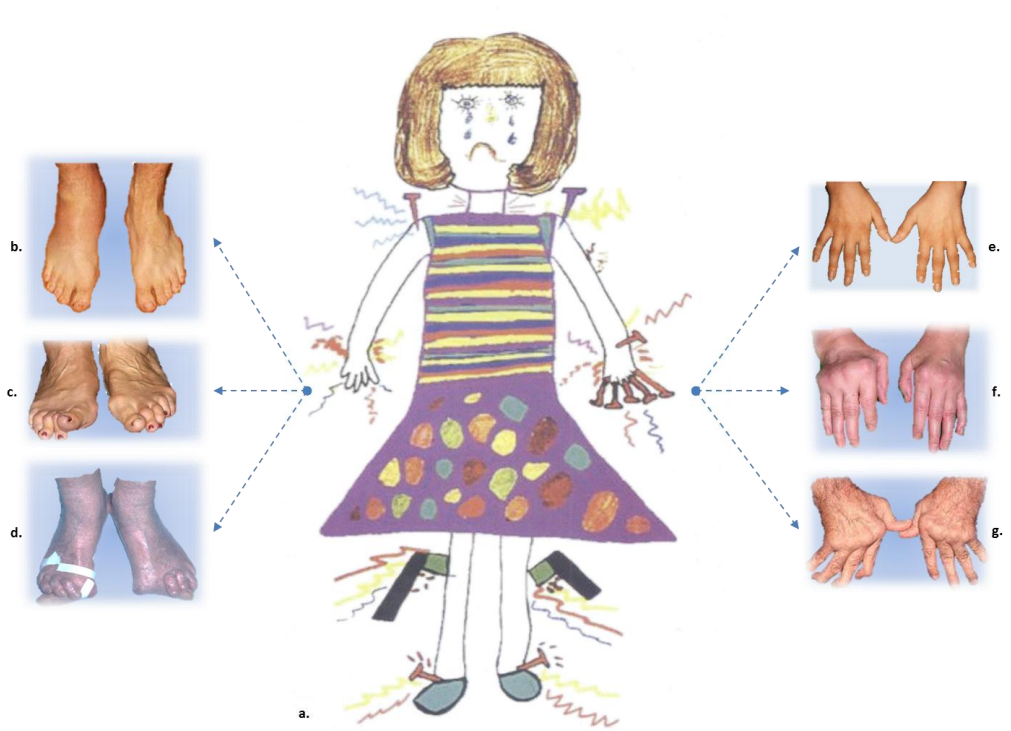


Figure 1: The clinical presentation of RA
Where 1a illustrates a child's perception of the experience of having arthritis, 1b-d illustrate mild, moderate and severe examples of RA disease in the feet, and 1e-g illustrate mild, moderate and severe examples of RA disease in the hands. *Images reproduced with permission from Peterson (2011) in association with the National Rheumatoid Arthritis Society (NRAS), Dr Mechanik (1998), Dr Agnihotri (2010), Medscape.com (2011) and Rumatory-Arthritis.com (2010).*

RA disease activity was traditionally assessed clinically using composite measures of disease activity (Anderson *et al.* 2012, Dougados and Gossec 2007). These include evaluation of multiple joint swelling or tenderness, (although not typically including the feet), serological markers of systemic inflammation and patient reported overall wellbeing (Anderson *et al.* 2012, Arnett *et al.* 1988). Disease activity was traditionally managed using disease modifying anti-rheumatic drugs (DMARDs) which aim to suppress inflammation, thereby easing the burden of disease on the patient (NICE 2009a, NICE 2009b, Edwards *et al.* 2005). The aim of pharmacological treatment was to suppress inflammation responsively and *slow* joint decay (Edwards *et al.* 2005, Brown *et al.* 2008). The aim of adjunctive podiatric treatment was to accommodate deformity where possible and provide palliative care of ulcerative sites or callus lesions (Rome *et al.* 2009, Turner *et al.* 2007, Williams *et al.* 2011, Mejjad *et al.* 2004). However, recent advances in the understanding of the aetiology and pathophysiology of RA have been made (Soderlin *et al.* 2011, van de Sande *et al.* 2011). Differing inflammatory pathways have been mapped and pharmacological treatment now aims to suppress inflammation early in the disease process *preventing* joint decay (Toonen *et al.* 2012, Mantovani 2000, Daikh and St Clair 2012, Singh *et al.* 2012).

While great progress in the management of RA has been made, a number of limitations to complete remission from disease for all patients remain (Kekow *et al.* 2011, Zhang *et al.* 2011, Tak and Kalden 2011). There is a need to identify and monitor minimal disease activity, to differentiate between those patients who have aggressive disease and have greater likelihood of developing life limiting complications, and to tailor and deliver targeted therapies for the individual patient in a timely manner (Tak and Kalden 2011, Schett *et al.* 2011, Breedveld and Combe 2011). Evaluation of disease activity within the foot may inform these current limitations.

2.1.1 Aetiology & pathophysiology

The monitoring and regulation of RA is inhibited by the unknown immunological pathways by which the disease is mediated; to date the precise aetiology of RA remains unclear (Choy and Panayi 2001, Edwards 2005, Feldmann *et al.* 1996, Jenkins *et al.* 2002, Panayi 1993a, Schett and Firestein 2010). Some authors have suggested a genetic predisposition (MacGregor *et al.* 2000, Macgregor and Steer 2006), others suggest environmental triggers, while the predominant current hypothesis is a combination of such factors (MacGregor *et al.* 2002). However, the greatest recent development in our understanding of RA has been made in the field of immunology, and thus this area forms the basis of this review (Zimmerman and Weyrich 2010, Schett and Firestein 2010, McGonagle and Georgouli 2008, Jenkins *et al.* 2002).

In RA, tissue and joint damage occur via the immuno-regulated invasion of synovial tissue by a milieu of inflammatory cells and cytokines (figure two) (Jenkins *et al.* 2002, Athanasou *et al.* 1988). There is a certain amount of synergy between inflammatory modulators, resulting in over-expression of cytokines and a primarily up-regulatory effect (figure two) (Athanasou *et al.* 1988, Choy and Panayi 2001). Of note is the positive feedback mechanism, characteristic of this type IV delayed hypersensitivity reaction, between T-cells and macrophages via the release of and activation by TNFα cytokines (Takaya 2000). TNFα is a key pro-inflammatory cytokine produced by T-cells (Jenkins *et al.* 2002, Panayi 1993a), which has received a lot of research attention because of the tremendous beneficial effect of anti-TNFα pharmacological treatments (Houkin *et al.* 1994, Feldmann and Maini 2003, Kogutt *et al.* 1994). However, as illustrated in figure two, this is one of many up-regulatory cytokines which may contribute to RA disease or equally represent further therapeutic targets (American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines 2002, Panayi 2005, Edwards and Cambridge 2005, Keystone 2005, Marston *et al.* 2010). In particular, B-cells have been demonstrated to display antigen presenting behaviour, produce both TNFα cytokines and antibodies, in addition to their well-documented role in autoantibody production in sero-positive RA patients (Panayi 2005, Di Paolo *et al.* 2011, Marston *et al.* 2010). Destruction of joint cartilage and bone occur latterly and are typically mediated via the adaptive immune system (Athanasou *et al.* 1988, Houkin *et al.* 1994, Choy and Panayi 2001, Martel-Pelletier *et al.* 2001, McHugh *et al.* 2010, Paradowska-Gorycka *et al.* 2010). Those factors which mediate activation and control of down-regulatory cellular responses, or maintenance of cellular ‘tolerance’, remain unclear.

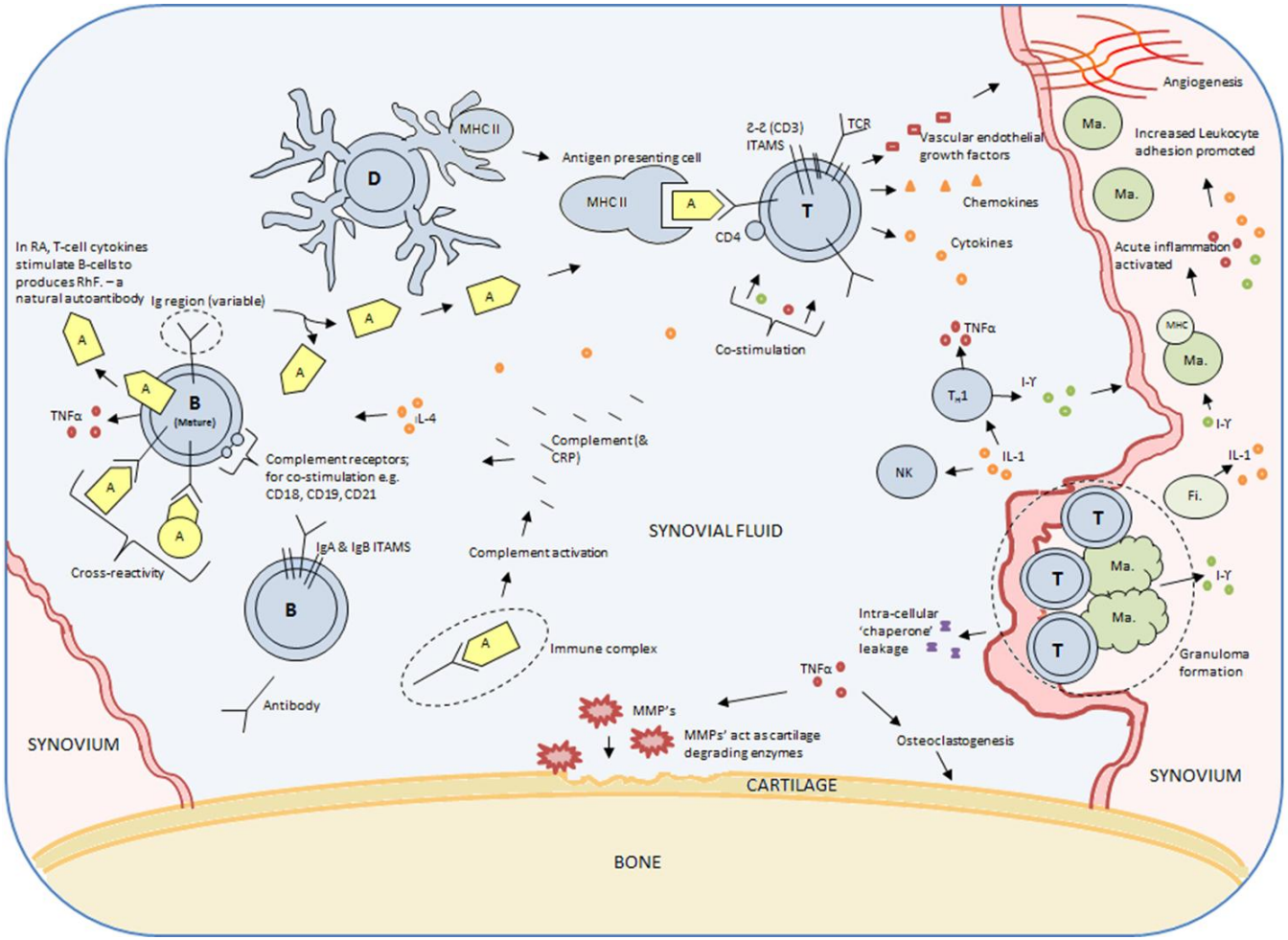


Figure 2: Patho-physiological cellular activity within an active rheumatoid joint

Where A= Antigen, B= B-cell ('bursal-cell'), CD= cellular surface recognition molecules – T-cells have *either* CD4 or CD8, CRP= C-reactive protein, D= dendritic cell, Fi= Fibroblast, Ig region= membrane bound immunoglobulin acting as B-cell receptor with aid of ITAMS, IL= Interleukin, Interferon Y= interferon gamma, ITAMs= immuno-receptor tyrosine-based activation motifs, Ma=Macrophage, MHC= major histocompatibility complex (also known as human leukocyte antigen (HLA) in humans), MMP = matrix metallo-proteases, NK= natural killer cell, T= T-cell ('thymus-cell'), TCR= T-cell receptor, Th1= Differentiated T helper cell, TNFα= tumour necrosis factor alpha. *Image author's own; information collated from Segal et al., (2000), Athanasou et al., (1988), Choy and Panayi (2001), Edwards (2005), Feldman et al., (1996), Panayi (1993b) and Schett and Firestein (2010).*

Of particular relevance to this thesis is the up-regulated formation of pannus (chronically hypertrophied synovial tissue), granuloma or rheumatoid nodules (Athanasou *et al.* 1988, Choy and Panayi 2001). In granuloma formation, as illustrated in figure two, Lymphocytes and Macrophages mature into giant or epitheloid cells, following stimulation from localised interferon-$_{Y}$ and other cytokines in response to chronic stress (Athanasou *et al.* 1988, Takaya 2000). Athanasou (1988) demonstrated that rheumatoid nodules and hypertrophied (or hyperplastic) synovium also demonstrate a high prevalence of several Monocyte-Macrophage markers and HLA-DR. This suggests that similar patho-physiological processes may be involved in the development of extra-articular nodules as intra-articular pannus. However, there is relatively little histological literature exploring the possibility of shared patho-physiological pathways common to hypertrophied synovial tissues. None the less, it is plausible to suggest the presence of a self-propagating positive-feedback mechanism within the extra-articular synovial tissues. There is therefore a plausible biological mechanism by which synovial structures of the forefoot may become problematic in patients with RA.

An improved understanding of the cellular mechanisms underpinning the development of soft tissue pathology within the forefoot may further inform management strategies; as shown in figure three, understanding the concept of the pathway between cellular activity and disability, and identifying potential causative mechanisms or therapeutic targets will help improve patient outcome. Thus there is clear benefit in the early diagnosis and management of RA.

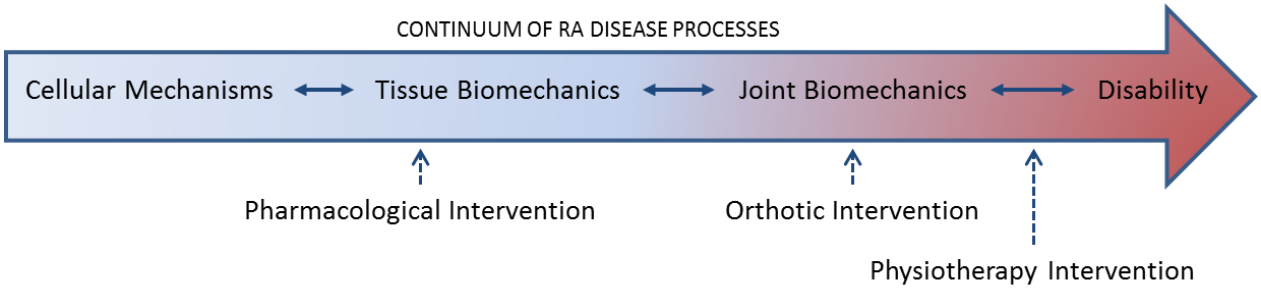


Figure 3: A theoretical concept of RA disease progression and management
Image author's own.

2.1.2 Diagnosis & classification

The use of diagnostic criteria allow early identification of a disease with good sensitivity (Dougados and Gossec 2007). Conversely, the use of classification criteria within a rheumatological research study allows repeatable cohort definition, with good specificity at a group level, particularly in late stage disease (Banal *et al.* 2009). However, until the recent publication of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA diagnosis guidelines (Aletaha *et al.* 2010, Anderson *et al.* 2012, Felson *et al.* 2011), few diagnostic criteria had been proposed or externally validated. As such research classification criteria were adopted for use clinically (Aletaha *et al.* 2011). Consequently, the majority of RA cohort studies have been based upon the superseded 1987

ACR disease classification criteria (table one), (Visser *et al.* 2002, Arnett *et al.* 1988, Moens *et al.* 1992), about which much discontent has been published.

Table 1: Disease classification
ACR 1987 classification criteria for Rheumatoid Arthritis (Arnett *et al.* 1988).

Criteria	Definition
Morning stiffness	Morning stiffness in and around the joints, lasting for at least 1hour
Arthritis of ≥3 joint areas	Soft tissue swelling or fluid in at least 3 of the following areas: the left or right MCP, wrist, elbow, knee, ankle or MTP joints
Arthritis of the hand joints	Swelling of the wrist, MCP or PIP joints
Symmetrical arthritis	Simultaneous involvement of the same joint areas (as above) on both sides of the body (at least 50% of affected joint areas affected symmetrically)
Rheumatoid nodules	Subcutaneous nodules present
Rheumatoid factor	Detected by a method which yields positive findings in <5% of normal controls
Radiographic changes	Erosions or unequivocal decalcification localised to the joints of the hands and wrists

The composite design of the criteria reflects the multifaceted presentation of rheumatoid disease, allowing a diagnosis to be made based on the cumulative presentation of some of the many possible associated symptoms or serological markers. However, a recent meta-analysis of 19 peer-reviewed publications (N=7438pts, 3883 with RA), has questioned the sensitivity and specificity of the criteria, noting that these are of little benefit in identifying early stage RA (Banal *et al.* 2009). Banal et al (2009) have captured and summarised a widely reported range in sensitivity (25-95%) and specificity (50-90%) and what was arguably a recurring theme of discontent regarding classification over the last decade (Saraux *et al.* 2001, Liao *et al.* 2008, Aridogan *et al.* 2008, Banal *et al.* 2009, Levin *et al.* 1996).

With an improved understanding of the immunological mechanisms of disease, numerous authors called for a review of RA diagnostic criteria. This is to reflect the biological advances in antibody detection, specifically anti-cyclic citrullinated peptide antibodies (anti-ccp), with a concomitant introduction of exclusion criteria and removal of markers associated with chronicity such as nodule formation (Berthelot *et al.* 2001, Berthelot *et al.* 2002, Caro-Oleas *et al.* 2008). Ironically however, authors continuing to compare the predictive value of different criteria, for example rheumatoid factor or specific antibody presence, continue to use the ACR criteria to define their sample populations (Aridogan *et al.* 2008, Lemos *et al.* 2007), or to retrospectively review sensitivity (Hulsemann and Zeidler 1999). This does render the question, ‘how can we determine if these markers are really more applicable in early RA detection?’ This highlights the current paradigm regarding classification; the criteria are limited yet there is a notable absence

of a more palatable alternative. Similarly, the crossover and merging of diagnostic and classification criteria has further confused this literature.

As Emery *et al*. (1997) suggest, a pathognomic feature of RA is persistence, therefore it is perhaps unsurprising that cumulatively the ACR criteria are reported as more sensitive and specific for those patients with early but aggressive disease than for those with an initially more subtle presentation, but who may gain a positive diagnosis in time (Jacobsson *et al.* 1994). This perhaps reflects a more pertinent question; 'is diagnosis enough?' Current literature suggests a trend towards diagnosis with identification of predictors of disease severity/aggression and prognosis (Rantapaa-Dahlqvist 2005). Tissue typing and a greater understanding of cellular activity, along with improved clinical imaging may be a positive step towards identifying early and/or aggressive disease. That is until prospective studies such as 'SERA' (Studies of the Etiology of RA), currently in its infancy, can provide further information (Kolfenbach *et al.* 2009, Knoss *et al.* 2007, Rantapaa-Dahlqvist 2005).

The ACR/EULAR 2010 criteria incorporate synovitis, serological markers of inflammation and symptom duration, in an attempt to facilitate earlier diagnosis without the need to identify features associated with later stage disease. The use of a weighted grading system for these three key features is arguably a response to the previously discussed criticisms of the 1987 ACR criteria (Aletaha *et al.* 2010). However, the ability of the criteria to achieve their additional aim of distinguishing between those newly diagnosed patients with more aggressive erosive disease is yet to be demonstrated. The implications for research design are that where possible the inclusion of an inception cohort of patients, presenting initially with undifferentiated inflammatory arthritis, would continue to be of benefit for the longitudinal evaluation of disease pathogenesis (Liao and Costenbader 2009).

2.1.3 Monitoring

The fluctuant nature of rheumatoid disease activity requires careful regular evaluation of disease state (Aletaha *et al.* 2008, Shaver *et al.* 2008). However, given the complexities of diagnosing and classifying disease previously mentioned, achieving rigour in disease state evaluation can pose a clinical challenge (Rintelen *et al.* 2009, Wolfe *et al.* 2009). Furthermore, the need to determine disease activity within research participants is particularly important for the determination of disease progression or treatment evaluation (Shaver *et al.* 2008, van Tuyl *et al.* 2009, Felson and Anderson 2001). Unsurprisingly therefore, common clinical and research tools for the determination of disease state are often composite measures with varying focus, again reflecting the multifaceted nature of RA (van Tuyl *et al.* 2009, Linde *et al.* 2008).

The 28 part disease activity score (DAS 28 (Van der Heijde *et al.* 1990)) is arguably the most commonly used composite measure of disease activity in both research and clinical practice (Leeb *et al.* 2007). However, since the advent of this tool the variability of scores, dependent

upon the individual component parts, has been a recurrent criticism by numerous authors (Leeb *et al.* 2007, Kirwan *et al.* 2009, Kievit *et al.* 2006, Neogi and Felson 2008). Măkinen (2007) attempted to quantify such variability, identifying that erythrocyte sedimentation rate (ESR), tender joint count (TJC), general health (GH) and swollen joint count (SJC) had the greatest effect on overall score respectively (mean score=0.71, 0.23, 1.56, 0.28 respectively, N=195) (MÃkinen *et al.* 2007). However, this criticism is not unique to the DAS 28, indeed most alternative disease activity measures do inherently have the same complication due to their composite design (Balsa *et al.* 2004, Aletaha *et al.* 2005).

The search for independent indicative variables has identified that patient reported outcome measures such as 'general health' and 'disease activity' visual analogue scales (VAS) may be good indicators of disease state (Linde *et al.* 2008, Shaver *et al.* 2008). These variables are also becoming increasingly identified as key in emerging alternative patient centred assessment tools such as the RADAI-5 and CDAI (Leeb *et al.* 2008), where traditional measures such as joint count are excluded. Arguably, the emerging tools are starting to reflect the current government emphases on early detection, intervention and preservation of activity discussed earlier, as well as consistency in outcome measures for clinical trials (The National Audit Office 2009, Molenaar *et al.* 2000). However, despite a growing body of evidence in support of these outcome measures, they still remain highly contended within the current literature (Shaver *et al.* 2008).

Particular contention surrounds the definition or classification of remission and minimal disease activity (MDA) (Aletaha *et al.* 2012, Lafeber and Van der Laan 2012, Khan *et al.* 2012, Anderson *et al.* 2012). Currently, the ACR and EULAR bodies are collaborating in an attempt to define criteria for remission and MDA, "so that we are all saying the same thing" (van Tuyl *et al.* 2009). Until such a time, for the purposes of this study the DAS 28, with CRP composite (Wolfe and Michaud 1994, Wolfe *et al.* 2001, Anderson *et al.* 2012), is arguably the most appropriate tool. Importantly though, while the overall theme within the current literature suggests the use of a composite tool, the additional identification of physiological phenomena within a clinical setting that help indicate minimal disease activity (MDA) would be a valuable asset to patient care.

2.1.4 Management

The management of RA has undergone a recent paradigm shift away from the gradual and progressive use of medicines towards earlier more aggressive pharmacological intervention with a number of relatively newer biological agents (Edwards *et al.* 2005, Singh *et al.* 2009, Singh *et al.* 2012). Indeed there is an increasing number of new biologics with differing immunological targets being identified and tested, reflecting the improved understanding of molecular processes involved in RA pathogenesis (Singh *et al.* 2009). Table two documents some of the current immunological (biologic) therapies and their intended molecular targets for inhibition.

Table 2: Current therapeutic biologic agents

	Agent: Generic drug name (market name)	Molecular target	Mode of action
TNFα inhibitors	Infliximab (Remicade) (Janka *et al.* 2000, Weiger *et al.* 2000)	TNFα/T-cell activation	Mouse derived monoclonal TNFα antibody
	Etanercept (Embrel) (Holland *et al.* 2000, Westenberg *et al.* 2000)	TNFα	Modulation of membrane-bound receptors bound to Fc portion of IgG antibody
	Adalimumab (Humira) 114, 115]	TNFα	Fully human monoclonal TNFα antibody (Moller Dohn *et al.* 2009)
	Certolizumab Pegol (Cimzia) (Kaushik and Moots 2005)	TNFα	Fully human monoclonal TNFα antibody (Connock *et al.* 2010, Patel and Moreland 2010)
	Abatacept (Orencia) (Teng *et al.* 2005, Kremer *et al.* 2005)	T-cell co-stimulation modulation	Inhibits co-stimulation thereby preventing secondary messenger activation of B and T-cells (Genant *et al.* 2008, Maxwell and Singh 2010, Schiff and Bessette 2010)
	Golimumab (Simponi) (Zhou *et al.* 2007)	TNFα	Fully human monoclonal TNFα antibody (Voulgari 2010)
B-cell inhibitors	Rituximab (MabThera) (Shaw *et al.* 2003)	CD20 (B-cell surface molecule)	CD20 antibody thereby preventing B-cell immunoglobulin recognition/ activation & thus initiation of immune cascade (Tanaka 2009)
	Ocrelizumab (Genovese *et al.* 2008, Genovese *et al.* 2010) (Genovese *et al.* 2008, Genovese *et al.* 2010)	CD20 (B-cell surface molecule)	CD20 antibody thereby preventing B-cell immunoglobulin recognition of antigens & thus activation and initiation of immune cascade
Cytokine inhibitors	Anakinra (Okuda and Takasugi 2006, Guntinas-Lichius *et al.* 2000)	IL-1	IL-1 receptor antagonist inhibiting endogenous binding of IL-1 & thus cytokine messenger activity
	MRA (Nishimoto *et al.* 2003)	IL-6	Anti-IL-6 receptor monoclonal antibody-acting as IL-6 antagonist thus inhibiting cytokine messenger activity
	Tocilizumab (Roactemra) (Maini *et al.* 2006)	IL-6	Anti-IL-6 receptor monoclonal antibody-acting as IL-6 antagonist thus inhibiting cytokine messenger activity (Schafer *et al.* 2010)
Other	Fostamatinib Disodium (Baluom *et al.* 2011)	Syk kinase (T-cell specific)	Spleen Tyrosine kinase inhibition – inhibiting intra-cellular messages of surface activation to lymphocyte cell nucleus (binds to ITAM sequences) (Genovese *et al.* 2010)

As documented in table two, a number of these medicines have been demonstrated as efficacious when compared to the management 'norm' of Methotrexate. However, the relative efficacy of comparative biologic agents remains unclear (Tak and Kalden 2011, Devine *et al.* 2011). Perhaps this is partly because the head-to-head trials have not been completed but also partly because of the difficulty in evaluating minimal disease activity, discussed previously in section 2.1.3. Alternative outcome measures of intervention effectiveness would be of considerable benefit in this area of study. In particular, outcome measures that help inform which regimen best suits individual patients are required.

2.1.5 Prevalence, incidence & impact

It is currently unclear what effect the new diagnostic guidelines have had on the reported prevalence of RA. The current documented prevalence of RA is globally inconsistent (Alamanos *et al.* 2006, Andrianakos *et al.* 2006, Gabriel 2001) and the reported UK national variation is between 0.44% and 1.16%, with a 3:1 female to male ratio (MacGregor *et al.* 1994a, Symmons *et al.* 2002). These ranges are however, similar to those reported for Northern Europe, North America and Greece, but higher than for Asia or for developing countries (Andrianakos *et al.* 2006). Reasons for such variation have been extensively discussed although a conclusive rationale remains elusive. MacGregor *et al.* (1994b), previously identified ethnic variation within the Norfolk region of England. However, despite ongoing work using this Norfolk Arthritis Register (NOAR) further explanation for regional or ethnic variation remains hypothetical to date.

The overall incidence of RA is reportedly declining in the UK to around 0.8% (N=26,000) (Symmons *et al.* 2002, Kvien *et al.* 2006, The National Audit Office 2009). However, the overall decline reported by Symmons *et al.* (2002) is somewhat skewed by the reduction in female incidence, a proportionally larger group; where further exploration of the male cohort shows no significant decline over the same period. It remains unclear why such gender related differences in incidence may occur. A further methodological complication in RA incidence analysis is the time taken to ascertain a positive diagnosis. For example, Wiles *et al.* (1999) highlight how a 5-year retrospective review of incidence based on the American College of Rheumatology (ACR) 1987 criteria can significantly adjust the reported incidence values (from 30.8/100,000 to 54/100,000 for females and 12.7/100,000 to 24.5/100,000 for males). Furthermore, despite the growing age of this publication few subsequent researchers appear to have adopted this approach and as such any published values for incidence and prevalence can only be considered a guide towards the current actual disease burden. Arguably the differences are contextually slight, however, when considering the burden of disease not just to patients but also their friends, family, co-workers, or care-workers the difference in impact is significant (Lajas *et al.* 2003).

The direct cost of RA to the NHS has risen considerably over the past decade to ~£560million with the increased use of biologic therapy (The National Audit Office 2009). The estimated indirect national economic cost of RA through sick leave and work related disability has risen from ~£1billion to ~£2billion since the turn of the century (The National Audit Office 2009), this is exclusive of further 'household' losses (Verstappen *et al.* 2005). However, such a snapshot does demonstrate the overall economic situation; indeed estimations from the national audit office's annual review (The National Audit Office 2009) suggest that if the number of patients treated within the first three months of diagnosis rises from the current 10% to 20%, the initial direct cost of treatment will increase by £11million over a 5 year period. However, the economic productivity gained through reduction in sick leave and work related disability is ~£31million. Furthermore, each patient has an estimated 4% increase in quality adjusted life years (QALYs) (The National

Audit Office 2009). This highlights the importance of early diagnosis and management, particularly for the retention of quality of life and the maintenance of activity.

It is unclear what proportion of the reported impact of RA disease is attributable to foot-related disability. There is increasing evidence that foot problems in patients with RA are highly prevalent, even when classical measures of disease activity, such as the DAS 28 score, suggest clinical remission (van der Leeden *et al.* 2010, Rome *et al.* 2009, Otter *et al.* 2010, Katz *et al.* 2006). A population survey by Otter *et al*. (2010) demonstrated that this is true for many patients with RA, regardless of disease duration or therapy, and may even be evident in those receiving biologic therapy (Grondal *et al.* 2008, Nagasawa *et al.* 2010). It appears that despite great advances in disease management, a large proportion of patients remain significantly affected by foot complications (van der Leeden *et al.* 2007, van der Leeden *et al.* 2010). This potentially has a major continued impact on a patients' ability to return to work or complete tasks of daily living (Klareskog *et al.* 2009, Katz *et al.* 2008, Puolakka *et al.* 2006). Furthermore, the natural history of foot related disability in patients with RA has received little investigation to date. Despite recent advances in systemic disease management, the longitudinal relationship between the prevalence of foot complications, disease state and disability remains unclear (van der Leeden *et al.* 2008). There is an ongoing need to determine the natural history and prognostic indicators of foot-related disability in patients with RA.

2.2 Complications of RA in the foot

Arguably, foot related complications in patients with RA are arguably poorly understood by both clinicians and researchers in comparison to problems with the hand or systemic disease, as evidenced by the comparative lack of reported literature (Williams and Graham 2012, Grondal *et al.* 2008, Wechalekar *et al.* 2012). Of those complications which are documented, metatarsal head erosion, metatarsophalangeal joint deformity and midfoot collapse are amongst the most frequent (figure four) (Loveday *et al.* 2012, van der Leeden *et al.* 2008, Otter *et al.* 2009).

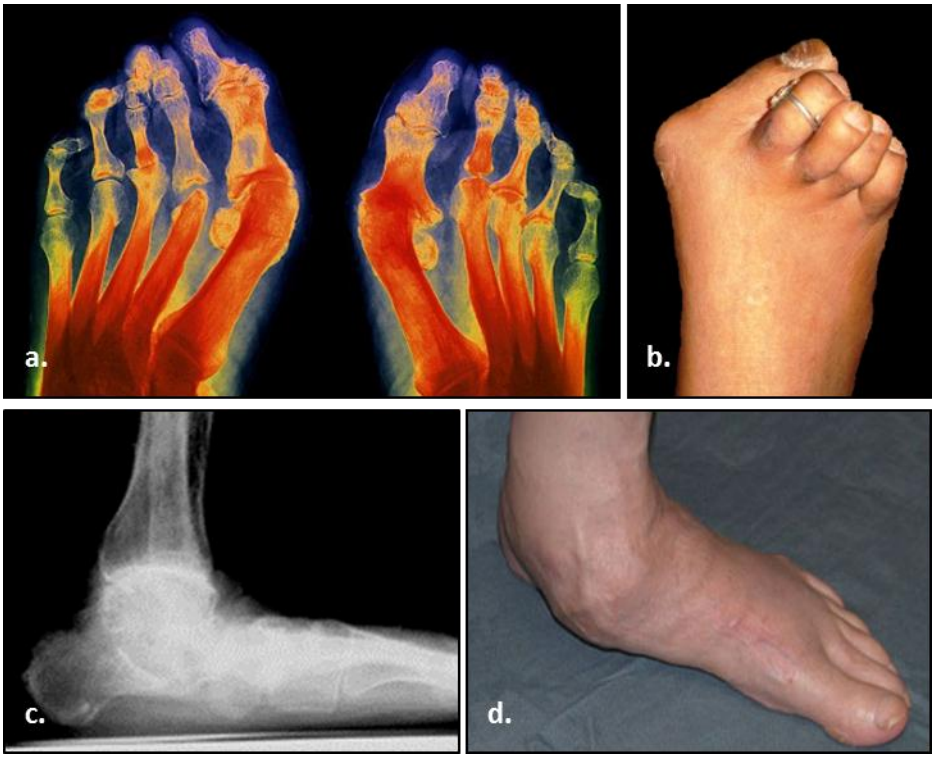


Figure 4: Deformities of the foot associated with RA
Where 4a illustrates bilateral colour-enhanced radiograph of the foot, note the extensive peripheral osteopenia and destruction to nearly all forefoot joints, 4b illustrates right foot deformity, note the grade three hallux abducto valgus deformity and lesser digit retraction, 4c illustrates a left foot sagittal plain radiograph (COFAS 2010), note the collapse of the midfoot joints, and 4d illustrates left midfoot deformity (COFAS 2010), note the prominent bulging of the navicular, classically associated with progressive midfoot medial-longitudinal arch collapse. *Images reproduced with permission from the London Science Museum (Song et al. 2010, Wellcome 2010) Medscape.com (2011), Dr Agnihotri (2010) and the Canadian Orthopaedic Foot and Ankle Society (2010).*

It is largely hypothesised and accepted by most reporting authors that the pathological processes of RA disease common to the hand, are likely similar and equally applicable to the foot (van der Leeden *et al.* 2006, Helliwell *et al.* 2007, Costa *et al.* 2004, Woodburn and Helliwell 2004). Helliwell et al (2000) amongst other authors (Turner *et al.* 2006, Turner and Woodburn 2008, Costa *et al.* 2004, Fuhrmann 2002), have documented that early aggressive involvement of the metatarsophalangeal (MTP) joints was as frequent as that of the metacarpals of the hand in a subset of 93 RA participants. It is estimated that within this sample population approximately eight forefoot joints were affected by pain, swelling or erosion in early disease, progressing to a statistically increased 15 or more after just one year ($p \leq 0.001$). This demonstrates the often rapid onset and progression of early disease in the foot, highlighting this as an area warranting further investigation. Importantly, patients with mild to moderate RA disease affecting their feet become significantly disabled when compared with the general population (Wickman *et al.* 2004).

Conversely, Van der Leeden *et al.* (2008) note a reduction in reported symptoms in one or more forefoot joints from 70% of participants to 45% after one year, in an inception cohort of patients with RA (N=848). This is on trend with similar studies of early disease activity in the hand. A reduction in reported mild walking disability was also noted from 57% to 40% after one year. This suggests that there may be potential for early patient-reported foot-related complications to be interrupted (van der Leeden *et al.* 2008). After eight years however, it was noted that MTP joint erosion had dramatically progressed from 19% to 60% presence. In addition a trend towards foot deformity in the mid and rearfoot joints, with significantly associated walking disability, was again increasing (p=0.02-0.001), a finding reinforced by other authors (Mizumura *et al.* 2000, van der Leeden *et al.* 2007, Turner *et al.* 2008). This is in contrast to sustained reductions in disease activity reported in studies of the hand. The extent to which disease activity continues within the foot compared to the hand remains unclear as does the rationale for such differences in treatment response. It is possible that improvements in overall wellbeing result in greater physical activity, therefore placing greater biomechanical demand upon the foot. Thus, generalised systemic improvement is reported while foot complications are exacerbated. Conversely, episodes of high systemic disease activity may result in increased rest periods and reduced functional demand upon the foot. There is a need therefore to consider the patient-reported complications of RA disease alongside the biomechanical and structural articular or extra-articular complications.

2.2.1 Patient reported foot complications

Reported foot complications in patients with RA are typically multifactorial in nature and include pain, deformity, functional impairment and activity limitation (Landorf and Radford 2008, Otter *et al.* 2004, Walmsley *et al.* 2010). As such, patient-reported complications are typically evaluated using multi-domain questionnaires (Walmsley *et al.* 2010, Otter *et al.* 2004). These facilitate patient-focused reporting of disease impact, providing an adjunct to the OMERACT (outcome measures in rheumatology) influenced biomedical model, classically used in the evaluation of disease state (DoH 2005, DoH 2003a). There are however relatively few appropriate and validated tools available for use in this patient group. In a review by Walmsley *et al.* (2010), 11 tools appropriate for the assessment of foot health in RA were identified. Of these, the Foot Impact Scale (FIS) was the only tool specifically validated for use in patients with RA (Helliwell *et al.* 2005). The remaining tools explore various domains in an aged or general ailing population. As shown in table three, the domains explored ranged from functional impairment, footwear limitation and social isolation to anxiety and depression, although the predominant constructs are those of pain and activity limitation (Bazzichi *et al.* 2005).

Table 3: Foot-specific patient-reported outcome tools
Patient reported outcome tools applicable to the evaluation of foot health status.

Primary Author	Year	Sample size	Tool	Domains	Number of items	Benefits	Limitations
Barnett (Barnett *et al.* 2005)	2005	400	**BFS:** Bristol Foot Score	Pain Function	15	Sensitive to change	Limited evidence to support item validation
Bennett (Bennett *et al.* 1998)	1998	111	**FHSQ:** Foot Health Status Questionnaire	Pain Function Footwear General foot health	13	Sensitive to change (intended for post-op evaluation). Includes psychometric properties. Comprehensive and well validated, with additional footwear component available.	Not condition specific
Budiman-Mak (Budiman-Mak *et al.* 1991)	1991	87	**FFI:** Foot Function Index	Function	23	Three subscales all independently validated	No patient involvement in generation. Therefore poor construct validity.
Budiman-Mak (Budiman-Mak *et al.* 2006)	2006	92	**FFI-R:** Revised Foot Function Index	Function Footwear and related psycho-social impact	Short: ~20 Long: ~30	Construction better allied with ICF recommendations	No psychometric evaluation included, therefore evaluation limited to pain and activity limitation
Garrow (Garrow *et al.* 2000)	2000	1,078	**MFPDQ:** Manchester Foot Pain and Disability Questionnaire	Pain Disability	19	Good construct validity	Psycho-social impact not evaluated
Helliwell (Helliwell *et al.* 2005)	2005	192	**FIS:** Foot Impact Scale	Impairment/footwear Activity limitation/participation restriction	51	Specifically designed for use in foot evaluation in RA populations. Closely associated with ICF domains. Well validated. Potential application for intervention evaluation or change in foot health status evaluation.	Little reported evaluation of sensitivity to change
Johanson (Johanson *et al.* 2004)	2004	290	**FAM:** Foot and Ankle Module	Pain Stiffness Swelling Function	10 ± ~10	Acute and long-term impact reviewed. Developed for broad application to musculoskeletal pathology and intervention. Modifiable upon user needs.	Focuses mainly on structure and function domains

Macran (Macran *et al.* 2003)	2003	2,361	**PHQ:** Podiatry Health Questionnaire	Pain Function Foot hygiene Nail care Quality of life	8	Well validated, with extensive patient engagement	Podiatry focussed but with little applicability to a rheumatoid population

2.2.1.1 Foot pain, impairment & activity limitation

Of the symptoms most frequently reported at both the onset and throughout RA disease, pain appears paramount. The forefoot presents as the initial symptomatic region in approximately 15% of all cases (Rojas-Villarraga *et al.* 2009), and was cited as the primary cause for walking impairment, four times more often than knee or hip joint complications, in 71% of patients with RA (N=1000), when surveyed by Grondal *et al.* (2008). Furthermore, a cross sectional survey of patients with RA completed by Otter *et al.* (2009) (disease duration 12.7yrs ±12.5yrs, N=585), reported 93.5% of respondents to have experienced severe foot pain at some point, with this pain being most prevalent in the forefoot (63.9%, n=376) and ankle (42.7%, n=251). This finding is reinforced by previous authors also noting a similarly high frequency of reported pain across the forefoot (range 65-86%; (Shi *et al.* 2000, Grondal *et al.* 2008)) and rearfoot/ankle (range 52-66%; (Shi *et al.* 2000, Grondal *et al.* 2008)). Interestingly the main predictive factors for increased forefoot pain identified by Otter *et al.* (2009) were longer disease duration ($p=0.009$) and increased body mass index (BMI; $p \leq 0.001$). There again appears to be an interesting juxtaposition of increased inflammatory stress and increased biomechanical stress; disease chronicity has been demonstrated to be associated with perpetuated inflammation while increased BMI has been suggested to pathologically raise lower limb integral joint forces during weight bearing activity.

The reported close association between pain and functional impairment in musculoskeletal disease is not novel, with themes of this kind echoed throughout the rheumatological literature (van der Waal *et al.* 2003, Badlissi *et al.* 2005, Barton *et al.* 2008, Hamilton *et al.* 2001). For example, Rojas-Villaraga *et al.* (2009) report a significant association between a positive metatarsal squeeze test (pain on medial-lateral compression of the forefoot at the level of the MTPJs), and patient reported disability. These two themes are also echoed throughout the various patient-reported outcome measures (PROMs) developed to evaluate an individual's perception of the impact of disease (Landorf and Radford 2008, Otter *et al.* 2004, Walmsley *et al.*). Of the available PROMS, the Manchester Foot Pain and Disability Questionnaire (MFPDQ (Garrow *et al.* 2000)), Bristol Foot Score (BFS; (Barnett *et al.* 2005)), Rowan Foot Pain Assessment Questionnaire (ROFPAQ (Rowan 2001)) and the American Academy of Orthopaedic Surgeons Foot and Ankle Module (FAM (Johanson *et al.* 2004)) all closely integrate pain and activity limitation sub-scales. Much of the merging of these constructs is reportedly as a consequence of patient engagement during item development, as recommended by the 2001 World Health Organisation (WHO) guidelines for the international classification of functioning, disability and health (World 2001). Conversely, the authors of the MFPDQ used an alternative approach of principal component analysis to derive the final three included constructs: pain intensity, functional limitation and personal appearance (Garrow *et al.* 2000).

It would appear that foot pain and activity limitation are inextricably linked. However, further review of the MFPDQ protocol for item development demonstrates a bias in design through the non-uniform weighting of factors. The latter use and evaluation of the modified MFPD Index by Menz *et al.* (2006) continued to demonstrate high internal consistency of the tool (Cronbach's alpha=0.89), whilst also demonstrating a significant association between the three primary constructs and depression or mental health status as assessed by the Goldberg Anxiety and Depression Scale (Goldberg *et al.* 1988) or Medical Outcomes Study Short Form–36 (McCallum 1995) respectively. However, this inadvertently reinforces the summative statement proposed by Otter *et al*. (2004) that at present no single tool is both specific and sensitive to the patient reported impact of foot complications in RA. Arguably, even fewer tools are sensitive to *change* in foot health status, despite a number being designed in response to the need for post-operative surgical evaluation, as highlighted in table 2. Indeed the Bristol Foot Score and FHSQ are the only tools that have been evaluated for sensitivity to change (Barnett *et al.* 2005).

While the FIS has not been validated for the evaluation of change in foot health status, it has been validated in accordance with ICF criterion (N=192, test-retest ICC analysis for each subscale=0.84, CI=0.75-0.9 and ICC=0.96, CI=0.93-0.98 respectively) (Helliwell *et al.* 2005, World 2001). The two subscales of the FIS questionnaire facilitate comprehensive evaluation of foot impairment (including pain), footwear restriction, activity limitation, participation restriction and psycho-social impact. Turner *et al.* (2007) have suggested a meaningful change in FIS score of 3 or more (with mean SD≤5) in the longitudinal use of this tool. However, the data upon which this is inferred is not presented for review, although it is cited as a clinically beneficial indicator sensitive to changes in foot health status. None the less, with the overall rounded appraisal of foot health status and baseline validation, this is arguably the most appropriate measure of disability for use in patients with RA at present.

2.2.2 Biomechanical foot complications

Biomechanical studies of the pedal articular manifestations of RA disease also note associations between reported pain and function (Bal *et al.* 2006, Helliwell *et al.* 2007, van der Leeden *et al.* 2008, Hamilton *et al.* 2001, Anders *et al.* 2007, Wickman *et al.* 2004). It has been extensively demonstrated that both foot deformity and activity limitation are significantly associated with extended disease duration or chronicity (p≤0.001 (Helliwell *et al.* 2000), p≤0.001 (Turner *et al.* 2008, Turner and Woodburn 2008) respectively). Rearfoot eversion, reduced ankle joint range of motion and excessive subtalar joint pronation are amongst the most frequently reported static biomechanical complications of RA in various cohort studies (Woodburn *et al.* 2002b, Khazzam *et al.* 2007, Turner *et al.* 2008, van der Leeden *et al.* 2008). Particularly clinically evident features include the characteristic reduction in medial longitudinal arch height, hallux-abducto-valgus deformity and forefoot metatarsal abduction (figure four) (Woodburn *et al.* 2002b). Reported functional biomechanical complications include a reduction in overall walking speed, from 1.28-1.30m/s in healthy controls to 0.96-1.05m/s in patients with RA (Turner *et al.* 2006,

Khazzam *et al.* 2007, van der Leeden *et al.* 2008), increased stance phase of gait from 62% to 66% of the gait cycle and increased periods of double limb support from 15.8% to 19.3% of the gait cycle (Khazzam *et al.* 2007, Turner *et al.* 2006, Woodburn *et al.* 2002a). It is suggested that these temporal changes are likely related to altered biomechanical loading patterns (centre of force trajectory or segmental rotational sequencing) through the foot (Semple *et al.* 2007, Turner *et al.* 2006, Lundgren *et al.* 2008, Wolf *et al.* 2008, Nester *et al.* 2007). However, the precise nature of these changes is yet to be fully understood. Indeed, while these latter stage biomechanical features of RA are well reported, their pathogenesis remains unclear. There is a paucity of longitudinal studies of foot disease in patients with RA; the current evidence base is mainly comprised of cross-sectional investigations of mid/rearfoot deformity and kinematic function in patients with established RA. It is unclear at present which patients are at greatest risk of developing adverse biomechanical function, which factors contribute to this, and which factors may be therapeutically modifiable. The relationship between adverse biomechanical function and inflammation in the foot remains unknown but it is thought to be potentially synergistic in nature.

2.2.2.1 Clinical assessment of foot alignment

A number of investigative techniques have been proposed to evaluate foot joint alignment and congruency with inferred implications for biomechanical function (Wolf *et al.* 2008, Turner *et al.* 2008, Nester *et al.* 2007, Woodburn *et al.* 2005, Fuller 2000, Dananberg 2000, Cavanagh *et al.* 1997). Clinically used static postural measures include navicular height, arch height and valgus index (Weiner-Ogilvie and Rome 1998, Menz and Munteanu 2005). However, these have been demonstrated to have poor inter-rater reliability (p=0.001-0.005) (Weiner-Ogilvie and Rome 1998, Menz and Munteanu 2005). Conversely the foot posture index (FPI-6) is a clinical static postural tool that has been validated using Rasch analysis (Redmond *et al.* 2006, Keenan *et al.* 2007). The authors acknowledge that the original FPI-8 was only able to predict 64% of the variance in static standing position and 41% of the postural variance during the stance phase of gait in patients with RA. None the less, with subsequent re-validation and removal of two items the tool has been shown to have good internal consistency (Cronbach's alpha=0.83) and allows multi-segment, multi-plane evaluation in a clinical setting. To our knowledge the FPI is the only validated measure of foot joint alignment published at the time of this investigation.

2.2.3 Articular foot complications

The prevalence of RA articular manifestations within the foot is high, reportedly affecting 90% of patients at some point (Michelson *et al.* 1994), and typically occurs in the forefoot metatarsophalangeal (MTP) joints (van der Leeden *et al.* 2008, Akerman *et al.* 1991, Bal *et al.* 2006, Costa *et al.* 2004). However, there is also limited evidence of articular involvement in other mid and rearfoot joints (Woodburn *et al.* 2002c, Helliwell *et al.* 2007). In analogue to the hand, synovitis and concomitant articular degradation (cartilage loss, joint space narrowing and marginal erosions) reportedly occur across all MTP joints, although a greater prevalence is reported in the more lateral joints (Umans and Elsinger 2001, Miller 2001, van der Leeden *et al.*

2006). Overall, the prevalence of MTP joint affectation is reportedly equal to or greater than the corresponding metacarpophalangeal hand joints in early RA disease (Hulsmans *et al.* 2000, van der Heijde *et al.* 1992, Mottonen 1988). A longitudinal study by Van der Leeden *et al.* (2006), however, demonstrated that, unlike the hand, a greater proportion of participants (40-50%) continued to have MTP joint erosive degradation after the first two years of disease despite continued treatment. Furthermore, Van der Leeden *et al.* (2010) have subsequently demonstrated that 40% of participants had active disease in one or more MTP joints despite achieving remission according to DAS 28 criteria, with an increase from 19-60% of participants reportedly having one or more MTP joint erosions from baseline to eight years. Conversely, recent data reported by Van Tuyl *et al.* (2012) suggests that inclusion of the forefoot joints does not alter identification of patients in remission from RA disease. This recent paper does appear to be in contrast with the majority of previous works, although further research into the added benefit of reviewing disease activity within the forefoot is warranted (Priolo *et al.* 1997).

Those factors which predict an individual patient's likelihood of developing greater articular involvement with disease chronicity are unclear. However, there does appear to be increasing evidence of continued, subclinical, minimal disease activity within the forefoot despite ongoing management (Felson *et al.* 2011, van der Heijde *et al.* 1992, van der Leeden *et al.* 2010). Continued biomechanical irritation through weight bearing activity and continued inflammation within extra-articular foot structures have been cited as potential causes (Shi *et al.* 2000, Platto *et al.* 1991, Turner *et al.* 2008, OBrien *et al.* 1997). There is a need therefore to consider the role of extra-articular features in the pathogenesis of foot complications in patients with RA.

2.2.4 Extra-articular foot complications

The forefoot is a relatively complex anatomical region housing a number of extra-articular structures with potential to be affected by the progress of RA disease (figure five) (Mahana-Borges *et al.* 2003). This may be as a consequence of excessive inflammation or adverse biomechanical function. However, there is notable obscurity within physiological or histological texts that document the anatomical detail of the adult forefoot. Figure five is an illustrative representation of the most frequently agreed structural anatomy of the forefoot, which will be used as the accepted anatomical reference for subsequent work presented within this thesis. It should be noted therefore that the obscurity in anatomical detail has posed a diagnostic challenge; abnormal tissues or structures have potentially been overlooked or misinterpreted by previous authors because of a lack of a standardised anatomical reference (Mahana-Borges *et al.* 2003, Chauveaux *et al.* 1987, Zanetti *et al.* 1997).

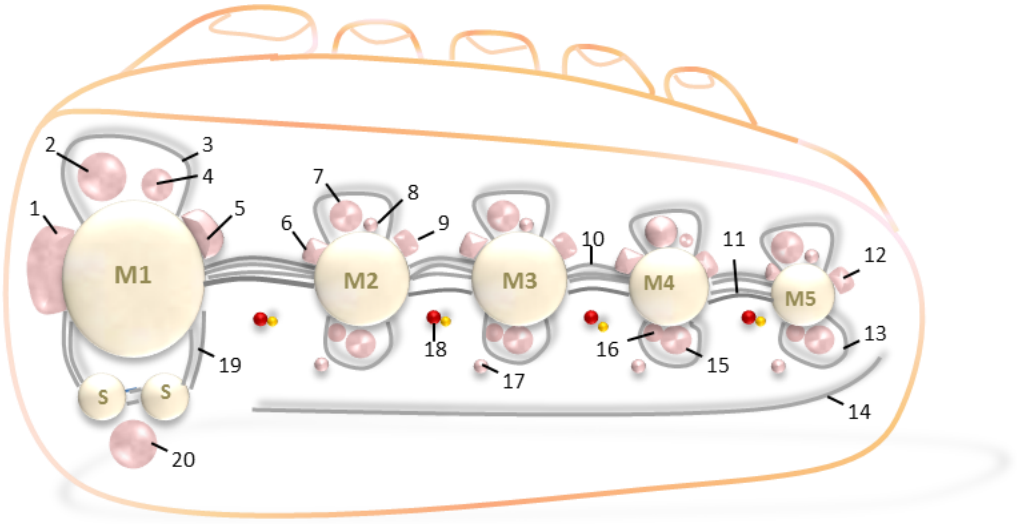


Figure 5: A transverse illustration of forefoot anatomy
Where 1= abductor hallucis tendon, 2 = extensor hallucis longus tendon, 3 = extensor hood, 4 = extensor hallucis brevis tendon, 5 = adductor hallucis tendon, 6 = dorsal interosseous tendon, 7 = extensor digitorum longus tendon, 8 = extensor digitorum brevis tendon, 9 = plantar interosseous tendon, 10 = deep transverse metatarsal ligament, 11 = section of plantar plate, 12 = abductor digiti minimi tendon, 13 = vertical fibres of plantarfascia, 14 = superficial transverse metatarsal ligament, 15 = flexor digitorum brevis tendon, 16 = flexor digitorum longus tendon, 17 = lumbrical tendon, 18 = neurovascular bundle, 19 = sesamoid ligament, 20 = flexor hallucis longus tendon. S = sesamoid bone, M1-5 = head of metatarsal bone 1-5. *Image author's own; anatomical detail collated from Mahana-Borges et al. (2003), Zanetti et al. (1997), Chauveaux et al. (1987).*

Table four details the known extra-articular complications of the forefoot that may be evident in patients with RA. The variety of differential diagnoses for complications of the forefoot in patients with RA is perhaps reflective of the anatomical complexity of the region.

Table 4: Differential diagnoses of the forefoot in RA
Differential diagnoses for commonly reported complications of the forefoot.

Diagnostic category	Differential diagnoses	Method of diagnosis	Reported clinical presentation in RA
Neurological	**Neuroma** (Ashman *et al.* 2001, Iagnocco *et al.* 2001, Zielaskowski *et al.* 2000, Alexander *et al.* 1987)	MRI (Ashman *et al.* 2001, Zielaskowski *et al.* 2000) US (Iagnocco *et al.* 2001)	Pain on medial to lateral compression of the forefoot. 'Sharp, shooting pain', regional numbness of the lesser digits.
	Neurofibrosis (Bossley and Cairney 1980, McElvenny 1943)	Dissection (Bossley and Cairney 1980) Radiography (Bossley and Cairney 1980) Surgical exploration (McElvenny 1943)	May be asymptomatic. Plantar capsulated, non-fluctuant swelling may be present in some cases.
	Ganglia (Ashman *et al.* 2001)	MRI (Ashman *et al.* 2001)	Small capsular, non-fluctuant swelling, typically dorsal and asymptomatic.
Tendonous	**Tendonosis/enthesopathy** (Ashman *et al.* 2001, Aronow 2005, Canoso 1998, Stiskal *et al.* 1997, Slobodin *et al.* 2007, Coakley *et al.* 1994, Falsetti *et al.* 2003)	Radiography (Falsetti *et al.* 2003) MRI (Ashman *et al.* 2001, Stiskal *et al.* 1997) US (Coakley *et al.* 1994, Falsetti *et al.* 2003) Surgical exploration (Aronow 2005)	Chronic manifestation at sites of tendon insertion. Low grade inflammation may be present. 'Dull ache on movement'.
	Tenosynovitis (Ashman *et al.* 2001, Suzuki *et al.* 2009, Baan *et al.* 2007, Caprotti *et al.* 1993)	Radiography (Baan *et al.* 2007) MRI (Ashman *et al.* 2001) US (Suzuki *et al.* 2009, Baan *et al.* 2007, Caprotti *et al.* 1993)	Acute manifestation along tendon tracks. Inflammation typically present. Regional tenderness on palpation or with movement. Estimated 7% prevalence in RA (Lauzon *et al.* 1987, Coakley *et al.* 1994), this although may be higher.
	Rupture/partial tear (Canoso 1998, Wanivenhaus 2007, Jernberg *et al.* 1999, Baan *et al.* 2007)	Radiography (Baan *et al.* 2007) MRI (Jernberg *et al.* 1999) US (Baan *et al.* 2007) Surgical exploration (Canoso 1998, Wanivenhaus 2007)	Acute manifestation along tendon tracks with associated regional inflammation. Extreme point tenderness on palpation. Functional impairment dependent upon degree of rupture.
Synovial	**Synovitis** (Mutlu *et al.* 2006, Burra and Katchis 1998, Joshua *et al.* 2007, Maillefert *et al.* 2003, Mulherin *et al.* 1996,	MRI (Mutlu *et al.* 2006, Maillefert *et al.* 2003) US (Joshua *et al.* 2007, Pascual-Ramos *et al.* 2009, Iagnocco *et*	Pain, swelling and erythema, local to synovial joints. Movement restricted. Typically affecting the MCP or MTP joints of the hands and feet.

Diagnostic category	Differential diagnoses	Method of diagnosis	Reported clinical presentation in RA
	Pascual-Ramos *et al.* 2009, Sattar 1990, Iagnocco *et al.* 2001)	*al.* 2001) Physical examination (Burra and Katchis 1998, Mulherin *et al.* 1996, Sattar 1990) Haematology (Mulherin *et al.* 1996)	
	Synovial cyst (Ashman *et al.* 2001, Bancroft *et al.* 2008)	MRI (Ashman *et al.* 2001)	Fluctuant, nodular swelling. Often located adjacent to DIP joints. Red/blue colouration. Typically asymptomatic.
	Peri-articular joint pannus (Caprotti *et al.* 1993)	US (Caprotti *et al.* 1993)	Subcutaneous, soft tissue masses extruding from the joints affected by RA (typically the MCP or MTP joints). Pannus itself may appear asymptomatic however is typically present alongside additional joint complications associated with RA.
	Pigmented villo-nodular synovitis (Sharma *et al.* 2005)	Histopathology (Sharma *et al.* 2005)	Sudden onset joint swelling, often disproportionate to the pain experienced. Less frequent slow onset manifestations, with gradual increases in tenderness may occur. Presentation is typically within the larger joints of the hip and knee, however the ankle or forefoot may be affected.
Vascular	**Vasculitis** (Maher and Wilson 2006, Iyngkaran *et al.* 2003, Pascual-Ramos *et al.* 2009)	US (Maher and Wilson 2006, Pascual-Ramos *et al.* 2009)	Purpura (red/purple discolouration), non-blanching with the application of pressure, noted. Systemic symptoms including, fever, weight loss and myalgia may be present. Glomerulonephritis and raised inflammatory markers indicated with further testing.
	Endarteritis (Bossley and Cairney 1980)	Dissection (Bossley and Cairney 1980) Radiography (Bossley and Cairney 1980)	Localised tissue necrosis, due to the collapse of small arterial vessel lumen. Severe pain and pallor on initial presentation, progressing to neuropathy and dark blue/black tissue discolouration.
	Angiofibromatosis (McElvenny 1943)	Surgical exploration (McElvenny 1943)	Small red/brown papules, apparent in only a few cases. Typically asymptomatic.
	Vascular calcification (Whiddon *et al.* 2008)	Radiography (Whiddon *et al.* 2008)	Often entirely asymptomatic unless severe, in which instance symptoms of peripheral vascular disease may be noted. Typically bilateral.
Bone	**Bony neoplasm** (Ashman *et al.* 2001)	MRI (Ashman *et al.* 2001)	Point tenderness present in some cases in addition to bony outgrowths or nodules. May be entirely asymptomatic. Unilateral.
	Freiberg's infarction (Ashman *et al.* 2001)	MRI (Ashman *et al.* 2001)	Point tenderness around the second or third metatarsal head region, often with small volumes of associated joint effusion. Pain on movement or palpation. Increased frequency of presentation in females (5:1) (Katcherian 1994). Typically unilateral.

Diagnostic category	Differential diagnoses	Method of diagnosis	Reported clinical presentation in RA
	Osteonecrosis (Berger *et al.* 2004)	Radiography (Berger *et al.* 2004)	Often localised to the epiphysis of long bones. Reduced joint congruency.
	Unspecified regional calcific deposition (Berger and Ziter 1972) (Whiddon *et al.* 2008)	Radiography (Berger and Ziter 1972, Whiddon *et al.* 2008)	Pain and swelling in one or more joints. Calcium deposition identified with further imaging or histological examination.
Fibrous	**Fibromatosis/plantar fibromatosis** (Ashman *et al.* 2001, Oliva *et al.* 2005)	Radiography (Oliva *et al.* 2005) MRI (Ashman *et al.* 2001) Physical examination (Oliva *et al.* 2005)	Nodular lesions associated with the deep plantar fascial tissue. May be benign at onset, however can functionally impair lesser digit extension in time.
	Granuloma (Knoss *et al.* 2006, Ashman *et al.* 2001, Caprotti *et al.* 1993, Campbell and Montgomery 2005)	MRI (Ashman *et al.* 2001) US (Caprotti *et al.* 1993) Histopathology (Knoss *et al.* 2006)	Small, spherical nodular mass. Histological examination further specifies sub type based upon necrotization and cell infiltration type.
Dermatological	**Ulceration** (Firth *et al.* 2008, Firth *et al.* 2007, Firth *et al.* 2006)	Physical examination (Firth *et al.* 2008, Firth *et al.* 2007, Firth *et al.* 2006)	Break in dermal tissue. May or may not have associated pain or inflammation.
	Pyoderma-gangrenosum (Pacifico *et al.* 2009)	Physical examination (Pacifico *et al.* 2009) Histopathology (Pacifico *et al.* 2009)	Small papules on initial presentation that may progress to large necrotic lesions, with yellow/green wound exudate.
Other	**Gouty tophi/cyst** (Canoso and Yood 1979a)	Combined physical examination & Histopathology (Canoso and Yood 1979a)	Swelling and erythema often local to a single joint, described as being exquisitely painful. Typically the first MTP joint of the foot is the primary site of manifestation. In chronic cases small white tophi may exude from the affected area.
	Infection (Ashman *et al.* 2001)	MRI (Ashman *et al.* 2001)	Swelling, erythema and tenderness local to the site of infection noted. May appear asymptomatic in heavily immune-compromised patients.
	Plantar plate disruption	MRI (Ashman *et al.* 2001, Umans and Elsinger 2001) US(Gregg *et al.* 2008)	Definitive presentation unknown. May be associated with unspecified metatarsalgia and forefoot instability.
	Sesamoiditis	Radiography (Kanatli *et al.* 2006) US (Ashman *et al.* 2001)	Inflammation local to the sesamoid bones, located plantar to the first MTP joint. Pain increased with weight-bearing activity.

The relative prevalence of the extra-articular complications of the forefoot in patients with RA is unclear. However, structures which incorporate a synovial membrane, such as joint linings, tendon sheaths or intermetatarsal bursae, are amongst the most frequently affected (Helliwell *et al.* 2007, Woodburn and Helliwell 2004, Shi *et al.* 2000, OBrien *et al.* 1997); as discussed in section 2.1, synovial structures may be preferentially responsive to excessive, disease-mediated, inflammation in patients with RA (OBrien *et al.* 1997).

Those factors which predict an individual patient's likelihood of developing greater extra-articular involvement with disease chronicity are unclear. However, as with the articular manifestations of RA, there appears to be increasing evidence of continued, subclinical, minimal disease activity within the extra-articular forefoot structures despite ongoing management (Wechalekar *et al.* 2012, van Tuyl *et al.* 2012, van der Leeden *et al.* 2010). In particular US-detected forefoot bursae (FFB) have been reported to be highly prevalent in patients with RA when compared to healthy volunteers (Bowen *et al.* 2009). Furthermore, Bowen *et al.* (2010c) have demonstrated a significant association between an increased US-detected presence of FFB and patient-reported foot-related disability. The rationale for this association remains hypothetical to date; FFB may be responsive to increased inflammation, or adverse biomechanical function, or both. The clinical importance of FFB longitudinally remains unclear. None the less, FFB do represent a potential prognostic indicator of foot-related disability, beyond existing measures of disease state, which warrant further investigation.

2.3 Forefoot bursae

Bursae are typically defined as encapsulated fluid filled spaces, often situated adjacent to synovial joints (Warwick *et al.* 1973). Their anatomical function is thought to be that of mechanical support by facilitating movement between closely aligned structures, enabling localised tissue compression or retraction when under pressure (Aguiar *et al.* 2005, Canoso *et al.* 1988, Meurman 1982). Within the forefoot however, the precise anatomical features of bursae remain contentious within the current literature (Awerbuch *et al.* 1982, Bossley and Cairney 1980, Chauveaux *et al.* 1987, Claustre *et al.* 1983). FFB are of particular interest in patients with RA, as they are potentially responsive to both disease mediated inflammation and adverse biomechanical function. Previous authors have reported the presence of synoviocytes lining the inner margins of intermetatarsal bursae, which may be responsive to RA in a similar manner to the synovium of joint linings (Jaganathan *et al.* 2012, Kachlik *et al.* 2008, Mutlu *et al.* 2006, Boutry *et al.* 2003a). Conversely, other researchers report fibrous connective tissue changes that encapsulate various fluid filled cavities across the intermetatarsal or plantar forefoot regions, which may be responsive to adverse mechanical function (Studler *et al.* 2008, Ahmed *et al.* 1994). None the less, preliminary work suggests that the presence of FFB may inform clinicians about changes in foot health or foot related disability (Bowen *et al.* 2009). Furthermore, it is also a biologically plausible hypothesis that FFB may themselves become

pathological. Further evaluation of the epidemiology and clinical importance of FFB in patients with RA is therefore warranted (Koski 1998).

2.3.1 Clinical importance of FFB

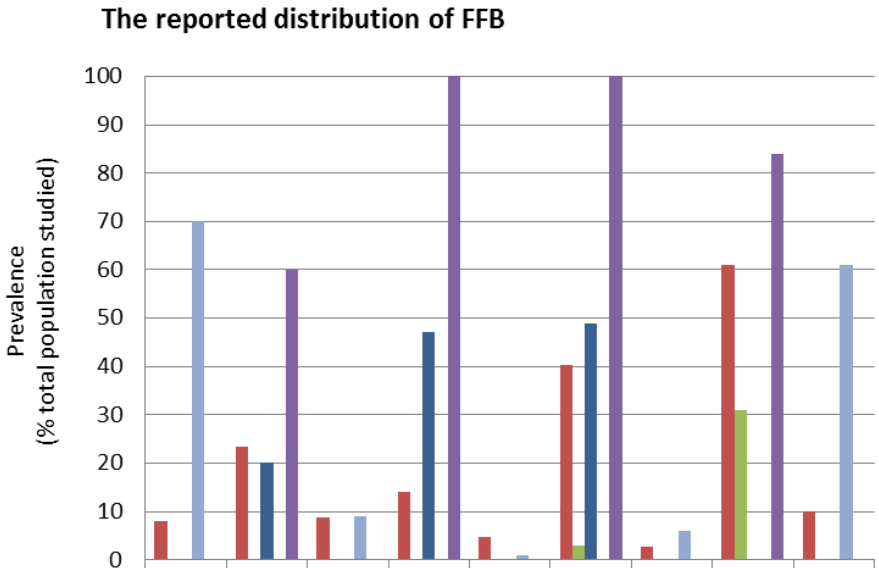
The clinical importance of FFB has been commented upon by only a few authors (Hertzler 1926, Iagnocco *et al.* 2001, Bowen *et al.*). Both Hertzler *et al.* (1926) and Iagnocco *et al.* (2001) report symptomatic bursae presenting as generalised metatarsalgia in patients with no comorbidity, where the majority of symptoms were characterised as 'burning' or 'walking on marbles'. Enlarged intermetatarsal bursae coexisting with neuroma have also been reported (Theumann *et al.* 2001). However, in all reports neurofibrosis is the primary pathological manifestation of interest and the bursa is frequently noted as an incidental but interesting finding, the relative clinical importance of which is unclear (Bossley and Cairney 1980, Chauveaux *et al.* 1987, Theumann *et al.* 2001, Alexander *et al.* 1987, Ashman *et al.* 2001, Scotti 1957). Bowen *et al.* (2009), document similar reported pain sensations in patients with RA, although again it is unclear to what extent these symptoms can be directly attributed to FFB. However, they do note a significant association between FFB presence and patient-reported foot-related disability (foot impairment p=0.026, activity limitation p=0.009). The reported relationship is independent of systemic markers of inflammation, suggesting perhaps a more biomechanical association. This would appear contrary to the findings of Hertzler *et al.* (1926) where reported pain is hypothesised to be directly related to actively inflamed bursae. Conversely, Bottger *et al.* (1998) as a result of their study of calcaneal bursae, hypothesise that an increase in the size of the bursal cavity is proportional to the pain experienced by the patient, without regard to inflammation presence or absence.

In the forefoot distinction between pathological tissues has perhaps been made more difficult because of the complex anatomical nature and close association of many structures. There is confusion within the available literature regarding the anatomy, physiology, aetiology and clinical presentation of FFB (Theumann *et al.* 2001, Studler *et al.* 2008, Chauveaux *et al.* 1987). The clinical importance of FFB in patients with RA is therefore unknown at present. It remains unclear as to whether size, location, tissue characterisation or inflammation is, either independently or in combination, clinically important in the manifestation of problematic FFB. Determination of the clinical importance of FFB and the factors which contribute to this will be beneficial in developing future management strategies for improving foot health or disability in patients with RA.

2.3.2 Epidemiology of FFB

The reported prevalence of one or more FFB in healthy volunteers ranges from 70-90% (Lohman *et al.* 2001, Studler *et al.* 2008, Zanetti *et al.* 1997). Similarly, the reported prevalence of one or more FFB in patients with RA ranges from 63-93% across authors (Boutry *et al.* 2003a, Bowen *et al.* 2009, Koski 1998). The natural history of FFB has not been detailed to date. None the less, FFB appear to be consistently reported as highly prevalent across cohort studies.

However, there is less consistency between authors regarding the distribution of observed FFB across forefoot sites, as illustrated in figure six (Roberts 1929, Bowen *et al.,* Boutry *et al.* 2003b, Koski 1998, Studler *et al.* 2008, Theumann *et al.* 2001, Bowen *et al.* 2009, Bowen *et al.* 2010b).



	S1	IM1-2	S2	IM2-3	S3	IM3-4	S4	IM4-5	S5
Bowen (2010) (RA: N=149)	8	24	9	14	5	40	3	61	10
Bowen (2010) (healthy:N=50)	0	0	0	0	0	3	0	31	0
Zanetti (1997) (healthy: N=70)	0	20	0	47	0	49	0	0	0
Studler (2008) (healthy: N=70)	70	0	9	0	1	0	6	0	61
Chauveaux (1987) (healthy: N=25)	0	60	0	100	0	100	0	84	0

Figure 6: Previously reported forefoot bursae distribution
The reported frequency of forefoot bursae presence is illustrated and classified according to anatomical location. Where S = plantar metatarsophalangeal joint region, IM = inter-metatarsophalangeal region. *Image author's own*.

Of note, Chauveaux *et al.* (1987) have a far greater overall estimation of FFB presence, which is relatively evenly distributed across intermetatarsal sites. In contrast, Studler *et al.* (2008) report a particularly high FFB presence plantar to the first and fifth metatarsal heads. Discrepancies between reports could be attributable to differences in observed populations, recruitment strategy or method of identification. Conversely, as suggested by Studler *et al.* (2008), discrepancies could be indicative of differences between natural anatomical and acquired FFB. It is suggested that altered or acquired FFB can be distinguished from anatomical FFB, becoming either advantageous or problematic in nature (Ahmed *et al.* 1994, Studler *et al.* 2008). No further work has been completed to date to systematically explore the characterisation of FFB in patients with RA. Characterising FFB may improve treatment targeting, where those FFB identified as clinically relevant can be reliably differentiated and preferentially treated.

2.3.3 Characterisation of FFB

Various methods of characterising FFB have been adopted in previous works and have largely centred on the perceived importance or aetiology of the identified FFB. The differing methods of proposed characterisation can be grouped into three main categories:

- Anatomical FFB
- Mechanical/adventitial FFB
- Symptomatic/pathological FFB

Within each category, the further characterisation of FFB has arguably become a complex exercise. As demonstrated in table five, a number of different subtypes of FFB have been proposed.

Table 5: Summary of FFB characterisation strategies

Classification	Definition	Sub-classification	Definition
Anatomical	Fluid filled sacks, developed during intrauterine life (Warwick *et al.* 1973). Contain a synoviocytic cellular membrane.	Sub-tendonous (Warwick *et al.* 1973, Aguiar *et al.* 2005, Hernandez *et al.* 1991)	Facilitate distinct separation between tendons and adjacent structures
		Sub-muscular (Warwick *et al.* 1973)	Facilitate distinct separation between muscle fibres and adjacent structures
		Sub-fascial (Warwick *et al.* 1973, Siciliano and Mozen 1993, Theumann *et al.* 2001)	Facilitate distinct separation between fibrous tissues and adjacent structures – typically bone
		Inter-ligamentous (Warwick *et al.* 1973)	Facilitate distinct separation between ligaments and typically superior adjacent structures
		Between adjacent bones/joint structures (Chauveaux *et al.* 1987, Hernandez *et al.* 1991, Siciliano and Mozen 1993)	Facilitate distinct separation between adjacent bony structures
Mechanical/adventitial	Fluid filled cavities, developed in response to mechanical tissue stress (Studler *et al.* 2008, Ahmed *et al.* 1994)	Fibrous (Studler *et al.* 2008, Ahmed *et al.* 1994)	Fluid filled regions present at areas of fascial tearing, lacking a synovial lining
		Hypertrophied synovial (Harper 2003, Claustre *et al.* 1983, Lohman *et al.* 2001)	Enlarged synovially lined bursae. May be anatomical or acquired – aetiology unknown.
Symptomatic/pathological	Fluid filled sacs, the presence of which may be construed as negative indicator (Awerbuch *et al.* 1982)	Fibrous (Scotti 1957)	Large fluid filled regions, lacking a synovial lining. May contain floating elements of fibrous or necrotic tissue.
		Hypertrophied synovial (Canoso *et al.* 1988, Koski 1998, Meurman 1982, Scutellari and Orzincolo 1998, Awerbuch *et al.* 1982, Bottger *et al.* 1998)	Enlarged synovially lined bursae. May be anatomical or acquired – aetiology unknown.
		Associated with Neuroma (Bossley and Cairney 1980, Reed and Bliss 1973, Scotti 1957, Zanetti *et al.* 1997, Alexander *et al.* 1987)	Synovial lining may or may not be present. Fluid filled region closely associated with the presence of a neuroma, linear relationship between neuroma and bursae unknown.

A lack of standardisation in the characterisation of FFB makes comparative evaluation of studies in this area challenging. Figure seven summarises the various proposed FFB relative to anatomical reference positions of the forefoot, as previously depicted in figure five.

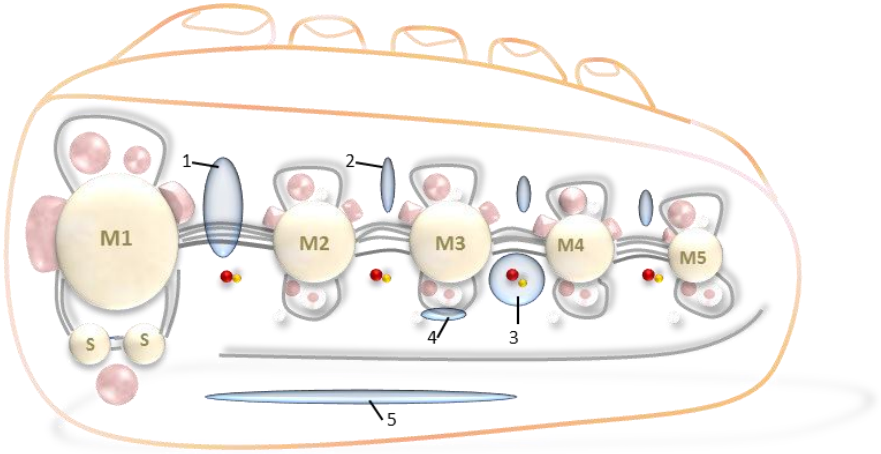


Figure 7: Forefoot anatomy & identification of reported bursae
Where 1 = 1-2 intermetatarsal bursa coursing adjacent to adductor hallucis tendon that may extend beyond the deep transverse intermetatarsal ligament, 2 = intermetatarsal bursae that may become hypertrophied extending beyond the deep transverse intermetatarsal ligament, 3 = bursae associated with neurovascular bundle, 4 = bursae associated with superior aspect of flexor digitorum brevis tendon, 5 = plantar mechanical bursae. *Image author's own; detail collated from Mahana-Borges et al. (2003), Zanetti et al. (1997), Chauveaux et al. (1987).*

Accurate characterisation of FFB may be of particular relevance when attempting to determine their relative clinical importance. In order to fully evaluate the role of FFB in RA, differentiation between closely associated anatomical structures, bursal hypertrophy, bursal fibrosis, bursitis, or inflammation in adjacent structures is required. There is a clear need for a standardised method of FFB characterisation, the use of which would allow better synthesis of clinical and research data in this area. The basis for future characterisation criteria can however be informed by previous literature.

2.3.3.1 Anatomical FFB

A generalised definition of anatomical FFB is that of an encapsulated, spherical or ellipsoid, fluid filled space situated between the metatarsal heads (Hernandez *et al.* 1991, Theumann *et al.* 2001). The FFB are situated superior to the deep transverse intermetatarsal ligament (DTML), which divides the intermetatarsal (IM) spaces into inferior and superior regions in the transverse plane (figure five) (Theumann *et al.* 2001). Based predominantly upon the findings of cadaveric studies it is thought that anatomical FFB do not typically extend beyond the head and base of the metatarsal (M) and proximal phalanx (PP) bones respectively, as shown in figure eight (Chauveaux *et al.* 1987, Claustre *et al.* 1983, Theumann *et al.* 2001).

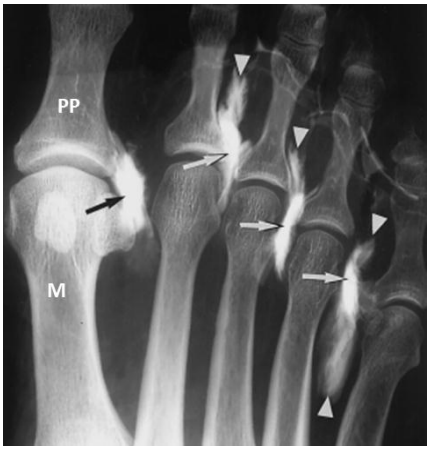


Figure 8: An anterior-posterior contrast enhanced right forefoot radiograph
The contrast media depict the IM bursae (arrows). Note the contrast leakage (arrowheads) distal to the second, third, and fourth bursae and proximal to the fourth bursa. *Image reproduced with permission from Professor Theumann* (Theumann *et al.* 2001).

Theumann *et al.* (2001) reported all IM FFB as situated superior to the DTML adjacent to the interosseous muscles, tendons and MTPJ collateral ligament complexes in non-pathological healthy cadaveric specimens (N=8), (figure nine: a). This is quite distinct from the neurovascular bundles (NVB) which are found plantarly. However as illustrated in figure nine (b), once distal to the DTML a closer association between the FFB and NVB may be seen. Indeed, as illustrated by Mohana-Borges *et al.* (2003) (figure nine: c), the uniformity of FFB positioning demonstrated by Theumann *et al.* (2001) may not always be the case, where the IM2-3 FFB appears far superiorly positioned than the IM1-2 FFB in this example. Conversely, Chauveaux *et al.* (1987) describe the IM1-2 bursa as uniquely and closely aligned with the adductor hallucis tendon in most cases, perhaps accounting for the presentation demonstrated by Mohana-Borges *et al.* (2003) in figure nine (c).

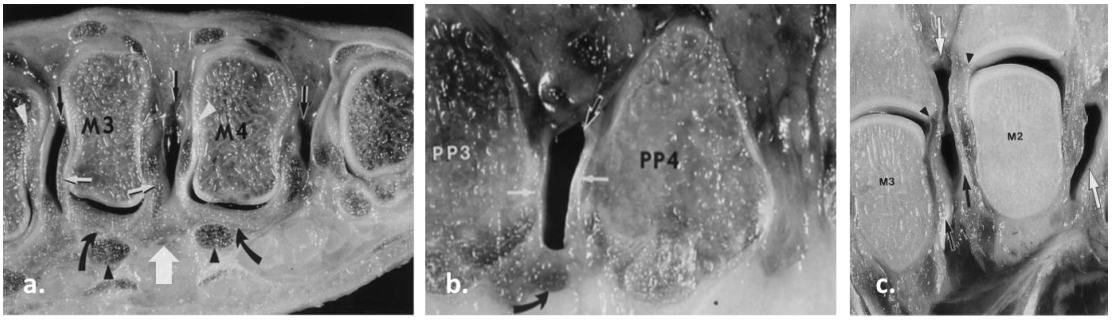


Figure 9: Cadaveric anatomical sections of the forefoot
Where 9a illustrates a transverse section of the forefoot, taken from the region proximal to the distal edge of the metatarsal head. The IM bursae (thin straight black arrows) lie between both interosseous tendons (straight white arrows). The collateral accessory ligaments (white arrowheads), arise in the depressions on the medial and lateral sides of the third and fourth metatarsal heads,(M3 & M4), and extend to the plantar plate (curved black arrows) below the interosseous tendons. The black arrow heads depict the flexor digitorum longus muscle. The neurovascular bundle is depicted by the thick straight white arrow (Theumann *et al.* 2001). 9b illustrates a transverse section of the forefoot, taken from the region distal to the base of the third and fourth proximal phalanx (PP3 & PP4 respectively). The IM bursa (straight black arrow) lies between both interosseous tendons (straight white arrows). Note the close relationship between the neurovascular bundle (curved arrow) and the bursa (actual size = smaller than 1mm). Proximal phalanges of the third (PP3) and fourth (PP4) rays are shown (Theumann *et al.* 2001). 9c illustrates a transverse section of the forefoot, taken at the middle inferior one-third of the metatarsal heads in a cadaveric left foot. The arrow heads show the phalangeal attachment of the main collateral component of the collateral ligament complex. The IM bursae (white arrows) are situated between the depressions of the metatarsal heads (M2 & M3) bordered by interosseous tendons (black arrows) which insert further into the phalangeal bases (Mahana-Borges *et al.* 2003). *Images reproduced with permission from Professor Theumann, and Dr Resnick on behalf of Dr Mohana-Borges et al. and the Journal of Radiology*.

Similarly, Chauveaux *et al.* (1987) and Bossley *et al.* (1980) also note the IM 2-3 and 3-4 bursae to be situated centrally and superiorly over the DTML, reporting these to arc either dorsally or plantarly once distal to the DTML, with the proximal fourth remaining at some distance from the NVB. In further contrast to Theumann (2001), Chauveaux *et al.* (1987) note that the IM 4-5 bursa may advance plantar to the DTML communicating directly with the subjacent plantar space, although reported findings are from a subset of participants presenting with neuroma-like symptoms. None the less, such plantar projections are not reported to protrude beyond the level of the plantar nerves or lumbrical muscles in any cases (N=25). In addition, various authors have also documented FFB as being located plantar to the metatarsal heads (Hernandez *et al.* 1991, Studler *et al.* 2008, Boutry *et al.* 2003b, Bowen *et al.,* Bowen *et al.,* Zanetti *et al.* 1997, Bowen *et al.* 2010b). However, the latter appear in imaging and pathological studies only and none to date have been reported in any non-pathological cadaveric human dissection works.

2.3.3.2 Hypertrophied synovial FFB

Bossley *et al.* (1980), among other authors, propose that anatomical bursae may become hypertrophied with excessive protrusion either dorsally or plantarly. Bossley *et al.* (1980), hypothesise that the synovial lining, proposed as common to all anatomical bursae (Hernandez *et al.* 1991, Bottger *et al.* 1998, Haller *et al.* 1988, Weston 1970b, Weston 1970a), may be susceptible to the processes of hypertrophy in a similar manner to the synovial tissues of MTP

joints in inflammatory joint disease (Scutellari and Orzincolo 1998, Awerbuch *et al.* 1982, O'Brien *et al.* 1997, Palmer 1995, Palmer 1970). Indeed, a number of authors have documented the presence of either an inner synovial membrane with projecting villi (Hernandez *et al.* 1991), or a fibro-collagenous membrane present with some superficial synoviocytic cellular elements, within anatomical bursae (Chauveaux *et al.* 1987, Meenagh *et al.* 2006).

Claustre *et al.* (1983), first explicitly report the possible association between hypertrophied IM FFB and RA specifically, a theory reinforced by the earlier work of Awerbuch *et al.* (1982) who demonstrated 20% (N=10) of RA patients to have histopathological changes within the synovial bursae consistent with inflammatory disease. Interestingly, the histopathological works by Koski *et al.* (1998) (N=25) identified 14 RA patients with inflamed IM FFB (bursitis), 8 with associated inflammation within the adjacent synovial tissue structures, thus 6 with inflammation local to the FFB only and no instances of inflammation in adjacent structures without the involvement of FFB. This is reinforced by the FFB findings of Scutellari *et al.* (1998) and Harper *et al.* (2003), in their studies of retrocalcaneal bursae, whereby bursitis is present in isolation. Despite this, the rationale for bursae affectation remains unclear.

Of note, the presence of connective tissue or integrated fibrosis appears to be as frequently reported as that of synovium (Chauveaux *et al.* 1987, Meenagh *et al.* 2006, Hernandez *et al.* 1991). Bossley *et al.* (1980) describe the bursal wall as often showing fibrinoid necrosis (in conjunction with lymphocytic infiltration). Perhaps, as both Palmer *et al.* (1995) and Reed *et al.* (1973) suggest, the distinction between rheumatoid nodules and hypertrophied synovial/fibrous lesions is less clear than initially thought in this population. Alternatively, Reed *et al.* (1973) propose links between the pathogenesis of vasculitic disease in RA and bursal lesion development, documenting hypertrophied synovial/fibrous FFB as being closely associated with the localised vasculature via hyalinised fronds. However, 38 years on, no further authors have documented this phenomenon.

Jahs *et al.* (1972) suggest that the frequently reported fibrosis is an additional traumatic response of anatomical bursae generated by chronic external compressive/torsional forces or inflammation. Both Alexander *et al.* (1987) and Coackley *et al.* (1994) hypothesise that distension of the DTML or adjacent ligamentous/tendonous structures, secondary to MTP joint deformity or inflammation respectively, causes attenuation of the bursal cavity, thus distorting the IM FFB. However the exact longitudinal cause and effect relationship between changes in forefoot structure has not been demonstrated to date and this does not appear to satisfactorily explain the hypertrophy previously demonstrated in the absence of other structural change. In contrast, Dedrick *et al.* (1990) hypothesises that IM FFB hypertrophy in RA exerts compressive force thereby distorting the neighbouring tissues and joints. Again, however, there is no longitudinal evidence to support this hypothesis. Conversely, the close integration between FFB

and fibrous or connective tissues has also led to the development of an entirely alternative hypothesis for the generation and hypertrophy of FFB.

2.3.3.3 Biomechanical FFB

A number of authors propose that a subset of bursae are generated following biomechanical irritation (Aguiar *et al.* 2005, Claustre *et al.* 1983, Meurman 1982, Studler *et al.* 2008). For example, Ahmed *et al.* (1994) report the development of biomechanical bursae at the socket interface in four below knee amputation patients. In such instances biomechanical bursae are often referred to as advantageous, allowing compression or torsion between otherwise densely fibrous rigid tissues. The proposed aetiology is mechanically induced separation of the fibro-collagenous tissues resulting in the accumulation of extra-cellular fluid in these spaces (Hernandez *et al.* 1991). Indeed, Ahmed *et al.* (1994) also note that with socket repositioning, the presence of bursae in two patients fully resolved. Studler *et al.* (2008) describe such bursae as slit-like cavities of fluid when observed within the forefoot, that manifest predominantly in areas of torsional stress and lack a synovial membrane.

Chauveaux *et al.* (1987) observe that the anatomical region in which biomechanical FFB are most frequently reported (inferior to the superior transverse IM ligament and superior to the DTML) is often referred to as the fibrous channel. It is hypothesised that the pathological changes within the local fibrous tissues of this region play an important role is the development of biomechanical FFB. The proposed pathological process is quite distinct from the hypertrophy of synovial tissue. The historical works of Scotti *et al.* (1957) appear to support this hypothesis, documenting evidence of fibrin within bursal cavities in this region. Additionally, the MRI work of Studler *et al.* (2008) (figures ten: a-c) appears to offer preliminary support for this hypothesis, demonstrating 90% of participants to have plantar fibrosis (>14mm), and 75% to have plantar FFB. The accompanying histopathological analysis supports these findings (figure ten: d).

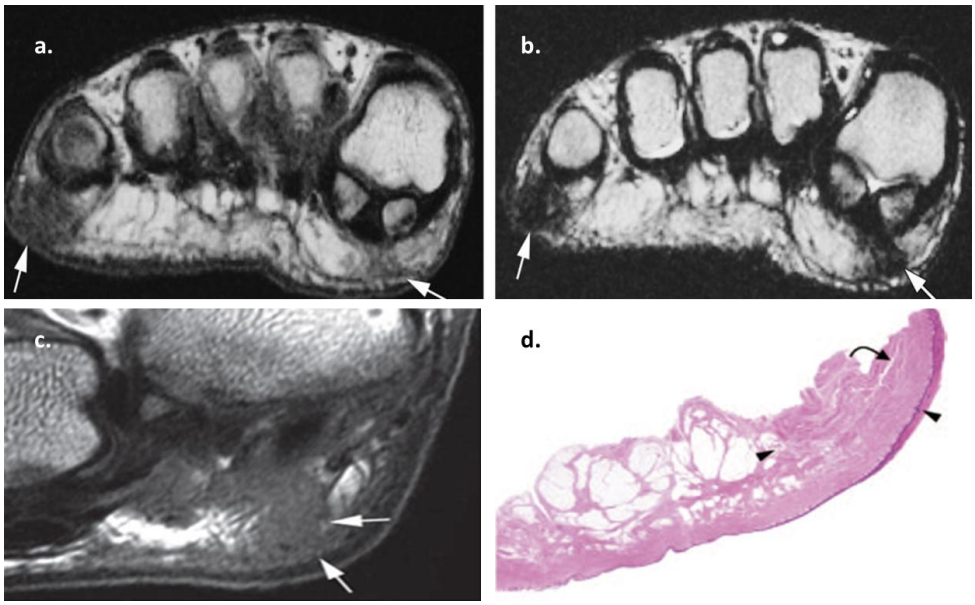


Figure 10: MRI & histological specimen comparison
Where figures 10a and 10b illustrate plantar fat pad signal alterations detected with MRI in a 35-year-old asymptomatic female; **(a)** Transverse T1-weighted image (400/15) showing continuous signal intensity alterations with blurred margins (white arrows) in plantar fat pad under the first and fifth metatarsal head regions of the right forefoot. **(b)** Transverse T2-weighted image (4500/119) showing similar signal intensity alterations (white arrows). Figures 10c and 10d illustrate the correlation between MRI findings and histological tissue sample removed plantar to the first metatarsal head region in a cadaveric specimen; **(c)** Transverse T1-weighted MRI (470/20) showing fat pad signal intensity alterations (white arrows) with blurred margins under the first metatarsal head. **(d)** Histopathologic specimen demonstrating fibrosis (arrowheads) and a slit-like cavity within collagen sheets that represents an adventitial bursa (black arrow), (Hema-toxylin-eosin stain, original magnification x 1) (Studler *et al.* 2008). *Images reproduced with the permission of Dr Studler*.

In a study of marathon runners (N=19), Lohman *et al.* (2001) similarly identified 68% of runners as having excessive fluid in the retrocalcaneal bursae. However, 53% of non-running healthy participants also had increases in bursal fluid volume. Perhaps therefore, the differing volume of bursae may be nothing more than a natural physiological characteristic. In pathological populations however, the presence of excessive fluid may inhibit an anatomical synovial bursa's mechanical function. For example, Canoso *et al.* (1988) discuss the inhibited movement of the rearfoot in a patient with inflammatory spondyloarthropathy, for whom the retrocalcaneal bursa has become hypertrophied, preventing the typical upward movement of the tongue-like projection of the plantar fat pad of the heel with ankle joint plantarflexion. Arguably, in such instances the hypertrophy may interfere with the mechanical role of the bursae, in contrast to generation of bursae to facilitate mechanical function. However, this poses the question of how one might differentiate between when a bursa, either anatomical synovial or mechanical, is advantageous or problematic.

2.3.3.4 Pathological FFB

Clinically, excessively hypertrophied FFB are considered to present symptomatically in most cases, as a sharp shooting pain, burning pain or the sensation of walking on marbles (Hertzler

1926, Iagnocco *et al.* 2001, Koski 1998). Associated visible plantar swelling, such as that shown in figure 11, has also been reported.

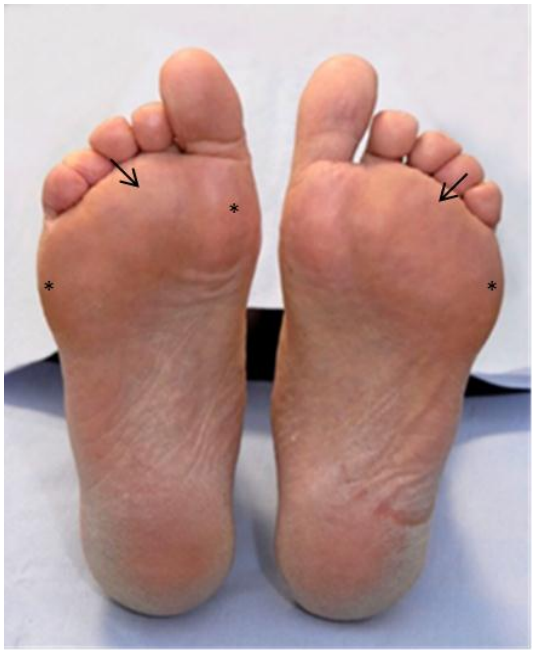


Figure 11: Plantar forefoot swelling in a patient with RA
Note the distal shift of the plantar fibro-fatty padding tissue with particular bulging distal to the second and third MTP joint regions bilaterally (black arrows). Large, fluctuant subcutaneous fluid-filled pouches are palpable plantar to the first MTP joint of the right foot and the fifth MTP joints bilaterally (black *). *Image author's own*.

In patients with RA, it is unclear to what extent FFB are pathological or just indicative of associated pathology. Furthermore it is unclear which particular FFB characteristics could result in an FFB being considered pathological.

A number of authors hypothesise that FFB are symptomatic because of their close association with the intermetatarsal neurovascular bundle, particularly in the region of common plantar digital nerve bifurcation in the IM 3-4 space (Zanetti *et al.* 1997, Awerbuch *et al.* 1982, Bossley and Cairney 1980, Chauveaux *et al.* 1987, McGlamery 1987). Awerbuch *et al.* (1982) reported 10 case-based symptomatic examples of close associations between neuroma and hypertrophied anatomical bursae (with histologically demonstrated synovial lining). Awerbuch *et al.* (1982) propose that the symptomatic development of a neuroma may be co-linear with increasing FFB volume, and that the resultant dorso-plantar pressure of the enlarged lesion contributes to reported pain. However, following excision of the neurofibrotic lesions, patchy de-myelination of the nerve tissue was evident in all cases (n=20) and was considered to be the primary symptomatic factor. Nissen *et al.* (1951) alternatively hypothesise that physiological damage to the nerve tissue is entirely secondary to bursal hypertrophy and inflammation. After extensive literature review, no further epidemiological studies of FFB to provide support or

counter-argument to these previously proposed hypotheses have been reported. As such, the symptomatic relevance of FFB remains unclear.

In contrast, Studler *et al.* (2008) suggest that plantar FFB are not associated with neuroma but instead are biomechanically mediated and occur advantageously. The FFB demonstrated by Studler *et al.* are located inferior to the superficial transverse IM ligament, and thus beyond the region of the neurovascular bundle. This may account for the asymptomatic presentation reported within the observed cohort, despite the reported high prevalence of bursa-like lesions. There is limited further evidence to support or refute the hypothesis that plantar FFB are adventitial and not pathological. Thus previous literature would appear to suggest that IM FFB are the most likely to be pathological, while plantar FFB may be indicative of biomechanical function but are themselves advantageous. Such hypotheses have not been definitively explored to date.

2.3.4 Identification

Within rheumatology, the traditional use of radiography to identify disease progression is being surpassed with the greater uptake of musculoskeletal ultrasound (US) and magnetic resonance imaging (MRI) (Cimmino 2008a, Cimmino *et al.* 2008, Meenagh *et al.* 2009, Suter *et al.* 2010). Both US and MRI have been shown to have improved efficacy of use relative to radiography in the determination and evaluation of early inflammatory arthritis (Cimmino 2008a, Brown 2007b, Joshua *et al.* 2007, katz *et al.* 2009, Meenagh *et al.* 2007, Szkudlarek *et al.* 2006). These modalities enable the imaging of soft tissue pathology, active inflammation and bone marrow oedema as well as changes within bone structure associated with RA progression (Varsamidis *et al.* 2005, Wakefield 2007). However, there remains a paucity of data regarding the intra and inter-rater reliability of image acquisition and interpretation for these modalities (Wakefield 2007, Koski 2006, Naredo 2006, Ostergaard *et al.* 2005b). Additionally there is scarce documentation of appropriate imaging techniques for the identification of FFB or other soft tissue lesions of the forefoot (Cimmino 2008a, Fessell and van Holsbeeck, Gregg *et al.* 2008, Iagnocco *et al.* 2001, Koski 1998, Bowen *et al.*). To date, there is no standardised method of identifying and characterising FFB in patients with RA. Bowen *et al.* (2009) have demonstrated that a number of clinically relevant FFB may be undetectable by clinical palpation alone and therefore the use of imaging techniques is warranted and development of robust methodologies required.

2.3.4.1 Musculoskeletal ultrasound

As noted by Wakefield *et al.* (2007), the uptake of US has been marred by a persistent paucity of data regarding the metric properties of US as an outcome measure in the evaluation of inflammatory disease. However, as shown in table six, while there is concerted international effort to address these issues, there are few studies to date demonstrating the use of US as a longitudinal evaluative tool. None the less, US-determined disease activity is emerging as an outcome measure, particularly in early disease or minimal disease activity (Cimmino 2008b).

Table 6: The development of musculoskeletal ultrasound as an outcome measure
Adapted from the findings of the OMERACT 7 and 8 working group for US (Wakefield 2007).

	Timeline	Event	
2004	OMERACT US SIG formed	The group was formed to address the metric qualities of US as a potential outcome measure in rheumatology (Wakefield 2003).	
2004	Systematic literature review	Highlighted deficiencies in the following areas	Intra-rater reliability
			Inter-rater reliability
			Inter-machine reliability
			Learning and teaching requirements
			Detecting and scoring synovitis
			Scanning protocol standardisation
2004	OMERACT agreement	Agreement that the OMERACT filter (incorporating truth, discrimination and feasibility) should be applied to developed US methodologies	
2004	Pilot pathology definitions agreed	Definitions by US findings for erosion, synovitis, tenosynovitis and enthesopathy agreed (Wakefield *et al.* 2005)	
2005-10	Intra/inter-rater reliability studies	Scheel (2005), (N=14): Good agreement with MRI (82%). Inter-rater reliability of foot and ankle low (kappa=0.28). Conclusion=standardised techniques required.	
		D'Agostino (2005), (N=17): Binary agreement good. Synovitis grading (0-3) had poor inter-rater reliability; attributed to lack of standardisation in scanning technique, particularly for semi-quantitative values.	
		Naredo (2006), (N=23): Good general agreement (kappa: 0.61-0.54), however, synovitis grading system and pathology definitions required	
		Cheung (2010), (N=35): Inter-rater reliability high, intra-rater reliability of image acquisition poor	
		Dougados (2010), (N=76): intra and inter-rater reliability grey-scale US high. Reliability of synovitis grading no better than clinical examination.	
2006	Efficacy of clinical use	Szkudlarek (2006), (N=60): US more sensitive, specific & accurate than clinical examination (kappa: 0.7, 0.78, 0.76 vs. 0.4, 0.85, 0.72 respectively, MRI=reference method)	
2006	US pathology definitions agreed	Final definitions agreed by expert consensus published (Wakefield 2007, Wakefield 2006).	Erosion: intra-articular discontinuation of bone surface apparent in 2 planes
			Synovial fluid: hypo or anechoic intra-articular material, compressible, without PD signal
			Synovial hypertrophy: hypoechoic non-displaceable, poorly compressible, may have PD signal apparent
			Tenosynovitis: hypo or anechoic thickened tissue, with or without fluid within the tendon sheath, apparent in 2 perpendicular planes, may have PD signal
			Enthesopathy: hypoechoic with loss of normal fibrillar architecture and/or thickened tendon or ligament at its bony attachment. May contain hyperechoic foci consistent with calcification, apparent in 2 perpendicular planes. May have

		PD signal, enthesophytes, erosion or irregularity at attachment.
2007	OMERACT synovitis scoring	OMERACT US group review synovitis scoring methodologies. Systematic review completed; highlighted lack of reliability and standardisation measures (D'Agostino *et al.* 2005, Taylor *et al.* 2004).
2007	OMERACT group meeting	Current status and research agenda formalised by OMERACT US SIG. To focus on US protocol standardisation (Wakefield 2007).
2009	OMERACT 9	Current status and research objectives reviewed. Further meeting documentation pending (D'Agostino *et al.* 2009).

Indeed, while the first report of the use of US in RA treatment evaluation was by Cooperberg in 1978 , the uptake of this modality as a routine methodology did not begin until the mid-late 1990s, with formal recognition only occurring in 2004. None the less, US is consistently reported to be advantageous in comparison to MRI due to its real-time imaging capabilities, chair-side accessibility, reduced scanning time, low acquisition cost and ability to simultaneously scan bone and soft tissues in grey-scale or with enhanced inflammatory feedback (Wakefield *et al.* 2008, Wakefield 2007, Szkudlarek *et al.* 2004, Cimmino 2008a, Grassi and Cervini 1998, katz *et al.* 2009). Comparative sensitivity, specificity and accuracy of US versus MRI range from 80-97% across various anatomical pathological details to 60-98% respectively, suggesting comparable clinical and research usage (Wakefield *et al.* 2008, Wakefield 2007, Szkudlarek *et al.* 2004, Cimmino 2008a, Grassi and Cervini 1998, katz *et al.* 2009).

A number of recent training recommendations for the use of US within rheumatological practice have been debated (Backhaus *et al.* 2001, Brown 2005, Brown 2006, Filippucci 2003, Filippucci 2007, Naredo 2008), although despite such proposals there remains no formal training route for rheumatologists or allied health professionals within rheumatology to date (Brown 2007a, Brown 2007b). However, Bowen *et al.* (2008) have demonstrated the efficacy of US use for the evaluation of forefoot structures by a podiatrist. Similarly, Riente *et al.* (2006) provide detailed documentation of a proposed scanning protocol for the foot and ankle. Thus, despite the well documented limitations, US use has potential efficacy in the evaluation of FFB in patients with RA, although careful demonstration of user reliability is required.

A particular challenge, consistently highlighted throughout the training literature, is that of tissue typing and structural recognition or differentiation (Bianchi *et al.* 2005, Ernst 1993, Gregg *et al.* 2008). As highlighted by Riente *et al.* (Riente *et al.* 2006) and Bianchi *et al.* (2005), this is particularly relevant to the complex anatomical structure of the forefoot. Classical grey-scale US appearances of joint structures demonstrate hyper-echogenicity at the bony margins due to the increased refraction of sound waves off the dense cortical bone, with hypoechoic joint centres (Cimmino 2008b, Hau *et al.* 1999). Comparative early and late pathological rheumatoid joint appearances are illustrated in figure 12.

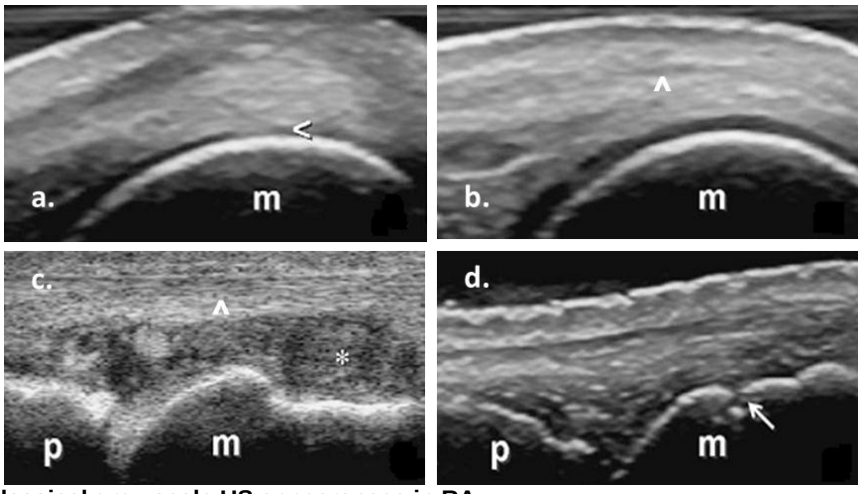


Figure 12: Classical grey-scale US appearances in RA
Where 12a and 12b illustrate right and left comparison of metacarpal head, with dorsal transverse linear transducer orientation, showing thinning of the cartilage layer (<), 12c illustrates synovial proliferation, with hypertrophy extending proximally from the joint cavity (*), with longitudinal linear transducer orientation over the second MCP joint, 12d illustrates an erosion of the metacarpal head <1 mm in size, with longitudinal orientation of the linear transducer. M=metacarpal head; p=proximal phalanx. *Images reproduced with permission from Professor Cimmino and the Journal of Best Practice and Research in Clinical Rheumatology (2008b).*

Such images demonstrate uniformity in acoustic feedback, where there is homogeneity across the cortical bone surface, despite marginal cartilage loss (figure 12a; <), erosion (figure 12d; white arrow), or throughout the fibrillar superficial tendon structures, despite small linear fissuring (figure 12b and c; ^) (Cimmino 2008b, katz *et al.* 2009, Ernst 1993). However, with inaccurate transducer orientation complications such as anisotropy (excessive acoustic feedback), shadowing (altered signal loss due to changing tissue densities) or ghosting (refracted non-perpendicular sound waves giving the false appearance of the presence of hyperechoic tissues) can occur (Hau *et al.* 1999, Gregg *et al.* 2008, Riente *et al.* 2006). User techniques such as transducer non-perpendicular orientation or 'heel-toeing' (the rocking of the transducer to displace soft tissues) may be used beneficially to enhance tissue recognition (Riente *et al.* 2006). It is also recommended that real-time dynamic imaging and tissue compression are used to improve US scanning specificity (Riente *et al.* 2006, Jousse-Joulin *et al.* 2010). Tissues such as the plantar flexor digitorum brevis tendons (appearing as fibrillar structures with or without superficial acoustic shadowing) or fibrous tissue around the neurovascular bundles (a complex anechoic mass with regions of hyperechogenicity consistent with non-pathological nerve tissue) are particularly susceptible to user error, making the clear diagnosis of FFB challenging (Riente *et al.* 2006, D'Agostino *et al.* 2005, Falsetti *et al.* 2006, Gregg *et al.* 2008). In these instances the use of real-time dynamic imaging for the assessment of compressibility may also improve diagnostic accuracy.

Furthermore, there are few textual references clearly depicting the US presentation of FFB. Iagnocco *et al.* (2001) demonstrate grey scale comparison of FFB and neuroma (figure 13)

however, the image quality in the printed text is poor and structural differentiation is challenging. Furthermore, FFB have not been included within the agreed depiction of structures by the EULAR/OMERACT expert consensus panel (Wakefield 2003).

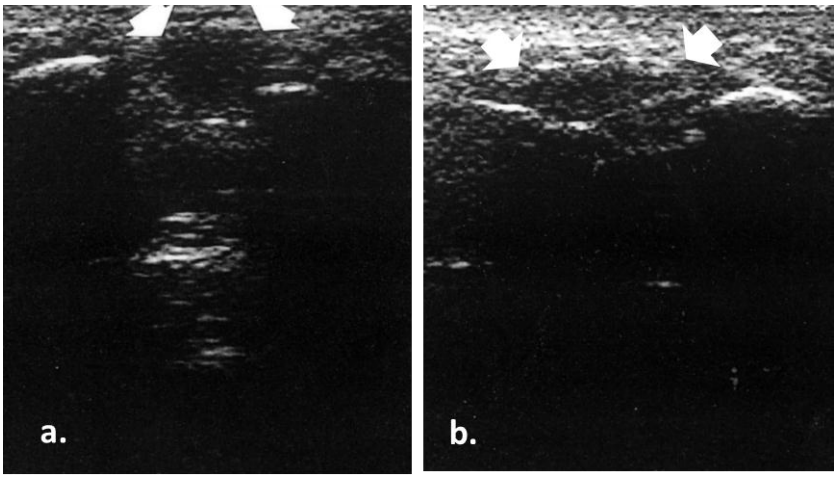


Figure 13: US appearance of an intermetatarsal neuroma & bursa
Where 13a illustrates a grey-scale transverse linear scan from the plantar aspect with identification of a centralised hypoechoic mass (neuroma is indicated by the white arrows) between metatarsal heads, 13b illustrates a grey-scale transverse linear scan from the plantar aspect with identification of a non-homogenous, anechoic signal (bursa is indicated by the white arrows) between metatarsal heads. *Images reproduced with permission from Professor Iagnocco and the Journal of Rheumatology (Iagnocco et al. 2001).*

Koski *et al.* (1998) summarise the commonly reported differentiating characteristics of US detectable FFB, whereby identification of a compressible mass with anechoic central body during dynamic imaging is reported as a key diagnostic feature. However, echoed throughout much of the imaging literature is the need for continued training to allow reliable dynamic differentiation of anatomical structures and clear characterisation of the tissue of interest a priori (Brown 2006, Cimmino 2008b, Filippucci *et al.* 2006, Naredo 2008, Taggart 2006, Valentin and Jager 2003). Thus, for the purposes of this thesis and in accordance with published recommendations, US detectable FFB will be declared present if:

- A hypoechoic discontinuation (with or without an anechoic centre), within the homogenous intermetatarsal or plantar fibro-fatty tissue is observed in two perpendicular planes.

Where FFB extend across multiple joint regions, the region containing the largest volume of FFB in the transverse scanning plane will be noted as the primary location, as recommended by Chauveaux *et al.* (1987). Additionally, given the complexity of classification, the appearance and association of FFB with adjacent structures will be noted, however FFB will not be classified at the data collection stage.

2.3.4.2 Magnetic resonance imaging

Unlike US, MRI has been considered the gold standard imaging modality for much of musculoskeletal medicine since its advent (Hornak 1996, Suter *et al.* 2010, Ostergaard and Szkudlarek 2003). The gold standard label is arguably given because of the ability of MRI to provide detailed, multi-planar, anatomical images which allow differentiation and characterisation of the tissues under scrutiny (Ostergaard *et al.* 2005b). As demonstrated in table seven (a), the development of MRI as a diagnostic tool within rheumatology is marked by the ability of MRI scans to both differentiate and characterise adjacent tissues. A large proportion of the literature pertaining to the use of MRI within rheumatology focuses upon systematic tissue differentiation or the development of the 'rheumatoid arthritis magnetic resonance imaging score' (RAMRIS) (Ostergaard *et al.* 2005a, Ostergaard *et al.* 2003). Only in recent years have longitudinal evaluations of MRI efficacy in inflammatory disease been reported.

Conversely, the chronological literature documenting the application of MRI to the study of the foot, summarised in table seven (b), demonstrates an altogether different trend; the focus of this research appears to be the identification of a single pathology and its diagnostic criteria. To date, no tools or systematic scoring methods have been proposed for use in the foot. However, Baan *et al.* (2011) have reported user reliability when applying RAMRIS to the foot joints.

Table 7a: The development of magnetic resonance imaging in RA

Timeline		Article type	Event
1998	Scutellari (1998)	RA evaluation	MRI reported as useful in the differentiation of synovial fluid from inflammatory pannus in RA soft tissue pathology
1999	Weishaupt (1999)	Diagnosis	MRI reported to provide good tissue differentiation in RA
2003	Ostergaard (2003)	Tool	OMERACT-RAMRIS tool proposed: initial core set of sequences and definitions are published which detail a methodological approach to MRI use in RA
	Conaghan (2003)	Tool	RAMRIS proposed: inter-rater reliability of the tool published
	Lassere (2003)	Tool	RAMRIS MCP inter-rater reliability published
2004	Ostergaard (2004)	*Review*	*Review:* value of MRI in peripheral joint exam; MR is beneficial in RA *Review:* the validity of imaging synovium – MR is proposed as the gold standard modality
2005	Conaghan (2005a)	Tool	RAMRIS: image atlas specific to the hand published
	Woertler (2005)	Diagnosis	Appearances of soft tissue masses on MRI characterised
	Ostergaard (Ostergaard *et al.* 2005a, Ostergaard *et al.* 2005c)	Tool	OMERACT-RAMRIS: introduction to the associated image atlas for the wrist and MCP joints *Review:* update on research priorities
	Haarvardsholm(2005)	Tool	RAMRIS: sensitivity to change analysis completed – determined to be suitable for use in RA monitoring
	Conaghan (2005b)	*Review*	*Review:* MRI as an outcome measure – rigour in studies completed to date is reported to be of a poor standard

	Bird (2005)	Tool	OMERACT-RAMRIS; reliability of proposed scoring system published
	Ejbjerg (2005)	Tool	OMERACT-RAMRIS wrist specific score published
2008	Dohn (2008)	RA evaluation	Semi-quantitative MRI of the wrist in RA proposed
	Cimmino (2008a)	*Review*	*Review:* RAMRIS good tool, bone oedema strongest independent predictor of radiographic progression at two years
2009	Conaghan (2009)	Tool	OMERACT MRI inflammatory group meeting: future research priorities should include feasibility studies and the imaging of remission
	Duer-Jensen (2008)	Use	Use of extremity MRI: efficacy of use unclear
	Boesen (2009)	Use	Protocol guidelines for the semi-quantitative analysis of MRI in RA
	Haavardsholm (2009)	RA evaluation	MRI shown to be a highly responsive method of determining biologic treatment effect in RA
	Katz (2009)	*Review*	*Review:* MRI 3D volumetric measures may be a useful outcome measure
	Kubassova (2010)	RA evaluation	Semi-quantitative MRI use in the evaluation of synovitis
	Machado (2010)	UIA evaluation	3E initiative launched: review and expert consensus regarding the investigation and follow-up of UIA.
	Boyesen (2011)	RA evaluation	Comparison of evaluative modalities: MRI is superior to other imaging modalities and serological markers of disease state in the evaluation of RA activity
2010	Suter (2010)	*Review*	*Review:* a lack of good research to support the use of MRI as either a diagnostic or prognostic tool in RA is reported

Table 7b: The development of magnetic resonance imaging of the foot & ankle

Timeline		Article type	Event
1994	Schweitzer (1994)	Diagnosis	MRI use proposed for tendon pathology evaluation in the foot and ankle
1997	Zanetti (1997)	Diagnosis	MRI use proposed for forefoot neuroma detection – demonstrated to be a highly accurate tool when validated with histology
	Stiskal (1997)	Diagnosis	MRI use proposed for chronic heel pain evaluation – patients with RA all had retrocalcaneal bursitis and no tendon abnormalities
	Forslind (1997)	RA evaluation	MRI in early RA: MRI of fifth MTP joint showed earliest detectable structural change, therefore MRI of the forefoot proposed as highly efficacious in patients with RA
1999	Kainberger (1999)	*Review*	*Review*: imaging the foot with MRI
2001	Theumann (2001)	Diagnosis	Detailed account of MRI findings in the forefoot of non-pathological feet – documentation of forefoot bursae verified with histological samples
	Ashman (2001)	Diagnosis	MRI protocol guidelines for the differential diagnosis of forefoot structures proposed
2003	Boutry (2003a)	Diagnosis	Common MRI findings in the hands and feet: FFB noted as common
	Maillefert (2003)	Diagnosis	MRI of hind foot in RA: criteria for synovitis identification proposed
	Mohana-Borges (2003)	Diagnosis	MRI and Bursography: MRI good for differentiating between structures
2004	Ostergaard (2004)	*Review*	*Review:* value of MRI in peripheral joint exam: MR is beneficial in RA *Review:* the validity of imaging synovium – MR is proposed as the gold standard modality

	Ostendorf (2004)	RA evaluation	MRI revealed RA activity in the forefoot but not the hands – recommends the forefoot is included in clinical evaluation of RA disease
2005	Falsetti (2006)	Diagnosis	Imaging the heel in RA: comparison of MR and PD-US; PD-US determined to have better clinical utility
2008	Wakefield (2008)	Diagnosis and use	Optimal assessment of the rearfoot with MRI: MRI used as reference modality - reader variability highlighted as an important consideration
	Gregg (2008)	Diagnosis	MRI of metatarsalgia: MRI reported to be a highly valuable tool, with good differentiation between anatomical structures and areas of inflammation
	Bancroft (2008)	Diagnosis	Methodological considerations for imaging soft tissue lesions in the foot
2011	Baan (2011)	Tool	RAMRIS can be reliably applied to the foot

The use of MRI for the identification of FFB has been reported by only a few authors (Gregg *et al.* 2008, Narvaez *et al.* 2002, Boutry *et al.* 2003a, Boutry *et al.* 2005, Studler *et al.* 2008) and there is currently no standardised protocol or technique for doing so. Despite this, MRI has provided useful insight regarding the contentious area of FFB characterisation; authors such as Mohana-Borges *et al.* (2003) and Studler *et al.* (2008) have both accurately demonstrated MRI determined FFB which are consistent with concomitant anatomical or histological examination respectively (figure 14).

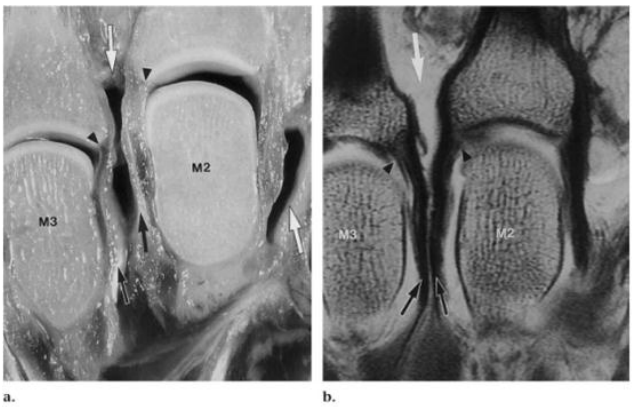


Figure 14: Imaging and anatomical section comparisons
Correlation between anatomical section **(a)** and MRI **(b)** findings in the transverse plane at the level of the metatarsal heads (M1-M3 depicted), in a cadaveric foot **(a)** 3mm thick gross anatomic section and **(b)** combined MR arthrographic and bursographic T1 weighted spin echo MR image (500/12) showing the phalangeal attachment of the main collateral component of the collateral ligament complex (arrowheads). The interosseous tendons (black arrows) insert further into the phalangeal bases and border the collateral ligament complex. Note the intermetatarsal bursa (white arrow) between the interosseous tendons, with leakage of the contrast agent in 14b**.** *Images reproduced with permission from Mohana-Borges et al. (2003)*.

Boutry *et al.* (2003a) clearly describe the hypertrophied synovium of intermetatarsal bursae (figure 15). Interestingly Chauveaux *et al.* (1987) demonstrated in eight patient cases, that injection with a contrast medium highlighted direct communication between the bursal cavity of interest and the MTP joints, a presentation quite distinct from that shown by Boutry *et al.*

(2003a). However, despite disagreement between the reported findings both authors conclude that there are distinct anatomical variations in position, physiology and associated characteristics of FFB.

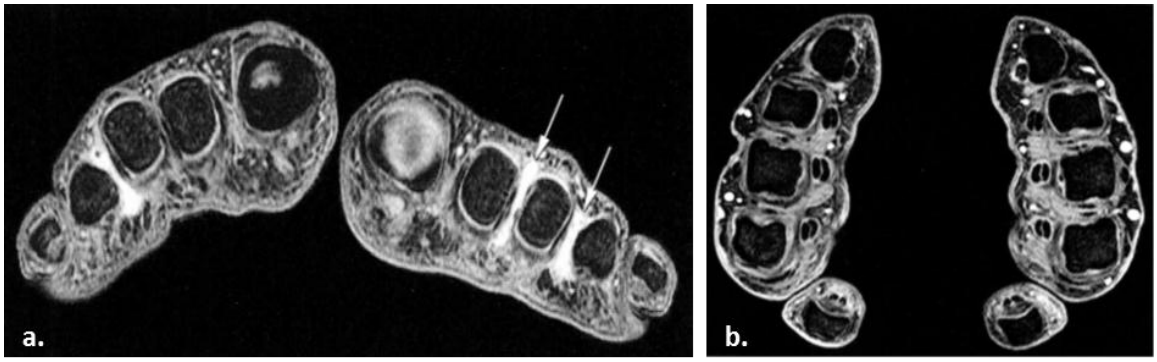


Figure 15: MRI appearance of forefoot bursae in patients with RA
Where 15a illustrates an axial, fat suppressed, gadolinium enhanced, three-dimensional, FLASH MR image of MTP joints in a 45-year-old man with early RA, revealing bilateral intermetatarsal bursitis (arrows). It is also noteworthy that no abnormality was found in the wrists (15b). *Images reproduced with permission from Boutry et al. (2003a).*

In contrast, Studler *et al.* (2008) clearly detail the fibrotic changes associated with plantar metatarsal bursae (figure 16). Such lesions are reported as distinct masses, occurring plantar to the inferior aspect of the deep transverse intermetatarsal ligament, with a fluid element encapsulated within an enhancing fibrotic mesh.

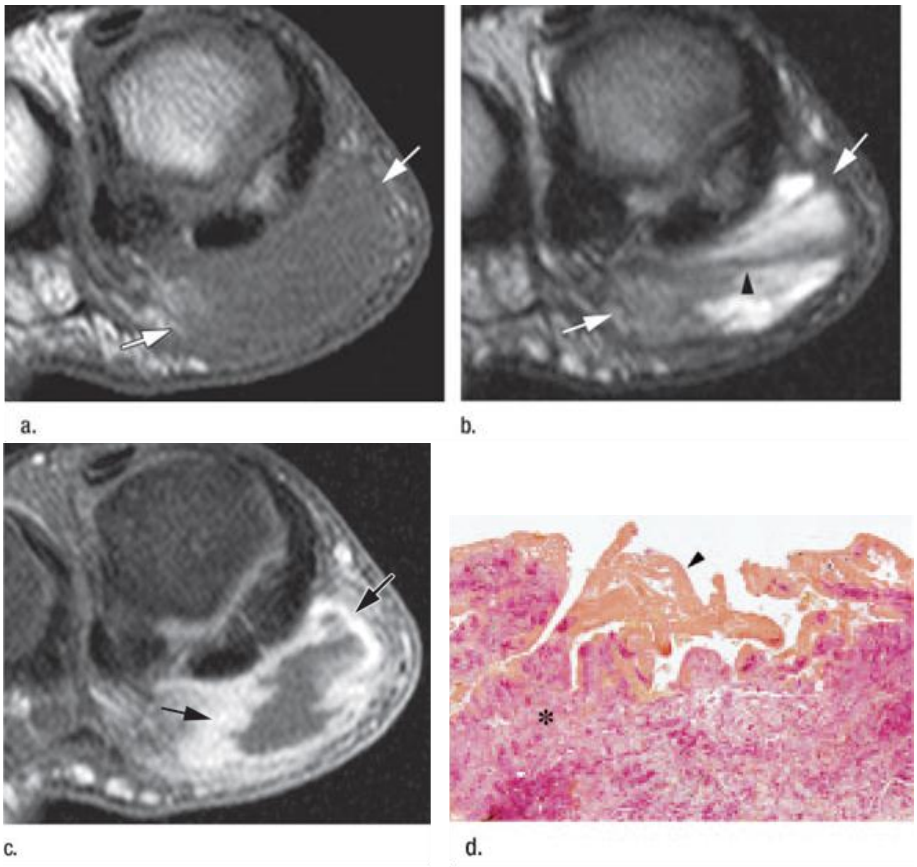


Figure 16: Plantar fat pad signal alterations with MRI and histological comparison
MRI findings of plantar fat pad signal alterations in a 59-year-old symptomatic male. Where 16a illustrates a transverse T1 weighted image, (600/15), showing a signal intensity alteration (white arrows) with indistinct margins in the plantar fat pad beneath the first metatarsal head region of the right forefoot. On a T2 weighted image (figure 16b), (4500/96), the majority of the signal intensity alteration (white arrows) is hyper-intense. Band-like structures of low signal intensity (black arrowhead) are apparent within the fat pad alteration. 16c illustrates a T1 weighted, contrast enhanced, fat suppressed image (735/15), showing peripheral enhancement (black arrows). 16d is a photomicrograph of a histological specimen showing fibrous collagen bundles (black *). Within the cavity, fibrin-lined papillary projections (black arrowhead) are seen and correspond to the band-like structures in image 16b. (Elastin-van Gieson stain; original magnification x 32). *Images and annotation reproduced with permission from Studler et al. (2008).*

The aetiology and clinical importance of differences in FFB tissue characteristics remains unclear. However MRI does appear to offer a potential method of further FFB epidemiological study. MRI has potential to provide an observer-independent, multi-planar, reliable and valid method of characterising FFB in patients with RA.

Characterisation of tissues is achieved by translating the different magnetic properties of tissue into differing radio frequency signals (Hornak 1996). These are subsequently Fourier transformed to generate grey scale images (Hornak 1996). The principles underpinning image generation are of particular relevance to this thesis, where the manipulation of magnetic fields is of paramount importance to the resultant accurate characterisation of FFB; the relaxation properties of excited hydrogen nuclei in water (for example bursal fluid) and lipids (for example plantar adipose tissue), after alignment using large magnetic field gradients which orientate the precessing isocromats to be either parallel (longitudinal magnetism) or antiparallel (transverse

magnetism) to the B0 axis, generate the signal to be Fourier transformed into an image (figure 17) (Hornak 1996).

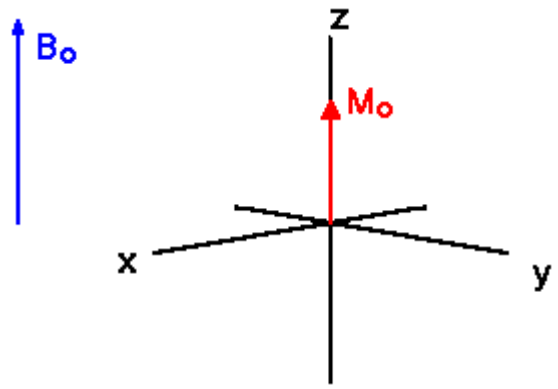


Figure 17: MRI T1 processes
Where x/y/z = orthoganol field gradients; Mo = equilibrium of magnetisation within the rotating frame (perspective of isocromat orientation); Bo = orientation of overall magnetic field. *Image reproduced with permission from JP Hornak (1996).*

The strength of the magnetic field gradients (Tesla), in addition to the magnitude, number and length of secondary magnetisation (radio frequency pulse) and length of relaxation time (longitudinal: T1 and transverse: T2) will therefore all lead to differences in the generated image contrast (Lisle 1996). The image contrast can be adjusted by changing the flip angle (direction of RF pulse), time of applied magnetisation, or number of applied pulses (Lisle 1996). This will re-orientate the precessing isocromats, and thus the signal generated by their return characteristics towards B0 is altered (Lisle 1996). Image contrast is therefore a result of TR/TE relaxation parameters (figure 18), and importantly an increased flip angle will improve tissue differentiation but will take longer and therefore there will also be more signal decay and loss of image clarity (Hornak 1996, Reiser *et al.* 2008).

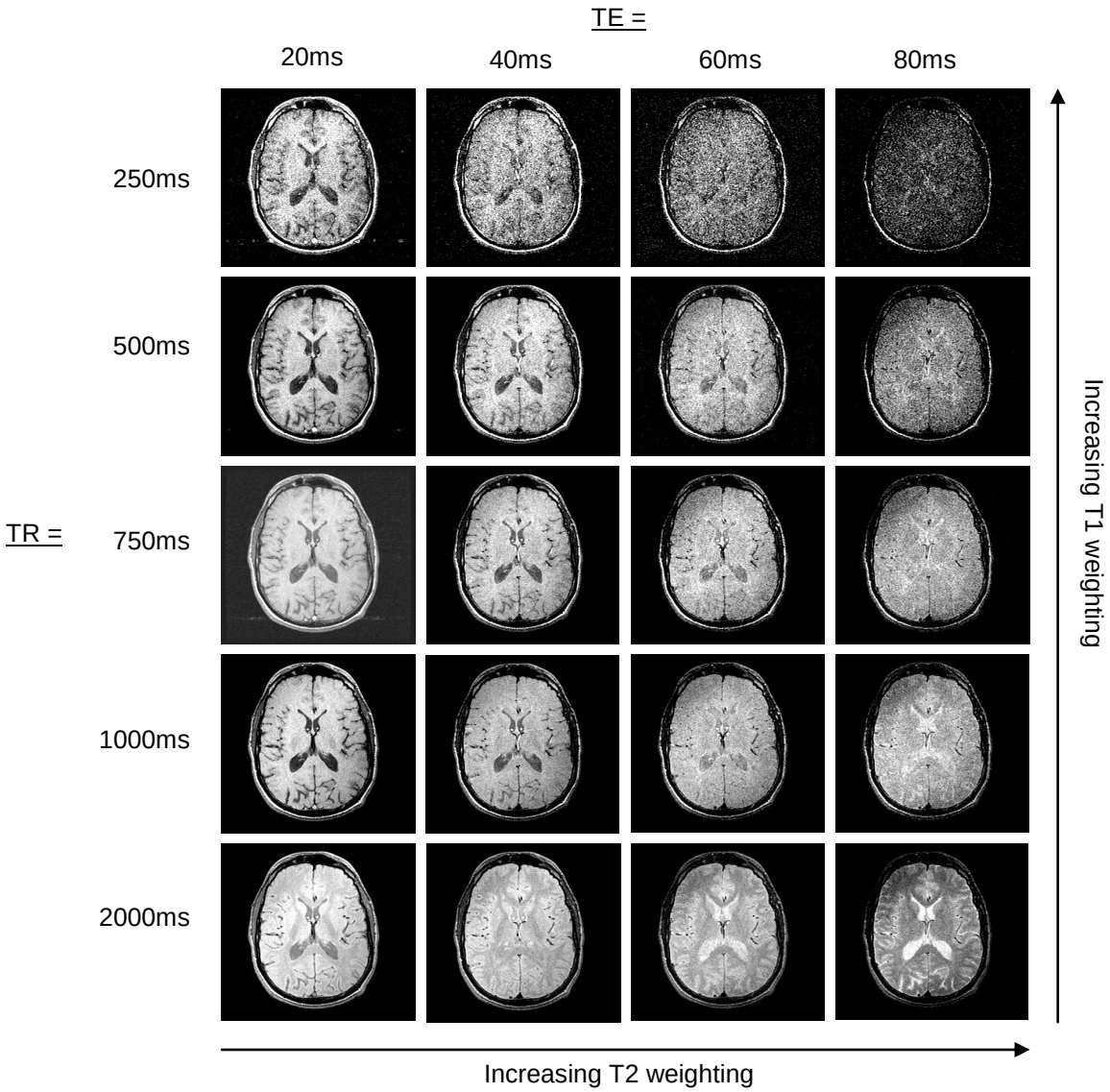


Figure 18: MRI TR/TE relaxation ratios & image contrast
Where TR=Relaxation time; TE=Echo time; T1=Longitudinal magnetisation; T2=Transverse magnetisation.
Image reproduced with permission from JP Hornak (1996).

The differing response rate of tissues to magnetisation, because of their variable hydrogen content, improves image contrast (Hornak 1996). In the case of FFB characterisation, a good sequence of images will therefore be selected in order to show sharp anatomical detail (avoiding excessive signal decay), the presence/absence of inflammation, the presence/absence of fluid, and differentiation between synovium and fibrous tissue. To date, there is no standardised definition of MRI-detected FFB and as such, for the purposes of this thesis, a fluid collection was defined as:

- A homogeneous hyperintense mass with fluid-equivalent signal on pd/T2 sequence and homogenous hypo-intensity in contrast to true 'mass' defined as non-fluid equivalent/intermediate signal on T1 and T2.

Differentiation between fluid/fibrous intermetatarsal lesions and neuroma was determined primarily by anatomical location, in addition to review of lesion margins and T1/T2 characteristics as above.

2.4 Summary

RA is a systemic, complex disease affecting multiple body tissues and organs that has a significant impact on the lives of patients and their families. The disease is typified by painful swelling and deformity of the joints of the hands and feet. However, the exact epidemiology of RA foot complications is unclear and under-reported in comparison to those of the hand. None the less, there is a growing body of evidence highlighting the epidemiology of foot problems in this patient group. Furthermore, evaluation of the presence of disease activity within the foot may help inform the new therapeutic target of complete remission from RA disease. In particular forefoot bursae have recently been highlighted as associated with RA disease activity and as potentially clinically relevant based upon cross sectional study. However, the natural history and longitudinal clinical importance of FFB in patients with RA remains unclear. Furthermore the biological mechanisms by which FFB are clinically relevant requires further investigation. This could improve the targeting of future intervention strategies. There is currently a clinical need for a user-independent, reliable and valid method of identifying and characterising potentially pathological and non-pathological FFB. There is confusion within the current literature regarding the exact epidemiology, aetiology and clinical importance of FFB in patients with RA. Further investigation of this area is warranted in order to inform future treatment strategies.

2.5 Research aim & hypothesis

This thesis aims to utilise novel US and MRI imaging techniques to determine the epidemiology and clinical importance of FFB in patients with RA. The four experimental studies completed as part of this thesis will: 1) contribute to the current understanding of the clinical importance of US-detectable FFB, 2) contribute to the current understanding of the biological mechanisms by which US-detectable FFB are clinically relevant, 3) provide a robust tool for the identification, characterisation and evaluation of pathological FFB, and 4) contribute to the current understanding of which FFB are pathological and why, providing an evidence-based framework for future clinical intervention. The research hypothesis central to this thesis, and underpinning the basis of study, is therefore:

- H_1: ‘FFB are clinically relevant in patients with RA’
- H_0: ‘FFB are not clinically relevant in patients with RA’

The main research question is thus:

What is the epidemiology and clinical importance of forefoot bursae in patients with rheumatoid arthritis?

Chapter three

Methodology

3.0 Introduction

The preceding chapter has identified an area of unmet clinical need in patients with rheumatoid arthritis (RA) who experience foot complications. The literature review completed has identified forefoot bursae (FFB) as a potential clinically relevant factor in the development or propagation of foot complications in this patient group. However, to date little is known about the longitudinal epidemiology, aetiology and clinical importance of FFB in patients with RA. This chapter therefore discusses the philosophical approach and research methodology used in the four experimental studies that form this thesis, the overall aim of which was to determine the epidemiology and clinical importance of forefoot bursae in patients with RA.

In order to achieve the main study aim a series of four experimental studies were completed. The methods for the completion of the experimental studies were thus designed to address the following objectives: 1) to describe the natural history of musculoskeletal ultrasound (US) detectable forefoot bursae (FFB) over a three-year period in patients with RA (Chapter four), 2) to describe and compare the presence of US-detectable FFB between patients with RA, OA and healthy individuals (Chapter five), 3) to create and evaluate a novel MR imaging methodology for use in the identification of FFB in patients with RA (Chapter six) and 4) to determine the clinical importance of MR detectable FFB in patients with RA (Chapter seven).

3.1 Main thesis aim & objectives

The main aim of the thesis was to determine the epidemiology and clinical importance of forefoot bursae in patients with rheumatoid arthritis (RA). The main objectives were thus:

1. To determine the natural history and clinical importance of US-detectable FFB in patients with RA (Chapter four)
2. To explore the relationship between US-detectable FFB and inflammation or biomechanical impairment in patients with RA (Chapter five)
3. To determine the reliability and validity of a novel MRI-based score for the identification and characterisation of FFB in patients with RA (Chapter six)
4. To determine the epidemiology and clinical importance of MRI-detectable FFB in patients with RA (Chapter seven)

3.1.1 Rationale for overall study design

A positivistic philosophical approach to this work was adopted (Giddings and Grant 2007, Silman and Hochberg 2001, Segura del Pozo 2006). As such, a prospective cohort study design was selected as the main methodological approach. Subsequently the methodologies developed are

reductionist in nature and grounded within a quantitative analytical approach, to facilitate the objective exploration of observed phenomena.

A step-wise pragmatic determination of the appropriate methodology was used, following the algorithm outlined in table eight. Arguably the majority of this work is based within the field of epidemiology (the study of the distribution of disease and its determinants) (Silman and Macfarlan 1995), and thus may be considered inductive. However, the methodological design is such that the research hypotheses may be tested, and therefore the completed research can be considered as deductive. None the less, it is anticipated that a substantial contribution of this work may be towards theory generation via the determination of disease occurrence and associated factors in a sequence of four novel experimental studies.

Table 8: Methodological design
Considerations in epidemiological research design (Silman and Macfarlan 1995).

Consideration factor	Example
Study design	What is the question posed – what type of study can best answer the question and is most practicable?
Population selection	Who should be studied? How many should be studied?
Information gathering	How should the information be obtained? Is the information obtained correct? Is the method used to obtain the information consistent?
Analysis	How should the data gathered be prepared for analysis? What are the appropriate analytical methods?
Interpretation of results	Can any associations observed be explained by confounding? Are the results explained by bias? Are the results generalisable?
Logistics	Is the research ethical? Is the research affordable?

3.2 Study specific research aims, objectives & methodological designs

To achieve the overall thesis aim a series of four experimental studies were completed:

Experimental study one: The main aim of this study was to determine the natural history and clinical importance of FFB in patients with RA. To achieve this aim the following objectives were set:

1. To determine the natural history of US-detectable FFB over three years
2. To describe potential differences in the US characteristics of identified FFB
3. To determine the clinical importance of US-detectable FFB

Experimental study one is a longitudinal, prospective three year follow-up study of US-detectable FFB, in a known cohort of patients with rheumatoid arthritis, for whom baseline and year-one follow-up phenotypic data have previously been collected (Bowen *et al.* 2009, Bowen *et al.* 2010c, Bowen *et al.* 2010b).

Experimental study two: The main aim of this study was to explore the potential relationship between US-detectable FFB and inflammation or biomechanical impairment in patients with RA. To achieve this aim the following objectives were set:

1. To compare the prevalence and distribution of US-detectable FFB between patients with medial knee osteoarthritis (OA), as a surrogate biomechanically impaired patient group, and healthy volunteers (HV)
2. To compare the prevalence and distribution of US-detectable FFB between patients with Rheumatoid arthritis (RA), as a surrogate inflammatory and biomechanically impaired patient group, and HV
3. To compare the prevalence and distribution of US-detectable FFB between patients with RA and OA
4. To explore the potential relationship between FFB distribution and biomechanical impairment or inflammation

Experimental study two is a comparative, cross-sectional, observational study of US-detectable FFB in participants with RA, OA or HV.

Experimental study three: The main aim of this study was to determine the reliability and validity of a novel MRI-based score for the identification and characterisation of FFB in patients with RA. The following study objectives were set:

1. To complete an iterative process of MRI-based semi-quantitative score design: development of the *FFB-Score*
2. To collate an *FFB-score* reference image atlas
3. To determine the reliability and validity of the *FFB-score*

Experimental study three utilises a collaborative process of score design by a team of rheumatologists, radiologists, and a podiatrist from centres within the UK and Germany. A cross-sectional cohort study design was used, with repeated MRI data generation by multiple readers.

Experimental study four*:* The main aim of this study was to determine the epidemiology and clinical importance of MRI-detectable FFB in patients with RA. To achieve this aim the following objectives were set:

1. To determine the prevalence of MRI-detectable FFB
2. To describe differences in the MRI characteristics of identified FFB
3. To determine the clinical importance of MRI-detectable FFB in patients with RA

Experimental study four is a cross-sectional observational study of MRI-detectable FFB in patients with RA.

The overall contribution of each experimental study towards the main thesis aim was subsequently considered in the final discussion chapter.

3.3 Ethical considerations & research governance

Southampton University Hospitals NHS Trust (SUHT) agreed sponsorship of all patient related studies in May 2009 (see appendix section A1). Professional indemnity insurance was also granted at this time (see appendix section A1). The programme of work was accepted onto the NIHR portfolio register in June 2009. The study was also registered with the UK central research network at this time in accordance with the declaration of Helsinki of the World Medical Association (2008), and reported on the central research network database. Full ethical approval for the program of work entitled 'The clinical importance of forefoot bursae in patients with rheumatoid arthritis' was obtained from the South Central Local Research Ethics Committee (B) in August 2009 (see appendix section A2). The study was accepted for completion within the Wellcome Trust Clinical Research Facility (WTCRF) in August 2009. Full approval from the local research and development department within SUHT was obtained in December 2009 (see appendix section A3). Approval for the additional completion of MRI works, reported in experimental studies three and four, was sought from the South Central Local Research Ethics Committee (B) and granted in December 2010 subsequent to the submission and approval of a substantial amendment request (see appendix section A3).

The University of Southampton agreed sponsorship of the study entitled 'The prevalence of forefoot bursae in healthy volunteers' in July 2011 (see appendix section A1). Ethical approval for this study was granted in July 2011 by the University of Southampton, Faculty of Health Sciences ethics committee (see appendix section A2). Insurance for the study was granted by the University of Southampton research governance office in July 2011 (see appendix section A1).

3.3.1 Study specific considerations

The following were identified and acknowledged as potential ethical issues applicable to the experimental studies included within this thesis:

1. Human participants were required as part of this population based study, and therefore appropriate informed consent procedures were adhered to. The year-three follow-up study was dependent upon the use of a previous cohort within which gender inequality had been demonstrated. However, this inequality was considered to be reflective of the gender inequality present within this regional population.

2. Data collected contained sensitive personal information regarding patient care. However, only clinicians and researchers actively involved in the study had access to this information, which was anonymised and held in a secure cabinet on the hospital site or on encrypted hardware/software. Patient anonymity was observed in all publications arising from this study. All participants were seen within the Wellcome Trust Clinical Research Facility (WTCRF), in an individually dedicated consultation room.

3. There is currently no formal training route, with associated assessment of competency, in the use of US or MRI by allied health professionals. As such, it is possible that error or bias may have been introduced into the study results by poor acquisition or interpretation of the imaging data. To minimise this, the study researcher (LH) completed a series of nationally recognised training courses and a programme of supervised training (as recommended by the lead radiologist contributing to this work). Inter-rater agreement between LH and a previous investigator (for US) or experienced radiologist (for MRI) was established and further training completed until satistfactory agreement was demonstrated.

4. Previous studies have shown a risk of tissue damage with US use, although this is related to levels of exposure never used within clinical practice. To ensure patient safety, all US exposure was managed in accordance with 'ALARA' principles of use (Fitzpatrick *et al.* 1998).

5. In patients with poor renal function there is a known risk of nephrogenic systemic fibrois associated with the use of gadolinium-based contrast agents during the acqusition of MR images. The renal function of all participants was screened prior to the undertaking of the MRI data collection, in line with MHRA guidance (MHRA 2007). All participants were also screened for additional contra-indications to MRI prior to final recruitment.

6. It was possible that lesions other than those associated with rheumatoid arthritis may have been identified during image analysis of the forefoot. Such lesions were reviewed by a senior radiologist/ rheumatologist for their evaluation, action and further discussion with the patient where applicable. Identification of these lesions was not made apparent to the patient at the time of image acquisition. However, a subsequent imaging session was arranged in conjunction with clinical follow-up by other medical specialists if appropriate.

7. Participant involvement in this study provided no direct benfit or gain to any patient, although did facilitate the development of new knowledge, that is applicable to the larger rheumatological community. Participants were able to have layman access to the findings of this study at key stages of completion. Participant involvement or withdrawal from the study was fully discussed, optional at any time, and had no direct consequence to ongoing clinical care.

3.3.2 Consent

Formal consent to participate in a study was obtained in writing on the day of data collection (see appendix section A4). Prior to this, participants were issued with a written information sheet (see appendix sections A5 and A6), asked to consider their participation and encouraged to discuss this with a friend/family member. At the time of obtaining consent participants were given the opportunity to discuss any concerns or questions with the investigator. Participants were reminded at this time that withdrawal from the study was possible at any stage, for any

reason, and that this would have no adverse consequence to their ongoing rheumatological care.

3.3.3 Data coding, handling & storage

The NHS code of confidentiality was adhered to during recruitment, data collection, analysis, dissemination or any other activity pertaining to the conduct of this study. All participants were anonymised at the time of recruitment, using an alpha-numerical code that was used on all subsequent documentation. Access to the coding criteria was limited to the immediate research team. All data and anonymisation details were kept in a locked cabinet within the hospital site if in hard copy or on encrypted, password protected hardware/software in accordance with the Data Protection Act (1998). Access to confidential information was permitted only to recognised persons for monitoring/audit/quality assurance or research purposes. Access to patient medical records was required to facilitate the review of relevant medical information (for example past pharmacological therapy). Participants were advised of this and were asked to acknowledge this directly as part of the process of granting informed consent. The principal investigator for the study (LH) was nominated as chief custodian of all collected data.

3.3.4 Conflicts of interest

The PhD candidature completed in conjunction with this thesis was supported by a clinical doctoral research fellowship award from the National Institute of Health Research (NIHR). The epidemiological work completed in experimental studies one and two was supported by a research grant from the Southampton Rheumatology Research Trust. The MRI-based investigations completed in experimental studies three and four were supported by a project grant from Pfizer UK. No personal benefits of any form were or will be received from any commercial party as a consequence of direct or indirect association with this research.

3.4 Study population

The main study population that forms the focus of this thesis is a cohort of consecutively, prospectively recruited patients with rheumatoid arthritis (RA) who have contributed to the 'FeeTURA' programme of work from 2007–2011. Two additional participant groups, including those with medial knee osteoarthritis (OA) or healthy volunteers (HV) were also included in a comparative study, reported in chapter five.

3.4.1 Target populations & recruitment strategy

Experimental study one: This study is a longitudinal evaluation of patients with RA who have contributed to the 'FeeTURA' research project over three-years, for whom baseline and one-year follow-up data has been previously reported (Bowen *et al.* 2010c, Bowen *et al.* 2009). At baseline, patients with a consultant confirmed diagnosis of RA, (according to 1987 ACR criteria (Arnett *et al.* 1988)), attending a Southampton based outpatient rheumatology clinic, were prospectively, consecutively recruited to the study between July 2006 and January 2007. Patients were given information about the study at the time of their clinical appointment and

invited to contact the research team for further information or to declare their interest in participation. Participants who completed the baseline appointment were invited to return for subsequent year-one follow-up by way of letter of invitation. Participants who attended both baseline and year-one appointments were considered eligible for entry into the year-three follow-up study and again contacted by way of a letter of invitation and reply slip (see appendix section A6).

Experimental study two: This study is a comparative evaluation of patients with RA, medial knee osteoarthritis (OA) or healthy volunteers (HV). Those patients with RA who contributed to experimental study one, were also included within this study. Patients with a consultant confirmed diagnosis of medial compartment knee OA of Kellgren and Lawrence grade≥2, in at least one knee, were recruited from a known cohort who had previously participated in a trial of vitamin D supplementation (the 'VIDEO' study). Participants were originally consecutively, prospectively recruited to the VIDEO study from a population of patients attending a general rheumatology outpatient clinic in Southampton between December 2005 and April 2009. Participants from the VIDEO study were consecutively, retrospectively identified from those completing the final episode of data collection within the trial and invited to participate within this study by way of letter of invitation. Recruitment of patients with OA to this study was completed in phases, from December 2009 to December 2010, until the target sample size was achieved. Healthy volunteers were recruited from staff and students attending the University of Southampton between July 2011 and November 2011. Potential participants were informed of the study by way of poster displays which contained researcher contact information. Following receipt of an expression of interest the researcher contacted the potential participants to complete eligibility checks and arrange an appointment.

Experimental studies three and four: Those patients with RA who contributed to experimental study one, were eligible for screening to studies three and four. Eligible participants were invited to complete this study by way of letter of invitation and reply slip, and accompanying patient information sheet (see appendix sections A5 and A6). Upon receipt of the reply slip, participants were contacted by the researcher to complete final screening checks and to arrange an appointment.

3.4.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the patient groups contributing to this thesis were defined as follows:

Inclusion criteria

For RA participants, patients were included who:

- had a diagnosis of RA according to the ACR criteria
- were attending a SUHT rheumatology outpatients' clinic between Jul 2006 and Jan 2007
- took part in the baseline FeeTURA study

- were aged between 18-80 years at the time of initial recruitment into the previous baseline FeeTURA study

For OA participants, patients were included in who:

- had radiological evidence of early OA disease at medial tibio-femoral knee compartment (based upon a modified Kellgren and Lawrence score of 2-3 (Lawrence *et al.* 1966), and Joint space width of >1mm)
- were able and willing to attend or comply with treatment and follow-up
- had pain in the knee for most days of the previous month
- were ambulatory at the time of recruitment into the VIDEO study
- were aged 50 years or over at the time of initial recruitment into the VIDEO study
- had taken part in the baseline VIDEO study

For HV, individuals were included who:

- have no diagnosis of a musculoskeletal condition
- are a student or staff member at Southampton University
- are willing to participant in the study, providing full informed consent

Exclusion criteria

For RA participants, patients were excluded who:

- had received corticosteroid injection therapy to the forefoot within the 12 weeks prior to the commencement of the initial FeeTURA study
- were unable to walk a distance of 5metres
- had concomitant musculoskeletal disease (e.g. primary osteoarthritis, gout, Paget's disease, systemic lupus erythematous)
- had a serious medical or psychological disorder that would prevent compliance with the study protocol
- were unable to provide informed consent

Additional exclusion criteria applicable to patients with RA otherwise eligible to complete MRI included:

- have a pacemaker fitted
- have other electronically, magnetically or mechanically activated medical device or implant that may be adversely affected by the MRI procedure
- have a history of eye injury involving metal fragments
- have a cochlear implant
- have renal dysfunction
- were pregnant
- are claustrophobic

- have a history of forefoot surgery with metallic fixation devices still in situ

For OA participants, patients were excluded who:

- had secondary OA subsequent to any of the following: septic arthritis, gout, pseudo-gout, Wilson's disease, Paget's disease, hyperparathyroidism, hypothyroidism, sarcoidosis, osteomalacia, osteoporotic fracture, a history of inflammatory disease, hypercalcaemia or hypercalciuria
- were using any of the following at the time of initial recruitment into the VIDEO study: glucosamine or chondroitin within the 12 weeks prior to recruitment, bisphosphonates, vitamin D supplementation with at total vitamin D content>200iμ, any anti-epileptic medication
- had received any intra-articular corticosteroid injection therapy within the 12 weeks prior to recruitment into the VIDEO study
- had received injection of Hyalgan within the 24 weeks prior to recruitment into the VIDEO study
- had undergone any surgical procedure to the knee in the 24 weeks prior to recruitment into the VIDEO study
- were pregnant at the time of recruitment into the VIDEO study

For HV, individuals were excluded who:

- Have had corticosteroid injection therapies to the forefoot within the previous 3 months prior to commencement of the study
- Have a musculoskeletal/rheumatological disease (e.g. primary osteoarthritis, rheumatoid arthritis, gout, Paget's disease, systemic lupus erythematous)
- Have a serious medical or psychological disorder that would affect the study protocol
- Are unable to comply, understand or are unwilling to participate in the requirements of this investigation
- Are unable to give informed consent

3.4.2 Withdrawal of participants

Participants were able to withdraw from the study at any time without providing a reason for doing so. At the time of consent all participants were reminded that they were able to withdraw at any point and that, if applicable, this would have no adverse consequence to their ongoing clinical care.

In the event of a participant with RA wishing to withdraw from the study they would not be replaced because all possible participants from the original FeeTURA study will already have been invited to participate. In the event of a participant with OA wishing to withdraw from the study, it was possible to fill this opportunity to participate via further consecutive, retrospective

recruitment from the VIDEO study population. In the event of a healthy volunteer wishing to withdraw from the study, they could be replaced by continued recruitment.

3.5 Sample size determinants

The following sections discuss the calculation, clinical reasoning and previously reported literature considered when determining the appropriate sample size for each experimental study.

3.5.1 Experimental study one

The sample size calculation used for independent group analysis with binary data (bursa presence/absence) was as follows:

$$N \textit{ (per group)} = \frac{2 \times [z_{(1-\alpha/2)} + z_{(1-\beta)}]^2}{\Delta^2}$$

Where α = level of statistical significance, β = power, Δ^2 = proportional difference, adjusted for variability between groups (effect size).
Calculation 1: Sample size

However, for this longitudinal investigation the target population is known and has been previously reported (Bowen *et al.* 2010b). This initial sample size was constructed using Pearson's correlation coefficient estimates of association between patient reported foot complications and bursae presence/absence (PCC=0.211; p=0.371). At baseline 150 participants were enrolled into the study with a subsequent recruitment rate of 86% (N=129) at the one-year follow-up visit. With a continued annual trend in loss to follow-up rates, the estimated recruitment for this study was approximately 90 participants. Therefore, with a known population size, the above calculation can be simultaneously equated thus (assuming the estimate of effect size obtained at baseline is consistent):

$$Z_{(1-\beta)} = \sqrt{\left[\frac{N\Delta^2}{2}\right]} - z_{(1-\alpha/2)}$$

Where α = level of statistical significance, β = power, Δ^2 = proportional difference, adjusted for variability between groups (effect size).
Calculation 2: Statistical power

Assuming a sample size of 90, there will be over 95% power to detect a difference of 0.55 in the proportion of participants with one or more bursae, using a two-sided 5% significance level. This power is greatly increased due to the large proportional difference between groups in presence/absence of bursae (effect size) observed at baseline. Thus the likelihood of detecting a false positive or incorrectly omitting a true positive finding is reduced.

3.5.2 Experimental study two

There is currently no known data regarding the prevalence of FFB in patients with OA. It was not possible therefore to estimate proportional effect in order to calculate a required sample size for this population, thus a pragmatic sample of 50 candidates was selected. Similarly, there is limited evidence available regarding the prevalence of US-detectable FFB in healthy volunteers and therefore a comparative control sample of 50 participants was recruited. This sample size

was reflective of the sample size of non-arthritic populations previously reported in studies of FFB (Bowen *et al.* 2010b).

3.5.3 Experimental study three

Previous research regarding the development of MRI-based tools, designed for use in patients with rheumatological conditions, have ranged from 10 in a developmental study for a semi-quantitative OA hand MRI score (Haugen *et al.* 2011), to 32 in an evaluative study of semi-quantitative MRI modalities for the assessment of knee OA (Roemer *et al.* 2010). However, previous research has also highlighted that an increased sample size is beneficial in imaging studies of inflammatory or erosive disease, in which distortion of anatomical features is common (Bird *et al.* 2003, Boesen *et al.* 2009, Cohen *et al.* 2011, Ostergaard *et al.* 2005c). As such, a target sample size of 50 participants was considered appropriate for this study. However, the potential size of the targeted population is bounded by the number of participants who are both eligible to undergo MRI and have completed the year-three follow-up appointment in experimental study one.

3.5.4 Experimental study four

The size of the potential sample available for analysis within this study is dependent upon those participants who completed experimental studies one and three. However, based upon the proportional difference in US-detectable FFB presence/absence a sample size of approximately 20 participants would be required, assuming 80% power and 5% significance level, for the determination of FFB presence or absence. These estimations are potentially of academic value only, as the prevalence of MRI-detectable FFB has not been previously reported to date.

3.6 Study outcome measures

A number of variables were recorded in order to achieve the proposed experimental study outcomes. The outcome measures were selected to provide information on the following: participant demographical information, the presence/absence of forefoot bursae or other forefoot soft tissue lesions, the evaluation of disease state, foot health or posture, and the determination of patient-reported foot-related disability. The following sections provide further detail regarding the methodological considerations for each identified outcome measure.

3.6.1 Demographical information

The demographical information collected includes age (years), height (centimetres/cm), weight (kilograms/Kg), gender (male/female), arthritis diagnosis and disease duration (years), and current pharmacology. These measures were obtained either by the review of patient records on the day of data collection, participant interviewing or by using standardised laboratory measures. The information was recorded on the participant demographical information sheet (see appendix sections A7a and A7b), to be used in subsequent analyses of interactions or confounding.

3.6.2 Monitoring of disease state

As discussed in Chapter two (section 2.1), a number of tools for the evaluation of disease state in RA have been developed. However for the purposes of this thesis both the DAS 28-CRP and DAS 28-ESR scores were used. These measures are consistent with those reported as routinely used within current rheumatological clinical practice and allow the evaluation of fluctuations in disease state (Wolfe *et al.* 2001).

Participants were asked to complete a visual analogue scale indicating their perceived overall well-being on the day of assessment. This was transformed linearly from a millimetre scale into a score of 0-100. The 28 joints assessed included both shoulders, both elbows, both radiocarpal joints, metacarpophalangeal joints 1-5 of both hands, proximal interphalangeal joints 1-5 of both hands, distal interphalangeal joints 2-5 of both hands and both knees (Van der Heijde *et al.* 1990). The joints were palpated for fluctuant swelling using a standardised technique and the patient was asked to report any tenderness felt during this process. Figure 19a-d illustrates the palpation techniques used for some of the upper body joints. Figure 19e-f illustrates the additional ankle and proximal interphalangeal joint palpation completed as part of the assessment of disease activity within the foot.

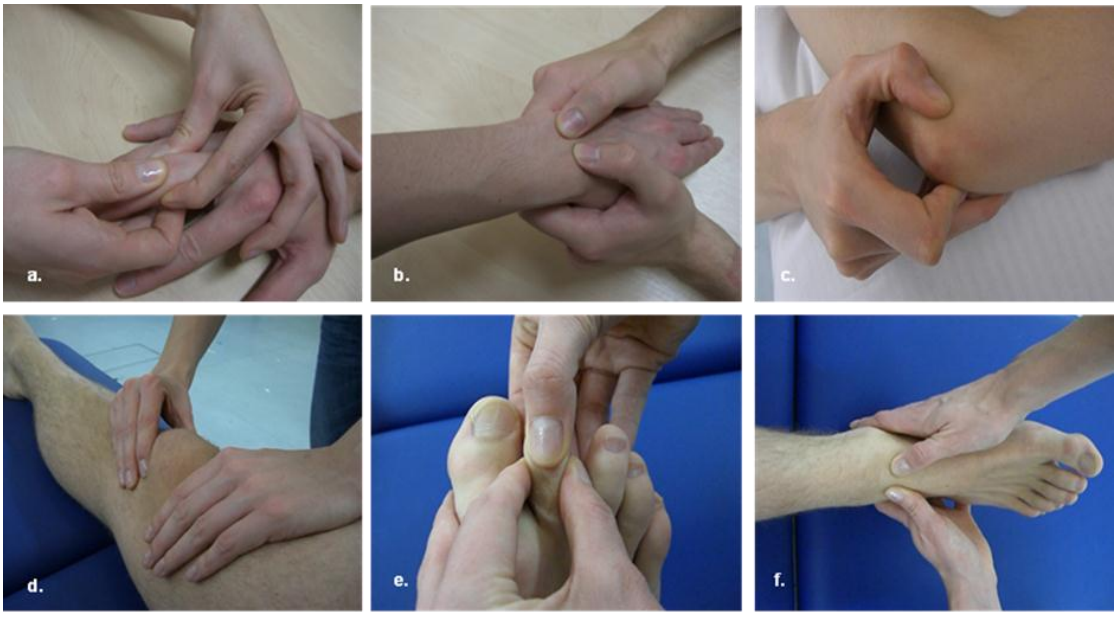


Figure 19: Joint Palpation
Joint palpation technique at a) the right 3rd proximal interphalangeal joint, b) the left radiocarpal joint, c) the left elbow joint, d) the right knee, e) the right 2nd proximal interphalangeal joint and f) the right talo-crural joint. *Images author's own.*

Blood samples were taken using standardised venesection techniques by the study researcher (LH), in accordance with local trust policy and good clinical practice guidelines (Bird *et al.* 2005). Samples were then labelled for ESR/CRP calculation or spun for plasma and serum separation (using a Beckman Coulter centrifuge, Allegra 6R® model, at 5,000rpm, 5°C, for 10 minutes), and prepared for storage (figure 20).

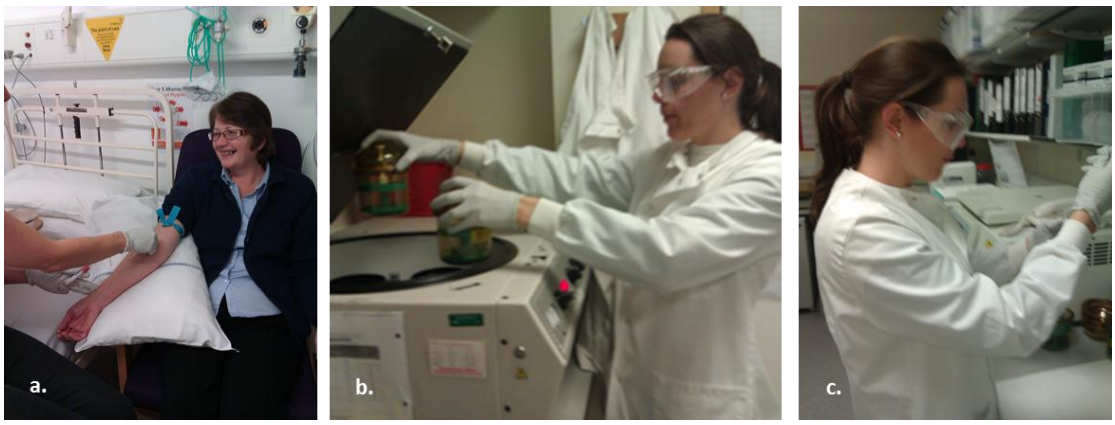


Figure 20: Sample preparation
Sample preparation where, 20a illustrates venesection technique, 20b illustrates plasma/serum separation via centrifuge at 5,000rpm, 5°C, for 10minutes, and 20c illustrates sample transfer into aliquots for storage. I*mages author's own.*

Further to the joint swelling and tenderness count, visual analogue scale (VAS) of overall wellbeing completion and CRP or ESR analysis, the composite DAS 28-CRP or DAS 28-ESR

scores were calculated. All information was recorded on the disease activity assessment form (see appendix section A14d), (Lynch *et al.* 2010). The DAS 28 scores and change in scores were subsequently interpreted in accordance with the guidelines listed in table nine.

Table 9: The scoring of disease activity in RA
DAS 28 scoring and interpretation (Lynch *et al.* 2010, Hayashi *et al.* 2010, Ostergaard *et al.* 2005a)

DAS score at baseline		**Change in DAS score after baseline**		
DAS score	Interpretation	>1.2	>0.06 + ≤1.2	≤0.06
≤3.2	inactive	good improvement	moderate improvement	no improvement
>3.2 ≤5.1	moderate activity	moderate improvement	moderate improvement	no improvement
>5.1	high activity	moderate improvement	no improvement	no improvement

3.6.3 Musculoskeletal ultrasound

A Diasus® diagnostic musculoskeletal ultrasound (US) scanner (System 8, Dynamic imaging, Livingston, Scotland, UK), was used for both studies one and two (figure 21a). Scanning was completed in B-Mode to provide real-time grey-scale images, sampled at a maximum frame rate of 30 frames per second. The return echo signals were automatically processed using Diasus® 2D spline filtering. Image pixilation was standardised at 640 x 440 pixels, the optimum settings for fine image resolution available using this software. The overall transmit power and gain was set at ≤50 and ≤30 respectively, in accordance with the European League Against Rheumatism (EULAR) working group for US in rheumatology scanning recommendations (Backhaus 2001). However, grey-scale contrast was continually adjusted during image acquisition in real-time using multiple fine gain control and focus points. Where possible the least amount of focus points were used and centred at the intermetatarsal level for plantar foot scans and the upper third of the joint space for dorsal foot scans. This enabled the transmit frequency to be as high as possible to achieve good image resolution whilst also maintaining a suitable wave penetration depth aimed at the level of anatomical interest.

All US scanning was performed in accordance with the British Medical Ultrasound Society (BMUS) guidelines for safe use (Fitzpatrick *et al.* 1998). In addition, the image acquisition protocol was designed to reflect the ALARA principles (as low as reasonably achievable) reported by the American Institute of Ultrasound in Medicine (AIUM), (Fitzpatrick *et al.* 1998). Thus, the minimum amount of US exposure was used to reasonably fulfil the objectives of the US scan.

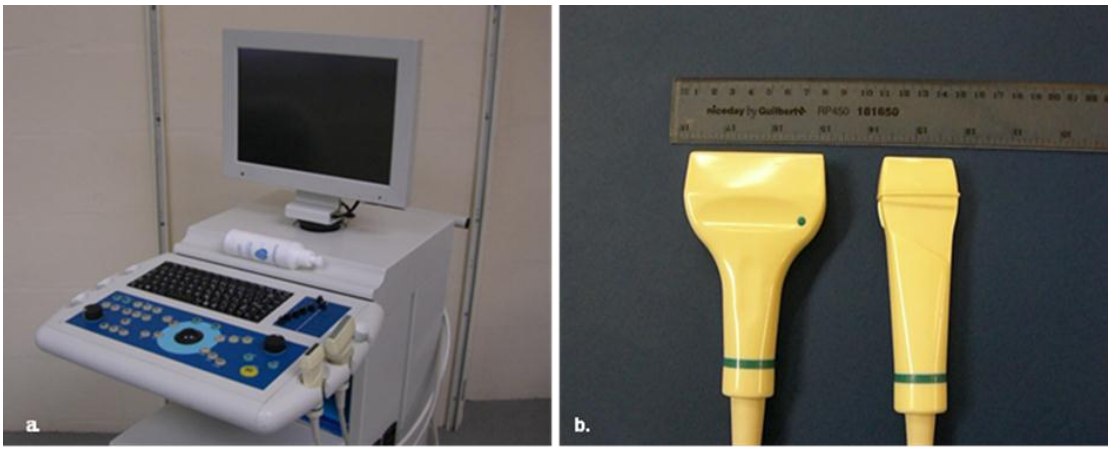


Figure 21: US equipment
Where 21a illustrates the Diasus® portable US unit, system 8, 21b illustrates the 5-10MHz ultra wideband linear-array transducer, active length 40mm (left) and the 8-16MHz transducer, active length 26mm (right). *Images author's own.*

The dual probe system operates with two linear array transducers (figure 21b). This enabled specific sound wave frequency use and thus optimised image resolution where possible whilst also ensuring accurate wave penetration depth when required, as demonstrated in figure 22. For example, the 8-16MHz transducer was not sufficient to accurately review the intermetatarsal spaces at the level of the deep transverse intermetatarsal ligament and therefore the 5-10MHz transducer was used for these scans.

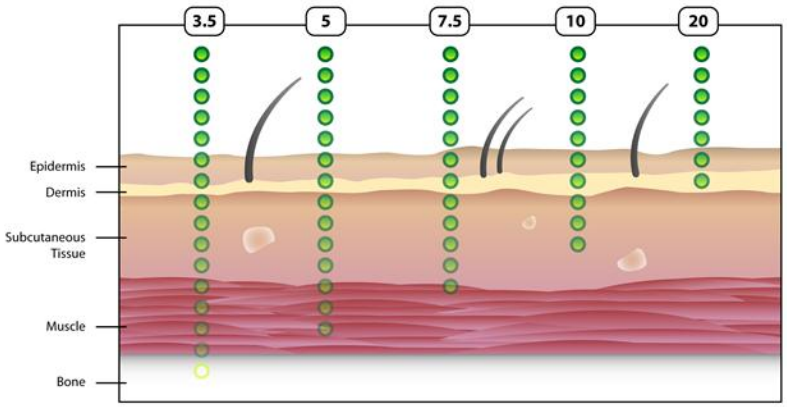


Figure 22: US transducer frequency & tissue depth penetration
A Longitudinal skin section demonstrating US frequency compared to depth of tissue penetrated in a large joint. *Image reproduced with permission from RH09 schematic design, Southampton (2009)*

3.6.3.1 US protocol

The US foot scan was completed prior to the podiatric assessment or evaluation of disease state, to minimise the potential for observer bias; the researcher completed the scan without prior knowledge of the participant's foot health or disease activity status. An overview of the US

scanning protocol is shown in figure 23. Hypo-allergenic, alcohol free coupling gel was liberally used throughout to improve transducer to skin contact.

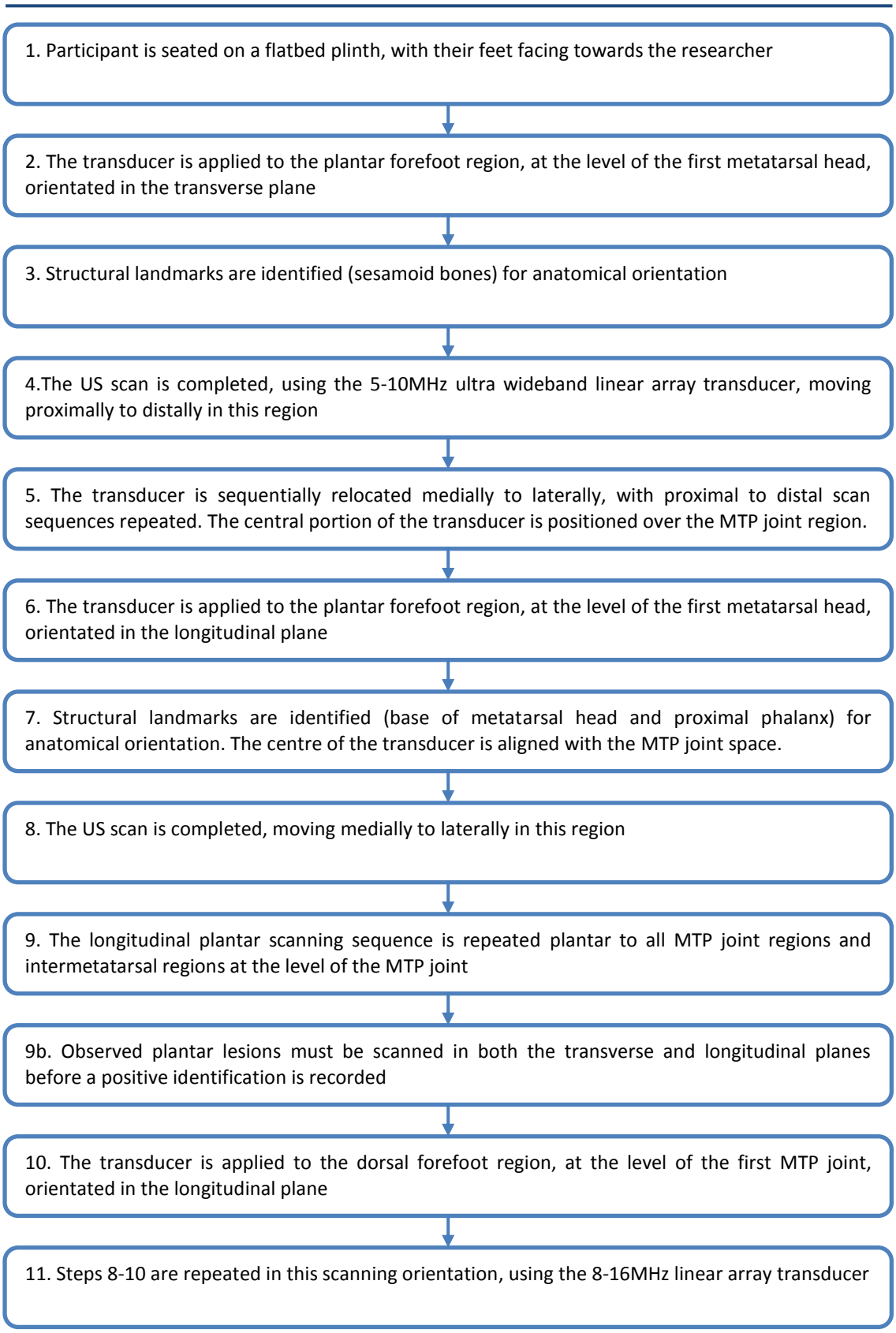


Figure 23: US scanning protocol

Forefoot bursae were noted as present if detectable in both the transverse and longitudinal planes, when scanning from a plantar approach, as illustrated in figures 24a and 24b. There are no standardised documented approaches for the determination of intermetatarsal or plantar bursae in the forefoot. However, common differential diagnoses include intermetatarsal neuroma and flexor digitorum longus tenosynovitis, for which a plantar US approach is recommended (Backhaus 2001, Baker *et al.,* Brown 2005, Fitzpatrick *et al.* 1998, Koski 1998, Chauveaux *et al.* 1987). The proposed plantar approach is consistent with that used by Bowen *et al.* (Bowen *et al.* 2008, Bowen *et al.*), who demonstrated reliable detection of FFB in the baseline and year-one follow-up studies.

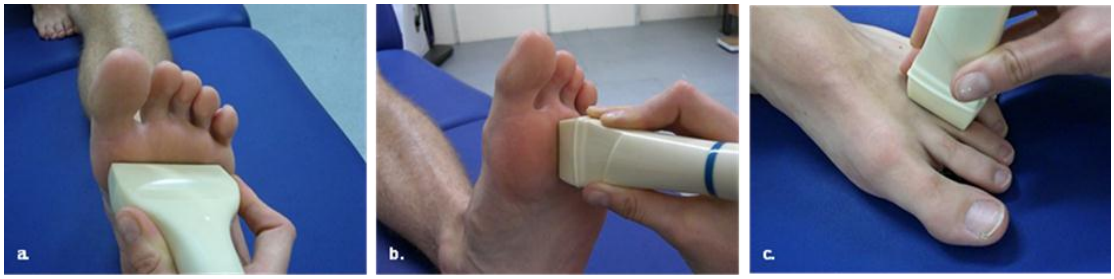


Figure 24: US transducer orientations
Where 24a illustrates the plantar transverse scan at the level of the MTP joint region, 24b illustrates the plantar longitudinal scan at the level of the second MTP joint region, and 24c illustrates the dorsal longitudinal scan at the level of the third MTP joint region. *Images author's own.*

MTP joint synovitis was noted as present if detectable in both the transverse and longitudinal planes when scanning from a dorsal approach (figure 24c). The selected approach conforms to those proposed by the EULAR working group for US in rheumatology (Backhaus 2001). Metatarsal head erosion was noted as present if detectable in either the dorsal or plantar scanning approach. However, a positive annotation was only given if the erosion was detectable in both the transverse and longitudinal plane, in accordance with EULAR guidelines (Backhaus 2001). Findings were recorded on the US assessment form (see appendix section A7c).

3.6.3.2 Benefits & limitations of US

Real-time multi-planar grey-scale US, in B-Mode, allows accurate detection of bone and soft tissue lesions within the forefoot. The use of Power Doppler would provide additional benefit for the identification of active inflammation. However, this Power Doppler was not available in this study. Image artefact, particularly anisotropy (disparity in acoustic feedback with changes in transducer orientation) was problematic when scanning plantarly due to the large number of converging, differently orientated, anatomical structures. To overcome this, the transducer was applied perpendicularly to the sole of the foot and then angled over a range of -45° to +45° about this original 90° position thus altering acoustic enhancement. The use of positional acoustic variation over striated tendonous structures provided further clarification regarding tissue detection and differentiation. Where fluid filled cavities were detected, the transducer was

held in a still position for a minimum of 5 seconds to observe any potential blood vessel pulsation. Gentle pressure was applied to the transducer to compress observed fluid to identify capsulation or distribution.

For dorsal MTP joint scanning, good transducer to skin contact was often difficult due to the presence of forefoot deformity, particularly lesser digit retraction or subluxation. The use of a smaller 'hockey-stick' transducer may have improved image acquisition in this area by improving transducer to skin coupling (Backhaus 2001). However, this transducer was not available in this study. Stand-off pad use was trialled prior to data collection in order to improve transducer to skin coupling over the lesser digits (Warner *et al.* 2008, Brown 2005, Riente *et al.* 2006). However the frequency reduction required to image at sufficient depth when using a stand-off pad noticeably reduced image quality. Thus, the smaller linear 8-16MHz transducer was preferentially chosen.

3.6.4 Magnetic resonance imaging

A 1.5 Tesla (T) whole body scanner (Siemens AG Medical Solutions, Germany), was used for all magnetic resonance image (MRI) acquisition (figure 25). A four channel flex extremity radio frequency (RF) surface coil (Siemens AG Medical Solutions, Germany; circularly polarised array), was used to image the mid and forefoot region only.

Figure 25: MRI hardware
The Siemens Avanto Syngo® scanner. *Images courtesy of Spire Healthcare Southampton.*

Prior to data collection initial capacitor tuning was completed to ensure that the RF coil frequency was synchronised with the magnetic field (B_0). Overall system calibration was completed as per the standard protocol for the radiology department. An extremity RF surface coil was selected in order to minimise the field of view to the region of interest only, thereby reducing the signal to noise ratio (SNR) during image acquisition and thus potential image artefact. As illustrated in figure 26, the region of interest (ROI) was centralised within the

superconducting magnet, reducing eddy current noise (external electrical signal interference), with the aid of a light localiser.

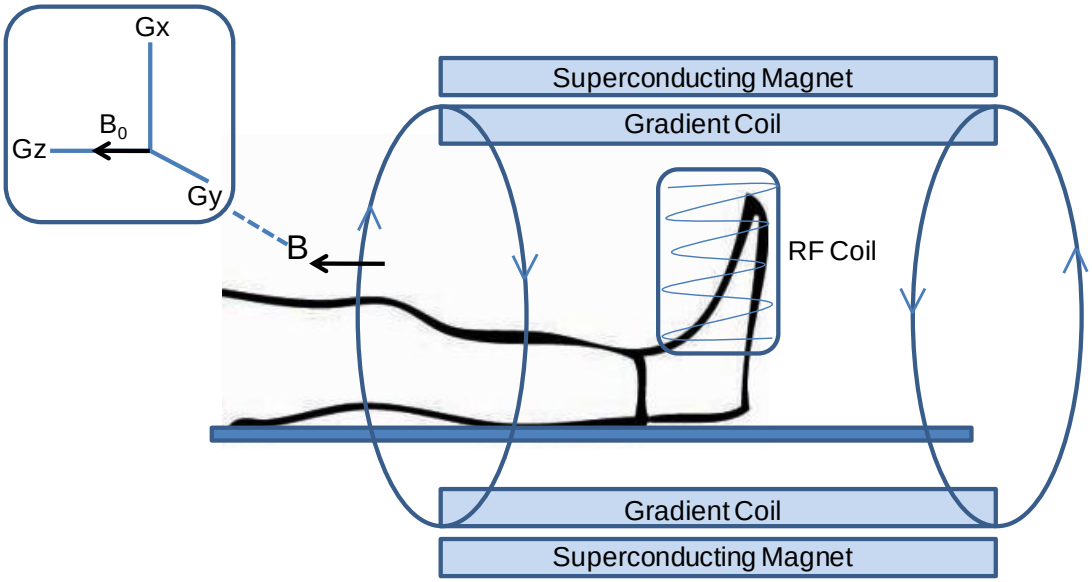


Figure 26: Schematic diagram of magnetic field gradient & coil arrangement
Where Gx= reference vertical (also the read direction); Gy= reference coronal (also the phase encode direction); Gz= reference horizontal; B_0=horizontal magnetic field about which isocromats precess prior to RF pulse exposure; B=applied static magnetic field; RF=Radio frequency. The alternate spin directions in the gradient coil create polarisation in the linear bore. *Image author's own.*

Figure 26 also demonstrates the arrangement of the magnetic fields, where B_0 (horizontal static magnetic field), about which the isocromats precess prior to the application of a RF pulse, is orthogonal to B_1 (transverse field after RF pulse is applied perpendicularly). The ROI is therefore defined in the read direction by Gx and in the phase encode direction by Gy. Overall, two-dimensional and three-dimensional sequences, of between 29 and 96 slices with 3mm to 0.6mm slice thickness respectively, were completed after orientation with a T1 sagittal localiser image. Alignment and positioning was manually orientated by the study radiologist (LK); coronal scans were orientated with the metatarsal parabola, sagittal scans were approximately orientated perpendicular to the coronal slice profile and with the shaft of the third metatarsal. The field of view (FoV) in the read direction was determined as the base of first metatarsal to the distal aspect of the hallux. The FoV in the phase-encode direction was defined as extending from the medial to the lateral foot borders.

3.6.4.1 MRI protocol

In order to establish a sufficient matrix of sequences to adequately identify soft tissue and bony structures with sufficient image clarity, a number of sequences were used. The protocol used adhered to International Radiation Protection Association (IRPA) (1991) recommendations and Medicines and Healthcare Products Regulatory Agency (MHRA) guidance (2007). However, to

date there are no published guidelines for the MRI of the forefoot in patients with RA. As such, a proportion of this thesis is devoted to the development of an appropriate MRI sequence protocol. The iterative development process and efficacy of the proposed semi-quantitative score are discussed in Chapter six. The main focus of sequence design was the accurate differentiation between soft tissue structures of the forefoot, achieved by review of the following:

- Sample properties (proton density/T1 or T2 characteristics of tissues; non-adjustable)
- Pulse sequence type (inversion recovery/spin echo etc.; adjustable)
- Pulse sequence timing (TR/TE; adjustable)

Pulse sequence type and timing were therefore selected to visualise a) anatomical structure (sequence 1: coronal T1 SE) b) high contrast between fluid and soft tissue (sequence 2: coronal STIR), and c) synovial inflammation (sequences 3 and 4: coronal and sagittal T1 weighted, fat suppressed, sequences after intravenous contrast administration). The 3D volumetric sequence allowed the three-dimensional reconstruction of identified lesions and orientation with adjacent features (sequence 5). Coronal scans were orientated with the metatarsal parabola and sagittal scans were approximately orientated perpendicular to the coronal slice profile and with the shaft of the third metatarsal. The field of view (FoV) in the read direction was determined as the base of first metatarsal to the distal aspect of the hallux. The FoV in the phase-encode direction was defined as extending from the medial to the lateral foot borders. The TE/TR ratios were adjusted in an iterative process by the radiologist until appropriate image clarity or contrast was achieved. For sequences 1-4 k-space was mapped linearly, and for sequence 5 was mapped using a sequential multi-slice selection method.

3.6.4.2 MR image reading

Images were viewed using Siemens *Syngo*© Fast view software (Siemens AG 2004-2006) and clinically reported by a consultant radiologist (LK) at the time of acquisition, in accordance with the ethical protocol. Images were read by two consultant radiologists (LK and MT) and a podiatrist (LH). All readers were blinded to each other's findings, unless explicitly stated as part of an educational or reliability exercise, to the corresponding patient clinical data. The protocol for image reading is discussed fully in Chapter six (section 6.3).

3.6.4.3 Safety in MR image acquisition

All imaging was completed in accordance with guidance from IRPA (1991). Contra-indications for MRI were reviewed with participants to confirm inclusion eligibility (see section 3.4 for participant inclusion/exclusion details). In accordance with MHRA guidance (2007) all participants completed a Glomerular Filtration Rate (GFR) screening test prior to the administration of IV Gadolinium. Gadolinium is a commonly used contrast agent however its dissociated form is toxic. Therefore renal function needs to be sufficient to filter the contrast

agent before it dissociates to avoid side effects such as nausea, headache, or in severe cases nephrogenic systemic fibrosis.

Highly concentrated absorption of RF energy at a single focal point, resulting in deep tissue burn, is a previously reported adverse event for MRI (Knopp *et al.* 1996, Dempsey *et al.* 2001). In order to minimise the risk of RF burn, the operating radiologist checked that no current loops were formed inside the magnetic bore during image acquisition, either by external wires or by touching extremities. Foam padding was used to secure the RF coil away from contact with the patient's skin as well as ensuring the feet were not touching during image acquisition.

3.6.4.4 Benefits & limitations of MRI

The use of paramagnetic contrast agents provides a rapid pathway for nearby water protons to give up longitudinal magnetisation, effectively reducing T1. Thus highly perfused tissues appear brighter on T1 weighted images. However, with time delay the contrast agent will diffuse across tissues, blurring anatomical tissue margins. It was important that post-contrast sequences are performed in a timely manner to allow adequate differentiation between highly vascularised synovium and fluid located within the bursal cavity. MR acquired images are vulnerable to distortion as a consequence of external RF interference. To overcome this, all image acquisition was performed within a Faraday cage. The use of a flex extremity RF coil allowed reduction in SNR by increasing the coil fill factor; the flex coil was closely aligned to the ROI only. Aliasing, where an image outside of the FoV is mapped over the ROI can occur when there is a demodulated signal frequency; the sampling frequency is unable to differentiate between high and low image frequencies. To overcome this, a low pass filter was applied to remove frequencies outside of the read direction FoV.

3.6.5 Foot & ankle assessment

All foot health information was recorded on the assessment sheet (see appendix section A7d). Tissue viability was reviewed and current or previous ulcer presence recorded. Participants were asked to report any current foot health concerns, episodes of podiatric or lower limb surgical intervention (past or present) or bespoke footwear/orthotic use (past or present).

Foot function was reviewed and range, direction and quality of motion in the ankle, subtalar, mid-tarsal (calcaneo-cuboid and talo-navicular joints), and first MTP joints bilaterally recorded. Foot structure was reviewed and the presence of hallux abducto-valgus deformity, fifth MTP joint exostoses, lesser digital retraction or MTP joint subluxation (2-4 only) was recorded. Foot posture was assessed using the foot posture index (Redmond *et al.* 2006). The FPI provided a composite measure of overall foot posture, (-12 to +12), based upon the degree of adjacent joint alignment (figure 27).

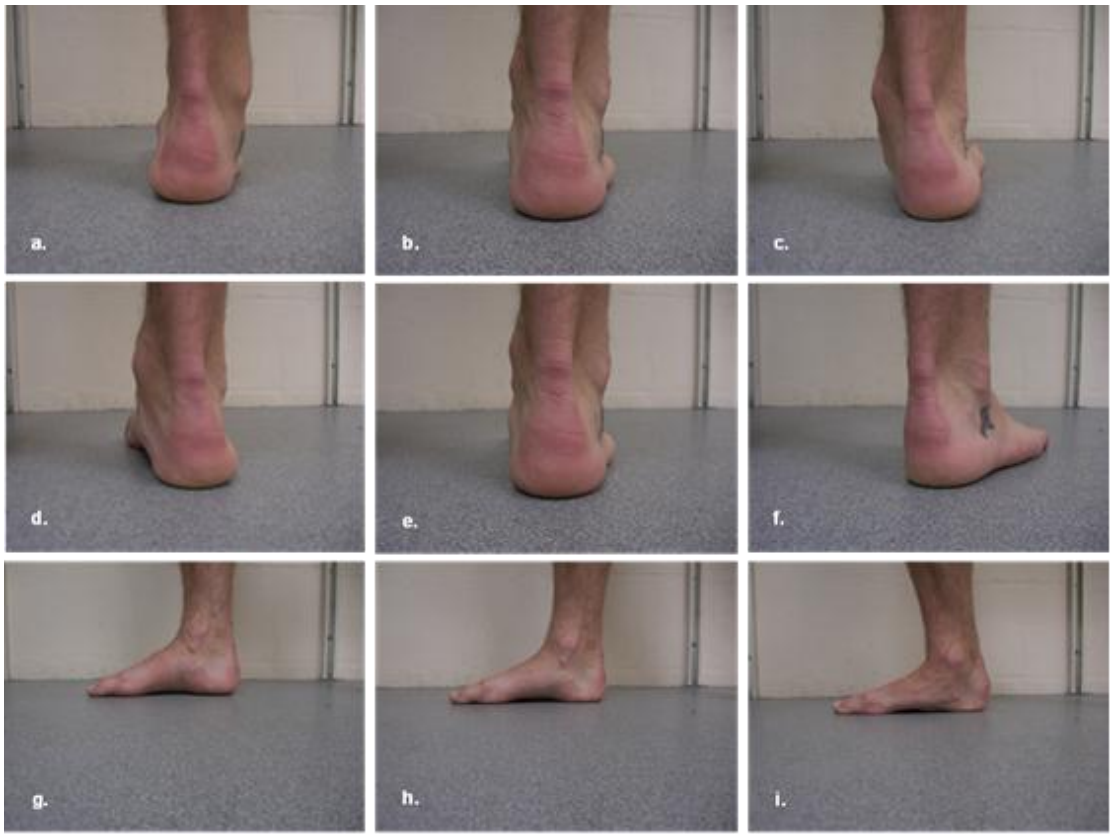


Figure 27: The foot posture index
Example images of right foot posture used for FPI calculation, where 27a illustrates an inverted rearfoot relative to leg (-1), 27b illustrates a rectus rearfoot relative to leg (0), 27c illustrates an everted rearfoot relative to leg (+2), 27d illustrates forefoot adduction relative to the rearfoot (-1), 27e illustrates straight forefoot to rearfoot alignment (0),27 f illustrates forefoot abduction relative to the rearfoot (+2), 27g illustrates a high arched foot position (-1), 27h illustrates a medium arched foot position (0), and 27i illustrates a low arched foot position (+1). *Images author's own.*

3.6.6 Patient-reported foot-related disability

Patient-reported foot-related disability was evaluated using the two subscales of the Foot Impairment Score (FIS); a) FIS_{IF}, 0-21: foot impairment and footwear restriction, b) FIS_{AP}, 0-29: activity limitation and participation restriction (Helliwell *et al.* 2005). An elevated FIS_{IF} or FIS_{AP} score indicates greater foot impairment or activity limitation respectively. For $FIS_{IF,}$ scores ≤6 were considered mild, 7-13 moderate and ≥14 severe. For $FIS_{AP,}$ scores ≤9 were considered mild, 10-19 moderate and ≥20 severe. Score ranges were pragmatically derived by the division of the total score in to approximate thirds. The FIS score has not been validated for longitudinal use. However, Turner *et al.* (2007) suggest that a score change of three or more, in either direction is clinically meaningful, and as such these margins will be used to evaluate clinically meaningful change in reported disability. For the purposes of reporting, the FIS_{IF} subscale will be referred to as 'foot impairment' and the FIS_{AP} subscale as 'activity limitation'. The FIS questionnaire was selected as the primary measure of disability because this is the only tool to our knowledge, with foot-related disability subscales that differentiate between disability and pain, which has been validated for use in patients with RA.

3.6.7 Summary of outcome measures

A summary of the outcome measures used throughout this thesis is given in table ten.

Table 10: Summary of outcome variables
Summary of outcomes including factors, measures, tests and expected results.

Factor	Outcome measure	Population to whom test is applicable	Test	Expected result
Demographical information	age	all	record review	continuous score; years
	gender	all	record review	nominal; male/female
	height	all	standardised laboratory measure	continuous score; cm
	weight	all	standardised laboratory measure	continuous score; Kg
	BMI	all	standardised calculation	continuous score; Kg/m^2
	disease duration	RA and OA	record review	continuous score; years
Dependent variable of interest	forefoot bursae (FFB)	US: all MRI: RA	US determined presence/absence	cumulative continuous score; 0-18
		US: all MRI: RA	MRI determined presence/absence and characteristics	cumulative continuous score; 0-18
Clinical variables	joint hypertrophy (JH)	US: all MRI: RA	US/MRI determined presence/absence	cumulative continuous score; 0-10
	erosion (ER)	US: all MRI: RA	US/MRI determined presence/absence	cumulative continuous score; 0-10
	overall score for disease state	all	DAS 28-CRP	continuous score; 0-5
	systemic inflammation	RA and OA	ESR and CRP	continuous score;
Mechanical variables	forefoot deformity	all	podiatrist examination	categorical score; 1-3
	foot and ankle joint ranges of motion (ROM)	all	podiatrist examination	cumulative continuous score; 0-6
	overall foot alignment and posture	all	FPI	continuous score; -12 to +12
Impact variables	patient-reported foot impairment	all	FIS_{IF}	continuous score; 0-21
	patient-reported activity limitation	all	FIS_{AP}	continuous score; 0-29
	Overall wellbeing	All	VAS	continuous score; 0-100

3.7 Quality assurance & control

Throughout this thesis, care has been taken to identify, consider, adjust for and interpret potential errors or biases inherent within the design of each experimental study. The following section documents potential sources of error or bias, methods used to negate these, and where possible the steps taken to quantify likely inaccuracy (Silman and Macfarlan 1995).

3.7.1 Agreement in data collection & interpretation

Estimations of reporting error, as a consequence of longitudinal researcher variability, have been estimated for both imaging modalities and completion of the FPI. The term agreement has been used throughout the following text to refer to the quantifiable extent to which scores taken on two occasions by the same researcher or by two researchers are the same or differ.

3.7.1.1 Agreement in US data

Within the limits of the study protocol it was not possible to recall patients or extend their visit to include multiple scans, in order to determine the intra-reader reliability of US for the study investigator (LH). Inter-rater reliability regarding the US detection of FFB was established between the investigator who collected the baseline and year-one follow-up data reported in Chapter four (CB) and the current investigator (LH). Ten participants were consecutively, prospectively recruited from those attending the year-three data collection appointment. Both raters independently completed an US scan of the same sequence of patients using a predefined standard operating procedure, without prior knowledge of the participant's disease state or reported foot health. After completion of the first three participants, raters were given opportunity to justify their reported findings and to discuss any potential discrepancies. Raters were then blinded to each other's reports for the remaining participants. FFB were recorded as either present or absent. If present, observed FFB were recorded as occurring in one of nine pre-defined forefoot regions. Inter-rater agreement regarding FFB presence/ absence at each site was evaluated using kappa analysis. Thus, the inter-rater agreement regarding the location of bursae, when both raters identified a bursae as being present, was moderate to substantial (left foot: kappa=0.8; right foot: kappa=0.8; both feet combined: kappa=0.71), (see appendix section A10 for details).

3.7.1.2 Agreement in MRI data

Intra-reader agreement for the study investigator (LH) was established. This was considered as representative of the potential for learning and transference of skills from a radiologist (LK) to podiatrist (LH), particularly with regard to the interpretation and synthesis of a number of key MRI sequences. Evaluation of intra-rater agreement was completed on two occasions after progressive stages of training. A potential learning effect was noted and agreement continued to improve to moderate levels with training (table 11). However, the grading or identification of metatarsal erosion and bone marrow oedema was reported to be consistently challenging respectively. Difficulty in the synthesis of multiple sequences and optimum slice selection were cited as the main reasons for this.

Table 11: MRI reading intra-reader agreement (LH)
Where PEA= percentage exact agreement; PCA= percentage close agreement; IM= intermetatarsal region; PL= plantar region. For all factors N=10.

Factor		After initial training			After additional training		
		Mean score (range)	PEA	PCA	Mean score (range)	PEA	PCA
Metatarsal erosion		8.2, (2-19)	0	50	7.5, (2-19)	20	40
Bone marrow oedema		-	-	-	-	-	-
Synovitis		1.2, (0-4)	30	100	1.1, (0-3)	80	100
IM – fluid	Presence	1.7, (0-4)	30	100	1.6, (1-3)	50	90
	Shape	1.8, (0-4)	30	100	1.7, (1-4)	50	100
	Enhancement	1.8, (0-5)	40	90	1, (0-3)	20	90
	T1	3.4, (0-8)	30	90	3.2, (2-9)	50	50
	T2	4.6, (0-10)	20	30	4.8, (2-9)	50	100
IM - soft tissue	Presence	0.1, (0-3)	20	100	1.8, (0-6)	50	50
	Shape	1.7, (0-6)	30	70	0.8, (0-3)	40	100
	Enhancement	0.7, (0-3)	40	100	1.8, (0-6)	60	90
	T1	1.5, (0-6)	30	80	2.1, (0-9)	50	80
	T2	1.9, (0-9)	20	50	0, (0)	30	100
PL – fluid	Presence	0, (0)	100	100	0, (0)	100	100
	Shape	0, (0)	100	100	0, (0)	100	100
	Enhancement	0, (0)	100	100	0, (0)	100	100
	T1	0, (0)	100	100	0, (0)	100	100
	T2	0, (0)	100	100	0, (0)	100	100
PL – soft tissue	Presence	0.2, (0-1)	60	100	0.2, (0-1)	90	100
	Shape	0.5, (0-3)	60	90	0.3, (0-2)	90	100
	Enhancement	0.1, (0-1)	90	100	0.1, (0-1)	90	100
	T1	0.4, (0-2)	60	100	0.3, (0-2)	90	100
	T2	0.5, (0-3)	60	90	0.3, (0-2)	90	100

Inter-rater agreement between the podiatrist (LH) and radiologist (LK) was evaluated on two occasions after progressive stages of training. LK was considered the expert reader. A potential learning effect was noted and agreement continued to improve to moderate levels with training (table 12). Again, the grading or identification of metatarsal erosion and bone marrow oedema by LH were reported to be consistently challenging.

Table 12: MRI reading inter-reader agreement (LH & LK)
Where PEA= percentage exact agreement; PCA= percentage close agreement; IM= intermetatarsal region; PL= plantar region. For all factors N=10.

Factor		After initial training			After additional training		
		Mean score (range)	PEA	PCA	Mean score (range)	PEA	PCA
Bone erosion		8.15 (2,19)	0	50	7.5, (2-19)	20	40
Bone oedema		-	-	-	-	-	-
Synovitis		1.2, (0-4)	30	100	1.1, (0-3)	80	100
IM – fluid	Presence	1.7, (0-4)	30	100	1.6, (1-3)	50	100
	Shape	1.8, (0-4)	30	100	1.7, (1-4)	50	90
	Enhancement	1.8, (0-5)	40	90	1, (0-3)	20	100
	T1	3.4, (0-8)	30	90	3.2, (2-6)	50	90
	T2	4.6, (0-10)	20	30	4.8, (0-3)	50	50
IM - soft tissue	Presence	0.8, (0-3)	20	100	0.9, (0-3)	50	100
	Shape	1.7, (0-3)	30	70	1.8, (0-6)	40	50
	Enhancement	0.7, (0-3)	40	100	0.8, (0-3)	60	100
	T1	1.5, (0-6)	30	80	1.8, (0-6)	50	90
	T2	1.9, (0-9)	20	50	2.1, (0-9)	30	80
PL – fluid	Presence	0, (0)	100	100	0, (0)	100	100
	Shape	0, (0)	100	100	0, (0)	100	100
	Enhancement	0, (0)	100	100	0, (0)	100	100
	T1	0, (0)	100	100	0, (0)	100	100
	T2	0, (0)	100	100	0, (0)	100	100
PL – soft tissue	Presence	0.2, (0-1)	60	100	0.2, (0-1)	90	100
	Shape	0.5, (0-3)	60	90	0.3, (0-2)	90	100
	Enhancement	0, (0-1)	90	100	0.1, (0-1)	90	100
	T1	0.4, (0-2)	60	100	0.3, (0-2)	90	100
	T2	0.5, (0-3)	60	90	0.3, (0-2)	90	100

3.7.1.3 Agreement in FPI data

The FPI requires semi-quantitative scoring of multiple joint alignments to derive a final composite score. The subjective nature of scoring alignment may introduce observer bias to the study results thus the intra- and inter-reader agreement of FPI scores were established.

A subset of 13 participants, consecutively recruited from the larger study population, was seen on two occasions, with a four week interval, by the same researcher (LH). After completion of the first three participants differences between scores were reviewed to identify large potential discrepancies, although none were identified. Review of the following ten participants was then completed. Intra-rater agreement was demonstrated by calculation of the mean difference between scores, with the range of disagreement expressed as +/- 2 standard deviations. The standard error of the mean was calculated to provide 95% confidence intervals for the likely mean disagreement between scores on occasions one and two. The results of the FPI intra-rater

agreement analysis are presented using Bland-Altman plots in figure 28 (Bland and Altman 1986). Additional agreement calculations are documented in appendix sections A9 and A10.

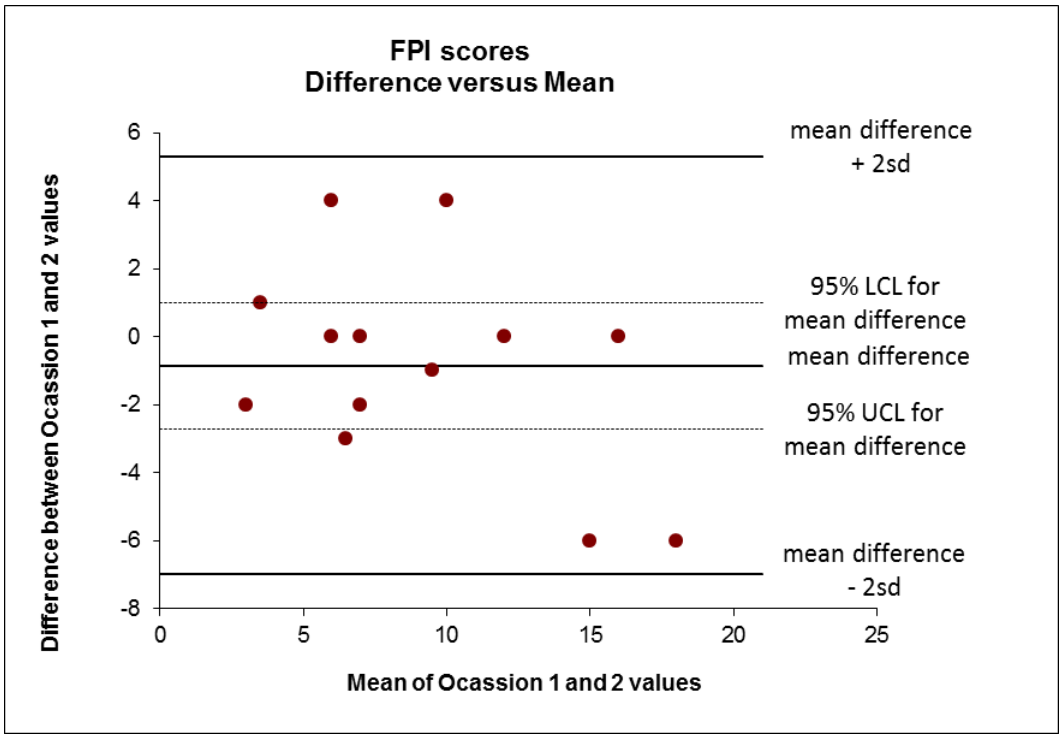


Figure 28: FPI Intra-rater reliability
Bland & Altman plot demonstrating intra-rater (LH) agreement for FPI scores for left and right feet combined (Bland and Altman 1986).

The intra-rater agreement for FPI use is therefore as follows:

- The standard error mean difference between scores at observation times one and two is 0.85, across a score range of -24 to 24
- The 95% confidence interval for this estimation is -2.71 to 1.01, for example 95% of all scores are within this limit of agreement
- All scores are within the upper and lower limits of two standard deviations from the mean, suggesting that there is good agreement between observations
- Agreement appears consistent across all score ranges, although this is a small sample size (N=13)

These results suggest there is good intra-rater agreement, with small potential variation in scores of >1, across a range of 24. The potential variation is neither positively nor negatively skewed suggesting that this is random error.

3.7.2 Confounding & interactive effects

It is possible that spurious relationships, (statistically inferred relationships between two variables when in fact no relationship exists), may be demonstrated when investigating

associations between FFB and explanatory variables, as illustrated in figure 29. Consequently, identification of putative risk factors (most likely explanatory variables) and investigation of possible confounders (explanatory, equally associated variables) was completed as part of the statistical analysis process.

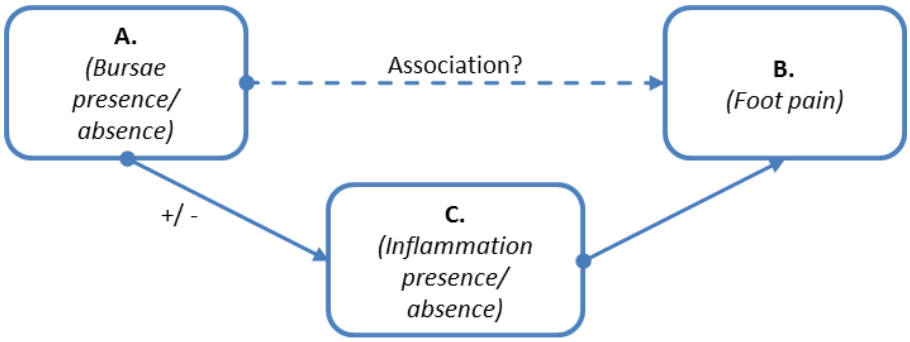


Figure 29: The identification of confounding variables
Where A = Exposure/ risk factor of interest (e.g. bursae presence), B = outcome of interest (e.g. foot pain), C = possible putative or confounding risk factor (e.g. presence of localised inflammation). *Image author's own*.

Possible putative factors included in association analyses were age, gender, height, weight, disease duration, disease activity (DAS 28-CRP or DAS 28-ESR), ESR, CRP, FPI and patient-reported foot-related disability. The conceptual framework for the definition of interaction, based on the homogeneity concept proposed by Szklo *et al.* (2005a), was adopted to allow for the consideration of interactive factors as either positive or negative effect modifiers. An example application of this concept to factors explored within this thesis is illustrated in figure 30.

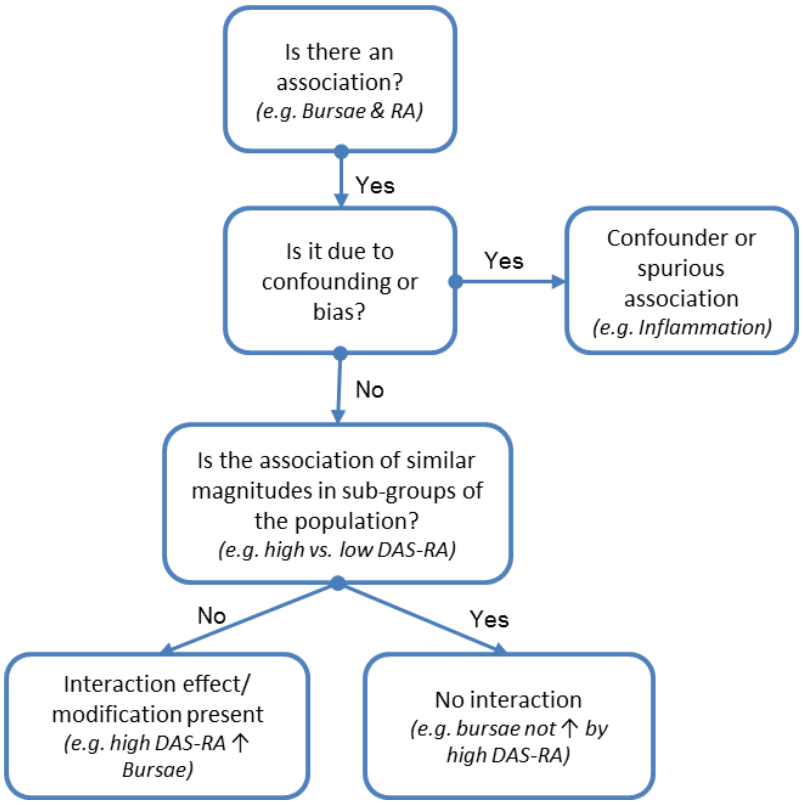


Figure 30: The conceptual framework for determining interactive effect
Where, in this example, it is assumed that RA is the effect modifer as bursae are potentially able to be eliminated. *Image author's own; adapted from Campbell and Machin (1999).*

3.8 Overview of statistical methodologies

The following sections provide an overview of the information processing techniques used for data entry, checking and analysis. All techniques were completed by the study researcher (LH) and reviewed by a senior statistician (DC) or data manager (JM).

3.8.1 Data preparation & analysis software

For studies one and two, the relational database Access (version 2, Microsoft Corporation, 2007) was used for data entry and all forms were configured to reflect that of the data collection sheets. The database tables created were: participant demographical data, US assessment, podiatry assessment, DAS 28 and FIS. The participant code was used as the primary key (unique person identifier) and also selected as the foreign key (used to link individuals across different tables). Within the database, the podiatry assessment, DAS 28 and FIS data was expressed as a sub-form within the master demographical form. Data was prepared for extraction or reporting using concatenated queries (for combining fields), calculated queries (for additive outcome variables) and parameter queries (to refine items extracted for analysis). A proportion of the collected data was double entered by two researchers (LH and PC), and subsequently checked for inconsistencies, outliers and missing information. Identified errors were checked against the original hard copy datasheets for clarification. Where information was confirmed as missing this was annotated as such within the database. Prior to statistical analysis

data distribution was checked for normality using histograms or scatter plots, the findings of which were used to inform statistical test selection.

For experimental study one, baseline, year-one and year-three datasets were merged using SAS® software (Statistical Analysis System, Version 9.3, SAS Institute Inc.). Statistical analysis was completed using either SPSS (Statistical Package for Social Sciences software, version 18.0, Chicago, Il, 2009) or Stata (version 11.0, Statacorp, College Station, Texas, USA). The MRI data collected for studies three and four was entered directly into multiple Excell pages (version 14.0, Microsoft Corporation, 2010) to reflect those of the data collection sheets and automatically re-configured into a larger single file. Data was checked for inconsistencies, outlier and missing information, and where appropriate the original record sheets referred to for clarification. The basic algorithm used for the clustering of data throughout this thesis is shown in figure 31. Variables of interest were defined at either the episode level (for longitudinal analysis), the participant level (for cross-sectional analysis), foot level (for agreement analysis) or site level (for FFB MRI characterisation).

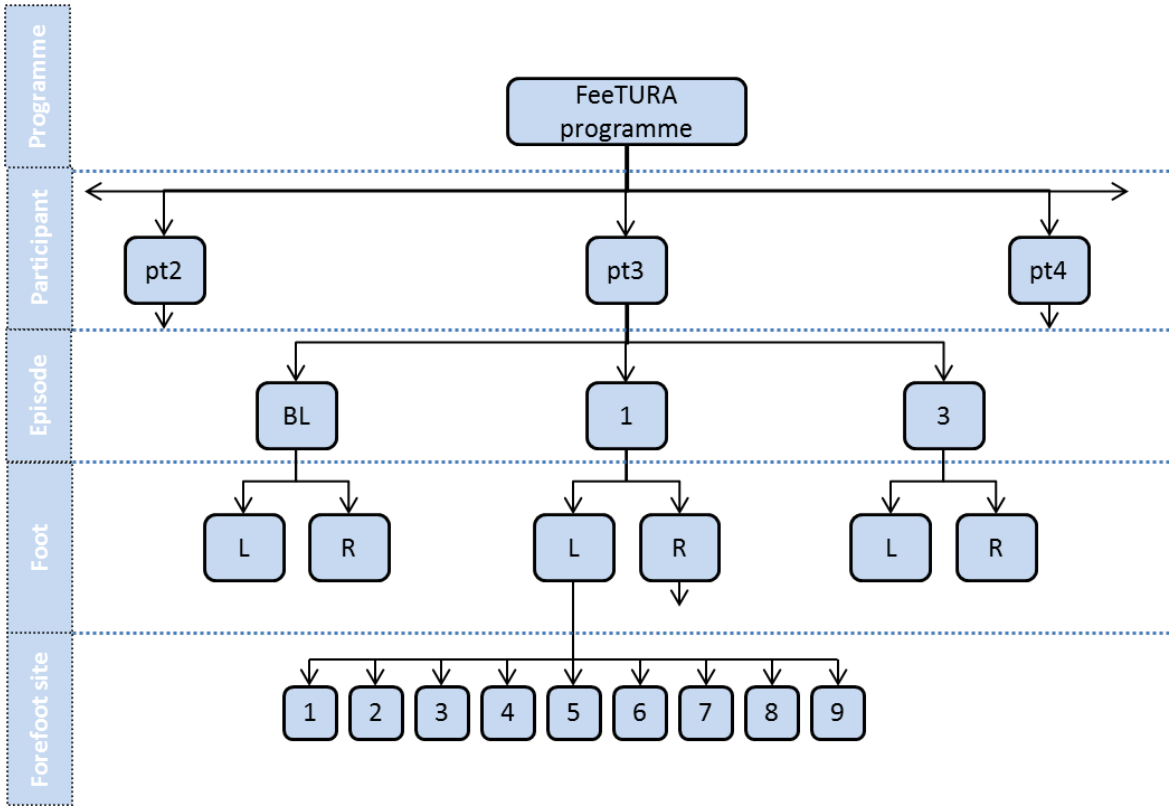


Figure 31: Data clustering
Where FeeTURA = Foot & Ankle Ultrasound studies in Rheumatoid Arthritis, pt = participant, BL = baseline data collection point, L = left foot, R = right foot, 1-9 = forefoot sites of interest. N.B. At the participant level N=159, however, not all participants have data for BL, year-one and year-three inclusively. *Image author's own*.

3.8.2 Descriptive statistics

The demographical and clinical characteristics of the study participants are presented as the mean or median, and standard deviation (SD) or range, dependent upon data distribution. For the reported longitudinal study (Chapter four), participants were coded as either responders (participated within follow-up data collection) or non-responders (did not participate). A Levenes test was completed to evaluate equality within group variances. Estimations of differences in demographic or clinical characteristics between those patients who did or did not respond to invitation for inclusion at year-three are presented as mean and 95% confidence intervals. Statistically significant differences in measured variables between response groups were determined using independent samples t-tests. For the reported comparative cross-sectional study (Chapter five), statistically significant differences in demographic characteristics between cohorts were determined using independent sample t-tests.

3.8.3 Inferential statistics

The following sections provide detail regarding the main statistical techniques used within the four experimental thesis chapters, to determine the epidemiology and clinical importance of FFB.

3.8.3.1 The epidemiology of FFB

The point prevalence proportion of US-detectable or MRI-detectable FFB was calculated by the division of the sum of identified cases by the sum of the total studied population and expressed per 100 patients. Longitudinal analysis of FFB was completed using an adjusted study cohort, which was inclusive of participants who attended all episodes of data collection only. The change in score value used for analysis purposes was an expression of the difference between baseline and year three scores. The comparative probability of FFB presence between different participant groups was expressed as an odds ratio (and 95% confidence interval), and calculated as follows:

$$\text{Odds ratio} = \frac{\text{number exposed in pop. A/ number not exposed in pop. A}}{\text{number exposed in pop. B/ number not exposed in pop. B}}$$

Calculation 3: Odds Ratio (Campbell and Machin 1999, Silman and Macfarlan 1995).

The distribution of FFB across nine predefined forefoot sites was expressed as a percentage of the total number of FFB and demonstrated figuratively using chloropleth maps. The nine investigated forefoot sites were grouped into medial (sites 1-3), central (sites 4-6) and lateral (sites 7-9). Statistically significant differences in the distribution of FFB between participant groups or MRI characteristics were evaluated using repeated Chi^2 analyses. Differences in the US or MRI appearance of FFB are discussed descriptively. Differences in the presence of FFB MRI determined enhancement between fluid and soft tissue lesions, within the same participant, across either intermetatarsal of plantar sites were determined using multiple matched-paired t-tests.

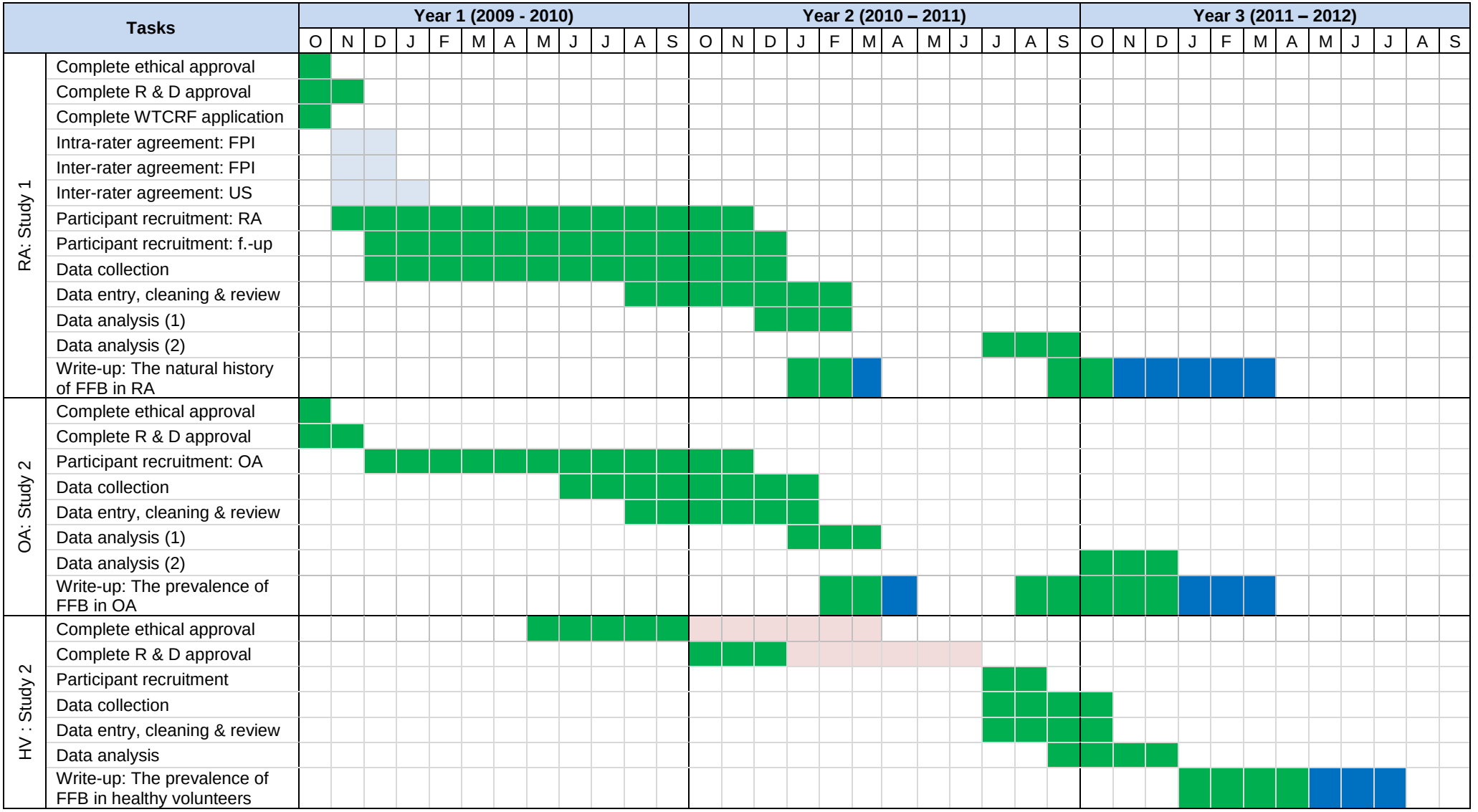
3.8.3.2 The clinical importance of FFB

Correlation coefficient analyses were used to determine the statistical significance of potential associations between the primary outcome of interest (FFB count), and measured explanatory variables (markers of disease activity, foot deformity/function and patient-reported foot-related disability) in each participant group.

Multiple linear regression techniques, with ordinary least squares estimation, adjusted for demographical data, were used to explore statistical relationships between the primary outcome of interest (FFB) and potential explanatory variables. Significant factors were subsequently entered into a multiple linear regression model to identify potential confounding or colinearity within the study findings. In Chapter five, multiple linear regression techniques were also used to explore the predictive value of FFB count, in each participant group, for alternate primary outcome measures including disease activity, foot deformity/function or disability. Multinomial logistic regression techniques were used to explore the potential relationships between FFB distribution and indicators of disease activity, foot deformity/function or disability. Significant factors were subsequently entered into a combined multinomial logistic regression model to identify potential confounding or colinearity within the study findings.

3.9 Timescale of research completion

Data collection for study one started in December 2009 and was completed in December 2010. Data collection for study two was completed in two phases; phase one started in June 2010 and was completed in January 2011, phase two started in July 2011 and was completed in October 2011. Data collection for studies three and four started in December 2010 and was completed in June 2011. Further detail regarding the timeline for the completion of specific research tasks is documented in table 13.


Tasks
Year 1 (2009 - 2010)
Year 2 (2010 – 2011)
Year 3 (2011 – 2012)
O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S
RA: Study 1
Complete ethical approval
Complete R & D approval
Complete WTCRF application
Intra-rater agreement: FPI
Inter-rater agreement: FPI
Inter-rater agreement: US
Participant recruitment: RA
Participant recruitment: f.-up
Data collection
Data entry, cleaning & review
Data analysis (1)
Data analysis (2)
Write-up: The natural history of FFB in RA
OA: Study 2
Complete ethical approval
Complete R & D approval
Participant recruitment: OA
Data collection
Data entry, cleaning & review
Data analysis (1)
Data analysis (2)
Write-up: The prevalence of FFB in OA
HV : Study 2
Complete ethical approval
Complete R & D approval
Participant recruitment
Data collection
Data entry, cleaning & review
Data analysis
Write-up: The prevalence of FFB in healthy volunteers

Tasks		Year 1 (2009-2010)												Year 2 (2010 – 2011)												Year 3 (2011 – 2012)											
		O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S
MRI score development: Study 3	Complete ethical approval																																				
	Complete R & D approval																																				
	Complete ethical amendment																																				
	Participant recruitment																																				
	Data collection																																				
	Intra-reader agreement																																				
	Inter-reader agreement																																				
	Data analysis planning																																				
	Pilot image reading																																				
	Image reading (LK & MT)																																				
	Image reading (LH)																																				
	Data entry, cleaning & review																																				
	Data analysis																																				
	Write up: Development of the FFB score																																				
MRI-detectable FFB Study 4	Data collection																																				
	Image reading																																				
	Data preparation																																				
	Data analysis planning																																				
	Data analysis																																				
	Write-up: The epidemiology of MRI-detectable FFB																																				

Research task undertaken	
Preliminary task	
Item associated with research dissemination	
Unanticipated research tasks	

Table 13: Gantt timeline of study completion

Chapter four

The epidemiology & clinical importance of US-detectable forefoot bursae in patients with rheumatoid arthritis

4.0 Chapter abstract

Background: Rheumatoid arthritis **(**RA) is a systemic, complex disease affecting multiple body tissues and organs that has a significant impact on the lives of patients and their families. The specific impact of RA on the foot is under-reported in comparison to the hand. However, there is a growing body of evidence highlighting the epidemiology of foot problems in this patient group. In particular forefoot bursae (FFB) have been recently highlighted as potentially clinically relevant and associated with RA disease. However, the natural history of FFB in patients with RA has not been reported previously. Furthermore, the longitudinal relationship between changes in RA disease activity and FFB is unclear. As such, longitudinal investigation of the natural history and clinical importance of FFB in patients with RA is warranted.

Aim: To determine the natural history and clinical importance of FFB in patients with RA.

Methods: A longitudinal, prospective, cohort study recruited patients with RA from a rheumatology outpatient clinic. Data were collected at baseline (N=149), one-year (n=120) and three-year follow-ups (n=60). The primary outcome of interest, the presence of forefoot bursae, was determined using musculoskeletal ultrasound. Point prevalence (PP) was used to describe the occurrence of FFB at each time point. The distribution of FFB across forefoot sites is expressed as a percentage of the total observed FFB. The US appearance of FFB is discussed descriptively. Correlation coefficient analysis was used to determine the statistical significance of potential associations between FFB count and indicators of disease activity or disability at year three. Linear regression was used to determine the predictive value of FFB count longitudinally.

Results: The mean (± SD) age, disease duration and DAS 28-CRP were 64 (±11.8) years, 15.1 (±10.3) years, and 2.9 (±1.2) respectively. FFB were consistently highly prevalent (baseline PP: 95 per 100 (mean: 3.58, SD: 2.36, range: 0-8); year 1 PP: 92 per 100 (mean: 3.80, SD: 2.44, range: 0-11); year 3 PP: 88 per 100 participants (mean: 3.05, SD: 2.14, range: 0-11)). Differences in the US appearance of FFB were noted, ranging from large spherical lesions to slit-like cavities. The presence of FFB at year three was significantly associated with metatarsal head erosion (r=0.419, p=0.001) but no other indicators of disease activity. A reduction in FFB count longitudinally was significantly associated with reduced DAS 28-CRP scores but no other indicators of disease activity (r=-0.331, p=0.030). Disease duration and forefoot bursae presence were significant prognostic indicators of foot impairment (p=0.009, p=0.012 respectively), explaining 16% of score variability in the final regression model. Disease duration, forefoot bursae and erosion presence were identified as significant prognostic indicators of

activity limitation (p=0.006, p=0.019, p=0.002 respectively), explaining 35% of score variability in the final regression model.

Conclusion: FFB are highly prevalent and clinically relevant longitudinally in patients with RA**.** FFB may be an indicator of therapeutic efficacy or themselves a therapeutic target, thereby improving patient outcome. Future research regarding the potential relationship between FFB and biomechanical impairment or inflammation is warranted.

4.1 Introduction

There is increasing evidence that foot problems in patients with rheumatoid arthritis (RA) are highly prevalent, even when classical measures of disease activity, such as the DAS-28 score, suggest clinical remission (van der Leeden *et al.* 2010, Rome *et al.* 2009, Otter *et al.* 2010, Katz *et al.* 2006). A population survey by Otter *et al*., (2010), demonstrated that this is true for many patients with RA, regardless of disease duration or therapy, and may be particularly evident in those receiving biologic therapy (Grondal *et al.* 2008, Nagasawa *et al.* 2010). It appears that despite great advances in disease management, a large proportion of patients remain significantly impaired by foot complications (van der Leeden *et al.* 2007, van der Leeden *et al.* 2010). This has a major impact on a patient's ability to return to work or complete tasks of daily living (Klareskog *et al.* 2009, Katz *et al.* 2008, Puolakka *et al.* 2006). Despite recent advances, the longitudinal relationship between the prevalence of foot complications, disease state and the impact of disease in terms of disability remains unclear (van der Leeden *et al.* 2008). Previous cross-sectional studies have suggested that forefoot bursae (FFB) are associated with RA disease activity and disability (Bowen *et al.* 2009, Bowen *et al.* 2010c). However, it is unclear whether these are spurious relationships, confounding effects or true physiological responses. Thus, further longitudinal investigation of the natural history and clinical importance of FFB in patients with RA is warranted as this may provide a potential therapeutic target.

4.1.1 Study aim & objectives

The main aim of this study was to determine the natural history and clinical importance of FFB in patients with RA. To achieve this aim the following objectives were set:

1. To determine the natural history of US-detectable FFB over three years
2. To describe potential differences in the US characteristics of identified FFB
3. To determine the clinical importance of US-detectable FFB

4.2 Materials & methods

4.2.1 Study design

A longitudinal, prospective, cohort study comprised of a series of cross-sectional observations at baseline, year-one and year-three follow-up time points was completed. Please note, the year-three follow-up data had been collected by the author for the purposes of this thesis while the baseline and year-one follow-up data had been previously collated and published (Bowen *et al.*

2010b). Thus, the data collected within this study is used as both a new cross-sectional data set and is also merged with data sets to facilitate longitudinal FFB evaluation.

The primary study outcome was an analysis of the presence of US-detected forefoot bursae (FFB). All intermetatarsal spaces (x4) and plantar metatarsal regions (x5) were imaged for the presence of FFB. The number of observed lesions for both feet was combined, thus a maximum score of 18 was possible. Explanatory variables of interest included those related to RA disease activity (joint hypertrophy (JH), metatarsal head erosion (ER), serological inflammatory markers (ESR, CRP) and disease activity score (DAS 28) or the impact of RA disease in terms of patient-reported foot-related disability (Foot Impact Score (FIS)). Disease activity was evaluated using markers of Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and calculation of a 28 joint Disease Activity Score (DAS 28) (Van der Heijde *et al.* 1990). Metatarsophalangeal JH and metatarsal head ER were determined using US and scored as present or absent for each location, thus a maximum score of 10 for either JH or ER was possible. Disability was evaluated using the two subscales of the Foot Impairment Score (FIS): 1. (FIS_{IF}, 0-21); Foot impairment and footwear restriction, 2. (FIS_{AP}, 0-29); Activity limitation and participation restriction (Helliwell *et al.* 2005). An elevated FIS_{IF} or FIS_{AP} score indicates greater foot impairment or activity limitation respectively. Explanatory variables were selected based upon the findings of previous work, literature review and potential clinical relevance. Detail regarding the selected measures is given in Chapters two (section 2.2), and three (section 3.6).

4.2.2 Study population

Patients included within this study were those with a consultant confirmed diagnosis of rheumatoid arthritis (RA; in accordance with 1987 ACR criteria), who were consecutively, prospectively recruited from a general rheumatology out-patient clinic within Southampton, and who have returned for all three data collection appointments. Detail regarding the recruitment, screening, inclusion/exclusion criteria and sample size determinants is documented in Chapter 3 (sections 3.4-3.5).

4.2.3 Protocol for data collection

The protocol for participant recruitment and data collection is summarised in figure 32.

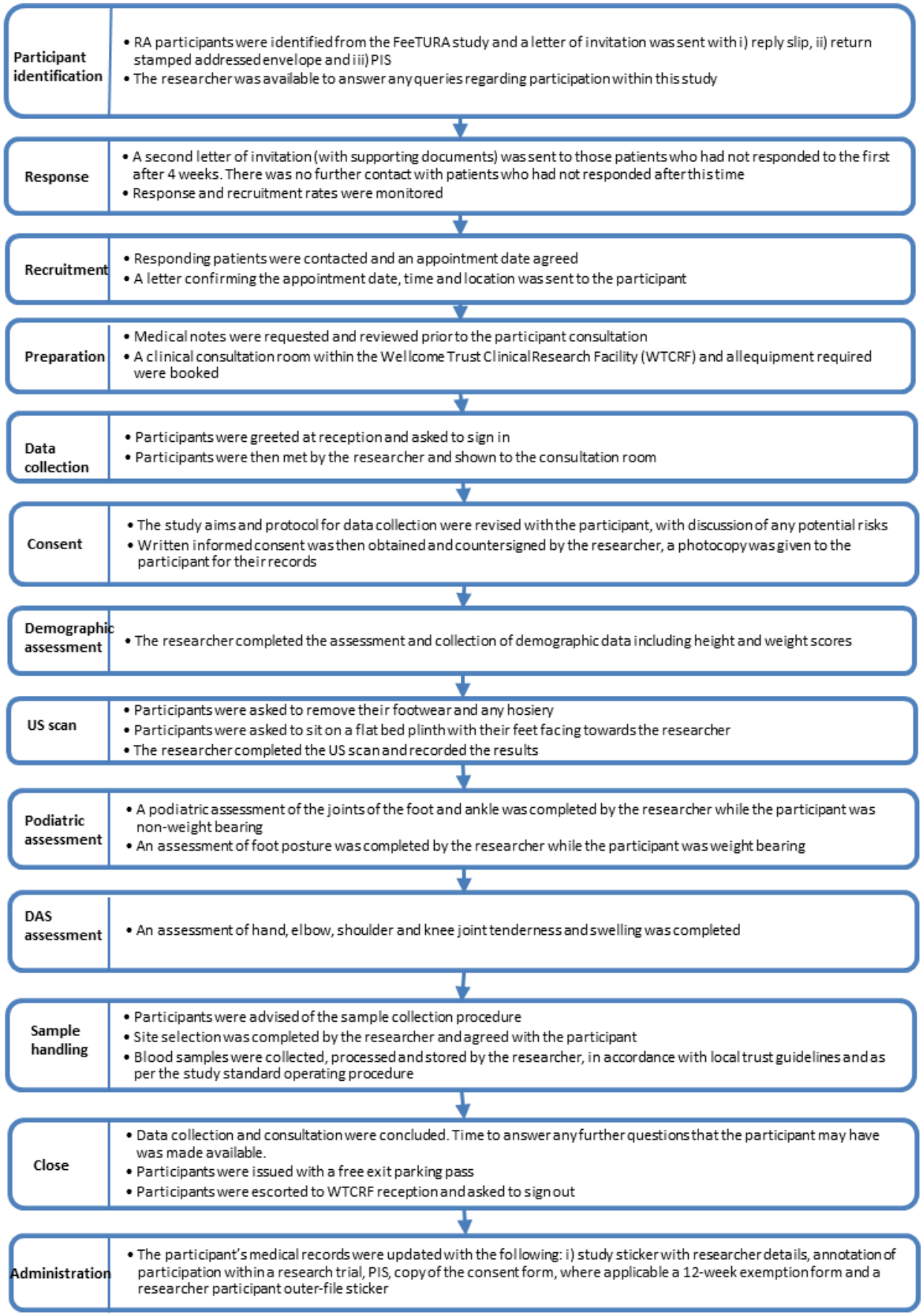


Figure 32: A schematic diagram of the protocol for study one
Where, FeeTURA = foot and ankle ultrasound research in rheumatoid arthritis; PIS = participant information sheet; ID = identification; US = ultrasound; DAS = disease activity score

4.2.4 Protocol for image collection & interpretation

Musculoskeletal ultrasound (US) scanning, using a Diasus® diagnostic scanner (System 8, Dynamic imaging, Livingston, Scotland, UK), was completed in B-Mode to provide real-time grey-scale images. The return echo signals were automatically processed using Diasus® 2D spline filtering. Image pixilation was standardised at 640 x 440 pixels, the optimum settings for fine image resolution available using this software. The overall transmit power and gain were set at ≤50 and ≤30 respectively, in accordance with the European League Against Rheumatism working group for US in rheumatology, scanning recommendations (Backhaus M. 2001). All metatarsophalangeal joints and intermetatarsal spaces, of both feet, were individually imaged from both a plantar and dorsal approach, in longitudinal and transverse scanning planes, using an 8-16MHz linear array transducer. All intermetatarsal spaces and plantar forefoot regions were additionally imaged from a plantar approach, in longitudinal and transverse scanning planes, using a 5-10MHz linear array transducer. Where possible the lowest number of focus points was used and centred at the level plantar to the deep transverse intermetatarsal ligament for plantar foot scans and the upper third of the joint space for dorsal foot scans. All US scanning was performed in accordance with the British Medical Ultrasound Society guidelines for safe use (Fitzpatrick *et al.* 1998) and completed by two trained podiatrists (LH and CJB), the reliability of which was determined to be substantial (kappa=0.7). Furthermore, the reliability of a podiatrist (CJB) and radiologist has been previously demonstrated and reported to be moderate-substantial (Bowen *et al.* 2008).

Intermetatarsal lesions were classified as bursae if a defined region of hypo-echogenicity, occurring within the IM spaces, either inferior or superior to the deep transverse intermetatarsal ligament, was observed in the perpendicular transverse and longitudinal plantar scanning planes. Plantar lesions were classified as bursae if a defined region of hypo-echogenicity, occurring inferior to the level of the base of the metatarsal heads, was observed in the perpendicular transverse and longitudinal scanning planes. Thus lesions were defined based upon location and grey-scale US properties and not size or shape. MTP joint hypertrophy was noted as present if distension of the dorsal synovial joint membrane, as a consequence of either increase in synovial fluid volume or membrane thickening, extended beyond the proximal or distal attachment sites at the metatarsal head or base of the proximal phalanx respectively. Metatarsal head erosion was noted as present if a distinct loss in cortical bone was observed in two perpendicular scanning planes.

4.2.5 Analysis

All analysis was completed using Stata version 11.0 (Stata Corp, College Station, Texas, USA), or SPSS version 18.0 (Chicago, Illinois, USA). The sample size for this study was determined using Pearsons' correlation coefficient estimates of association between bursae presence/absence and patient reported foot complications (r=0.211; p=0.371), based upon previously reported data (Bowen *et al.* 2009). Prior to analysis, data distribution was checked for

inconsistencies, outliers and missing information. Histograms and scatter plots were used to assess whether the data followed a normal distribution. The demographic and clinical characteristics of the study participants are presented as the mean/median, standard deviation (SD) and range. Estimations of differences in demographic or clinical characteristics between those patients who did or did not respond to invitation for inclusion at year-three are presented as mean and 95% confidence intervals. Statistically significant differences in measured variables between response groups were determined using independent sample t-tests.

The total number of US-detectable episodes of FFB, JH or ER for both feet combined was calculated for each patient; these count scores were treated as continuous variables for the purposes of analysis, although were bounded between 0-18 for FFB and 0-10 for JH and ER. Point prevalence was used to describe the occurrence of FFB at each time point. The distribution of FFB across forefoot sites is expressed as a percentage of the total observed FFB. The US appearance of FFB is discussed descriptively. Correlation coefficient analysis was used to determine the statistical significance of potential associations between FFB count and indicators of disease activity or disability at year three.

Longitudinal analysis was completed using an adjusted study cohort, which was inclusive of participants who attended all episodes of data collection only. The ‘change in score’ value used for analysis purposes was an expression of the difference between baseline and year three scores. Correlation coefficient analysis was used to determine the statistical significance of potential associations between changes in the primary outcome of interest (FFB count) and changes in other explanatory variables from baseline to year three (markers of disease activity and disability). Multiple linear regression techniques with ordinary least squares estimation were used to explore statistical relationships between the primary outcomes of interest and potential explanatory variables. Significant factors were subsequently entered into a multiple linear regression model to identify potential confounding or colinearity within the study findings. A pattern analysis technique was used to demonstrate the longitudinal variability of each measure of disability, specific to each participant. Participants were categorised based upon the manner in which the outcome of interest increased or decreased, by 1 score or more, or remained the same across time points, and were subsequently stratified into high (FFB>4) or low (FFB≤3) FFB count groups. Differences between groups were explored using Chi^2 analyses.

4.3 Results

4.3.1 Study cohort characteristics

At baseline 149 participants were recruited to the study. Of those, 120 returned at year one and of those 60 returned at year three. Five patients died between the year-one and three appointments. Respondents unable to attend the year-three appointment cited lack of time (n=6), unwillingness to travel (n=4), poor mobility (n=2) or other personal factors (n=5) as reasons for non-attendance. A summary of response analysis is shown in table 14. The

Levenes' test for equal variance identified that for both weight and DAS 28-CRP variables this could not be assumed and therefore adjusted values are reported.

Table 14: Response analysis
Results are reported for the comparative evaluation of responders and non-responders between stated time points.
Where BMI = Body Mass Index; CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; DAS = Disease Activity Score; FIS_{IF} = Foot Impact Score impairment/footwear subscale; FIS_{AP} = Foot Impact Score activity/participation limitation subscale.

	BASELINE→YEAR-THREE		YEAR-ONE→YEAR-THREE		BASELINE→YEAR-ONE	
	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
age (years)	1.1 (-3.0–5.2)	0.592	1.9 (-2.5-6.3)	0.402	-1.4 (-6.4-3.7)	0.588
weight (Kg)	0.2 (-4.8-5.2)	0.945	-0.9 (-6.4-4.7)	0.753	3.3 (-2.9-9.5)	0.297
BMI (Kg/m^2)	0.3 (-1.5-2.1)	0.745	-0.9 (-2.9-1.1)	0.394	1.6 (-0.9-4.0)	0.203
disease duration (years)	0.4 (-3.0-3.9)	0.808	0.2 (-3.6-4.0)	0.915	1.2 (-3.0-5.4)	0.570
CRP (mg/L)	0.6 (-5.6-6.8)	0.840	2.7 (-2.8-8.2)	0.333	-0.5 (-8.2-7.2)	0.900
ESR (mm/hr)	5.1 (-1.3-11.5)	0.116	2.0 (-5.4-9.4)	0.594	2.2 (-5.8-10.2)	0.580
DAS 28-CRP	0.5 (0.1-1.0)	0.029*	0.3 (-0.2-0.8)	0.256	0.3 (-0.3-1.0)	0.329
DAS 28-ESR	0.5 (0.02-1.0)	0.041*	-0.02 (-0.6-0.6)	0.938	0.6 (-0.1-1.2)	0.121
FIS_{IF}	-0.2 (-1.9-1.4)	0.794	-0.5 (-2.3-1.2)	0.543	0.9 (-1.1-2.9)	0.393
FIS_{AP}	-0.01 (-3.1-3.1)	0.993	-0.4 (-3.9-3.2)	0.837	3.0 (-0.8-6.8)	0.124

A further month-by-month summary of response and recruitment rates can be found in appendix section A8. Due to the number of participants responding but unable to attend the clinical appointment for US review from December 2009-March 2010, the recruitment criteria and associated ethical application were revised to allow completion of the FIS questionnaire only if patients were unable to attend the hospital. This change was implemented in April 2010. Three subsequent study participants completed the FIS questionnaire but did not attend any other assessment. At year one no significant differences between responders and non-responders for any tested variables were identified. The results of responder analysis at year three suggested that those patients with higher disease activity, as indicated by DAS 28-CRP and DAS 28-ESR, were more likely to return (p=0.029 and p=0.041 respectively). A summary of the demographic and clinical characteristics of the study population at each time point is given in table 15.

Table 15: Cohort demographic & clinical characteristics
N.B. data is reported following adjustment for cases completing all episodes of data collection.
Where MTP = metatarsophalangeal; DAS = disease activity score; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FIS_{IF} = foot impact score impairment/footwear subscale; FIS_{AP} = Foot Impact Score activity/participation limitation subscale.

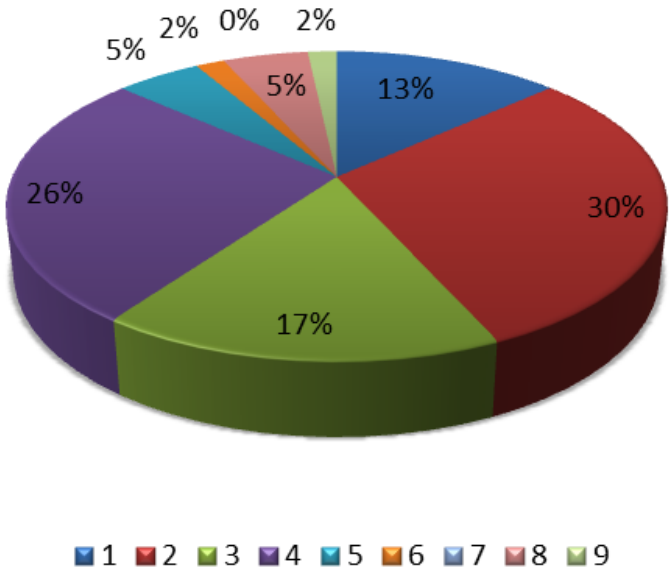
	BASELINE (N=149) **Mean**, (SD), Range	YEAR ONE (n=120) **Mean**, (SD), Range	YEAR THREE (n=60) **Mean**, (SD), Range
age (years)	**59.4**, (12.3), 25-87	**60.7**, (12.1), 26-88	**62**, (11.8), 28-89
height (m)	**1.6**, (0.1), 1.2-2.1	**1.6**, (0.1), 1.2-2.1	**1.7**, (0.1), 1.3-2.1
weight (Kg)	**73.3**, (16.1), 43.8-118.9	**71.9**, (15.9), 43.8-110.2	**71.0**, (13.6), 42.2-108
BMI (Kg/m^2)	**27.2**, (4.9), 18.5-41.6	**27**, (5.5), 16.8-48.2	**25.5**, (3.9), 19.1-33.4
disease duration (years)	**12.3**, (10.3), 1.0-43.0	**13.1**, (10.4), 2.0-44.0	**15.1**, (10.3), 3.0-45.0
gender	29 (M): 121 (F)	23 (M): 97 (F)	9 (M): 51 (F)
MTP joint hypertrophy	**2.8**, 2.7 (0-10)	**1.7**, (1.9), 0-7	**2.5**, (2.8), 0-10
erosion	**3.7**, (2.6), 0-10	**4.8**, (3.0), 0-10	**6.0**, (3.3), 0-10
CRP (mg/L)	**12.1**, (20.4), 2-100	**12.8**, (18.8), 1-122	**8.8**, (13.2), 1-73
ESR (mm/hr)	**20.3**, (16.5), 2-100	**22.5**, (16.9), 1-81	**20.1**, (20.5), 0-111
DAS 28-CRP	**3.1**, (1.2), 1.1-6.6	**3.1**, (1.2), 0.5-6.6	**2.9**, (1.2), 1-5.4
DAS 28-ESR	**3.6**, (1.3), 1.1-6.5	**4.1**, (1.5), 0.5-6.6	**3.1**, (1.3), 0.3-6
FIS_{IF}	**10.7**, (4.8), 0-20	**10.4**, (5.1), 0-20	**10.4**, (5.1), 0-20
FIS_{AP}	**16.9**, (10.3), 0-29	**17.3**, (9.9), 0-30	**17.4**, (9.8), 0-30

As shown in table 16, no significant differences in participant markers of RA disease activity were reported longitudinally.

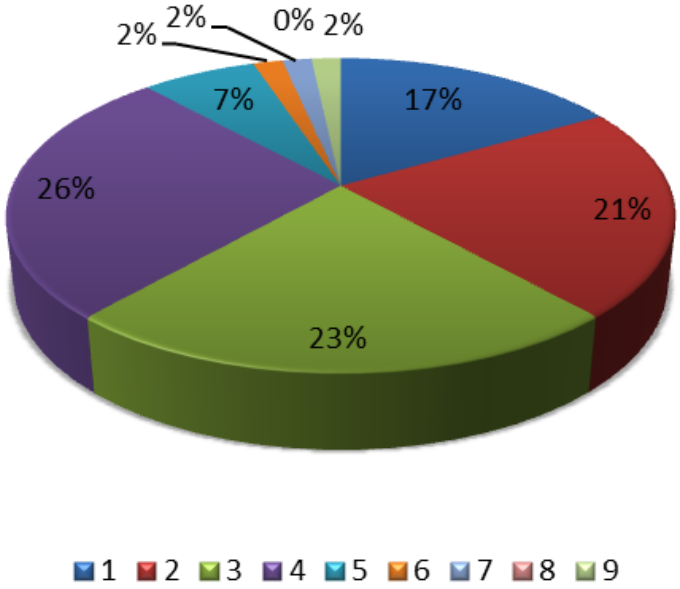
Table 16: Longitudinal changes in disease activity
Results are reported for evaluation of difference in scores between time points for the same participant. Therefore the maximum possible sample size for comparison with year one and year three data is 120 and 60 respectively. *= Significant at level of 5% probability (2-tailed).

	BASELINE→YEAR THREE		YEAR ONE→YEAR THREE		BASELINE→YEAR ONE	
	Mean difference (95% CI)	p-value	Mean Difference (95% CI)	p-value	Mean difference (95% CI)	p-value
MTP joint hypertrophy	-0.9 (-1.9 – 0.06)	0.066	0.4 (-0.5 – 1.4)	0.384	1.07 (0.2 – 1.9)	0.009*
erosion	1.4 (-2.5 – -1.4)	0.011*	-2.3 (-3.2 - -1.4)	0.000*	-1.1 (-2.0 - -2.0)	0.018*
DAS 28-CRP	-0.08 (-0.6 – 0.5)	0.751	0.1 (-0.4 – 0.7)	0.660	0.14 (-0.3 – 0.6)	0.534
CRP (mg/L)	5.8 (-3.5 – 15.2)	0.217	4.2 (-2.4 – 10.7)	0.207	-2.8 (-13.1 – 7.4)	0.580
ESR (mm/hr)	2.2 (-4.9 – 9.3)	0.539	-0.1 (-5.0 – 4.9)	0.977	-1.6 (-7.3 – 4.1)	0.582

As demonstrated in table 15, mean FIS_{IF} and FIS_{AP} scores remained moderate across all time points. Longitudinally, the change in mean FIS_{IF} score from baseline to year three suggests a slight improvement over time, while FIS_{AP} deteriorated, although reported changes in disability scores between time points were not significantly different. As illustrated in figure 33, few patients remained in a stable state of reported disability, with the majority of patients (98%, n=59) experiencing some fluctuation, with regards to both improvement and worsening. Overall, 15% of participants (n=9) reported deterioration in FIS_{IF} such that they changed severity classification from mild to moderate or from moderate to severe. Conversely, 14% of participants (n=8) reported improvement in FIS_{IF} such that they changed severity classification from severe to moderate or from moderate to mild. Similarly, 22% of participants (n=13) reported deterioration in FIS_{AP} such that they changed severity classification from mild to moderate or from moderate to severe. Conversely, 23% of participants (n=14) reported improvement in FIS_{AP} such that they changed severity classification from severe to moderate or from moderate to mild. Assuming a clinically meaningful change in score of 3 points or more (Turner *et al.* 2007), thus regardless of disability category, 10% of participants (n=6) reported worsening foot impairment while 9% of participants (n=15) reported improvement. Similarly, 23% of participants (n=14) reported a clinically meaningful increase in activity limitation, while 18% (n=11) reported improvement.



33a. FIS_{IF}



33b. FIS_{AP}

Figure 33: Frequency of pattern occurrence for changes in reported disability over time
Where 1=↓↓, 2=↓↑, 3=↑↑, 4=↑↓, 5=↔↓, 6=↔↑, 7=↔↔, 8=↓↔, 9=↑↔; where ↓= reduction in 1 score or more between time points, ↑= increase in 1 score or more between time points, ↔ = no change in score between time points. FIS_{IF} = foot impact score impairment/footwear subscale; FIS_{AP} = Foot Impact Score activity/participation limitation subscale

4.3.2 The natural history of FFB

The point prevalence of US-detectable FFB at baseline, year one and year three was calculated to be as follows:

- At baseline (N=150), the overall point prevalence of FFB was 93 per 100 RA participants (mean: 3.54, SD: 2.22, range: 0-9); (139/150).
- At year one (N=120), the overall point prevalence of FFB was 93 per 100 RA participants (mean: 3.70, SD: 2.20, range: 0-11); (112/120).

- At year three (N=56), the overall point prevalence of FFB was 88 per 100 RA participants (mean: 3.05, SD: 2.14, range: 0-11); (49/56).

However, due to participant drop-out from the study it was considered that adjusted time-matched point prevalence may be more representative of the true trend in FFB prevalence scores over time. The adjusted time-matched prevalence scores are therefore summarised as follows:

- At baseline, the adjusted point prevalence of FFB was 95 per 100 RA participants (mean: 3.58, SD: 2.36, range: 0-8); (57/60).
- At year-one, the adjusted point prevalence of FFB was 92 per 100 RA participants (mean: 3.80, SD: 2.44, range: 0-11); (55/60).

Changes in the prevalence of FFB were not statistically significantly different over time, as demonstrated in table 17.

Table 17: Longitudinal changes in FFB prevalence
N.B. data included within this analysis includes year-matched cases for whom only baseline, year-one and year-three data is available. Therefore the maximum possible sample size for comparison is 60 participants. However, due to missing data these totals are variable.
*= Significant at level of 5% probability (2-tailed).

	Mean diff (95% CI)	P-value
BASELINE→YEAR-THREE (N=56)	0.8 (-0.03 – 1.7)	0.058
YEAR-ONE→YEAR-THREE (N=56)	0.7 (-0.1 – 1.5)	0.760
BASELINE→YEAR-ONE (N=60)	-0.07 (-0.912 – 0.779)	0.875

A similar frequency of total FFB occurrence was noted across time points, however, the distribution of FFB across forefoot sites varied, as illustrated in figure 34. At baseline a greater proportion of the total FFB were located within the intermetatarsal spaces. A similar but less distinct trend is observed at year-three, with the greatest notable difference being an increase in FFB reported plantar to the first MTP joint with a concomitant reduction within the IM 1-2 space.

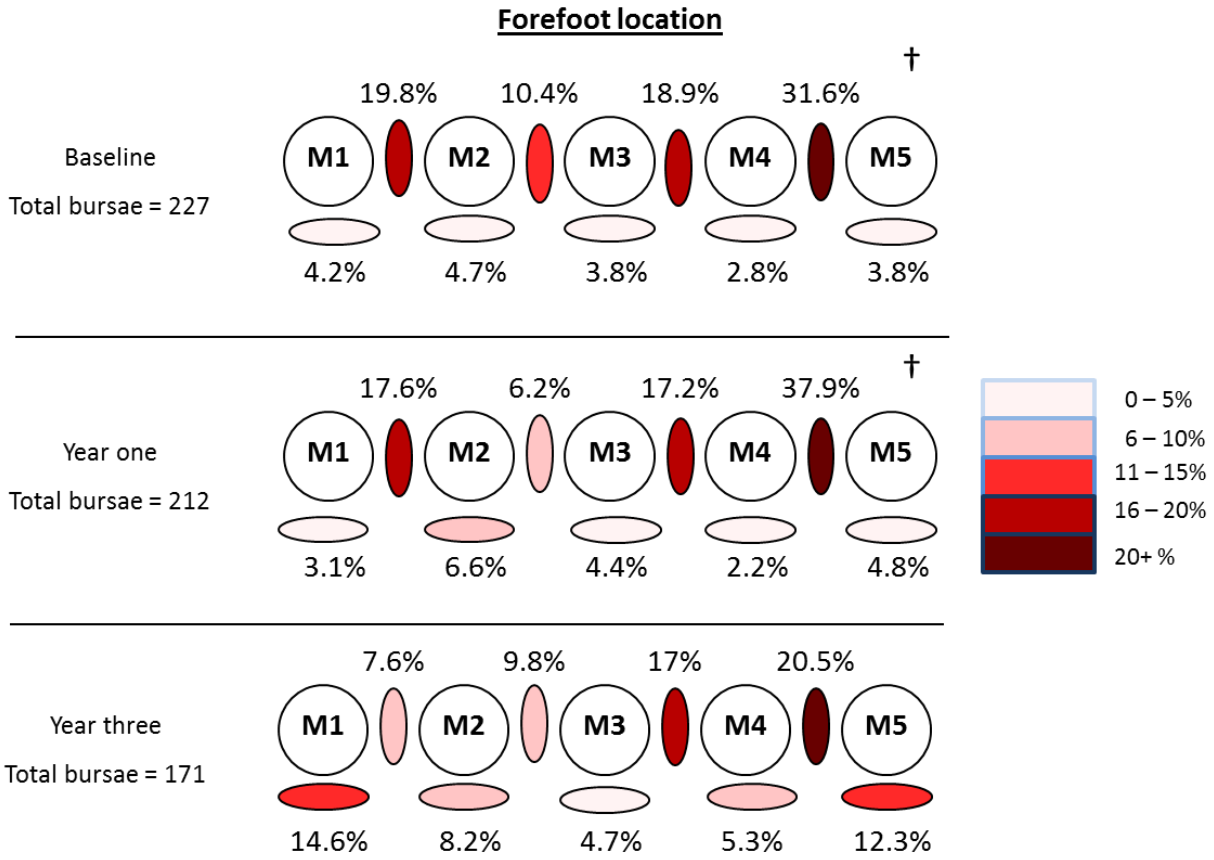


Figure 34: The distribution of FFB across forefoot sites at each time point
Values are expressed as percentage of total observed FFB in each location. Values are representative of the adjusted cohort of participants who completed all episodes of data collection only.
Where M1-5 = plantar metatarsophalangeal joint region.

Overall, bilateral FFB were detected in 87.5% of participants at the year-three follow-up visit (N=49)). Of the total FFB observed (n=171), 53.7% of FFB (n=43) were noted within the intermetatarsal region, whereas 46.2% of FFB (n=37) were noted plantar to the metatarsal heads. The most common location for FFB, when both feet were combined, was the intermetatarsal 4-5 space (62.5% of participants, n=35), closely followed by the intermetatarsal 3-4 space (51.8% of participants, n=29), however a range in distribution across all sites was observed. The least common sites for FFB occurrence were plantar to the third and fouth metatarsal head regions (14.3%, n=8 and 16.1%, n=9 respectively).

4.3.3 The US characteristics of FFB

Examples of intermetatarsal lesions, classified as bursae based on the presence of a defined region of hypo-echogenicity occurring within the IM spaces plantar to the DTML, are illustrated in figures 35a and b.

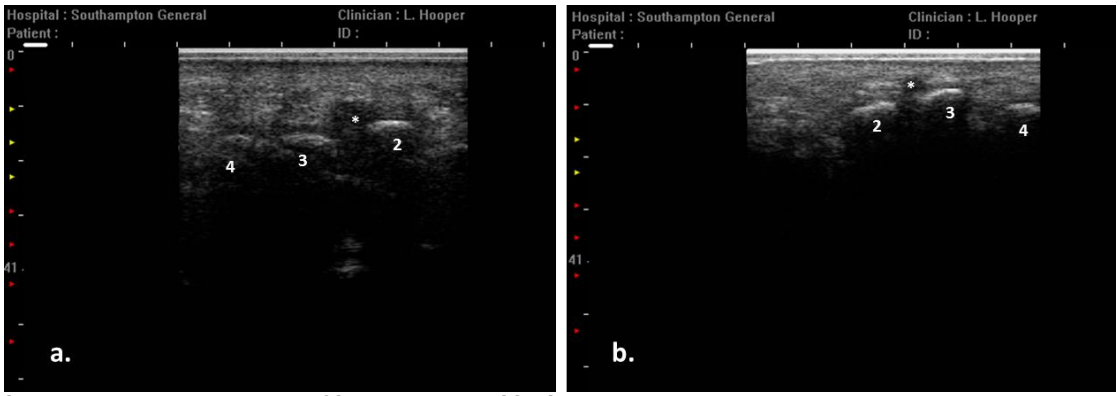


Figure 35: US appearances of intermetatarsal lesions
Where 35a illustrates a transverse scan of the right foot with identification of the bases of the metatarsal heads (2-4) and an intermetatarsal lesion (*), 35b) illustrates a transverse scan of the left foot with identification of the bases of the metatarsal heads (2-4) and an intermetatarsal lesion (*).

Differences in the ultrasound appearances of IM lesions were noted; a subset of FFB appeared as well defined homogeneously hypoechoic with well-defined and regular borders (figure 28a), while an alternate subset appeared as diffuse heterogeneously hypoechoic, containing an anechoic centre with irregular borders (figure 28b).

All plantar lesions were noted as being hypoechoic discontinuations within the plantar soft tissues of the forefoot, with a compressible, anechoic region at the centre, and were thus classified as FFB. However, the appearance of such lesions was also highly variable, ranging from superficial slit-like cavities (figure 36a) to larger spherical structures occurring either plantar or dorsal to the superficial transverse intermetatarsal ligament (figure 36b).

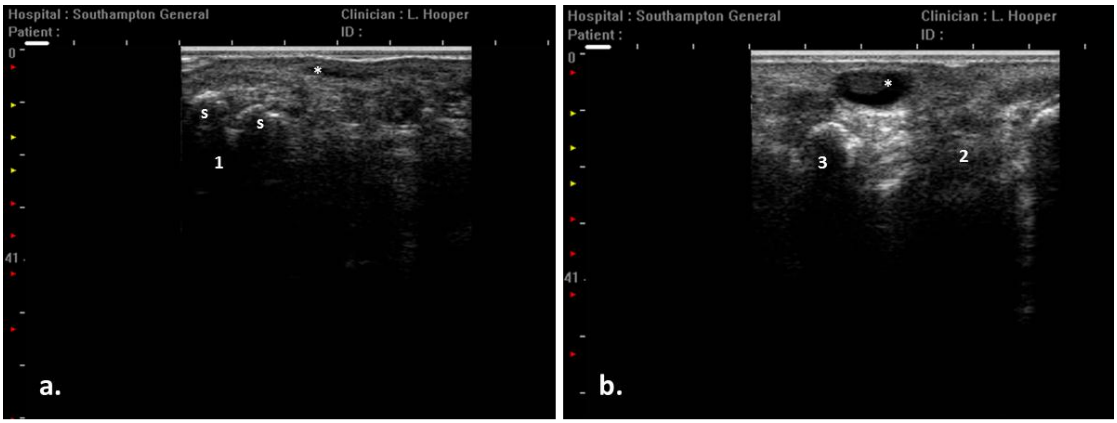


Figure 36: US appearances of plantar forefoot lesions
Where 36a illustrates a transverse scan of the left foot with identification of the sesamoids (s) and a slit-like fluctuant cavity superficial to the region of the 2nd metatarsal head, 36b illustrates a transverse scan of the right foot with identification of a large fluctuant spherical lesion, with anechoic fluid cavity enveloping a hypoechoic free floating central mass, plantar to the intermetatarsal 2-3 space.

In addition to lesions being located within the intermetatarsal and plantar metatarsal regions as previously reported, bursal-like cavities were also observed in association with and adjacent to

other forefoot structures. As illustrated in figures 37a and b, a bursal cavity (*) was also noted curving around the plantar and tibial borders of the medial sesamoid of the right foot. The lesion appears slit-like in figure 37a when viewed without the application of plantar compression. However, the same lesion, seen enlarged in figure 37b, demonstrates lateral capsular bulging when displaced by applying plantar compression with the ultrasound transducer. This exemplifies a number of cases where the still grey-scale image of the bursal cavity was highly fluctuant dependent upon operator transducer orientation or contact pressure.

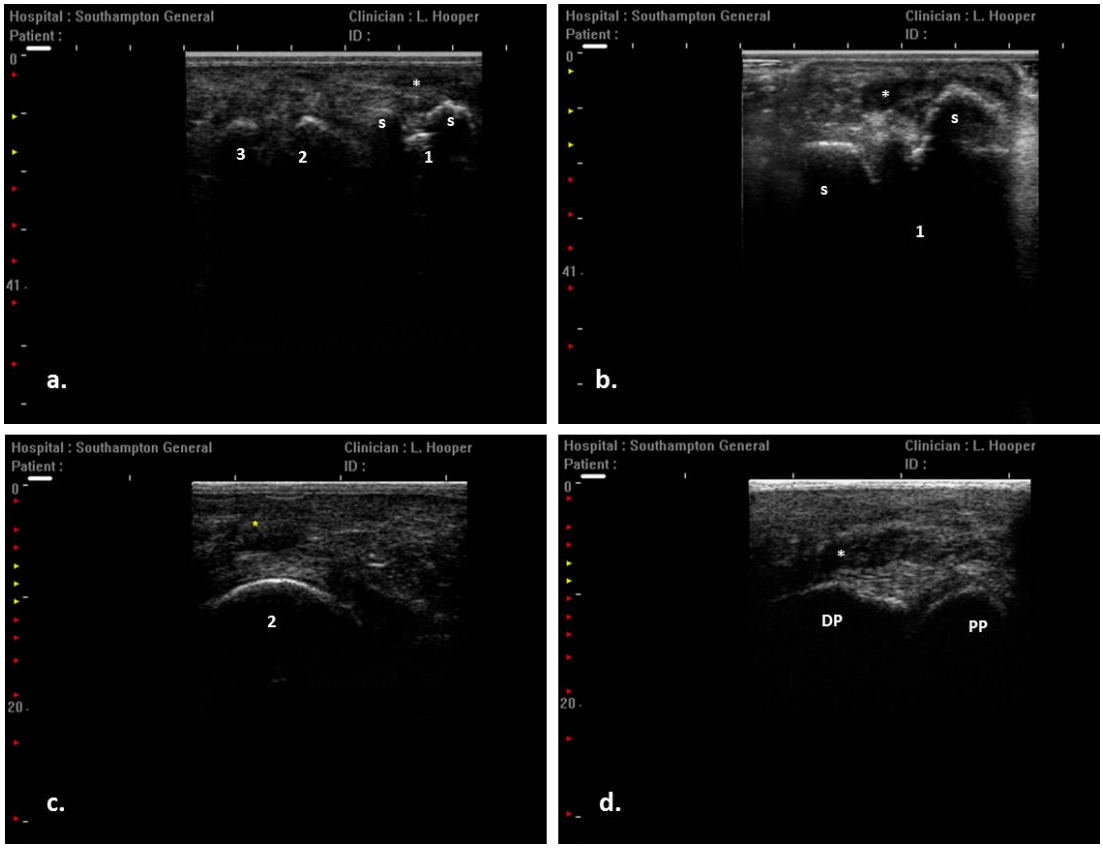


Figure 37: US appearances of other hypoechoic forefoot lesions
Where 37a illustrates a transverse scan at the level of the metatarsal heads using the 5-10MHz probe, with identification of the sesamoids (s) and metatarsal heads 1-3. The bursal cavity, located plantar to the medial sesamoid (*), appears slit-like without plantar compression with the transducer. However, the same lesion seen enlarged in figure 37b demonstrates lateral capsular bulging when displaced by applying plantar compression with the transducer (*). 37c Illustrates a longitudinal scan plantar to the 2nd metatarsal head of the right foot using the 8-16MHz probe, with identification of a capsular lesion superficial to the flexor digitorum longus tendon (*). 37d Illustrates a longitudinal plantar scan of the 1st interphalangeal joint of the right foot using the 8-16MHz probe, with identification of a lesion superficial to the inserting slip of the flexor hallucis longus tendon. DP= distal phalanx, PP= proximal phalanx**.**

The bursal cavity noted plantar to the second metatarsal head in figure 37c, exemplifies an instance of lesion occurrence, superficial to but remaining separate from, the underlying flexor digitorum longus tendon, which remained homogeneous with no discontinuation to fibrillar striation. This was the single detected occurrence of a separate lesion superficial and distinct from the tendon, with no interjecting fatty tissue. In all other cases of a possible bursal cavity being located immediately plantar to the tendon, scanning in perpendicular planes using the 8-

16 MHz transducer subsequently identified the tissue disruption as regions of tenosynovitis. The bursal cavity shown in figure 37d, illustrates the occurrence of a lesion within the soft tissues of the hallux, located plantar to the interphalangeal joint, which could be tracked proximally to the base of the phalanx. The lesion is separated from the inferior flexor hallucis longus tendon slip by fibro-fatty tissue, illustrating the distinct nature of this structure. The lesion appears as a heterogeneous hypoechoic mass with regions of total anechogenicity. Instances of plantar hallux lesions were noted in two study participants. A summary of all observed lesions is shown in figure 38.

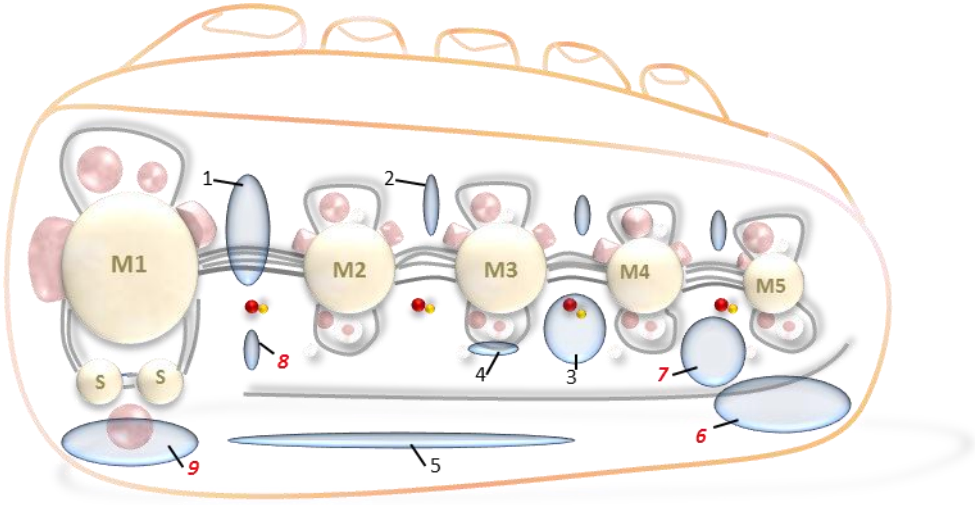


Figure 38: Forefoot anatomy & identification of observed bursae
Where FFB 1-5 were previously identified, FFB 6-9 are additionally identified within this study.
1 = 1-2 intermetatarsal bursa coursing adjacent to adductor hallucis tendon that may extend beyond the deep transverse intermetatarsal ligament, 2 = intermetatarsal bursae that may become hypertrophied extending beyond the deep transverse intermetatarsal ligament, 3 = bursae associated with neurovascular bundle, 4 = bursae associated with superior aspect of flexor digitorum brevis tendon, 5 = plantar mechanical bursae, 6 = large 'billowing' intermetatarsal bursae located plantar to the deep transverse intermetatarsal ligament, may appear as either an organised homogeneous hypoechoic mass, or diffuse hypoechoic region with or without an anechoic centre, 7 = large spherical encapsulated intermetatarsal bursae, may appear as either a hypoechoic mass with or without an anechoic centre, 8 = small intermetatarsal bursae, appearing as a well-defined region with hypoechoic signal, 9 = large encapsulated spherical bursae located plantar to the 1st MTPJ, often found plantar to the medial sesamoid bone. *Image author's own.*

4.3.4 The clinical importance of FFB

Increased FFB count was significantly associated with increased metatarsal head erosion (r=0.419, p=0.001) but no other indicators of disease activity at year-three. A reduction in FFB count longitudinally was associated with reduced DAS 28-CRP scores (r=-0.331, p=0.030), but no other indicators of disease activity.

The presence of FFB and disease duration at baseline were determined to be significant independent predictors of FIS_{IF} scores at year-three, where a high presence of FFB or increased

disease duration were indicative of worsening foot impairment longitudinally (R^2=0.10, p=0.012; R^2=0.11, p=0.009 respectively, table 18a). Similarly the presence of FFB and increased disease duration, in addition to the increased presence of ER and disease activity at baseline, were all determined to be significant predictors of FIS_{AP} at year-three, where a high presence of FFB or ER, increased disease duration and increased disease activity were indicative of increased activity limitation longitudinally (R^2=0.12, p=0.006; R^2=0.09, p=0.019; R^2=0.16, p=0.002; R^2=0.11, p=0.025 respectively, table 18a).

Table 18a: Predictors of disability: univariate, adjusted, linear regression analysis
Reported results were adjusted for age and disease duration.
FIS_{IF} = Foot Impact Score impairment/footwear subscale; FIS_{AP} = Foot Impact Score activity/participation limitation subscale; CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; DAS = Disease Activity Score.

	Impairment (FIS_{IF})				Activity limitation (FIS_{AP})			
EXPLANATORY VARIABLE	Reg. Coeff.	p-value (95% CI)	R^2	F-value	Reg. Coeff.	P-value (95% CI)	R^2	F-value
forefoot bursae	0.70	0.012 (0.02 – 1.23)	0.10	6.77	1.47	0.006 (0.44 – 2.5)	0.12	8.14
MTP joint hypertrophy	0.29	0.239 (-0.20 – 0.78)	0.02	1.42	0.25	0.608 (-0.71 – 1.2)	0.004	0.27
erosion	0.49	0.053 (-0.01 – 0.98)	0.01	3.89	1.14	0.019 (0.20 – 2.09)	0.09	5.84
DAS 28-CRP	1.23	0.051 (-0.07 – 2.47)	0.09	4.02	2.43	0.025 (0.32 – 4.54)	0.11	5.40
DAS 28-ESR	1.13	0.051 (-0.01 – 2.3)	0.08	4.0	2.12	0.035 (0.15 – 4.09)	0.09	4.70
CRP (mg/L)	0.002	0.941 (-0.07 – 0.07)	0.00	0.01	0.02	0.802 (-0.12 – 0.15)	0.001	0.06
ESR (mm/hr)	0.03	0.467 (-0.05 – 0.11)	0.01	0.54	0.17	0.033 (0.01 – 0.32)	0.08	4.75
disease duration	0.16	0.009 (0.04 – 0.27)	0.11	7.20	0.36	0.002 (0.14 – 0.58)	0.16	10.82

All identified independently significant explanatory variables were entered into a further multivariate regression model, adjusted for age and disease duration, in order to identify potential covariate factors. As shown in table 19, the significance of each independent predictor variable diminished, suggesting likely colinearity between the included model factors. Additionally, in each model, the increased adjusted model R^2 suggests that the colinearity between the included model factors may be synergistic in overall effect.

Table 19: Predictors of disability: multivariate linear regression analysis
Where 19a shows results of multivariate regression analysis for previously identified independent predictors of reported foot impairment; 19b shows results of multivariate analysis for previously identified predictors of activity limitation.
FIS_{IF} = Foot Impact Score impairment/footwear subscale; FIS_{AP} = Foot Impact Score activity/participation limitation subscale; CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; DAS = Disease Activity Score.

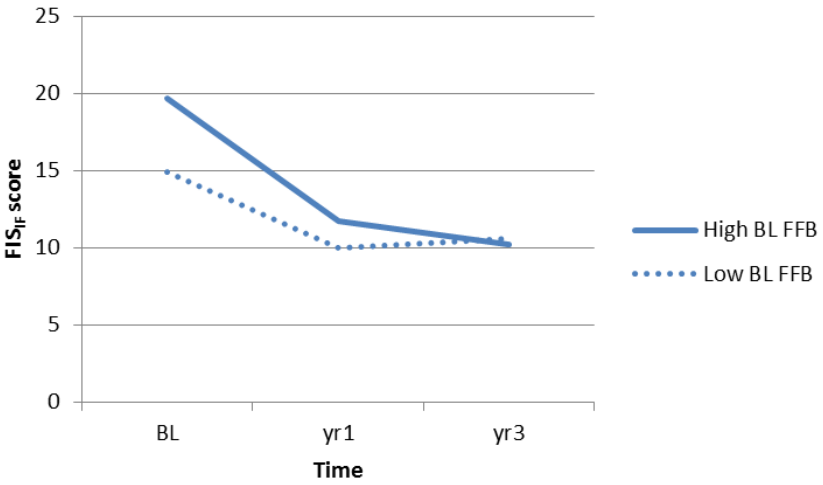
19a.

EXPLANATORY VARIABLE	Impairment (FIS_{IF}) β	p-value (95% CI)	R^2 (adj. R^2)	F-value
forefoot bursae	0.50	0.084 (-0.07 – 1.06)	0.16 (0.13)	5.28
Disease duration	0.12	0.067 (-0.01 – 0.24)		

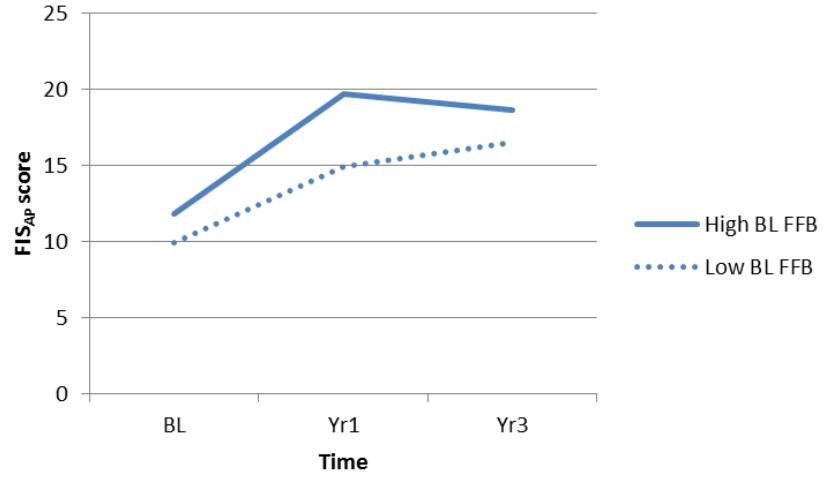
19b.

EXPLANATORY VARIABLE	Activity limitation (FIS_{AP}) β	P-value (95% CI)	R^2 (adj. R^2)	F-value
forefoot bursae	0.33	0.552 (-0.78 – 1.43)	0.35 (0.27)	4.22
erosion	0.87	0.083 (-0.12 – 1.87)		
DAS28-CRP	2.36	0.026 (0.30 – 4.43)		
ESR (mm/hr)	0.11	0.136 (-0.04 – 0.25)		
disease duration	0.18	0.147 (-0.07 – 0.43)		

Following identification of FFB as a novel predictor of both FIS_{IF} and FIS_{AP}, data were stratified into groups of high (n=25) and low (n=35) FFB count at baseline; where 0-3 was defined as low, and 4 or more as high based upon clinical observation and overall observed score range. As illustrated in figure 39, a trend towards increased reported disability in those patients with increased FFB presence at baseline was observed, however differences between groups were not significant.



39a. FIS$_{IF}$



39b. FIS$_{AP}$

Figure 39: FFB & changes in foot-related disability

Where patients were grouped by high (≥4)/low (≤3) FFB count at baseline. FIS = Foot Impact Score; IF = Foot impairment subscale; AP = Activity limitation subscale; BL = baseline; Yr = Year.

4.4 Discussion

This study has uniquely demonstrated the epidemiology of FFB in patients with RA. Differences in the US characteristics of observed FFB have been reported. Furthermore the clinical importance of FFB in patients with RA has been evaluated. In the studied cohort, FFB were consistently highly prevalent, albeit slightly reducing, longitudinally. This observed FFB prevalence was determined to be significantly associated with RA disease activity. The findings of this study therefore appear to reinforce the hypotheses of previous authors which suggest an association between FFB presence and RA disease activity ((Bowen *et al.* 2009, Bowen *et al.* 2010c, Mutlu *et al.* 2006, Koski 1998)). Uniquely however this study has demonstrated a longitudinal association between FFB and RA disease activity.

Furthermore, previous authors, such as Turner *et al*. (Turner *et al.* 2006, Turner *et al.* 2008), have highlighted the relationship between disease mediated inflammation, structural changes to joint integrity and functional decline, and cited these as probable causes for the high prevalence of disability observed in RA populations (Woodburn *et al.* 2002b, van der Leeden *et al.* 2006, van der Leeden *et al.* 2008). This study has uniquely proposed and demonstrated that FFB may additionally be a clinically relevant feature of RA disease related to disability; where the presence of FFB at baseline was identified as a significant independent predictor of disability after three years in this patient group. Additionally, changes in FFB presence and disease activity were both associated with changes in reported disability. Two plausible hypotheses, explaining the relationship between FFB presence and foot-related disability in patients with RA, have been proposed; 1. FFB synovium is susceptible to disease-mediated inflammatory processes in a similar manner to joint synovium, and FFB are therefore representative of disease activity (Bossley and Cairney 1980), 2. FFB occur or hypertrophy as a consequence of poor forefoot biomechanical function, and are therefore indicative of physical changes in joint function (Studler *et al.* 2008, Ahmed *et al.* 1994). A combination of both hypotheses is also plausible.

The association between FFB and inflammatory disease has been previously documented in both histological and cross-sectional imaging studies (1983, 1982, 1998). The identification of a synovial membrane within intermetatarsal FFB, with inwardly projecting villi (Hernandez *et al.* 1991), or a fibro-collagenous membrane which exhibits some superficial synoviocytic cellular elements (Chauveaux *et al.* 1987, Meenagh *et al.* 2006), appears to provide support for the notion that FFB are directly associated with disease activity. Additionally, a number of cross sectional imaging studies reinforce this theory, suggesting that the particular susceptibility of FFB, above other synovial structures, makes them a clinically useful, representative feature of minimal disease activity (Koski 1998, 1998, 2003). Conversely, a number of authors propose that at least a subset of plantar FFB may be entirely generated as a consequence of mechanical irritation (Aguiar *et al.* 2005, Claustre *et al.* 1983, Meurman 1982, Studler *et al.* 2008). Authors such as Studler *et al*. (2008) describe these as slit-like cavities of fluid, lacking a synovial membrane, that manifest predominantly in areas of torsional stress. This is perhaps reinforced by the findings of Ahmed *et al*. (1994), who report the development of mechanical bursae at the socket interface in four below knee amputees. In such instances mechanical FFB may be considered advantageous, allowing compression or torsion between otherwise densely fibrous, rigid tissues. The proposed aetiology is mechanically induced separation of the fibro-collagenous tissues, resulting in the accumulation of extra-cellular fluid in these spaces (Hernandez *et al.* 1991). It is currently unclear to what extent the observed differences in the US appearance of FFB demonstrated in this study may reflect alternate subsets of FFB in this patient group. Future research that explores the underlying aetiology or patho-physiology of FFB in patients with RA would identify future potential therapeutic targets.

4.4.1 Study limitations

This study has a number of strengths and potential limitations. The studied population is a consecutive sample of well phenotyped patients for whom unique longitudinal data is now available, who may be considered as representative of patients with RA attending secondary care in England. However, there is some loss to follow-up. None the less, the response analysis completed suggests that there is no systematic differential bias in any of the key measured variables introduced as a result of this. It is possible that some of the included participants have modified their responses regarding foot health as a consequence of inclusion within the study. However the reported values for both the primary and secondary outcome measures are consistent with those reported in previous works, thereby reducing the likelihood of the presence of this effect within the reported results. It is however possible that those patients with minimal RA disease, who do not attend a secondary care environment for their rheumatological care, will have been selectively omitted from recruitment to this study, resulting in a sampling bias. Given the unclear nature of the association between FFB, RA disease activity and biomechanical impairment, the likely modification to the external validity of the reported results made by omission of this group is unclear.

In order to minimise observer bias in the primary outcome measure, the US examination was completed prior to all other clinical assessment of foot health. Additionally the FIS questionnaire was graded after the completion of all other data collection activities. Of additional note, the FIS score used within this study was not originally intended for longitudinal use. However, in the absence of a validated longitudinal scoring system the authors felt that FIS use was appropriate in this preliminary work. The development of a clinical tool, sensitive to change and validated for use in this population would significantly enhance any subsequent work in this area. The use of Power Doppler (PD) for the determination of active inflammation, as an adjunct to US examination, would also enhance future work in this area. PD was not available at the time of this study and therefore it is not possible to determine whether identified FFB were actively inflamed (bursitis). None the less, this does not detract from the significant findings of this study which show that the US-detected FFB are indicative of disability and therefore should be considered a clinically relevant feature of RA disease.

The reduced sample size of this study may account for the lack of significant difference in disability reported between high and low FFB groups, via the introduction of a type II misclassification error. However, the upper categorical boundaries were selected based upon limited clinical understanding of FFB and as such stringent cut-off margins were selected. Of course, review of these boundaries may yield significant differences between groups. It should also be noted that, for some participants, inclusion within the study identified a number of previously untreated foot impairment and footwear complications at the baseline appointment, for which subsequent treatment was offered. This may account for the slight improvement in impairment scores reported over time, and therefore the generalisability of these results to

patients not receiving podiatric care should be considered. Similarly, the rationale for the potential association between disability and FFB remains unclear. It is possible that improvement in systemic disease activity may lead to an increase in weight bearing activity as patients undertake more tasks as part of daily living. Concomitantly with this however, the biomechanical stresses placed upon the foot may also be elevated. The relative contribution of elevated adverse biomechanical function to FFB prevalence remains unclear. Conversely, it is also plausible that a worsening of systemic disease activity may also see concomitant increases in the hypertrophy or inflammation of synovially lined structures such as FFB. Again the relative contribution of elevated inflammation to FFB prevalence also remains unclear.

Having identified FFB as clinically relevant in patients with RA, further exploration of the potential relationships between FFB and biomechanical impairment or disease mediated inflammation would improve the current understanding of the biological mechanisms contributing to the potentially pathological nature of observed FFB. Evaluation of the presence, distribution and characterisation of US-detectable FFB in healthy volunteers, for whom FFB may be potentially present but non-pathological, would also contribute to the advancement of knowledge in this area of study.

4.4.2 Conclusion & summary

This study has uniquely identified that forefoot bursae are highly prevalent and clinically relevant longitudinally in patients with RA. The association between reductions in FFB and reduced DAS 28-CRP longitudinally provides preliminary evidence to support the hypothesis that FFB may be a potential indicator of disease activity and long term therapeutic efficacy. Future research regarding the potential relationship between FFB and inflammation or biomechanical impairment is warranted.

The epidemiology & clinical importance of US-detectable FFB in patients with rheumatoid arthritis

Key points:

- FFB remain highly prevalent in patients with RA longitudinally
- The US characteristics of FFB in patients with RA are variable
- Changes in the prevalence of FFB are associated with changes in RA disease activity
- FFB are identified as a prognostic indicator of patient reported disability and represent a possible novel therapeutic target

Chapter five

The relationship between forefoot bursae & inflammation or biomechanical impairment

5.0 Chapter abstract

Background: Previous research has shown that musculoskeletal ultrasound (US) detectable forefoot bursae (FFB) are indicative of foot-related disability longitudinally in patients with RA. However, the pathological mechanisms associated with FFB presence in this patient group are unclear; two biologically plausible hypotheses have been proposed: 1. FFB are associated with biomechanical impairment, 2. FFB are associated with RA disease mediated inflammation.

Aim: To explore the relationship between US-detectable FFB and biomechanical impairment or inflammation in patients with RA.

Methods: A cross-sectional observational study was completed in three comparative cohorts: 1. Healthy volunteers (HV, n=50), 2. patients with medial knee osteoarthritis (OA, n=50), 3. patients with rheumatoid arthritis (RA, n=56). HV were selected as a comparative control group. Patients with knee OA were selected as a surrogate biomechanically impaired only group. Patients with RA were considered representative of a biomechanically impaired and inflammatory group. FFB were noted as present if detected in two scanning planes, when viewed with US. Indicators of biomechanical function included assessment of foot joint deformity, ranges of motion and overall posture. Indicators of inflammation included US-detected metatarsophalangeal joint hypertrophy or metatarsal head erosion, systemic serological markers (ESR and CRP) and a composite measure of disease activity (DAS 28). The probability of FFB presence was determined for each participant group and comparatively expressed as an odds ratio (inclusive of 95% confidence interval and p-value). Multiple linear regression analyses were used to determine the independent predictors of FFB in each participant group, in addition to the predictive value of FFB for impaired biomechanical function or disability. Multinomial logistic regression analyses were used to determine the relationship between FFB distribution and indicators of disease activity, biomechanical function or disability in each patient group.

Results: FFB were highly prevalent in both patients with RA and knee OA (PP=88 per 100 participants; mean=3.05, SD=2.14, range=0-11, and PP=94 per 100 participants; mean=2.8, SD=1.5, range=0-5, respectively), compared to HV (PP=56 per 100 participants; mean=1.3, SD=1.5, range=0-6). Increased FFB count was associated with biomechanical impairment in HV and patients with OA. Conversely in patients with RA FFB count was significantly associated with erosion presence only ($r=0.42$, $p \leq 0.01$). Comparatively, HV demonstrated a lateral FFB distribution, OA patients an even distribution and RA patients a lateral or central FFB distribution. Differences in FFB distribution were significantly different between all groups (RA-

HV: X^2=26.37, p≤0.01; RA-OA:. X^2=15.64, p≤0.01; OA-HV: X^2=16.02, p≤0.01). The distribution of FFB in patients with OA was not related to biomechanical impairment or foot-related disability. In patients with RA, the distribution of FFB was significantly related to markers of RA disease activity but not biomechanical impairment or foot-related disability.

Conclusion: Uniquely, this study has identified that, in patients with RA, US-detected FFB are highly prevalent and related to both inflammation and biomechanical impairment. The distribution pattern of FFB, unique to patients with RA, may be clinically relevant and related to metatarsal head erosion. The findings of this study suggest that both inflammation and biomechanical impairment are related to the prevalence of FFB. Further work is required to characterise which FFB are of greatest clinical relevance.

5.1 Introduction

Previous studies have demonstrated a high prevalence of musculoskeletal ultrasound (US) detected forefoot bursae (FFB) in patients with rheumatoid arthritis (RA) (Bowen *et al.* 2009, Bowen *et al.* 2010c). FFB prevalence has been demonstrated to be significantly associated with increased RA disease activity both in cross-sectional and longitudinal studies (Bowen *et al.* 2009, Bowen *et al.* 2010c, Koski 1998, Palmer 1970). Furthermore, FFB have been demonstrated to be a significant prognostic indicator of patient-reported foot-related disability longitudinally (Chapter four). However, the biological mechanisms underpinning this relationship are currently unclear. Previous researchers have suggested that, in patients with RA, an increased prevalence of FFB may be related to increased disease activity. It is hypothesised that the synovium, which lines the otherwise inconspicuous intermetatarsal anatomical bursae, is hypertrophied as a consequence of excessive inflammation (Koski 1998, Bowen *et al.* 2010a, Chauveaux *et al.* 1987). Conversely, there is evidence to suggest that an increased prevalence of FFB may be related to biomechanical impairment; it is hypothesised that adverse pressure and shearing forces result in the accumulation of interstitial fluid within degraded tissues (Ahmed *et al.* 1994, Studler *et al.* 2008, Aguiar *et al.* 2005). However, to date, the pathophysiological mechanism underpinning the previously reported clinical relevance of US-detected FFB in patients with RA is unclear. In order to target and optimise therapeutic intervention, an improved understanding of the potential inflammatory or biomechanical mechanisms underpinning the clinical importance of FFB in this patient population is required.

5.1.1 Study aim & objectives

The main aim of this study was to explore the potential relationship between US-detectable FFB and biomechanical impairment or inflammation in patients with RA. To achieve this aim the following objectives were set:

1. To compare the prevalence and distribution of US-detectable FFB between patients with medial knee osteoarthritis (OA), as a surrogate biomechanically impaired patient group, and healthy volunteers (HV)

2. To compare the prevalence and distribution of US-detectable FFB between patients with rheumatoid arthritis (RA), as a surrogate inflammatory and biomechanically impaired patient group, and HV
3. To compare the prevalence and distribution of US-detectable FFB between patients with RA and OA
4. To explore the potential relationship between FFB distribution and inflammation or biomechanical impairment

5.2 Materials & methods

5.2.1 Study design

To achieve the above objectives a comparative, cross-sectional observational study design was used. The primary study outcome was an analysis of the presence of US-detected forefoot bursae (FFB). All intermetatarsal spaces (x4) and plantar metatarsal regions (x5) were imaged for the presence of FFB. The number of observed lesions for both feet was combined, thus a maximum score of 18 was possible. Explanatory variables of interest included those related to biomechanical foot deformity (foot posture index (FPI), hallux abducto-valgus deformity (HAV), lesser digital deformity (LDD)), foot function (ankle, subtalar, midfoot, or metatarsophalangeal joint ranges of motion), patient-reported foot-related disability (FIS), or those related to RA disease activity (joint hypertrophy (JH), metatarsal head erosion (ER), serological inflammatory markers (ESR, CRP) and DAS 28).

The foot posture index was selected as a composite measure of weight-bearing foot joint alignment and scored for both feet combined (0-24). Deformity was scored as either present or absent for each joint assessed and the accumulative score for each foot combined (0-20). Joint range of motion was scored as full, limited or rigid for each joint of interest and the accumulative score for each foot combined (0-4). Disability was evaluated using the two subscales of the Foot Impairment Score (FIS); 1. (FIS_{IF}, 0-21): foot impairment and footwear restriction, 2. (FIS_{AP}, 0-29): activity limitation and participation restriction (Helliwell *et al.* 2005). An elevated FIS_{IF} or FIS_{AP} score indicates greater foot impairment or activity limitation respectively. Metatarsophalangeal JH and metatarsal head ER were determined using US and scored as present or absent for each location. An accumulative score for each foot combined was calculated (range=0-10). Disease activity was evaluated using markers of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and calculation of a 28 joint disease activity score (DAS 28) (Van der Heijde *et al.* 1990). Explanatory variables were selected based upon the findings of previous work, literature review and potential clinical relevance. Further detail regarding the selected measures is given in Chapters two (section 2.2) and three (section 3.6).

5.2.2 Study population

The study utilised three comparative cohorts: 1. healthy volunteers (HV; n=50), 2. patients with medial knee osteoarthritis (OA; n=50), 3. patients with rheumatoid arthritis (RA; n=56). HV were

recruited from the staff and student population at the University of Southampton via open advertisement. Patients with a consultant confirmed diagnosis of unilateral medial compartment knee OA, of Kellgren and Lawrence grade ≥2at the time of recruitment (Kellgren and Lawrence 1957), or consultant confirmed diagnosis of RA (consistent with 1987 ACR criteria), were recruited from known cohorts who had previously participated in either a trial of vitamin D supplementation (the 'VIDEO' study) or forefoot bursae (the 'FeeTURA' study). Participants from both the 'VIDEO' and 'FeeTURA' studies were originally consecutively, prospectively recruited from a population of patients attending a UK rheumatology outpatient clinic. Participants from the VIDEO study were consecutively, retrospectively identified from those completing the final episode of trial data collection until the target sample size was achieved. All FeeTURA study participants were invited to take part in this follow-up study. Please note, the participants with RA contributing to this study have also contributed to the study findings documented in Chapter four. Thus, a proportion of the data presented within this study may be a replication of that reported previously. However duplicate data is presented in a contextually different manner to that presented previously. Further details regarding the study population are given in Chapter three (sections 3.4-3.5).

5.2.3 Protocol for data collection

The participant recruitment and data collection protocol is summarised in figure 40.

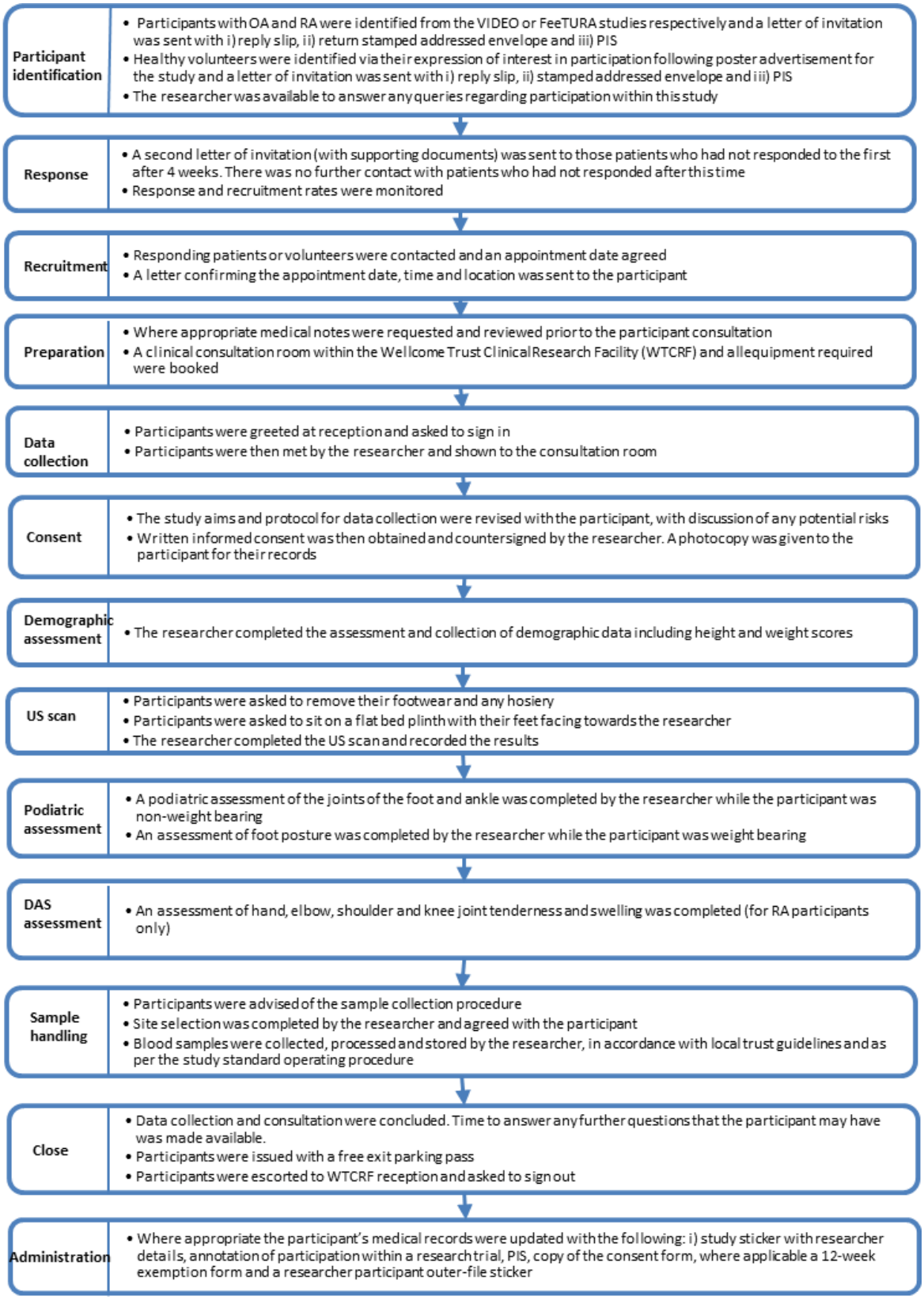


Figure 40: A schematic diagram of the study protocol
Where, VIDEO = Vitamin D in osteoarthritis research trial; FeeTURA = foot and ankle ultrasound research in rheumatoid arthritis; PIS = participant information sheet; ID = identification; US = ultrasound; DAS = disease activity score.

5.2.4 Protocol for image collection & interpretation

Musculoskeletal ultrasound (US) scanning, using a Diasus® diagnostic scanner (System 8, Dynamic imaging, Livingston, Scotland, UK), was completed in B-Mode to provide real-time grey-scale images. The return echo signals were automatically processed using Diasus® 2D spline filtering. Image pixilation was standardised at 640 x 440 pixels, the optimum settings for fine image resolution available using this software. The overall transmit power and gain were set at ≤50 and ≤30 respectively, in accordance with the European League Against Rheumatism working group for US in rheumatology scanning recommendations (Backhaus M. 2001). All metatarsophalangeal joints and intermetatarsal spaces, of both feet, were individually imaged from both a plantar and dorsal approach, in longitudinal and transverse scanning planes, using an 8-16MHz linear array transducer. All intermetatarsal spaces and plantar forefoot regions were additionally imaged from a plantar approach, in longitudinal and transverse scanning planes, using a 5-10MHz linear array transducer (see figure 24, Chapter three, section 3.6.3). Where possible the least amount of focus points were used and centred at the level plantar to the deep transverse intermetatarsal ligament for plantar foot scans and the upper third of the joint space for dorsal foot scans. All US scanning was performed in accordance with the British Medical Ultrasound Society guidelines for safe use (Fitzpatrick *et al.* 1998) and completed by two trained podiatrists (LH and CJB), the reliability of which has been previously reported and identified as moderate to substantial (kappa=0.7) (Bowen *et al.* 2008).

Intermetatarsal lesions were classified as bursae if a defined region of hypo-echogenicity, occurring within the IM spaces, either inferior or superior to the deep transverse intermetatarsal ligament, was observed in the perpendicular transverse and longitudinal plantar scanning planes. Plantar lesions were classified as bursae if a defined region of hypo-echogenicity, occurring inferior to the level of the base of the metatarsal heads, was observed in the perpendicular transverse and longitudinal scanning planes. Thus lesions were defined based upon location and grey-scale US properties and not size or shape. MTP joint hypertrophy was noted as present if distension of the dorsal synovial joint membrane, as a consequence of either increase in synovial fluid volume or membrane thickening, extended beyond the proximal or distal attachment sites at the metatarsal head or base of the proximal phalanx respectively. Metatarsal head erosion was noted as present if a distinct loss in cortical bone was observed in two perpendicular scanning planes.

5.2.5 Analysis

All analysis was completed using Stata version 11.0 (Stata Corp, College Station, Texas, USA), or SPSS version 18.0 (Chicago, Illinois, USA). Prior to analysis, data distribution was checked for inconsistencies, outliers and missing information. Histograms and scatter plots were used to assess whether the data followed a normal distribution. The demographic and clinical characteristics of the study participants are presented as the mean, standard deviation (SD) and range. Statistically significant differences in demographic characteristics between cohorts were

determined using independent sample t-tests. Statistical significance was reported at the 5% confidence level, based upon two-tailed analysis ($p \leq 0.05$).

The point prevalence proportion (PP) of US-detectable FFB was calculated by the division of the sum of identified cases by the sum of the total studied population and expressed per 100 patients. The probability of FFB presence was determined for each participant group and comparatively expressed as an odds ratio (inclusive of 95% confidence interval and p-value). Statistically significant differences in the distribution of FFB across forefoot regions between groups were determined using repeated chi squared analyses. Correlation coefficient analysis was used to determine the statistical significance of potential associations between the primary outcome of interest (FFB count), and measured explanatory variables (markers of foot deformity/function, patient-reported foot-related disability and disease activity) in each participant group. The total number of US-detectable episodes of FFB, JH or ER for both feet combined was calculated for each patient; these count scores were treated as continuous variables for the purposes of analysis, although they were bounded between 0-18 for FFB and 0-10 for JH and ER. Multiple linear regression techniques, with ordinary least squares estimation, were used to explore the predictive value of FFB count, in each patient group, for alternate primary outcome measures relating to disease state; including foot deformity/function, patient-reported foot-related disability and/or disease activity. Further linear regression, with ordinary least squares estimation, was used to explore statistical relationships between FFB count as the primary outcome of interest and potential explanatory variables. Significant factors were subsequently entered into a multiple linear regression model to identify potential confounding or colinearity within the study findings.

FFB were grouped into medial (sites 1-3), central (sites 4-6) or lateral (sites 7-9) scores (figure 41). Trends between medial, central and lateral FFB scores were then coded into one of four categories: 1. equal distribution of FFB across all sites, 2. increased distribution laterally, 3. increased distribution centrally, 4. other distribution. Categories were selected based upon observations of overall trends within the data for each group. It is noteworthy that few patients demonstrated an increasing distribution medially therefore this was not included as a category. Chi^2 analyses were used to determine statistically significant differences in pattern category between patient groups. Age-adjusted, multinomial, logistic regression techniques were used to explore the potential relationships between FFB pattern category and indicators of biomechanical function, disability or disease state in each patient group. Significant factors were subsequently entered into a combined multinomial logistic regression model to identify potential confounding or colinearity within the study findings.

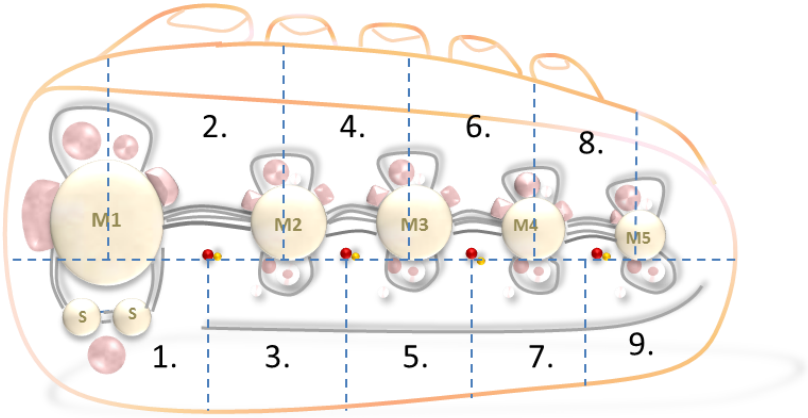


Figure 41: Lesion site definitions
Segmentation of intermetatarsal sites is by bisection of the midline of the metatarsal head, relative to the short axis of the foot, for medial-lateral boundaries and the base of the lesser metatarsal heads for plantar boundaries. Segmentation of plantar sites is by vertical bisection of the midline of the intermetatarsal space, relative to the short axis of the foot, for medial-lateral boundaries and the base of the lesser metatarsal heads for dorsal boundaries. 1-9 = derived intermetatarsal and plantar foot segments. *Image author's own*.

5.3 Results

5.3.1 Study cohort characteristics

A summary of the demographic and clinical characteristics of the study participants is shown in table 20. Participant age was significantly different between all groups (HV-OA p≤0.001; HV-RA p≤0.001; OA-RA p=0.006). Additionally, significant differences in participant weight, BMI and disease duration between patients with OA and RA were noted (p≤0.001, p≤0.001, p=0.043 respectively).

Table 20: Cohort demographic characteristics
Where SD = standard deviation, BMI = body mass index.

	HEALTHY VOLUNTEERS (N=50)	KNEE OA (N=50)	RA (N=60)
	Mean, (SD), Range	**Mean**, (SD), Range	**Mean**, (SD), Range
age (years)	**41**, (13), 20-65	**66.3**, (12.2), 53-80	**62**, (11.8), 28-89
height (m)	**1.7**, (0.09), 1.5-1.9	**1.7**, (0.1), 1.5-1.9	**1.7**, (0.1), 1.3-2.1
weight (Kg)	**69.5**, (13.3), 47-115	**81.4**, (15), 51.3-120.6	**70.7**, (13.6), 42.2-108
BMI	**24.6**, (4.5), 18.9-38.4	**28.6**, (5), 19.3-41.5	**25.5**, (3.9), 19.1-33.4
disease duration (years)	-	**11.2**, (9.3), 1-40	**15.1**, (10.3), 3-45

5.3.2 The comparative epidemiology of FFB between HV & patients with knee OA

The point prevalence of FFB in healthy volunteers and patients with OA was 56 per 100 participants (mean=1.3, SD=1.5, range=0-6) and 94 per 100 participants (mean=2.8, SD=1.5,

range=0-5) respectively. Thus, for each patient with OA without FFB, 15.7 patients are likely to have at least one FFB (47/3). Conversely, for each HV without FFB, 1.3 people are likely to have at least one FFB (28/22). Comparatively, patients with OA are 1.7 times more likely to have at least one FFB than HV (0.94/0.56). Similarly when considering the relative odds of occurrence, for every OA patient without FFB 2.7 (3.5/1.3) times as many OA patients will have at least one, relative to the number of HV with FFB for every HV without; the odds ratio for FFB occurrence relative to patients with OA and HV is 0.08 (95% CI=0.022-0.296, p≤0.001).

Significant differences between participant groups were observed in the distribution pattern of FFB across forefoot sites (X^2=16.02, p≤0.001). HV had a greater tendency towards a lateral FFB distribution, particularly at the IM 4/5 site, while patients with OA had a relatively more even distribution across the forefoot, although they also demonstrated a high frequency of FFB in the IM 4/5 site (figure 42).

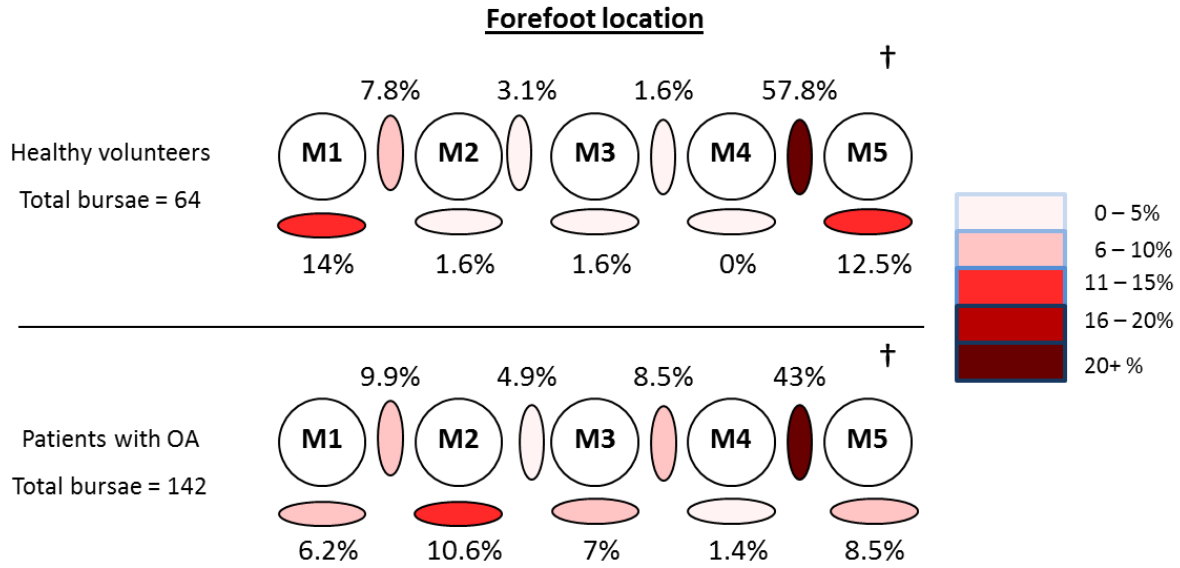


Figure 42: The distribution of FFB in HV & patients with OA
Values are expressed as percentage of sample with FFB in this location.
Where M1-5 = plantar metatarsophalangeal joint region.

5.3.3 The comparative epidemiology of FFB between HV & patients with RA

The point prevalence of FFB in HV and patients with RA was 56 per 100 participants (mean=1.3, SD=1.5, range=0-6) and 88 per 100 participants (mean=3.05, SD=2.14, range=0-11) respectively. Thus, for each patient with RA without FFB, 7 patients are likely to have at least one FFB (49/7). Conversely, for each HV without FFB, 1.3 patients are likely to have at least one FFB (28/22). Comparatively, patients with RA are 1.6 times more likely to have at least one FFB than HV (0.88/0.56). Similarly when considering the relative odds of occurrence, for every RA patient without FFB, 5.4 (7/1.3) times as many RA patients will have at least one, relative to the number of HV with FFB for every HV without; the odds ratio for FFB occurrence relative to patients with RA and HV is 0.18 (95% CI=0.069-0.479, p≤0.001).

Significant differences between participant groups were observed in the distribution pattern of FFB across forefoot sites (X^2=26.37, p≤0.001). HV had a greater tendency towards a lateral FFB distribution, particularly at the IM 4/5 site, while patients with RA had a tendency for FFB to also occur more centrally (figure 43).

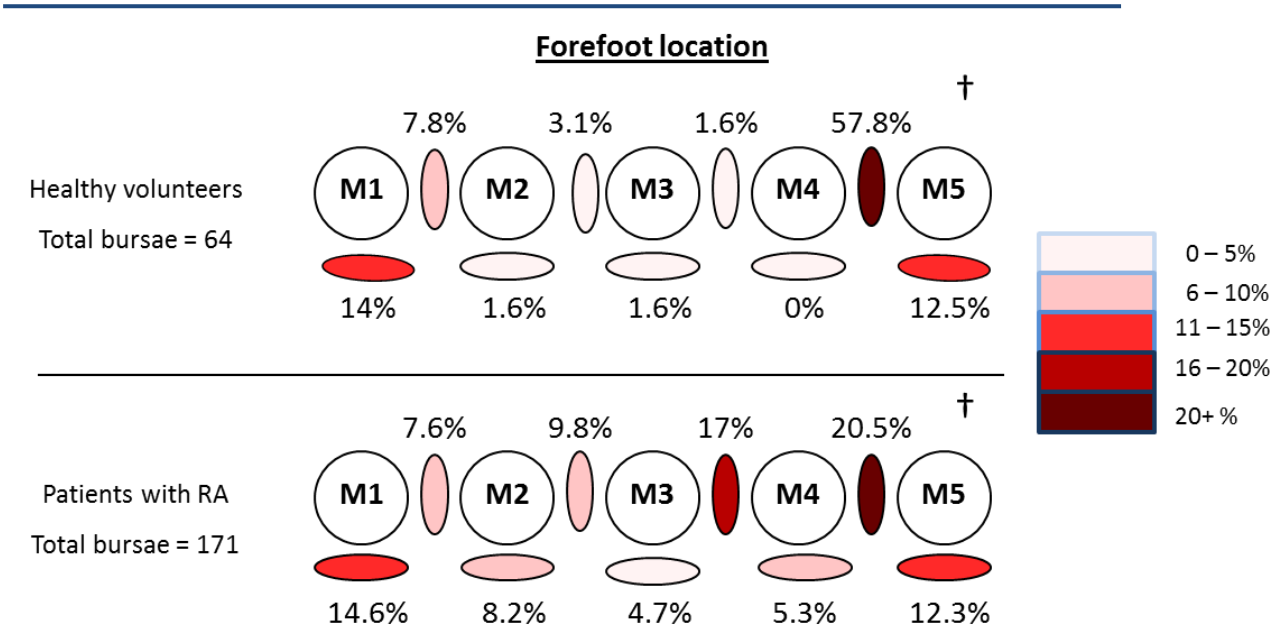


Figure 43: The distribution of FFB in healthy volunteers & patients with RA
Values are expressed as percentage of sample with FFB in this location.
Where M1-5 = plantar metatarsophalangeal joint region.

5.3.4 The comparative epidemiology of FFB between patients with RA & knee OA

The point prevalence of FFB in patients with RA and OA was 88 per 100 participants (mean=3.05, SD=2.14, range=0-11) and 94 per 100 participants (mean=2.8, SD=1.5, range=0-5) respectively. Comparatively, patients with OA are 1.1 times more likely to have FFB than patients with RA (0.94/0.88). Similarly when considering the relative odds of occurrence, for every RA patient without FFB, 0.4 (7/15.7) times as many RA patients will have at least one, relative to the number of OA patients with FFB for every OA patient without; the odds ratio for FFB occurrence relative to patients with RA and OA is 0.45 (95% CI=0.109-1.831, p=0.328).

Significant differences between participant groups were observed in the distribution pattern of FFB across forefoot sites (X^2=15.64, p≤0.001). Patients with RA had a greater frequency of FFB occurring within the intermetatarsal spaces or outer margins of the foot while patients with OA had a relatively more even distribution across the forefoot and high prevalence at IM 4/5 (figure 44).

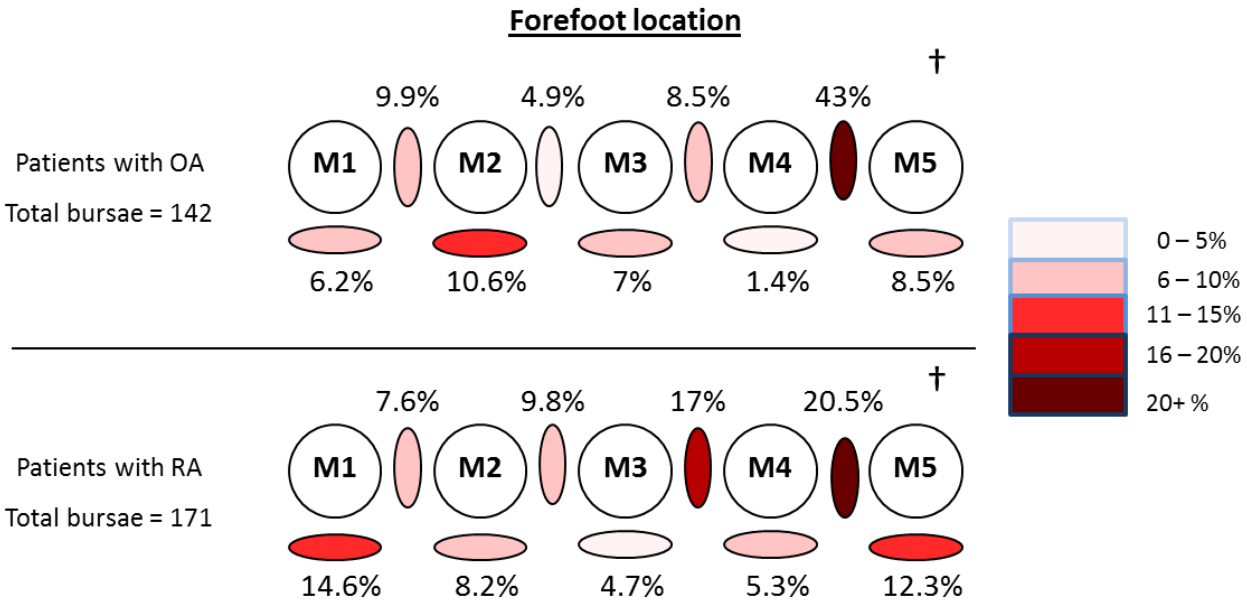


Figure 44: The distribution of FFB in patients with RA & OA
Values are expressed as percentage of sample with FFB in this location.
Where M1-5 = plantar metatarsophalangeal joint region.

5.3.5 The relationship between FFB distribution & inflammation or biomechanical impairment

In patients with OA, FFB pattern category was not determined to be significantly related to indicators of biomechanical impairment or foot-related disability (see appendix section A15 for details). In patients with RA, FFB pattern category was determined to be significantly related to disease activity; a more central FFB distribution was indicative of increased joint hypertrophy or metatarsal head erosion (Pseudo R^2=0.145, p=0.032; Pseudo R^2=0.240, p=0.002 respectively). When joint hypertrophy and erosion were entered into a further combined, age-adjusted, multinomial regression analysis, the resultant model accounted for 30.4% of the variability in FFB pattern category (table 21). FFB pattern category was not significantly related to biomechanical impairment or foot-related disability in this patient group (see appendix section A15 for details).

Table 21: Predictors of FFB pattern category: age-adjusted, multinomial, logistic regression analysis (RA)
Where df = degrees of freedom. * = Significant at the 0.05 level.

EXPLANATORY VARIABLE	FFB PATTERN CATEGORY				
	X^2	***df***	**p-value**	**Pseudo-R^2 (Cox & Snell)**	**Model p-value**
constant	9.24	3	0.026	0.304	0.002
joint hypertrophy	4.95	3	0.176		
***erosion**	11.49	3	0.009		
likelihood score	20.29	6	0.002		
goodness-of-fit	67.02	81	0.868		

5.3.6 The relationship between FFB count & inflammation or biomechanical impairment

For healthy volunteers, FFB count was significantly associated with increased biomechanical impairment; where increased FFB count was significantly associated with poorer foot posture ($r=0.41$, $p=0.003$), the presence of hallux abducto-valgus deformity ($r=0.30$, $p=0.032$) or lesser digital deformity ($r=0.46$, $p\leq0.001$) and reduced foot joint ranges of motion (ankle: $r=0.34$, $p=0.014$; subtalar: $r=0.37$, $p=0.009$; midfoot: $r=0.37$, $p=0.009$; metatarsophalangeal: $r=0.28$, $p=0.050$). For participants with OA, FFB count was significantly associated with reduced ankle joint range of motion ($r=-0.30$, $p=0.037$). For participants with RA, FFB count was significantly associated with increased US-detected metatarsal head erosion ($r=0.42$, $p\leq0.001$), but no other biomechanical or disease related variables (for full association analysis results see Appendix A13).

In patients with OA an increased number of FFB significantly predicted reduced ankle joint ranges of motion ($R^2=0.09$, $p=0.037$) but no other measures of biomechanical impairment or foot-related disability. In patients with RA an increased number of FFB significantly predicted reduced ankle joint range of motion ($R^2=0.08$, $p=0.039$) and increased metatarsal head erosion ($R^2=0.18$, $p\leq0.001$) but no other measures of biomechanical impairment, foot-related disability or disease activity (for full regression analysis results see Appendix A14).

5.3.7 Predicting FFB count in HV & patients with OA or RA

For HV, indicators of biomechanical function were determined to be significant predictors of FFB count. Increased foot posture, HAV, lesser digital deformity scores and reduced ankle, subtalar and midfoot joint ranges of motion were determined to be significant independent predictors of FFB count, where poorer foot structure and function were indicative of increased FFB count ($R^2=0.17$, $p=0.003$; $R^2=0.10$, $p=0.024$; $R^2=0.23$, $p\leq0.001$; $R^2=0.12$, $p=0.016$; $R^2=0.16$, $p=0.004$; $R^2=0.16$, $p=0.004$ respectively, table 22a; for full results see Appendix A12). All identified independently significant explanatory variables were entered into a further multiple regression analysis, with the resultant models explaining 24% of the variability in the observed number of FFB, of which foot posture and lesser digital deformity significantly accounted for 15% and 77% of the variance respectively (table 22b).

Table 22: Predictors of FFB count
Where 22a shows results of linear regression analyses for all dependent variables; 22b shows results of a multiple regression analysis for previously identified independent predictors of FFB count.
Where BMI = body mass index; jROM = joint range of motion; CI = confidence interval. *= Significant at the 0.05 level.

22a. Predictors of FFB count: univariate, age-adjusted, linear regression analysis (HV)

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**R^2**	**F-value**
***foot posture**	0.17	0.003 (0.06-0.27)	0.17	9.53
***hallux abducto-valgus**	0.88	0.024 (0.12-1.63)	0.10	5.44
***lesser digital deformity**	0.53	0.000 (0.25-0.80)	0.23	14.5
***ankle jROM**	1.09	0.016 (0.22-1.97)	0.12	6.29
***subtalar jROM**	1.27	0.004 (0.42-2.12)	0.16	8.91
***midfoot jROM**	1.27	0.004 (0.42-2.12)	0.16	8.91

22b. Predictors of FFB count: multivariate, age-adjusted, linear regression analysis (HV)

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**Adjusted R^2**	**F-value**
***foot posture**	0.15	0.022 (0.02-0.27)	0.24	4.16
***lesser digital deformity**	0.77	0.026 (0.1-1.43)		

For patients with knee OA, an increased presence of lesser digital deformity and reduced ankle joint range of motion were determined to be significant independent predictors of FFB count (R^2=0.07, p=0.057; R^2=0.09, p=0.037 respectively, table 23a). Both explanatory variables remained significant when entered into a multiple regression analysis, with the resultant model explaining 15% of the variability in the observed number of FFB (table 23b).

Table 23: Predictors of FFB count (OA)
a: Results of linear regression analyses for all dependent variables; b: Results of a multiple regression analysis for previously identified independent predictors of FFB count. *Significant at the 0.05 level.

23a. Predictors of FFB count: univariate, adjusted, linear regression analysis (OA)

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**R^2**	**F-value**
lesser digital deformity	0.31	0.057 (-0.01-0.64)	0.07	3.79
***ankle jROM**	-0.44	0.037 (-0.85- -0.03)	0.09	4.62

23b. Predictors of FFB count: multivariate linear regression analysis (OA)

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**Adjusted R^2**	**F-value**
***lesser digital deformity**	0.37	0.022 (0.06-0.68)	0.15	5.35
***ankle jROM**	-0.50	0.014 (-0.90- -0.11)		

For patients with RA, an increased presence of metatarsal head erosion and reduced ankle joint range of motion were determined to be significant independent predictors of FFB count (R^2=0.18, p≤0.001; R^2=0.08, p=0.039 respectively, table 24a). Both explanatory variables remained significant when entered into a multiple regression analysis, with the resultant model explaining 18% of the variability in the observed number of FFB (table 24b). No further biomechanical or disease related explanatory variables were identified as significant predictors of FFB count (for full analysis results see Appendix sections A12 to A15).

Table 24: Predictors of FFB count (RA)
Where 24a shows results of multiple linear regression analyses for all dependent variables; 24b shows results of a multiple regression analysis for previously identified independent predictors of FFB count. *Significant at the 0.05 level.

24a.Predictor of FFB count: univariate, adjusted, linear regression analysis (RA)

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**R^2**	**F-value**
***erosion**	0.27	0.001 (0.11-0.43)	0.18	11.49
***ankle jROM**	0.52	0.039 (0.03-1.01)	0.08	4.47

24b. Predictors of FFB count: multivariate, adjusted linear regression analysis (RA)

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**Adjusted R^2**	**F-value**
***erosion**	0.24	0.004 (0.08-0.41)	0.18	7.02
ankle jROM	0.36	0.137 (-0.12-0.83)		

5.4 Discussion

This is the first study to comparatively determine the prevalence of US-detectable FFB in patients with RA, medial knee OA and healthy volunteers. Uniquely, FFB were determined to be highly prevalent in both patients with RA and patients with medial knee OA. The results of this study suggest that patients with RA are 1.3 times more likely to have at least one FFB than a healthy volunteer, while those with medial knee OA are 1.7 times more likely. Comparatively, patients with OA are 1.1 times more likely to have at least one FFB than those with RA.

To our knowledge, there have been no previously reported studies of FFB in patients with medial knee OA and as such the surprisingly high prevalence of FFB cannot be compared to other works. However, Silva (2008) reported the presence of bursal hypertrophy in the absence of active inflammation in patients with biomechanically elicited trochanteric pain. In this work the authors hypothesise that biomechanical irritation contributed to bursal hypertrophy and the fibrotic changes seen in the associated histopathology of excised tissue. It is possible that a similar rationale of biomechanical irritation to the plantar fibro-fat pad of the forefoot, subsequent

to proximal/distal joint degradation and kinetic dysfunction, may account for the high presence of FFB reported in this study (Astephen and Deluzio 2004, Astephen and Deluzio 2005, Astephen *et al.* 2008a). The sensitivity and specificity of US for detecting and differentiating between FFB and fibrotic changes within the plantar fat pad has not been established. It is possible therefore, that misclassification of FFB and fibrotic lesions could be contributing to an over-reporting of FFB presence. Future work which determines the construct validity of US-reported FFB would be of significant benefit to this area of study.

The pattern of FFB distribution was significantly different between all groups. Healthy volunteers demonstrated a lateral FFB distribution, patients with OA an even distribution and patients with RA a lateral or central distribution. However, all groups had the highest prevalence of FFB in the 4/5 intermetatarsal space. In patients with OA, the distribution of FFB was not related to indicators of biomechanical impairment or foot-related disability. However in patients with RA, the distribution of FFB was related to MTP joint hypertrophy and metatarsal head erosion but not indicators of biomechanical impairment or foot-related disability. These findings suggest that in patients with OA, although elevated in number, the distribution of FFB is not clinically indicative. However in patients with RA, the distribution of FFB is associated with inflammatory disease activity and is potentially a clinically relevant feature in the pathogenesis of RA foot disease. Conversely, the high prevalence of FFB seen in all groups, including the healthy volunteers, perhaps suggests that a proportion of FFB are present yet clinically 'silent'. The findings of this study therefore appear to reinforce those of previous authors which suggest that different types of FFB may exist. Thus, patients with RA potentially demonstrate a number of coexisting FFB subtypes related to healthy foot anatomy, biomechanical irritation and disease activity. An observer-independent, reliable and valid method of characterising FFB in patients with RA, to differentiate between those which are potentially anatomical or pathological, would be of significant clinical benefit, providing a framework for future targeted intervention.

In patients with RA, metatarsal head erosion and ankle joint range of motion were both identified as significant independent predictors of FFB count. When entered into a multivariate model, the significance of ankle joint range of motion diminished, suggesting that these items are potentially co-linear. The interpretation of the consistently identified relationship between FFB and erosion should therefore be made with caution; it is unclear to what extent erosion should be considered as representative of disease activity, disease chronicity or biomechanical impairment of the MTP joints in this experimental context. Interestingly this concept is arguably reinforced by the findings of Woodburn *et al*. (2002c), who demonstrate changes in forefoot kinetics associated with impaired ankle joint architecture in patients with RA. Future use of Power Doppler (PD) to identify active inflammation would enhance subsequent study of the clinical importance of FFB in patients with RA.

The relative clinical importance of FFB that are associated with inflammation or biomechanical impairment remains unclear. Interestingly, a similarly high FFB prevalence between patient groups was observed. However, in contrast to patients with RA the relationship between FFB prevalence and disability was not evident in patients with OA. Thus, the clinical importance of US-detected FFB in terms of foot-related disability in patients with OA, when evaluated with outcome measures used in this study, appears negligible. However the prognostic value of FFB in patients with medial knee OA does appear to offer further avenues of investigation. Van der Leeden *et al.* (2008), amongst other authors, have previously identified significant reductions in weight-bearing activity with the course of RA disease activity (Cho *et al.* 2012, Hallert *et al.* 2012). It is possible that the RA population studied undertake less weight-bearing activity than the comparative OA group and therefore acquire less biomechanical irritation to the forefoot (Miyoshi *et al.* 2004). Alternatively, many of the patients with RA also demonstrated a generalised loss of plantar fibro-fatty tissue which may limit the extent of the biomechanically irritated tissue response that can be observed using US (Falsetti *et al.* 2006, Budiman-Mak *et al.* 1999). Conversely, the kinetic parameters of gait are likely to be significantly different between patient groups (van der Leeden *et al.* 2006, Turner *et al.* 2008, Turner and Woodburn 2008, Khazzam *et al.* 2007, Huang *et al.* 2008, Heiden *et al.* 2009b); previous researchers have demonstrated that patients with RA have reduced walking speed, increased stance phase of gait and widened base of support (Turner *et al.* 2008, Turner and Woodburn 2008, Woodburn *et al.* 2002b). Conversely patients with medial knee OA have been demonstrated to have a greater tendency towards lateral loading of the foot during the stance phase of gait (Huang *et al.* 2008, Heiden *et al.* 2009a, Astephen *et al.* 2008a). Such functional differences will have a concomitant effect upon the internal loading forces exerted upon joints and soft tissues during gait (Astephen and Deluzio 2005, Astephen *et al.* 2008b). Thus differences in the nature of biomechanical impairment between patient groups may account for the variation in FFB count and distribution observed. Future work may seek to investigate the relationship between FFB and dynamic markers of biomechanical impairment in addition to static markers such as those used within this work (Cavanagh *et al.* 1997).

5.4.1 Study limitations

This study has a number of strengths and potential limitations. The patients with OA or RA were consecutively, prospectively recruited from an outpatient secondary care setting and as such the study findings may be considered as generalisable to such patients within the UK. There is no known pathophysiological mechanism that would lead to regional variation in the reported prevalence of FFB in such patient groups. However, the generalisability of the study results to patients not reviewed within a secondary care setting should be considered (Silman and Hochberg 2001). In particular, there has been recent discussion regarding the under-representation of the elderly or people without a history of health service access within the study of OA epidemiology (Hoogeboom *et al.* 2012, Peat *et al.* 2011).

The patients with OA included within this study had a significantly greater BMI than the comparative participant groups. Previous research has suggested a link between elevated BMI and biomechanical impairment in terms of both kinematic and kinetic joint loading parameters (Goulston *et al.* 2011, Holliday *et al.* 2011, Oliveria *et al.* 1999). The additional loading and torsional stress exerted upon the soft tissues of the forefoot as a consequence of elevated BMI are unclear although such theoretical links provide a plausible pathophysiological rationale for an association between BMI and FFB presence (Astephen and Deluzio 2005). It is possible that the overall elevation in BMI present in patients with OA may contribute to the increased presence of FFB recorded. It is currently unclear whether elevated BMI may be an aetiological, putative or confounding factor in the development of FFB. Improved understanding of the relationship between FFB and BMI would help inform the further determination of the clinical importance of FFB in differing patient groups.

Throughout the course of data collection the researcher undertaking the US assessment was not blinded to the patient group of each participant, and as such there is potential for observer bias within the reported results (Silman and Hochberg 2001). However to minimise subjectivity in observation, a strict protocol of US procedure and FFB identification was adhered to throughout data collection and analysis. Additionally, the researcher undertaking the investigation completed a comprehensive formal training programme in the use of US. Inter-rater agreement in the use of US between the primary researcher and a second 'expert' researcher was confirmed as good-excellent on two occasions, suggesting that the likelihood of reporting error is minimal (see Chapter three, section 3.7). None the less, there is a need for a reliable and valid method of characterising FFB, which can subsequently be used to inform the clinical importance of FFB in patients with RA.

5.4.2 Conclusion & summary

Uniquely, this study has identified that, in patients with RA, US-detected FFB are highly prevalent and related to both inflammation and biomechanical impairment. The distribution pattern of FFB, unique to patients with RA, may be clinically relevant and related to metatarsal head erosion. The findings of this study suggest that both inflammation and biomechanical impairment are related to the prevalence of FFB. Further work is required to characterise which FFB are of greatest clinical relevance.

The relationship between FFB & Inflammation or biomechanical impairment

Key points:

- FFB are highly prevalent in patients with RA and medial knee OA
- In patients with RA, the presence of FFB is associated with inflammation and biomechanical impairment
- The central distribution pattern of FFB, unique to patients with RA, is clinically relevant and associated with metatarsal head erosion
- Further characterisation of FFB is required in order to fully determine their clinical importance

Chapter six
Detecting forefoot bursae in patients with rheumatoid arthritis using MRI: development of the '*FFB-score'*

6.0 Chapter abstract

Background: Previous studies have demonstrated a high prevalence of clinically relevant forefoot bursae (FFB) in patients with rheumatoid arthritis (RA) using musculoskeletal ultrasound (US). However, there is a need for an observer-independent, reliable and valid method of characterising FFB. Magnetic Resonance Imaging (MRI) allows improved visualisation and characterisation of FFB in multiple imaging planes.

Aim: To determine the reliability and validity of a novel MRI-based scoring tool for the identification and characterisation of FFB in patients with RA.

Methods: A collaborative process of tool design was completed by a team of rheumatologists, radiologists, and a podiatrist from centres within the UK and Germany. In an iterative process of tool design, items to be included, grading criteria, overall utility and MRI sequences were determined. The *FFB-score* assesses 9 distinct forefoot regions and contains 5 items; lesion presence, shape, enhancement, and T1/T2 characteristics. The final tool was evaluated on 42 consecutively recruited patients with RA (mean (±SD) age=62.2 (±12) years, disease duration=15.3 (±10.3) years, and DAS 28=3.1 (±1.4)), who were recruited from a UK rheumatology clinic. Images were obtained using a 1.5T whole body scanner and a 4-channel flex extremity coil. The final MRI protocol included coronal T1 and STIR, coronal and sagittal T1 post-gadolinium, and long axis 3D volumetric sequences. The intra and inter-reader agreement was evaluated using percentage exact/close agreement (PEA/PCA) and kappa analyses. Content validity was evaluated using Lawshe's content validity ratio (CVR). Discriminant validity, with regard to differentiation between high and low MRI-determined indicators of disease activity (erosion, bone marrow oedema and synovitis), clinical markers of disease activity (DAS 28), or foot-related disability (foot impact score), was evaluated using receiver operator characteristic curves and area under the curve analysis.

Results: The *FFB-score* was determine to have substantial overall intra-reader agreement (kappa range=5.5-9) and substantial inter-reader agreement (kappa range=4.7-8.7). The *FFB-score* was determined to have good content validity (CVR: 0.625) and good discriminant validity when differentiating between patients with high/low MRI-determined disease activity local to the forefoot (erosion: p=0.011, synovitis: p=0.004, oedema: p=0.018). The *FFB-score* has good discriminant validity when differentiating between patients with high/low foot-related disability (foot impairment p=0.006, activity limitation p=0.033).

Conclusion: The *FFB-score* is a reliable and valid MRI-based tool for the identification and characterisation of FFB in patients with RA. Further investigation of the clinical importance of

identified FFB characteristics may allow timely and targeted therapeutic intervention. Longitudinal validation, assessment of responsiveness and refinement of the scoring system is needed in order to maximise its potential utility in clinical trials and epidemiological studies.

6.1 Introduction

Previous studies have demonstrated a high prevalence of musculoskeletal ultrasound (US) detected forefoot bursae (FFB) in patients with rheumatoid arthritis (RA) (Bowen *et al.* 2009, Bowen *et al.* 2010c). FFB prevalence has been demonstrated to be significantly associated with increased RA disease activity both in cross-sectional and longitudinal studies (Bowen *et al.* 2009, Bowen *et al.* 2010c, Koski 1998, Palmer 1970). Furthermore, FFB have been demonstrated to be a significant prognostic indicator of patient-reported foot-related disability longitudinally (Chapter four). However, the underlying biological mechanisms linking FFB to disease activity or disability are currently unclear. Two plausible hypotheses have been suggested and explored in comparative study of patients with primarily inflammatory or degenerative arthritis: 1. FFB are associated with biomechanical impairment (Ahmed *et al.* 1994, Studler *et al.* 2008, Aguiar *et al.* 2005), 2. FFB are associated with RA disease mediated inflammation (Koski 1998, Bowen *et al.* 2010a). The work presented in Chapter five reinforces these disparate hypotheses, demonstrating comparatively different FFB counts and distributions between healthy volunteers and patients with predominantly inflammatory or degenerative arthritis. The findings of this work suggest that differing clinically relevant FFB distribution patterns or characteristics may coexist in patients with RA. Accurately identifying, and differentiating between, which FFB are related to inflammation or biomechanical impairment would allow better targeted intervention. There is a need for an observer-independent, reliable and valid method of identifying and characterising FFB in patients with RA. Magnetic Resonance Imaging (MRI) allows improved visualisation and characterisation of FFB in multiple imaging planes.

6.1.1 Study aim & objectives

The main aim of this study was to determine the reliability and validity of a novel MRI-based scoring tool for the identification and characterisation of FFB in patients with RA; the '*FFB-score'*. The following study objectives were set:

1. To complete an iterative process of MRI-based semi-quantitative tool design
2. To collate an *FFB-score* reference image atlas
3. To determine the reliability and validity of the *FFB-score*

6.2 Materials & methods

6.2.1 Study design

To achieve the above objectives a collaborative process of score design was completed by a team of rheumatologists, radiologists, and a podiatrist from centres within the UK and Germany.

A cross-sectional cohort study design was used, with repeated image data generation by multiple readers.

6.2.2 Study population

Patients included within this study were those with a consultant confirmed diagnosis of RA who were consecutively recruited from a UK rheumatology out-patient clinic. Those participants who completed all stages of the FeeTURA programme (three appointments) were eligible for screening into this study. Detail regarding the recruitment, screening, inclusion/exclusion criteria and sample size determinants is documented in Chapter three (sections 3.4-3.5).

6.2.3 Protocol for tool development

The protocol for score development adhered as closely as possible to the 2009 OMERACT recommendations for the MRI-based quantification of RA (Boesen *et al.* 2009). A schematic diagram of the four stages of score development is shown in figure 45. At stage one, selection of items initially proposed for inclusion within the FFB tool was based upon literature review, clinical utility, and agreed via panel consensus (panel members=LK, MT, FR, NA, CE and LH). Features determined as key following panel discussion included FFB anatomical location, size, shape, enhancement, and MR appearance. The categorisation of FFB based upon anatomical location, rather than perceived aetiology or clinical importance, was considered to be the most objective approach to documentation and is consistent with principles of radiological investigation. At stage two, image acquisition protocols were refined by the study senior radiographer (NR) in conjunction with the research team until an optimal sequence protocol was achieved. Image acquisition and interpretation were reviewed in conjunction with the proposed tool items for completeness, comprehensibility, time taken to complete, feasibility of clinical use and appropriateness of scoring ranges and criteria. At stages three and four the final version of the proposed tool was evaluated for reader agreement and validity.

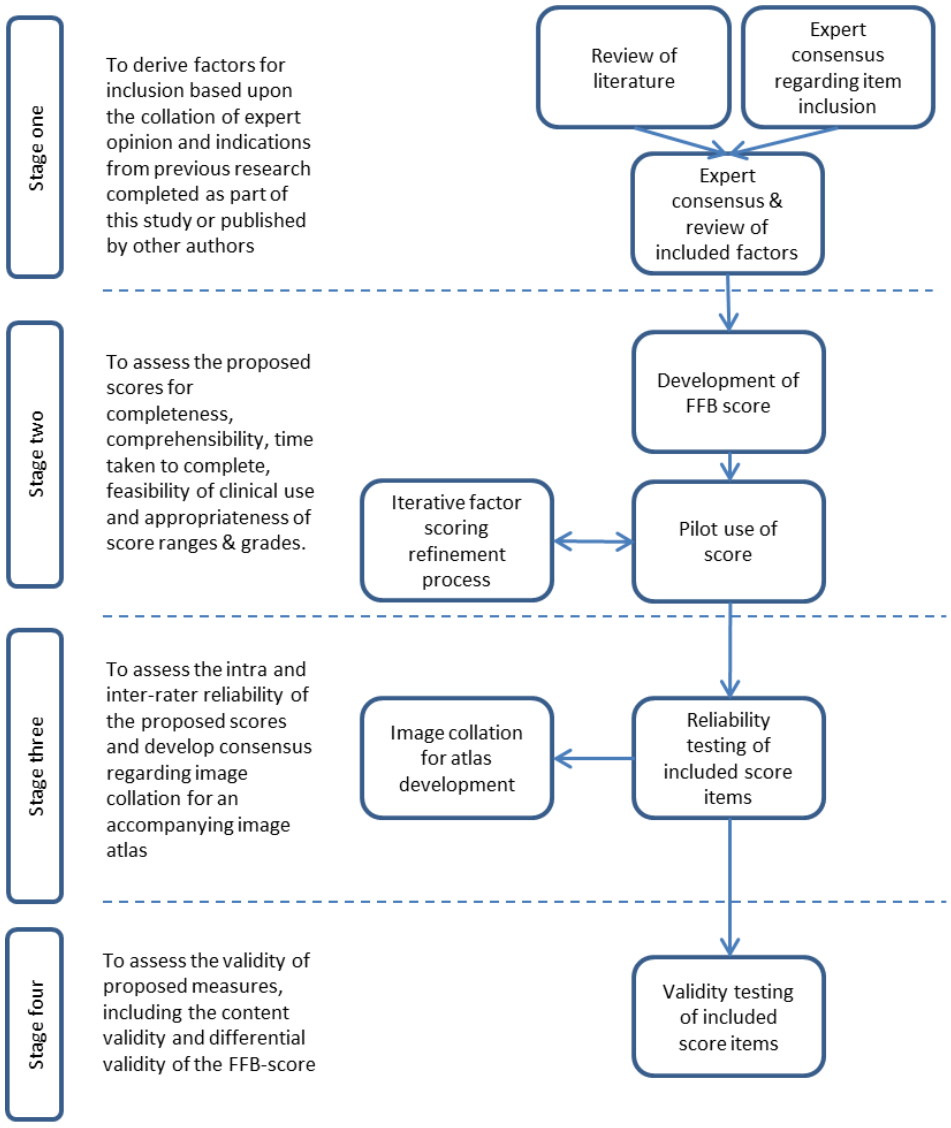


Figure 45: Protocol for *FFB-score* development

6.2.4 Protocol for data collection

The protocol for participant recruitment and MRI data acquisition is illustrated in figure 46.

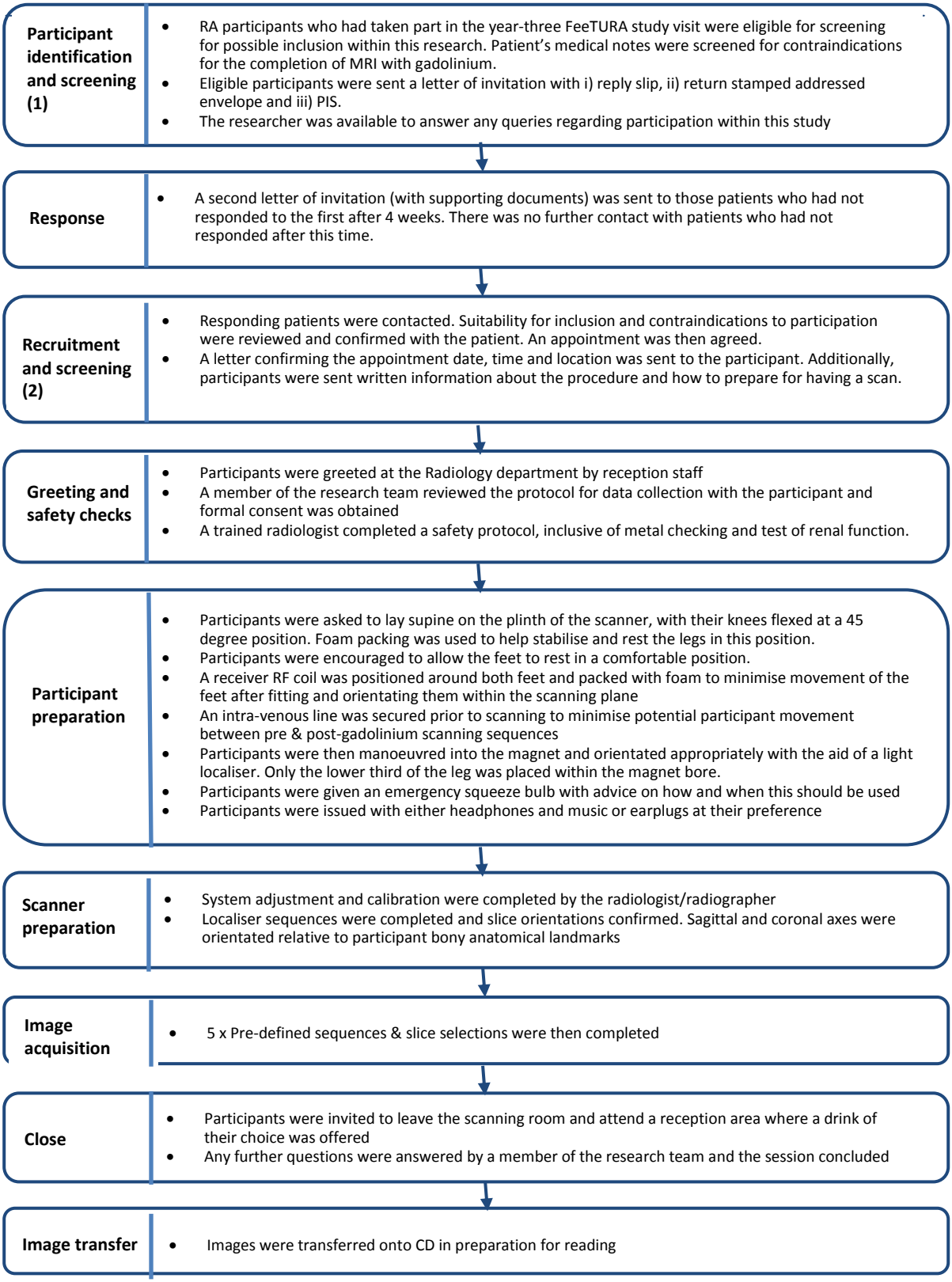


Figure 46: A schematic diagram of the protocol for MRI data acquisition

A 1.5 Tesla (T) whole body scanner (Siemens Avanto Syngo® MR B15, Siemens AG Medical Solutions, Erlangen, Germany) was used for all MRI acquisition. A four channel flex extremity radio frequency (RF) surface coil (Siemens, Siemens AG Medical Solutions; circularly polarised array) was used to image the mid and forefoot region only. Prior to data collection, initial capacitor tuning was completed to ensure that the RF coil frequency was synchronised with the magnetic field (B_0). System calibration was completed as per the standard protocol for the radiology department.

Overall, two-dimensional and three-dimensional sequences, of between 29 and 96 slices with 0.6mm to 3mm slice thickness respectively, were completed after orientation with a T1 sagittal locator image. Alignment and positioning were manually orientated by the radiologist; coronal scans were orientated with the metatarsal parabola, sagittal scans were orientated approximately perpendicular to the coronal slice profile and with the shaft of the third metatarsal. The field of view (FoV) in the read direction was determined as the base of the first metatarsal to the distal aspect of the hallux. The FoV in the phase-encode direction was defined as extending from the medial to the lateral foot borders. The TE/TR ratios were adjusted in an iterative process by the study senior radiographer until appropriate image clarity or contrast was achieved (dependent upon sequence and intended use). Further details regarding the protocol for image acquisition are documented in Chapter three, section 3.6.4, (including ROI definition/participant placement, mapping k-space and SNR management). A summary and rationale for the final MRI sequence protocol are given in table 25.

Table 25: Summary & rationale for MRI sequences
Where T1=Isocromat relaxation time; Cor=coronal; se=spin echo; STIR=short tau inversion recovery; fs=fat saturated; gad=gadolinium; Sag=sagittal; Ax=axial; pd=proton dense; sp=space.

Sequence number	Description	Abbreviation	Primary use
1	T1 weighted coronal spin echo pulse sequence	Cor_T1_se	Identification of bone erosion and anatomical landmarks
2	Coronal Short Tau Inversion Recovery	Cor_STIR	Differentiation between tissue types (fluid/fat/fibrous tissue)
3	T1 weighted fat saturated post-contrast coronal	Cor_T1_fs_(post-gad)	Identification of highly vascularised regions
4	T1 weighted fat saturated post-contrast sagittal	Sag_T1_fs_(post-gad)	Identification of highly vascularised regions
5	Long axis proton dense fat saturated three-dimensional volumetric space	Ax_pd_sp	Reconstructed calculation of lesion volume

The final MRI sequence protocol used in data acquisition is shown in table 26.

Table 26: MRI sequence protocol used in data acquisition
Where TR=relaxation time, TE=echo time, FoV=field of view; Cor=coronal; se=spin echo; STIR=short tau inversion recovery; fs=fat saturated; gad=gadolinium; Sag=sagittal; Ax=axial; pd=proton dense; sp=space.

Sequence	TR/TE (ms)	FoV (mm)	Acquisition matrix	Pixel size (mm)	Flip angle	Slice thickness (mm)	Inter-slice gap (mm)	Number of slices	Acquisition time
1 Cor_T1_Se	TR : 656 TE :15	200	384 x 182	0.7 x 0.5	90	3.0	1.5	29	2.04
2 Cor_STIR	TR : 4000 TE :15	200	384 x 160	0.7 x 0.5	150	3.0	1.5	29	2.46
3 Cor_T1_fs (post-gad)	TR:620 TE :15	200	384 x 182	0.7 x 0.5	90	3.0	1.5	29	3.53
4 Sag_T1_fs (post-gad)	TR :579 TE :18	200	384 x 140	0.9 x 0.5	90	3.0	1.0	2 x 19	5.26
5 Ax_PD_Sp	TR :1300 TE :37	180	320 x 278	0.6 x 0.6 x 0.6	160	0.6	N/A	96	4.35
								Total	17.64

Sequence key: 1: Coronal T1, 2: Coronal STIR, 3: Coronal T1 post-gadolinium fat saturated, 4: Sagittal T1 post-gadolinium fat-saturated, 5: Long axis proton dense 3D volumetric.

6.2.5 Protocol for image reading

Images were viewed using Siemens *Syngo*© Fast view software for Dicom images (Siemens AG 2004-2006). They were reviewed for anomalous findings by a consultant radiologist (LK) at the time of acquisition in order to conform to safety and quality control checking procedures. The first three complete sets of acquired images were read by two consultant radiologists (LK and MT) simultaneously. Image interpretation and scoring were discussed and agreed during this time. A further five images were read by each radiologist independently. Findings, scoring criteria and grading systems were reviewed for consistency and efficacy. The findings of this initial reading exercise were discussed by a panel of three national and international radiologists (LK, MT and FR), two consultant rheumatologists (NA and CE) and a podiatrist (LH). Consensus regarding image interpretation, item inclusion and grading criteria or ranges was sought. The itemised scoring tool was subsequently adjusted in response to this process. The remaining images were scored by each radiologist reader independently (LK and MT). A podiatrist (LH) underwent MRI image interpretation and scoring mentorship with the chief radiologist for the study (LK) over a period of 12 months, in addition to completing an adjunctive taught training course on MRI principles and practice. The podiatrist re-read and scored the first five complete sets of acquired images. Image interpretation and agreement between the podiatrist and a radiologist (LK) were evaluated. Further mentorship occurred over a six month period after which a supervised re-reading session, between LH and LK, of the original five complete sets of images, was completed to improve areas where inconsistency or poor-moderate agreement were identified. The following five complete sets of acquired images were then re-read by LH and a second evaluation of agreement between the LH and LK completed. Good agreement between the podiatrist (LH) and radiologist (LK) was established (see Chapter three, section 3.7.2 for details). All remaining images were subsequently independently re-read and scored by the podiatrist. All image readers (LK, MT and LH) were not blinded to the name of the study participant, however they were blinded to other reader findings, unless explicitly stated as part of the training, agreement analysis or expert consensus exercises. Both radiologists were blinded to the corresponding patient clinical data at the time of image reading.

Identified FFB were categorised to a single pre-defined site only (see figure 41, Chapter five, section 5.2.4). In the event of observed FFB extending across the pre-defined anatomical boundaries, the site in which the majority of the FFB was located was recorded. Differentiation between fluid and soft tissue lesions was determined by differences in T1/T2 contrast. However, after initial reading, it was observed that complex fibrous lesions with fluid elements were apparent. Fluid collection was therefore defined as a homogeneous hyperintense mass with fluid-equivalent signal on pd/T2 sequence and homogenous hypointensity in contrast to true ‘mass’, defined as non-fluid equivalent/intermediate signal on T1 and T2. Differentiation between fluid/fibrous intermetatarsal lesions and neuroma was determined primarily by anatomical

location, in addition to review of lesion margins and T1/T2 characteristics as described previously.

6.2.6 Protocol for image atlas development

Images considered to be of suitable quality and representative of each item grade were collated by LH for potential inclusion within the image atlas. Each was reviewed for quality, representativeness, site and grade. Included images were selected by panel consensus (LH, LK, MT, FR, NA and CE).

6.2.7 Analysis

All analysis was completed using Stata version 11.0 (Stata Corp, College Station, Texas, USA) or SPSS version 18.0 (Chicago, Illinois, USA). Prior to analysis, data distribution was checked for inconsistencies, outliers and missing information. Histograms and scatter plots were used to assess whether the data followed a normal distribution. The demographic and clinical characteristics of the study participants are presented as the mean, standard deviation (SD) and range. The arrangement and clustering of study data used for FFB analysis purposes is shown in figure 47.

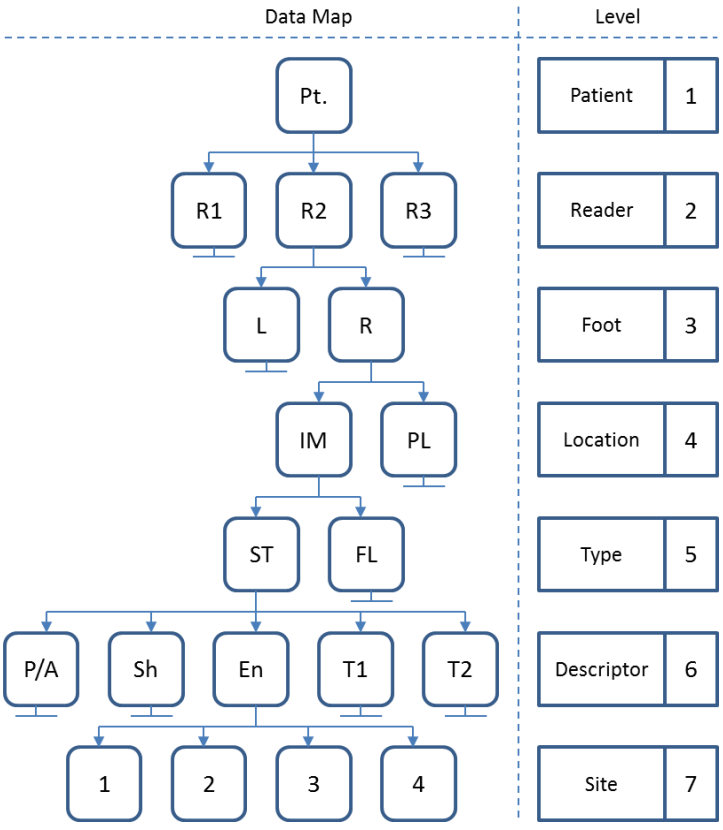


Figure 47: Data clustering map
Where Pt = patient, R1/2/3 = reader one to three, L = left, R = right, IM = intermetatarsal lesion, PL = plantar lesion, ST = soft tissue lesion, FL = fluid lesion, P/A = present/absent, Sh = shape, En = Enhancement, T1 = MRI T1 characteristic, T2 = MRI T2 characteristic. N.B. The number of sites present (level seven) is dependent upon location (level 4), where intermetatarsal lesions have four possible sites and plantar forefoot lesions have five possible sites.

The radiologist combined and radiologist/podiatrist combined mean score (and range) for each item was calculated. Intra-reader and inter-reader agreement were evaluated using estimations of percentage exact agreement (PEA) and percentage close agreement (PCA=within ± 2 scores) for all items and Kappa agreement for the determination of FFB presence or absence.

Content validity, defined as the extent to which a tool accounts for/includes all likely contributing components, was evaluated using Lawshe's content validity ratio (CVR). CVR was calculated for all items. The discriminant validity of the *FFB-score*, defined as the degree to which two total scores can reliably differentiate between two distinct groups or characteristics, was evaluated using receiver operator characteristics (ROC) curves plotted using Mann Whitney-U statistics and corresponding area under the curve analysis. The discriminant validity of the *FFB-score* to differentiate between patients with high/low disease activity or patient-reported foot-related disability was also assessed in this way. MRI-determined disease activity local to the forefoot was assessed via observations of metatarsal head and phalangeal base erosion or bone marrow oedema and MTP joint synovitis. Participants with erosion score ≥20, bone marrow oedema score ≥11 and synovitis score ≥2 were classified as having high disease activity. The margins for erosion and oedema were defined as 25% of the observed maximum score. The margin for synovitis was defined as being what was considered clinically meaningful by the expert consensus panel. Systemic disease activity was assessed using DAS 28. The margins for systemic disease activity were defined as per the previously validated DAS disease categories (Wolfe *et al.* 2001). Patient-reported foot-related disability was assessed using the two subscales of the foot impact score (FIS): 1. (FIS_{IF}, 0-21); foot impairment and footwear restriction, 2. (FIS_{AP}, 0-29): activity limitation and participation restriction (Helliwell *et al.* 2005). Participants with FIS_{IF} score ≥7 and FIS_{AP} score ≥10 were classified as having high foot impairment or activity limitation respectively. The margins for disability were pragmatically derived, as high, moderate or low, at 33% increments of the total score. The discriminant validity of the seven derived *FFB-score* items was assessed and included: 1. total FFB count, 2. total predominantly fluid lesion count, 3. total predominantly soft tissue lesion count, 4. total FFB enhancement, 5. total fluid lesion enhancement, 6. total soft tissue lesion enhancement, and 7. FFB shape.

6.3 Results

6.3.1 Study cohort characteristics

All invited patients took part in the study. A summary of the demographic and clinical characteristics of the study cohort (N=42) is given in table 27. A total of 840 joints and 1,512 possible FFB sites were reviewed by each reader.

Table 27: Cohort demographic & clinical characteristics
Where CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, DAS=disease activity score; FIS_{IF}=foot impact score impairment/footwear subscale; FIS_{AP}=foot impact score activity/participation limitation subscale; US=musculoskeletal ultrasound; FFB=forefoot bursae.

	Mean, (SD), Range
age (years)	**62.2,** (12), 28-89
height (m)	**1.7,** (0.1), 1.3-1.9
weight (Kg)	**71**, (13.7), 42.2-108
BMI (Kg/m^2)	**26**, (4.4), 19.1-39
disease duration (years)	**15.3,** (10.3), 4-42
CRP (mg/L)	**9.3,** (14.9), 1-73
ESR (mm/hr)	**20.8,** (21.9), 0-111
DAS 28-CRP	**3.5,** (4.6), 1-31
DAS 28-ESR	**3.1,** (1.4), 0.3-6
erosion	**17.9**, (17.4), 0-77
bone marrow oedema	**10,** (9.6), 0-44
synovitis	**3.5**, (4.7), 0-20
FIS_{IF}	**3,** (2.2), 0-8
FIS_{AP}	**7,** (3.2), 0-10
US-detectable FFB	**3,** (2.9), 0-10

6.3.2 The '*FFB-score*'

All originally proposed items and scoring criteria were included within the final version of the tool, with the exception of size for which the semi-quantitative reporting of values was highly inconsistent between readers due to difficulties in clear structural visualisation in three imaging planes. Four possible enhancement grading options were proposed and trialled during phases one-three of score development:

- Option 1: The scale is 0-3. Score 0 is no enhancement and scores 1-3 (mild, moderate, severe) are by thirds of the presumed maximum volume of enhancing tissue within the identified lesion
- Option 2: The scale is 0-2. Score 0=no enhancement, 1=patchy, 2=solid
- Option 3: The scale is 0-2. Score 0=no enhancement, 1=less than 2mm thickness, 2=greater than 2mm thickness (when measured from the widest portion of peripheral enhancement, avoiding partial voluming effect)
- Option 4: The scale is 0-4. Score 0=no enhancement, 1=1-25%, 2=26-50%, 3=51-75%, 4=76-100% of the presumed maximum volume of the potential enhancing tissue within the identified lesion

After completion of tool development stages 1-3, option two was selected as the most appropriate score for use. The final proposed *FFB-score* items, definitions and grading criteria

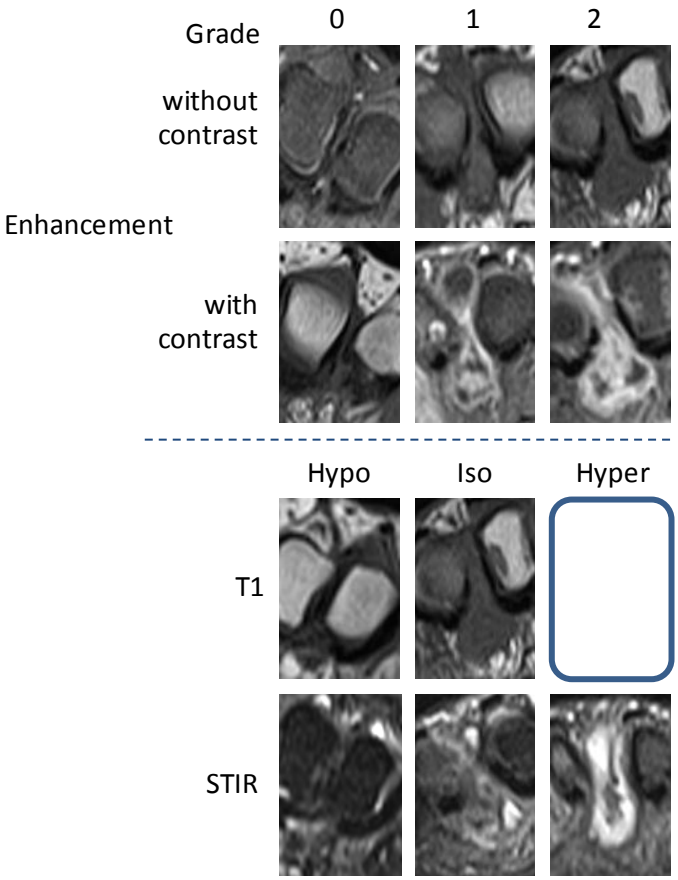
are presented in table 28. The *FFB-score* record sheet with user guide can be found in the appendix section A19.

Table 28: *FFB-score* items, definitions & grading criteria

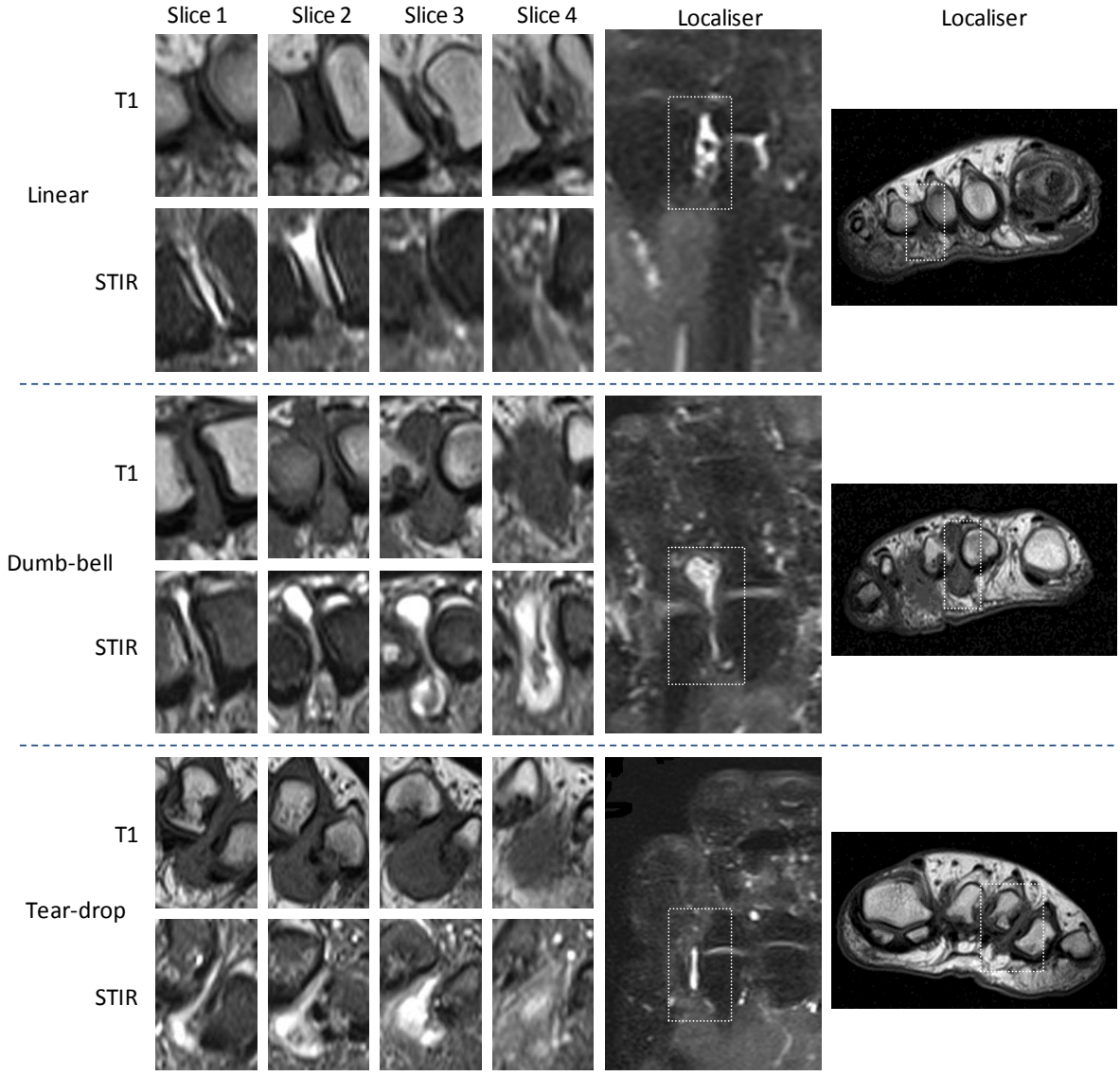
Factor	Definition	Scoring
Fluid collection	A fluid collection is defined as a homogeneous hyperintense extra-articular mass with a fluid-equivalent signal on PD/T2 weighted sequences, to be judged relative to synovial joint fluid.	Present (1)/Absent (0)
Extra articular soft tissue lesion	A fluid collection is defined as a homogeneous hyperintense extra-articular mass with a fluid-equivalent signal on PD/T2 weighted sequences, to be judged relative to synovial joint fluid.	Present (1)/Absent (0)
Shape	**Intermetatarsal lesions:** Lesions with an extended height and narrow width are described as linear. Lesions with bulbous rounded dorsal/plantar margins are described as 'dumb-bell'. Lesions with bulbous rounded plantar margins are described as 'teardrop'. **Plantar lesions:** Lesions with an extended width and narrow height are described as linear. Lesions with irregular borders projecting both in the transverse and frontal planes are described as reticular. Lesions with regular borders of near equal projection in both the transverse and frontal planes are described as mass-like.	**Intermetatarsal lesions:** Linear (1)/Dumb-bell (2)/Teardrop (3) **Plantar lesions:** Linear (1)/Reticular (2)/Mass-like (3)
Enhancement	Enhancement is judged by comparison of T1 weighted images obtained before and after intravenous gadolinium contrast.	No enhancement (0)/Patchy (1)/Solid (2)
MR characteristics	Lesions are defined as hypointense (Hypo) when appearing darker relative to muscle imaged within the same slice, Isointense (Iso) when appearing grey-scale equivalent or hyperintense (hyper) when appearing brighter.	Hypointense (1)/Isointense (2)/Hyperintense (3)
Intermetatarsal location	Lesions are defined as occurring within the intermetatarsal spaces if the major proportion of the lesion is located dorsal to the deep transverse intermetatarsal ligament.	IM 1-2/IM 2-3/IM 3-4/IM 4-5
Plantar metatarsal location	Lesions are defined as occurring plantarly if the major proportion of the lesion is located plantar to the deep transverse intermetatarsal ligament. The plantar area of the foot is divided into fifths in accordance with the area underlying each metatarsal head. The plantar intermetatarsal space is bisected in a line perpendicular to the sagittal image plane, equi-distant from each metatarsal head.	1/2/3/4/5

6.3.3 *FFB-score* image atlas

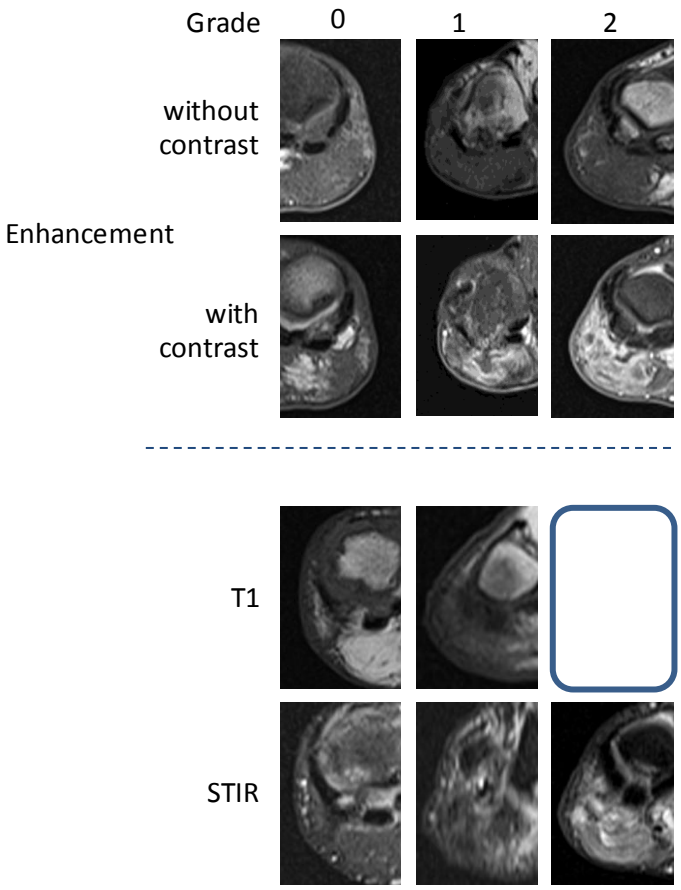
Figure 48 illustrates the collated images considered to be representative of item grading for the *FFB-score*. Each image set has a locator image in order to help orientate the user towards the area of interest.



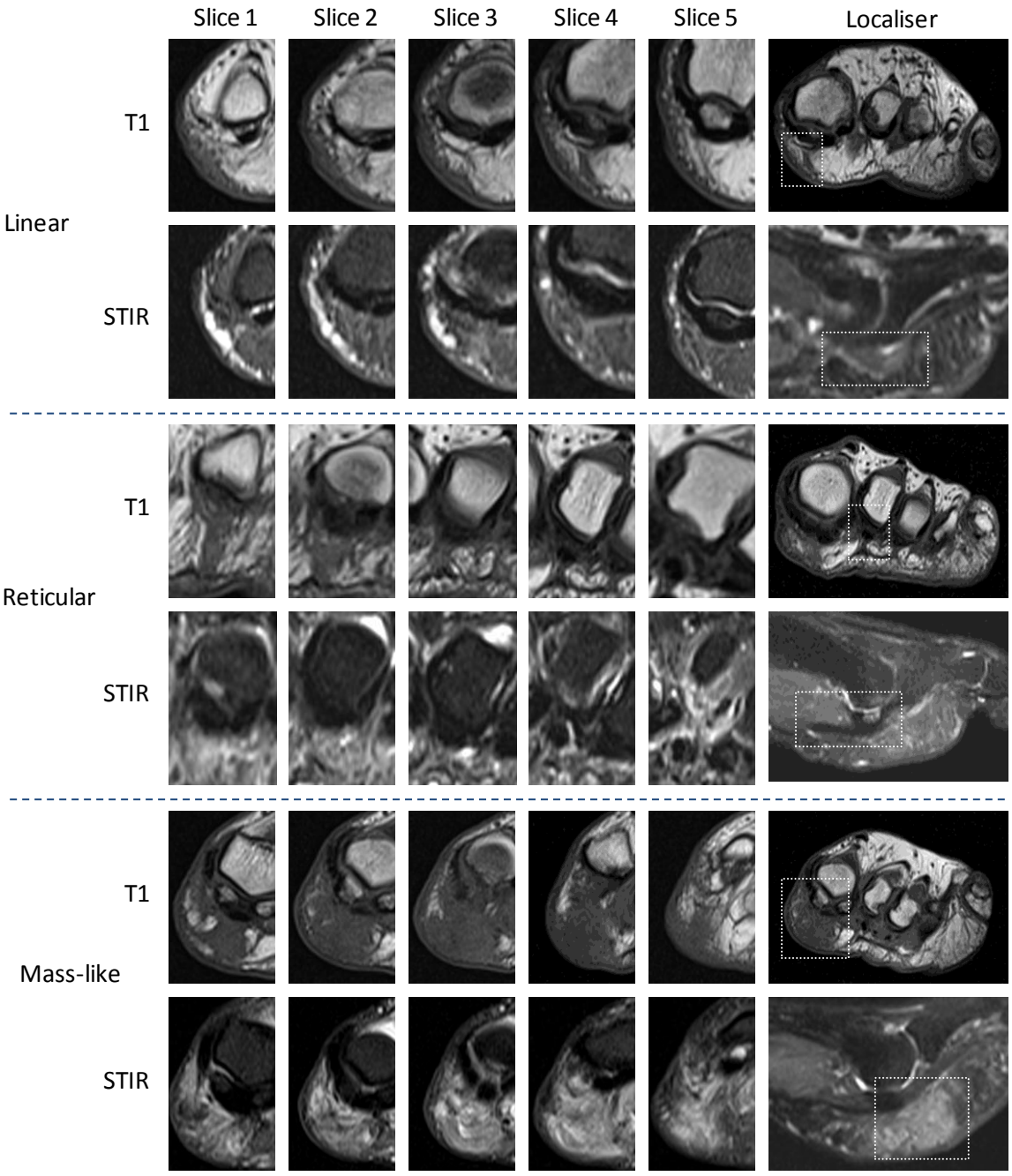
48a. Intermetatarsal lesions: enhancement & T1/ STIR characteristics



48b. Intermetatarsal lesions: shape



48c. Plantar lesions: enhancement & T1/STIR characteristics



48d. Plantar lesions: shape

Figure 48: The *FFB-score* image atlas
See table 28 for item grading definitions

6.3.4 *FFB-score* values & ranges

The combined mean score (and range) for all *FFB-score* items when evaluated both between radiologist readers and between a radiologist and podiatrist reader were similar (table 29).

Table 29: *FFB-Score* mean values & ranges

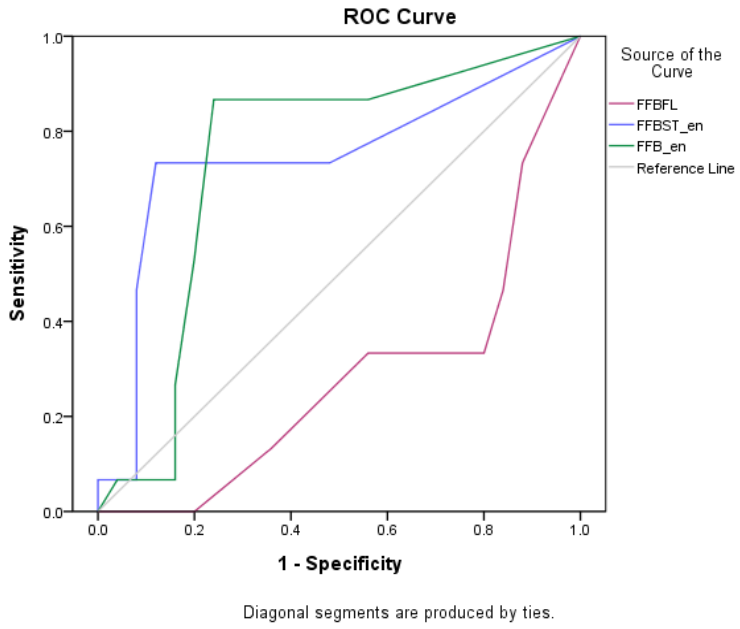
Lesion type		Factor	Radiologist combined **mean score,** (range)	Adjusted radiologist & podiatrist combined **mean score** (range)
Intermetatarsal	Fluid	Count	**3** (0-8)	**3** (0-8)
		Shape	**4** (0-14)	**4** (0-14)
		Enhancement	**1** (0-9)	**1** (0-9)
		MRI T1	**7** (0-14)	**7** (0-14)
		MRI T2	**10** (0-24)	**10** (0-24)
	Soft tissue	Count	**1** (0-5)	**1** (0-9)
		Shape	**0** (0-6)	**1** (0-6)
		Enhancement	**1** (0-6)	**1** (0-8)
		MRI T1	**2** (0-10)	**2** (0-10)
		MRI T2	**2** (0-12)	**2** (0-12)
Plantar lesion	Fluid	Count	**0** (0-2)	**0** (0-2)
		Shape	**6** (0-15)	**5** (0-15)
		Enhancement	**0** (0-3)	**0** (0-3)
		MRI T1	**0** (0-4)	**0** (0-4)
		MRI T2	**0** (0-6)	**0** (0-6)
	Soft tissue	Count	**5** (0-10)	**4** (0-10)
		Shape	**11** (0-25)	**9** (0-25)
		Enhancement	**1** (0-7)	**1** (0-7)
		MRI T1	**10** (0-20)	**8** (0-20)
		MRI T2	**12** (0-29)	**10** (0-29)

6.3.5 Intra & inter-reader agreement

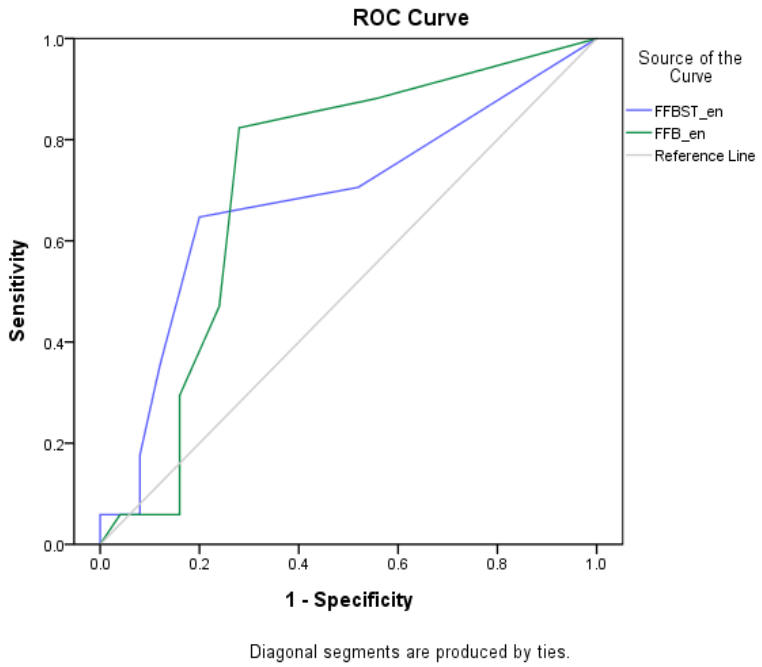
Overall, the *FFB-score* was demonstrated to have substantial intra-reader agreement. The detection of intermetatarsal fluid lesions was moderate (k=5.5), plantar fluid lesions excellent (k=7.5-8) and intermetatarsal and plantar soft tissue lesions substantial (k=9, k=7-8 respectively). Further agreement result details are tabulated in appendix section A16. Overall, the *FFB-score* was demonstrated to have substantial inter-reader agreement, with the exception of plantar soft tissue lesion shape and T1/T2 characteristics between readers LK and MT, for which agreement was poor-moderate. The detection of intermetatarsal fluid lesions was moderate (k=4.7-4.9), plantar fluid lesions substantial to excellent (k=6.6-8.7) and intermetatarsal and plantar soft tissue lesions substantial (k=7.3-7.5, k=6.4 respectively). Further agreement result details are tabulated in appendix section A16.

6.3.6 *FFB-score* validity

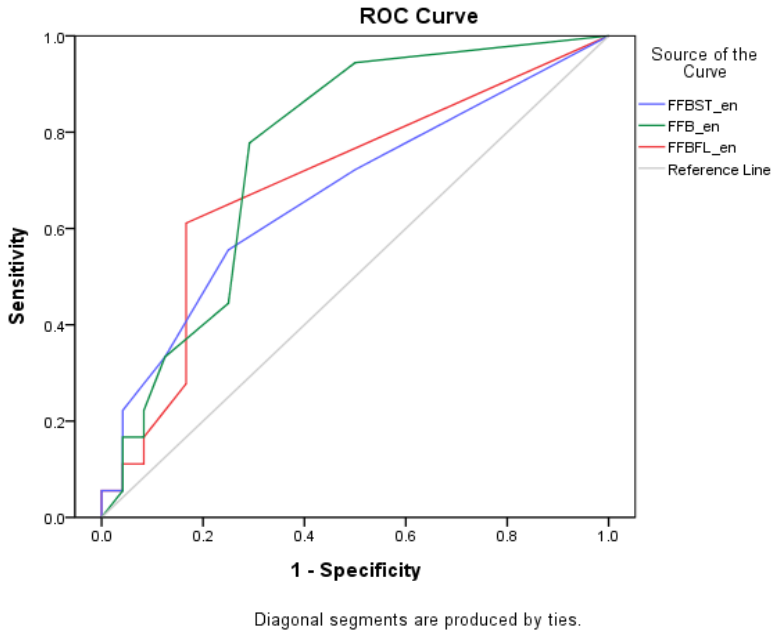
Estimations of *FFB-score* content validity, calculated using Lawshe's CVR, determined that all items have good validity (0.625; where N=5 and Ne=5 for all items). The FFB-score had poor discriminant validity for the differentiation of patients with high/low systemic disease activity (further discriminant validity result details are tabulated in appendix section A17). Conversely, FFB count and enhancement characteristics demonstrated good discriminant validity for the differentiation of patients with high/low MRI-determined disease activity local to the foot. Specifically, FFB fluid lesion count, FFB enhancement and soft tissue lesion enhancement significantly discriminated between high/low erosion scores (AUC= 0.281, p=0.022; AUC=0.741, p=0.011; AUC=0.744, p=0.011 respectively; figure 49a). FFB enhancement and soft tissue lesion enhancement significantly differentiated between high/low bone marrow oedema scores (AUC= 0.718, p=0.018; AUC=0.681, p=0.048 respectively; figure 49b). FFB enhancement and fluid lesion enhancement significantly differentiated between high/low synovitis scores (AUC= 0.759, p=0.004; AUC=0.697, p=0.031 respectively; figure 49c). Further discriminant validity result details are tabulated in appendix sections A17 and A18.



49a. Metatarsophalangeal joint erosion



49b. Bone marrow oedema



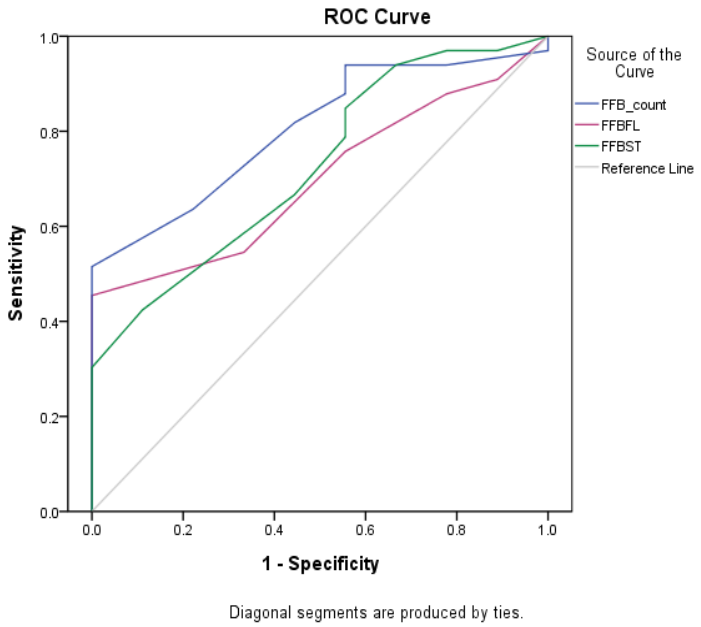
49c. Metatarsophalangeal joint synovitis

Figure 49: *FFB-score* discriminant validity: disease activity

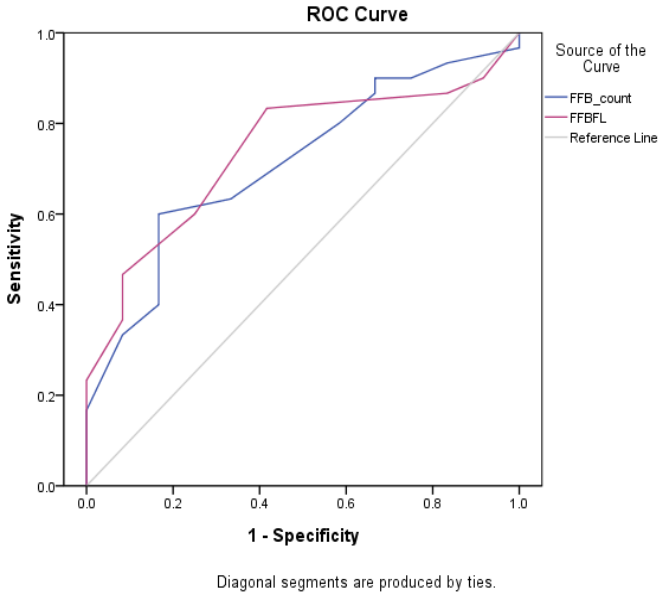
Where 49a shows discriminant validity for high/low erosion scores, 49b shows discriminant validity for high/low bone marrow oedema scores, 49c shows discriminant validity for high/low synovitis scores. FFB = forefoot bursae; FL = fluid lesion; ST = soft tissue lesion; en = enhancement.

The *FFB-score* was also determined to have good discriminant validity when differentiating between patients with high/low foot-related disability. Specifically, FFB count and FFB soft tissue lesion count significantly discriminated between high/low foot impairment (AUC=0.198, p=0.006;

AUC=0.274, p=0.040 respectively; figure 50a). FFB count and FFB fluid lesion count significantly differentiated between high/low activity limitation (AUC=0.288, p=0.033; AUC=0.260, p=0.016 respectively; figure 50b).



50a. FIS_{IF}



50b. FIS_{AP}

Figure 50: *FFB-score* discriminant validity: foot-related disability

Where 50a shows discriminant validity for high/low foot impairment scores, 50b shows discriminant validity for high/low activity limitation scores. FFB = forefoot bursae; FL = fluid lesion; ST = soft tissue lesion; en = enhancement; FIS_{IF} = foot impact score impairment/footwear subscale; FIS_{AP} = foot impact score activity/participation limitation subscale

6.4 Discussion

To our knowledge, this study is the first to propose a systematic method for the semi-quantitative characterisation of FFB in patients with RA. The *FFB-score,* created and evaluated in a multi-step process consistent with OMERACT recommendations, appears to have good content validity (OMERACT filter 1), discriminant validity (OMERACT filter 2) and feasibility of use (OMERACT filter 3) based upon the preliminary analyses completed in this work (Boesen *et al.* 2009, Tugwell *et al.* 2007). In particular, the *FFB-score* appears to have good discriminant validity when differentiating between patients with high/low foot-related disability or forefoot disease activity. The *FFB-score* also appeared to demonstrate good intra and inter-reader reliability for all score dimensions. The findings of this study therefore provide preliminary evidence in support of the use of this score for the identification and characterisation of potentially clinically relevant bursa-like lesions of the forefoot in patients with RA. The accompanying image atlas and user guide provides reference material that may aid the uptake and use of the *FFB-score* in future work.

The evaluation of FFB, completed as part of the *FFB-score* development, identified differences in the tissue characteristics of observed lesions. Previous authors have suggested that such differences are related to the FFB aetiology (Studler *et al.* 2008, Koski 1998), although characterisation by pathological or aetiological means has arguably contributed to confusion within the literature. It is therefore proposed that the *FFB-score* can be utilised to characterise a range of forefoot bursa-like lesions without assumption or bias towards their potential aetiology and clinical importance. However, it should be noted that despite all identified lesions meeting our study definition of bursa (fluid filled cavity), a range of bursa-like lesions were observed. Of particular note, are the complex lesions occurring within the plantar fibro-fatty tissues of the forefoot that demonstrated a mixture of enhanced synovium and dense fibrotic tissue around a fluid cavity. The clinical significance of the range of bursa-like lesions observed remains unclear and warrants further investigation. Further evaluation of the clinical importance of MRI-detected FFB, and the characteristics thereof, in patients with RA is also warranted.

The reduced agreement reported for intermetatarsal fluid lesions was attributed to difficulty in accurately differentiating between nerve, fibrous or synovial tissue and bursa. The close anatomical association between the intermetatarsal neurovascular bundles and FFB, evident throughout the course of this work, potentially confounds the symptomatic nature of lesions identified within this anatomical region (Theumann *et al.* 2001). Future work, systematically exploring the prevalence and histopathology of co-existing FFB and neuroma, may provide beneficial insight regarding the pathogenesis of such lesions (Zielaskowski *et al.* 2000, Mutlu *et al.* 2006, Zanetti *et al.* 1997).

Significant differences in FFB enhancement, related to RA disease activity, were noted. Thus, the score developed in this study has potential clinical value in identifying and characterising

bursa-like lesions of the forefoot that may be indicative of RA disease activity; it is feasible that FFB characterised using the *FFB-score* represent a surrogate indicator of disease activity within the forefoot. However, the mechanisms underpinning this relationship remain unclear.

6.4.1 Study limitations

This study has a number of strengths and potential limitations. The studied population is a consecutive sample of well phenotyped patients with established RA, receiving ongoing rheumatological care. As such, the generalisability of the study findings to those patients with early disease or high disease activity needs to be explored. It should also be noted that the measures of MRI-determined localised disease activity used within this study have not been previously validated for use within the forefoot, although they have been demonstrated to be reproducible at this site (Baan *et al.* 2011). It is unclear at this time whether the elevated proportion of localised disease activity identified within this cohort is due to measurement error or is a true indication of ongoing minimal disease activity within the forefoot. The evaluation of disease activity local to the foot, but not detected with traditional composite measures such as the DAS 28, is of particular clinical importance in the ongoing care of foot health in patients with RA. This work provides further evidence which supports the need for the future development of a reliable and valid tool for the evaluation of RA disease activity in the forefoot.

Kappa values were used to determine the agreement between readers for the overall presence or absence of a lesion. However, this method does not account for instances where the same lesion may be observed by each reader but scored as occurring in neighbouring locations, thereby reducing absolute agreement. As such, the kappa values reported are potentially an under-estimation of actual presence/absence agreement between readers. Evaluation of lesion size was omitted from the analysis of this study due to poor agreement between readers in the early iterative stages of score development. However, this should not be taken to infer that lesion size is of little clinical relevance. Moreover, the collaborators of this study agreed that the FFB-score may be enhanced with the inclusion of lesion size although the identification of alternate semi-quantitative methods to achieve this requires further work. Additionally, assessment of responsiveness and criterion validity (inclusive of predictive validity) and refinement of the scoring system are needed in order to maximise its' potential utility in clinical trials and epidemiological studies (Silman and Hochberg 2001). Furthermore, the construct validity of all identified bursa-like lesions could be developed with the completion of a concurrent histopathological investigation.

6.4.2 Conclusion & summary

The *FFB-score* is a reliable and valid MRI-based tool for the detection and evaluation of FFB in patients with RA. The proposed tool has potential to be used clinically to locate and characterise FFB. Additional investigation of the clinical importance of identified FFB characteristics would potentially allow timely and targeted therapeutic intervention. Further longitudinal validation,

assessment of responsiveness and refinement of the scoring system is needed in order to maximise its potential utility in clinical trials and epidemiological studies.

Detecting forefoot bursae using MRI: development of the '*FFB-score'*

Key points:

- The *FFB-score* is reliable and valid for the identification and characterisation of FFB in patients with RA
- The *FFB-score* can be used in future epidemiological studies of FFB in patients with RA
- Further longitudinal evaluation of the *FFB-score* is required

Chapter seven

The epidemiology & clinical importance of MRI-detectable forefoot bursae in patients with rheumatoid arthritis

7.0 Chapter abstract

Background: Previous studies have demonstrated a high prevalence of clinically relevant musculoskeletal ultrasound (US) detected forefoot bursae (FFB) in patients with rheumatoid arthritis (RA). Both increased inflammation and biomechanical impairment have been cited as potential pathophysiological mechanisms underpinning the clinical importance of FFB. However, further characterisation of FFB is required to better explore this hypotheses. The recently derived magnetic resonance imaging (MRI) based *FFB-score* allows improved identification and characterisation of FFB in multiple imaging planes, such that determination of the epidemiology and clinical importance of MRI-detectable FFB, and specific characteristics thereof, is feasible.

Aim: To determine the epidemiology and clinical importance of MRI-detectable FFB in patients with RA.

Methods: A cross-sectional observational study of FFB was completed in patients with a consultant confirmed diagnosis of RA recruited from a UK rheumatology clinic. The primary outcome of interest, the presence of FFB, was determined using a 1.5T whole body MRI scanner and 4-channel flex extremity coil. The MRI protocol included coronal T1 and STIR, coronal and sagittal T1 post-gadolinium, and long axis 3D volumetric sequences. The point prevalence proportion (PP) of FFB was calculated by the division of the sum of identified cases (FFB ≥1) by the sum of the total studied population and expressed per 100 patients. The distribution of FFB across 9 pre-defined forefoot sites was expressed as a percentage of the total observed FFB. The MRI-determined characterisation of FFB is discussed descriptively. Correlation coefficient analysis was used to determine the statistical significance of potential associations between FFB count, or characteristics thereof, and indicators of systemic (ESR, CRP, DAS 28) or localised disease activity (MRI-detected MTP joint synovitis, erosion or bone marrow oedema), biomechanical impairment (FPI, Joint range of motion), or patient-reported foot-related disability (FIS questionnaire).

Results: The mean participant (± SD) age, disease duration and DAS 28 was 62.2 (±12) years, 15.3 (±10.3) years and 3.1 (±1.4) respectively. MRI-detectable FFB were highly prevalent in this patient cohort (PP=100 per 100, mean=7.7, SD=3.9, range=1-18). Of all observed FFB (n=324), 41.7% were characterised as predominantly fluid and 58.3% as predominantly soft tissue lesions. Fluid lesions were typically distributed within the intermetatarsal spaces while soft tissue lesions were typically distributed across the plantar forefoot. An increased presence of plantar fluid lesions was associated with elevated systemic markers of disease activity as were

reductions in the presence of soft tissue lesions. An increased presence of intermetatarsal soft tissue lesions was associated with the presence of MTP joint synovitis. An increased presence of soft tissue lesions (predominantly plantar) was associated with markers of biomechanical impairment. A trend towards an association between Increased FFB enhancement and disease chronicity or greater patient-reported foot impairment was noted.

Conclusion: MRI-detectable FFB are highly prevalent in patients with RA. Characterisation of MRI-detected FFB is helpful in identifying those lesions of greatest clinical relevance; there is preliminary evidence to suggest that the presence of intermetatarsal soft tissue lesions and plantar fluid lesions are associated with RA disease activity, while plantar soft tissue lesions are associated with biomechanical impairment. Importantly, a trend towards an association between increased FFB enhancement and increased foot impairment was noted.

7.1 Introduction

Previous studies have demonstrated a high prevalence of musculoskeletal ultrasound (US) detected forefoot bursae (FFB) in patients with rheumatoid arthritis (RA) (Bowen *et al.* 2009, Bowen *et al.* 2010c). FFB prevalence has been demonstrated to be significantly associated with increased RA disease activity both in cross-sectional and longitudinal studies (Bowen *et al.* 2009, Bowen *et al.* 2010c, Koski 1998, Palmer 1970). Furthermore, FFB have been demonstrated to be a significant prognostic indicator of patient-reported foot-related disability longitudinally (Chapter four). Both increased inflammation and biomechanical impairment have been cited as potential pathophysiological mechanisms underpinning the clinical relevance of US-detectable FFB (Ahmed *et al.* 1994, Studler *et al.* 2008, Aguiar *et al.* 2005, Koski 1998, Harper 2003, Hernandez *et al.* 1991). The work presented in Chapter five has reinforced this hypothesis, demonstrating comparatively different FFB distributions between healthy volunteers and patients with predominantly inflammatory or degenerative arthritis. The findings of this work suggest that differing clinically relevant FFB distribution patterns or characteristics may coexist in patients with RA. The recently derived MRI-based *FFB-score*, unlike US, allows observer-independent, multi-planar, identification and characterisation of FFB in patients with RA (Chapter six). This study therefore aims to utilise the *FFB-score* to determine the epidemiology and clinical importance of MRI-detectable FFB, and characteristics thereof, in patients with RA.

7.1.1 Study aim & objectives

The main aim of this study was to determine the epidemiology and clinical importance of MRI-detectable FFB in patients with RA. To achieve this aim the following objectives were set:

1. To determine the prevalence of MRI-detectable FFB
2. To describe differences in the MRI characteristics of identified FFB
3. To determine the clinical importance of MRI-detectable FFB in patients with RA

7.2 Materials & methods

7.2.1 Study design

To achieve the above objectives a cross-sectional observational study design was used. The primary study outcome was an analysis of the presence of MRI-detected forefoot bursae (FFB), and their MRI characteristics. All intermetatarsal spaces (x4) and plantar metatarsal regions (x5) were imaged for the presence of FFB and characterised according to the '*FFB-score'*. The number of observed FFB for both feet was combined (0-18). Explanatory variables of interest included those related to systemic RA disease activity (serological inflammatory markers and composite disease activity score), disease activity localised to the forefoot (MRI-detected activity), biomechanical foot deformity (foot posture index (FPI), hallux abducto-valgus deformity (HAV), lesser digital deformity (LDD)), foot function (ankle, subtalar, midfoot, or metatarsophalangeal joint ranges of motion), or disease impact in terms of patient-reported foot-related disability (Foot Impact Score).

Systemic disease activity was evaluated using markers of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and calculation of a 28 joint disease activity score (DAS 28) (Van der Heijde *et al.* 1990). Disease activity localised to the forefoot was evaluated using MRI-detected metatarsophalangeal joint synovitis (SY), bone marrow oedema (OE), and metatarsophalangeal joint erosion (ER). Synovitis was graded 0-3 (normal, mild, moderate or severe), bone marrow oedema as 0-3 (by 33% volume increments) and erosion as 0-10 (by 10% volume increments), as per the recommendations for the EULAR-OMERACT '*RAMRIS'* score for the hand (Conaghan *et al.* 2005a). The foot posture index was selected as a composite measure of weight-bearing foot joint alignment and scored for both feet combined (0-24). Deformity was scored as either present or absent for each joint assessed and the accumulative score for each foot combined (0-20). Joint range of motion was scored as full, limited or rigid for each joint of interest and the accumulative score for each foot combined (0-4). Disability was evaluated using the two subscales of the foot impairment score (FIS): 1. (FIS_{IF}, 0-21); foot impairment and footwear restriction, 2. (FIS_{AP}, 0-29); activity limitation and participation restriction (Helliwell *et al.* 2005). An elevated FIS_{IF} or FIS_{AP} score indicates greater foot impairment or activity limitation respectively. Explanatory variables were selected based upon the findings of previous work, literature review and potential clinical relevance. Detail regarding the selected measures is given in Chapter two (section 2.2) and Chapter three (section 3.6).

7.2.2 Study population

Patients included within this study were those with a consultant confirmed diagnosis of RA who were consecutively recruited from a UK rheumatology out-patient clinic. All participants who completed the year-three 'FeeTURA' study were eligible for screening to this study. Further detail regarding the recruitment, screening, inclusion/exclusion criteria and sample size determinants is documented in Chapter three (sections 3.4-3.5).

7.2.3 Protocol for data collection

The protocol for participant recruitment and MRI data acquisition is illustrated in figure 51.

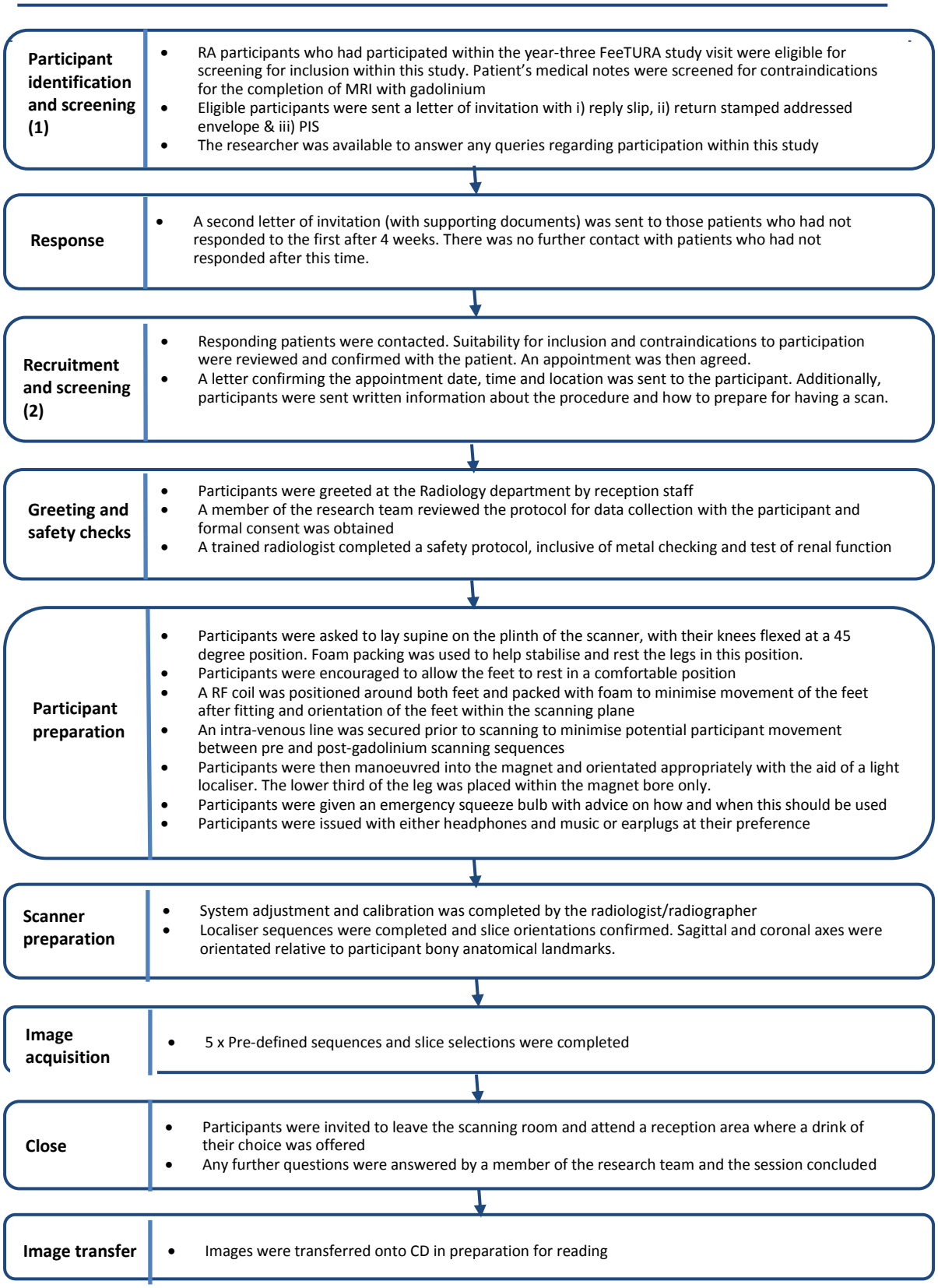


Figure 51: A schematic diagram of the protocol for MRI data acquisition

A 1.5 Tesla (T) whole body scanner (Siemens Avanto Syngo® MR B15, Siemens AG Medical Solutions, Erlangen, Germany) was used for all MRI acquisition. A four channel flex extremity radio frequency (RF) surface coil (Siemens, Siemens AG Medical Solutions; with circularly polarised array) was used to image the mid and forefoot region only. Prior to data collection initial capacitor tuning was completed to ensure that the RF coil frequency was synchronised with the magnetic field (B_0). System calibration was completed as per the standard protocol for the radiology department.

Five sequences were completed after orientation with a T1-weighted sagittal locator image: 1. T1 weighted coronal spin echo pulse sequence, 2. Coronal short Tau inversion recovery sequence, 3. T1-weighted fat-saturated post-gadolinium coronal, 4. T1-weighted fat-saturated post-gadolinium sagittal, 5. Long axis proton-dense fat-saturated 3D voxel sequence. Alignment and positioning was manually orientated by the radiologist; coronal scans were orientated with the metatarsal parabola, sagittal scans were approximately orientated perpendicular to the coronal slice profile and with the shaft of the third metatarsal. The field of view (FoV) in the read direction was determined as the base of 1st metatarsal to the distal aspect of the hallux. The FoV in the phase-encode direction was defined as extending from the medial to the lateral foot borders. Further details regarding the protocol for image acquisition is documented in Chapter three (section 3.6.4).

7.2.4 Protocol for image acquisition & reading

FFB images were scored according to previously derived *FFB-score* and graded for all items including presence/absence of a lesion, lesion location (intermetatarsal/plantar), tissue type (fluid/soft tissue), shape (linear/reticular/mass or linear/dumb-bell/teardrop), and enhancement (0-2) (Chapter 6). The metatarsophalangeal joints of the forefoot were scored for synovitis, bone marrow oedema and erosion. Synovitis was graded 0-3 (normal, mild, moderate or severe), bone marrow oedema as 0-3 (by 33% volume increments) and erosion as 0-10 (by 10% volume increments), as per the recommendations for the EULAR-OMERACT '*RAMRIS'* score for the hand (Conaghan *et al.* 2005a). Images were viewed using Siemens *Syngo*© fast view software for Dicom images (Siemens AG 2004-2006). Images were reviewed for anomalous findings by a consultant radiologist (LK) at the time of acquisition in order to conform to safety and quality control checking procedures. All MRI images were read and scored by a consultant radiologist (LK), familiar with the *FFB-score,* who was blinded to the patient's clinical presentation and disease state.

7.2.5 Analysis

All analysis was completed using Stata version 11.0 (Stata Corp, College Station, Texas, USA) or SPSS version 18.0 (Chicago, Illinois, USA). Prior to analysis, data distribution was checked for inconsistencies, outliers and missing information. Histograms and scatter plots were used to assess whether the data followed a normal distribution. The demographic and clinical

characteristics of the study participants are presented as the mean, standard deviation (SD) and range.

The point prevalence proportion of MRI-detectable FFB was calculated by the division of the sum of identified cases by the sum of the total studied population and expressed per 100 patients. The observed FFB presence mean, SD and range were also calculated. For the purposes of distribution analyses, MRI-detected FFB were grouped according to the predominant tissue characteristic of the observed lesion; group 1: predominantly fluid, group 2: predominantly soft tissue. The nine investigated forefoot sites were grouped into medial (sites 1-3), central (sites 4-6) and lateral (sites 7-9), (figure 41, Chapter five, section 5.2.4). Statistically significant differences in the distribution of FFB across forefoot regions between fluid and soft tissue lesions were explored using chi squared analyses. Differences in the MRI appearance of FFB are discussed descriptively. Differences in the presence of FFB enhancement between fluid and soft tissue lesions, within the same participant, across either intermetatarsal of plantar sites were determined using multiple matched-paired t-tests. Correlation coefficient analysis was used to determine the statistical significance of potential associations between the primary outcome of interest (FFB count), and measured explanatory variables (markers of systemic disease activity, local disease activity, biomechanical function and patient-reported foot-related disability). The total number of MRI-detectable episodes of FFB, JH or ER for both feet combined was calculated for each patient; these count scores were treated as continuous variables for the purposes of analysis, although were bounded between 0-18 for FFB and 0-10 for SY, OE and ER. For the purposes of clinical importance analyses, participants were pragmatically stratified into high (FIS_{IF}>5; ~25% of maximum score) or low (FIS_{IF}≤4) reported foot impairment and high (FIS_{AP}>8; ~25% of maximum score) or low (FIS_{AP}≤7) reported activity limitation. Statistically significant differences in total observed FFB, or characteristics thereof, between high and low levels of patient-reported foot impairment or activity limitation was subsequently determined using Chi^2 analysis.

7.3 Results

7.3.1 Study cohort characteristics

All invited patients participated within the study. A summary of the demographic and clinical characteristics of the study cohort (N=42) is given in table 30. A total of 840 joints and 1,512 possible FFB sites were reviewed.

Table 30: Cohort demographic & clinical characteristics
Where CRP=C - reactive protein, ESR=erythrocyte sedimentation rate, DAS=disease activity score; FIS_{IF}=foot impact score impairment/footwear subscale; FIS_{AP}=foot impact score activity/participation limitation subscale.

	Mean, (SD), Range
age (years)	**62.2,** (12), 28-89
height (m)	**1.7,** (0.1), 1.3-1.9
weight (Kg)	**71**, (13.7), 42.2-108
BMI (Kg/m^2)	**26**, (4.4), 19.1-39
disease duration (years)	**15.3,** (10.3), 4-42
CRP (mg/L)	**9.3,** (14.9), 1-73
ESR (mm/hr)	**20.8,** (21.9), 0-111
DAS 28-CRP	**3.5,** (4.6), 1-31
DAS 28-ESR	**3.1,** (1.4), 0.3-6
synovitis	**3.5**, (4.7), 0-20
bone marrow oedema	**10**, (19.6), 0-44
erosion	**17.9**, (17.4), 0-77
FIS $_{IF}$	**3,** (2.2), 0-8
FIS $_{AP}$	**7,** (3.2), 0-10

7.3.2 The prevalence of MRI-detectable FFB in patients with RA

MRI-detectable FFB were highly prevalent in patients with RA (table 31). Of all observed FFB, a greater number were detected within the plantar metatarsal region compared to the intermetatarsal region. Of all observed FFB, a greater number of observed lesions were predominantly soft tissue compared to fluid (table 31).

Table 31: The prevalence of MRI-detectable FFB

	Point prevalence (per 100 participants)	**Mean**, (SD), Range
Total observed FFB	100	**7.7**, (3.9), 1-18
Intermetatarsal FFB	88.1	**4.1**, (2.6), 0-11
Plantar FFB	92.9	**3.6**, (2.3), 0-10
Fluid FFB	83.3	**3.2**, (2.2), 0-7
Fluid intermetatarsal FFB	83.3	**3.1**, (2.1), 0-7
Fluid plantar FFB	7.1	**0.1**, (0.3), 0-1
Soft tissue FFB	97.6	**4.5**, (2.7), 0-11
Soft tissue intermetatarsal FFB	52.4	**0.9**, (1.2), 0-5
Soft tissue plantar FFB	92.9	**3.6**, (2.3), 0-10

The distribution of MRI-detectable FFB is shown in figure 52. A significant difference between the distribution of predominantly fluid and soft tissue lesions was observed (X^2=72.8, p≤0.001);

fluid lesions were distributed across the medial and central intermetatarsal spaces, while soft tissue lesions were distributed across the plantar forefoot region (figure 52).

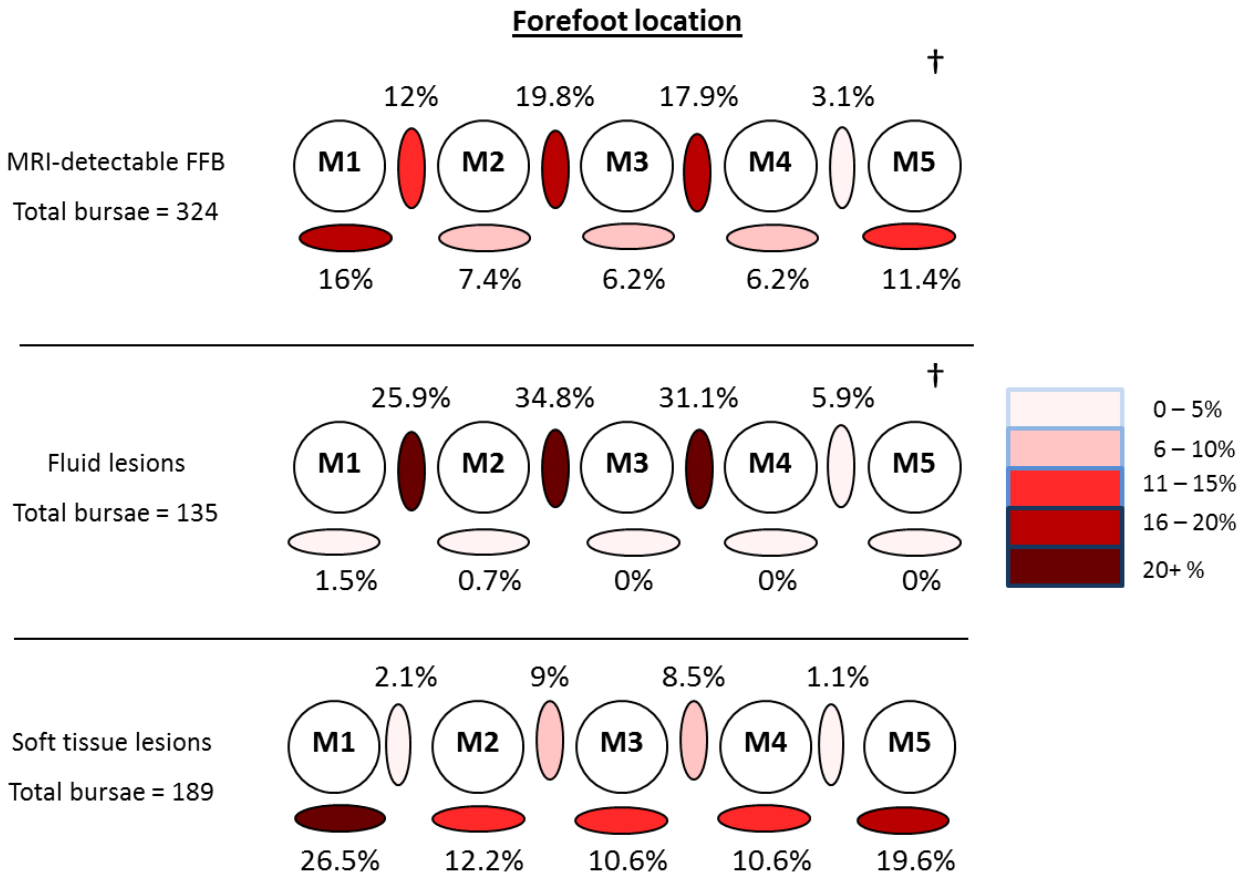


Figure 52: The distribution of MRI-detectable FFB & FFB-subtypes across the forefoot
Values are expressed as percentage of sample with FFB in this location.
Where M1-5 = plantar metatarsophalangeal joint region.

7.3.3 The MRI characteristics of FFB in patients with RA

Differences in the shape of observed FFB, for both fluid and soft tissue lesions, in both intermetatarsal and plantar metatarsal regions were observed (figure 53). Additionally both fluid and soft tissue lesions demonstrated ranges of enhancement (figure 54). No significant difference in enhancement between intermetatarsal fluid and soft tissue lesions was determined ($t=0.815$, $p=0.420$). However, a significant difference in enhancement between plantar fluid and soft tissue lesions was determined ($t=-3.65$, $p\leq0.001$), where predominantly soft tissue lesions were significantly more inflamed than predominantly fluid lesions.

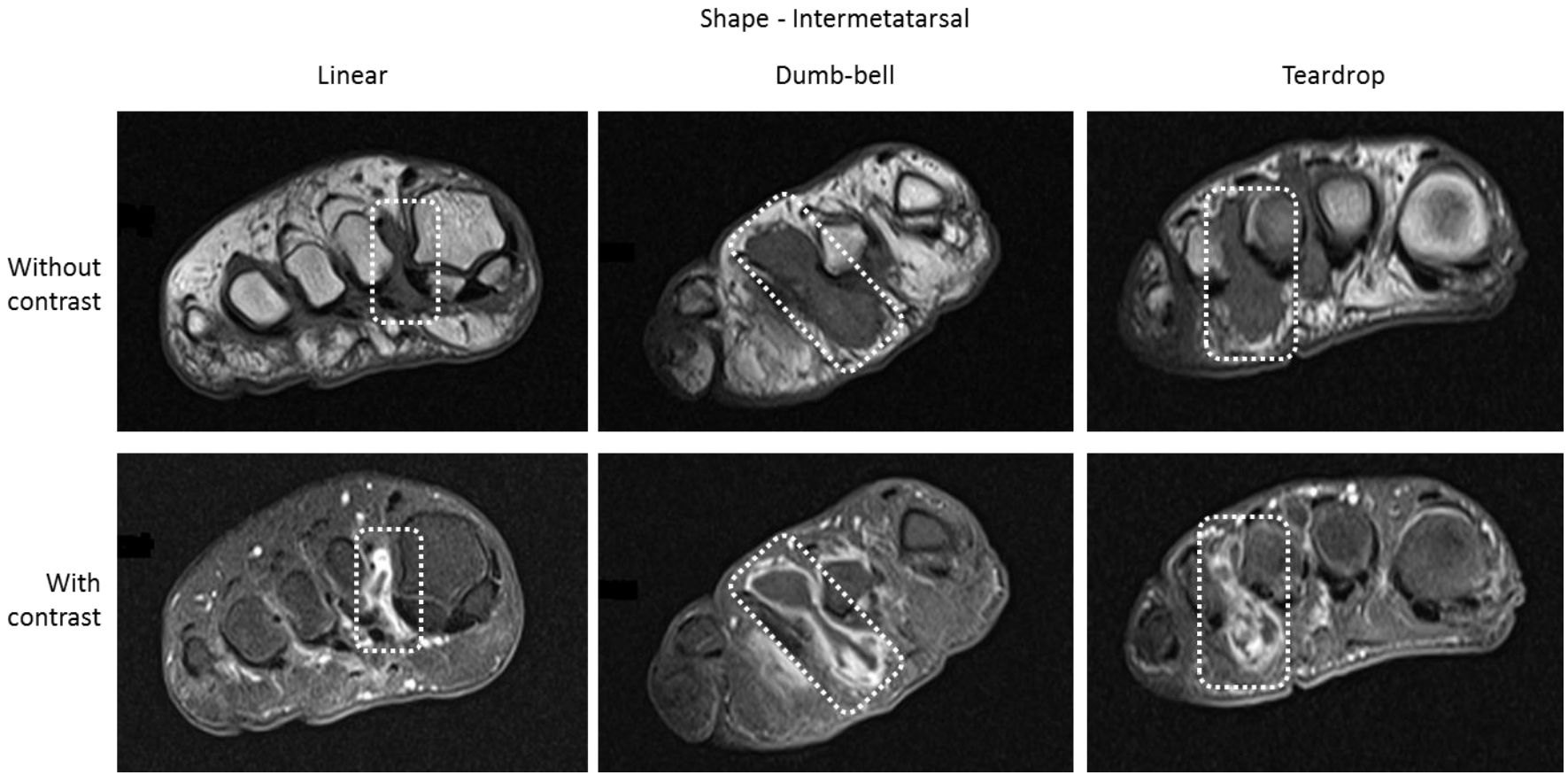


Figure 53a: Differences in MRI-detectable FFB shape

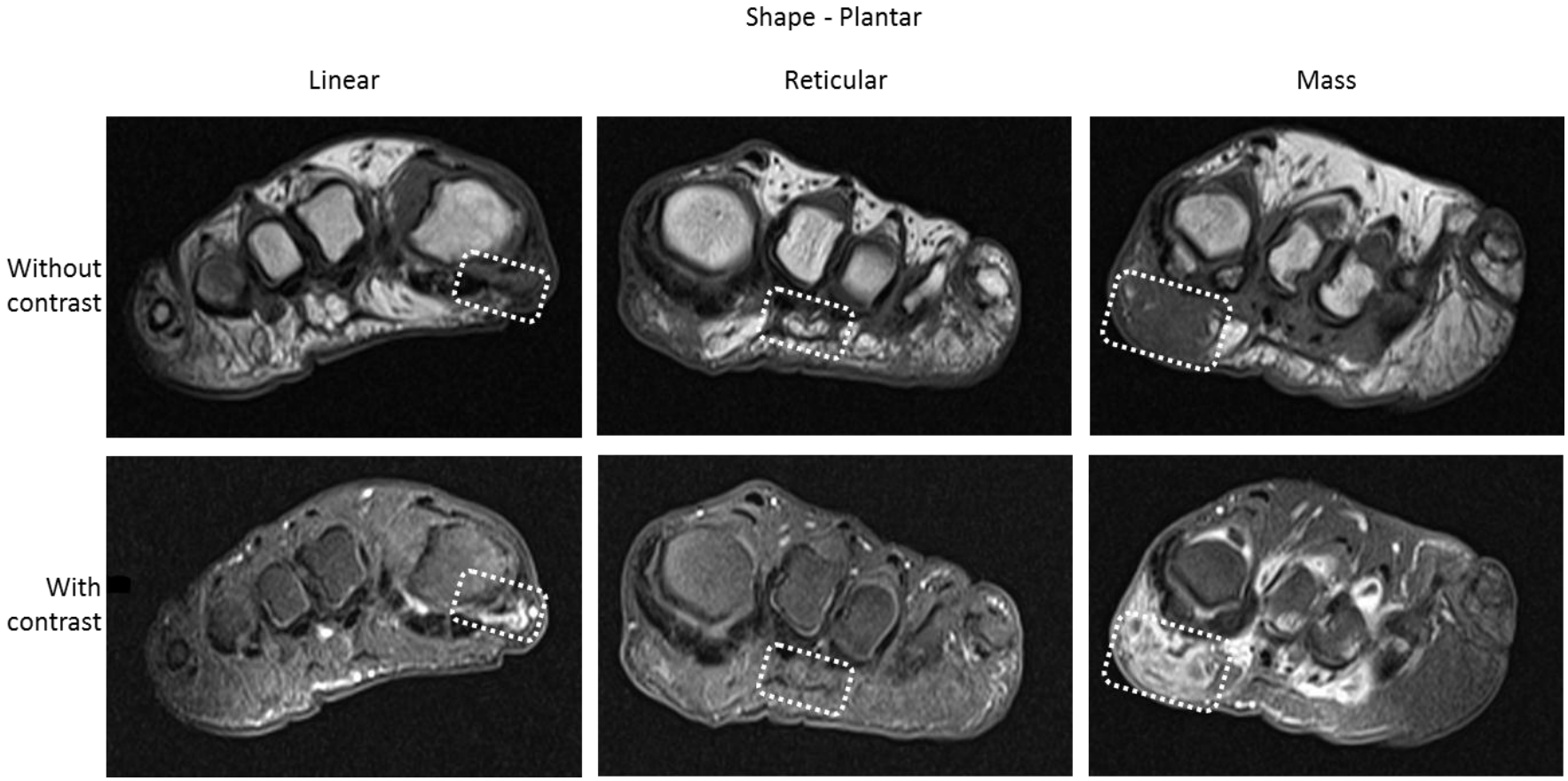


Figure 53b: Differences in plantar lesion shape
Where 53a illustrates differences in observed intermetatarsal lesion shape, 53b illustrates differences in observed plantar lesion shape. Areas of interest are denoted by an interrupted white line.

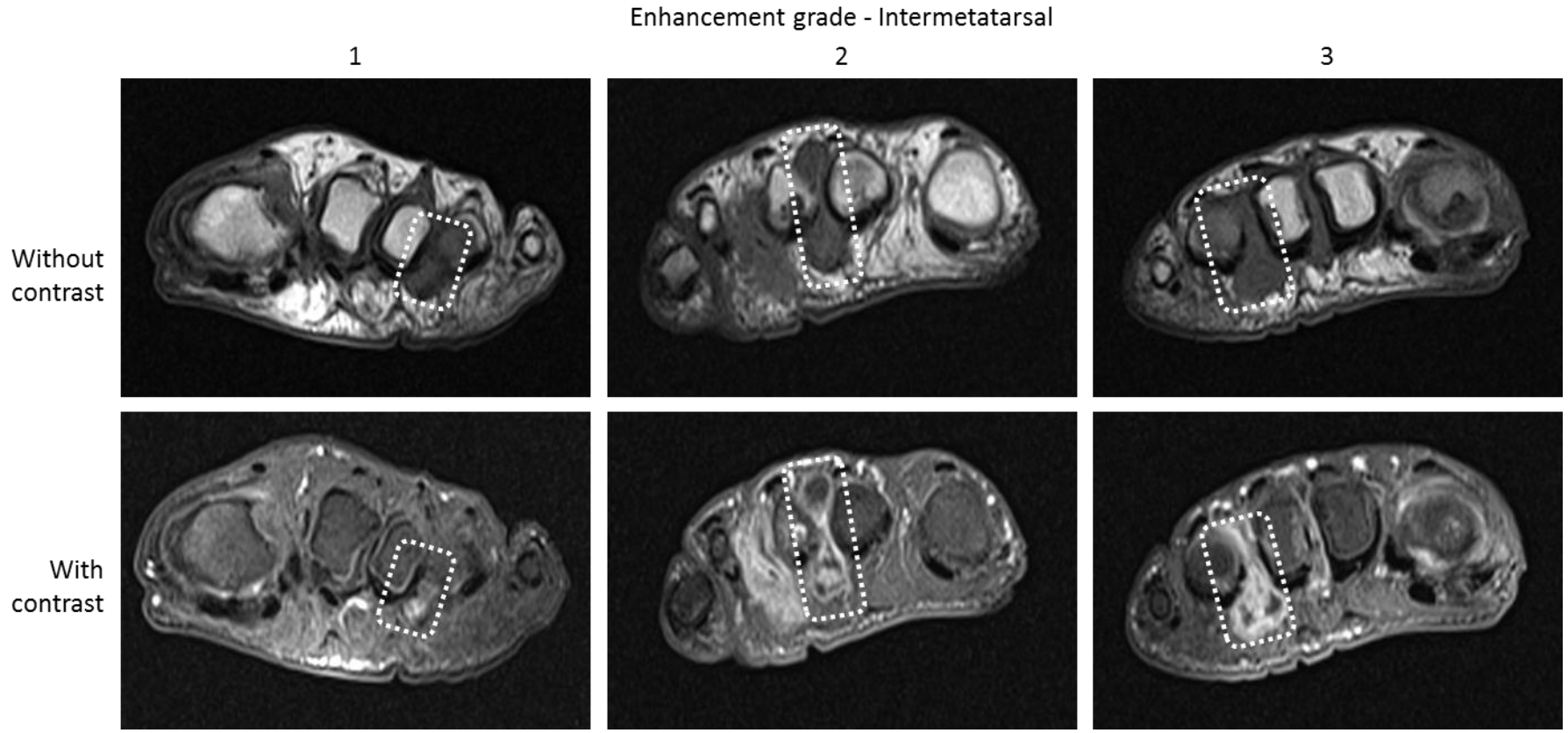


Figure 54a: Differences in MRI-detectable FFB enhancement: intermetatarsal lesions

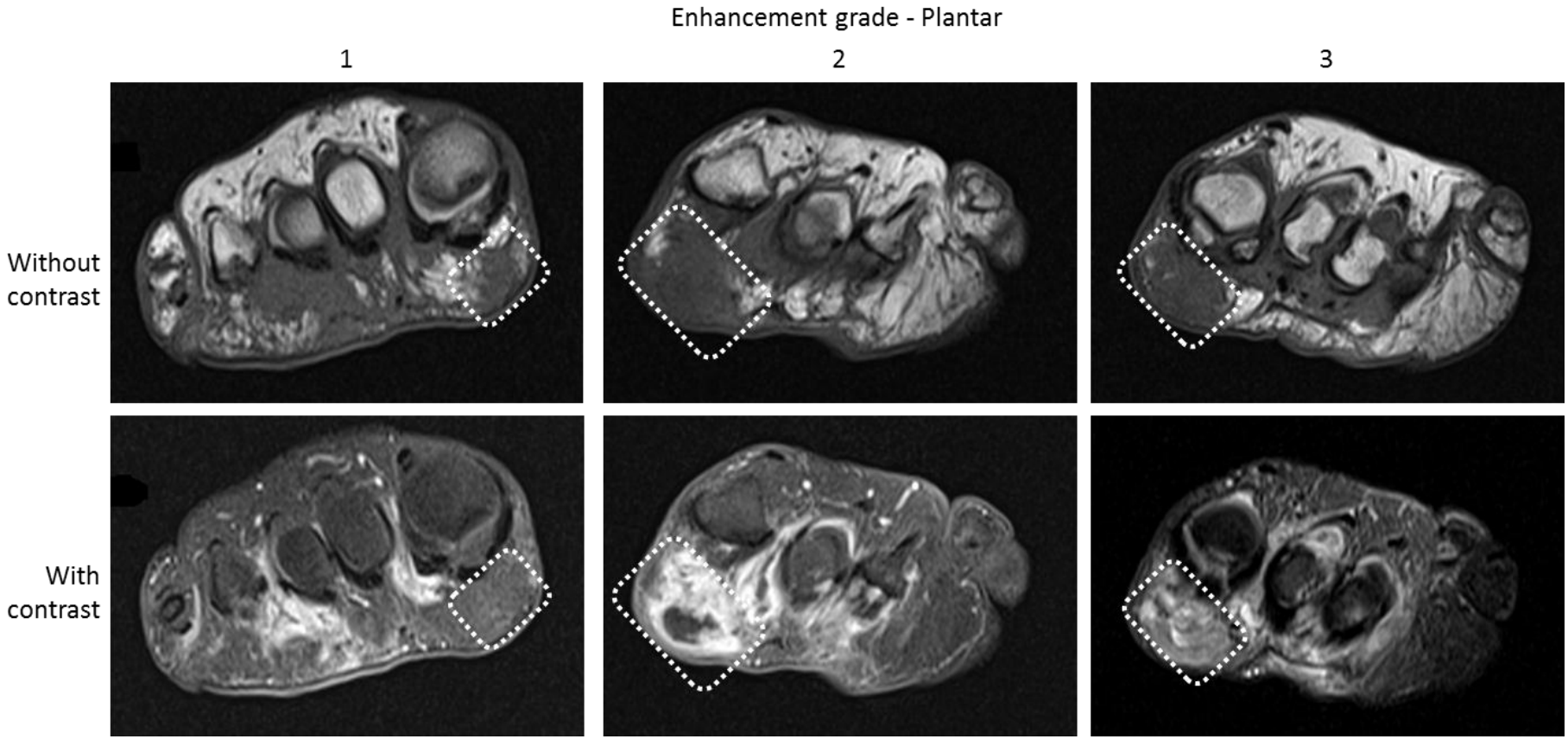


Figure 54b: Differences in MRI-detectable FFB enhancement: plantar lesions
Where 54a illustrates differences in observed intermetatarsal lesion shape, 54b illustrates differences in observed plantar lesion shape. Areas of interest are denoted by an interrupted white line.

7.3.4 The clinical importance of FFB in patients with RA

An increased number of plantar fluid lesions and reduced numbers of all soft tissue lesions (and specifically plantar soft tissue lesions) was significantly associated with increased CRP (r=0.33, p=0.035; r=-0.38, p=0.015; r=-0.34, p=0.029 respectively). Increased plantar soft tissue lesion enhancement was significantly associated with longer disease duration (r=0.38, p=0.015). No further FFB characteristics were associated with systemic markers of disease activity.

An increase in the number of intermetatarsal soft tissue lesions was significantly associated with metatarsophalangeal joint synovitis (r=0.37, p=0.017). Increased intermetatarsal fluid lesion enhancement was also approaching a significant correlation with synovitis (r=0.3, p=0.053). No further FFB characteristics were associated with localised markers of disease activity.

An increase in the number of soft tissue lesions was significantly associated with poorer foot posture (r=0.36, p=0.019) and reduced ankle joint range of motion (r=0.35, p=0.025). No further FFB characteristics were associated with markers of biomechanical impairment. Please note, disease duration, CRP, ESR, DAS 28-CRP and MRI-detected SY, OE and ER were all determined to be negatively skewed and as such Spearman's Rank association analyses are reported for these variables.

Participants were grouped according to low (<25% of maximum score) or high (≥25% of maximum score) erosion, bone marrow oedema, synovitis or reported foot-related disability. Significant differences in plantar soft tissue lesion enhancement were noted between those patients with low or high erosion scores (p=0.03, t=1.97, 95% CI=-0.02 – 1.31). Similarly, significant differences in plantar soft tissue lesion enhancement and the number of intermetatarsal soft tissue lesions were noted between patients with low or high bone marrow oedema scores (p=0.03, t=2.22, 95% CI=0.06-1.24; p=0.048, t=-2.07, 95% CI=-1.62-0.01 respectively). No significant differences in any MRI characteristics were noted between patients with low or high synovitis or foot-related disability. However a trend towards an increase in all MRI enhancement characteristic scores in those patients with greater foot impairment (FIS_{IF}) was noted. Additional detail related to the completed association analyses is presented in appendix section A20.

7.4 Discussion

To our knowledge, this study has uniquely reported the high prevalence of MRI-detected FFB in patients with RA. Furthermore, differences in the MRI characteristics of identified FFB in this patient group were demonstrated in this work. Identified bursa-like lesions appeared to exhibit a range of inflammatory and fibrotic tissue characteristics. Predominantly soft tissue lesions within the plantar tissue were the most prevalent lesion type (PP=92.9 per 100), followed by fluid and soft tissue lesions within the intermetatarsal spaces (PP=83.3 per 100, PP=52.4 per 100 respectively), with fluid lesions within the plantar tissue being the least prevalent (PP=7.1 per

100). Distribution analysis further revealed a trend for fluid lesions to be predominantly located within the intermetatarsal 1/2, 2/3 and 3/4 spaces, while soft tissue lesions were mainly distributed across the plantar forefoot regions. Thus the findings of this study suggest that two distinct and predominant groups of FFB may coexist in patients with RA: 1. intermetatarsal predominantly fluid lesions, 2. plantar predominantly soft tissue lesions. However, these groups are not absolute and do not represent those lesions of greatest potential clinical importance. This research has generated preliminary evidence to suggest that the presence of intermetatarsal soft tissue lesions and plantar fluid lesions are associated with RA disease activity, while plantar soft tissue lesions are associated with biomechanical impairment.

Previous authors have suggested that an increased presence of plantar soft tissue lesions is attributable to biomechanical irritation; it is hypothesised that repetitive and adverse biomechanical irritation distorts the structural integrity of the plantar fibro-fat pad and elevates a mechanism of tissue fibrosis (Ahmed *et al.* 1994, Studler *et al.* 2008, Lohman *et al.* 2001, Bottger *et al.* 1998, Cameron 1963). Overall, the findings of this study therefore appear to support this hypothesis. However, uniquely this work has also identified a significant association between inflamed plantar soft tissue lesions and elevated bone marrow oedema in patients with RA. The implications of this finding are unclear; it is possible that these findings illustrate a mechanism whereby repetitive biomechanical irritation results in the perpetuation of inflammation within the forefoot as suggested by Studler *et al*. (2008). Conversely, these findings may illustrate a mechanism whereby minimal disease activity within the forefoot is driving the development of fibrotic/synovial lesions within the plantar tissues or vice versa (Boutry *et al.* 2003a, Canoso and Yood 1979b, Hernandez *et al.* 1991, Zielaskowski *et al.* 2000). It would appear that majority of plantar soft tissue lesions are associated with biomechanical impairment, however a few, which can be differentiated via their MRI enhancement characteristics, appear to be related to RA disease activity.

The presence of intermetatarsal soft tissue lesions was also noted to be significantly associated with elevated counts of bone erosion. This would initially appear to reinforce the hypothesis that intermetatarsal soft tissue FFB are related to inflammation, perhaps by a process of synovial hypertrophy, and not biomechanical impairment (Awerbuch *et al.* 1982, Jaganathan *et al.* 2012, Boutry *et al.* 2003a). However, the biomechanical function of the intermetatarsal tissues remains unclear. This is arguably potentially relevant in patients with notable lesser digital deformity and potential rupture of the plantar plate or adjacent ligaments which may destabilise the forefoot during loading activity (Fuhrmann *et al.* 2005, Siddle *et al.* 2012). It is possible therefore, that biomechanical impairment may be a confounding driver for both intermetatarsal soft tissue hypertrophy and joint deterioration. The methods of identifying biomechanical impairment in this study largely focus's upon static measures of joint alignment and therefore may not be sensitive to the biomechanical stresses exerted upon the tissues of the forefoot. However, the presence of intermetatarsal soft tissue lesions was also noted to be significantly associated with MTP joint

synovitis, arguably reinforcing the inflammatory driven hypothesis of FFB hypertrophy. Future work that evaluates the pathogenesis of MRI-detectable FFB longitudinally, within an inception cohort without notable changes to the biomechanical structure and integrity of the foot, would significantly benefit study in this area. An improved understanding of the pathological mechanisms underpinning this relationship between FFB characteristics and RA disease will help evidence the clinical importance of FFB further.

It may however, be misleading to consider differences in the MRI characteristics of FFB to be indicative of distinct subtypes of bursa-like lesion. For the purposes of analysis, the identified FFB were categorised in this way, however a number of complex bursa-like lesions were observed with ranging fluid/soft tissue or enhancement presentation. It is plausible that the differing MRI characteristics observed may be representative of a range in the stages of lesion development rather than discrete subtypes of FFB (Studler *et al.* 2008, Awerbuch *et al.* 1982, Mutlu *et al.* 2006). Longitudinal evaluation of the pathogenesis of MRI-detectable FFB with concomitant histological examination would provide additional evidence in support of refute of this hypothesis. In particular further evaluation of the clinical importance of FFB enhancement may help direct future therapeutic strategies.

7.4.1 Study limitations

This study has a number of strengths and limitations. The studied population is a consecutive sample of well phenotyped patients with established RA, receiving ongoing rheumatological care. As such, the generalisability of the study findings to those patients with early disease or high disease activity needs to be explored. It should also be noted that the measures of MRI-determined localised disease activity used within this study have not been previously validated for use within the forefoot, although have been demonstrated to be reproducible at this site (Baan *et al.* 2011).

No previous investigations of the prevalence of MRI-detectable FFB have been reported to date. As such the sample size of this study was estimated based upon the proportional difference in US-detectable FFB presence/absence previously identified (Chapter four). Despite a high prevalence of FFB subsequently being observed within this study cohort, the statistical power to stratify FFB data based upon MRI characteristics should be questioned. For this reason the inferential statistics completed within this study have been limited to association analysis only (Bland and Altman 2009, Bland and Altman 1994a). Although completion of additional regression analyses, in order to identify clinically meaningful relationships between FFB characteristics and RA disease, would have benefit (Silman and Hochberg 2001). Furthermore, the identification of potential confounders or interactive effects within the reported data, such as treatment regimen/drug use, is required. Previous research has reported significant associations between methotrexate use and tissue fibrosis, although the exact mechanisms for this remain unclear (DiFrancesco *et al.* 1994, Mutlu *et al.* 2006, Matsushita *et al.* 2006, Patatanian and

Thompson 2002, Williams *et al.* 1998). None the less, there is potential biological plausibility to the suggestion that drug use may affect FFB prevalence in patients with RA.

In order to minimise reporting bias in the primary outcome measure, the MRI image sets were read without prior knowledge of the corresponding patient-reported foot-related disability scores. However, it was not possible to blind the reading researcher (LH) to the name of the study participant to whom the image set corresponded. As such it is possible that the reader may have been familiar with the participant's clinical characteristics in the 4-6 weeks previous to the scan being completed. However, inter-reader reliability with an experienced radiologist, blinded to the clinical history of the study participants, has been previously established and reported as good to excellent (Chapter six). The good inter-reader agreement reported previously suggests that there is minimal evidence of systematic observer bias as a consequence of familiarity with the clinical history of the study participants.

7.4.2 Conclusion & summary

MRI-detectable FFB are highly prevalent in patients with RA. Characterisation of MRI-detected FFB is helpful in identifying those lesions of greatest clinical relevance; there is preliminary evidence to suggest that the presence of intermetatarsal soft tissue lesions and plantar fluid lesions are associated with RA disease activity, while plantar soft tissue lesions are associated with biomechanical impairment. Importantly, a trend towards an association between increased FFB enhancement and increased foot impairment was noted.

The epidemiology & clinical importance of MRI-detectable FFB in patients with rheumatoid arthritis

Key points:

- MRI-detectable FFB are highly prevalent in patients with RA
- 41.7% of observed FFB were characterised as predominantly fluid & 58.3% as predominantly soft tissue
- An increased presence of intermetatarsal soft tissue FFB and plantar fluid FFB is associated with increased RA disease activity
- An increased presence of soft tissue FFB within the plantar fat pad is associated with biomechanical impairment, however these FFB can themselves become inflamed
- A trend towards those patients with the greatest number of inflamed FFB also reporting the greatest foot impairment was observed

Chapter eight

Discussion, conclusions & future research

8.0 Introduction

The preceding chapters have presented a series of four experimental studies that explore the epidemiology and clinical importance of US-detectable or MRI-detectable FFB in patients with RA. This chapter aims to draw together the findings of these four experimental studies and to discuss the presented body of work as an integrated programme of research. The advancement in knowledge and contribution towards clinical practice made by this research programme is considered. The conclusion is made that 'FFB are clinically relevant in patients with RA' and the alternate thesis hypothesis, originally outlined in Chapter two, is accepted. Limitations within the reported studies are acknowledged and recommendations for future research proposed.

8.1 The epidemiology & clinical importance of forefoot bursae in patients with RA

This programme of research has identified a high prevalence of FFB in patients with RA. Results from the longitudinal US evaluation suggest that the high prevalence of FFB is largely sustained over a period of time however some fluctuations in FFB number can occur. The disability status of a patient with RA can be predicted by the number of FFB that they have. However, further comparative evaluation of FFB between patients with predominantly inflammatory or degenerative arthritis suggests, that while the number of FFB may be clinically relevant, their location may also be clinically meaningful. Evaluation of FFB in healthy volunteers suggests that approximately 50% of those FFB identified in patients with RA may not be clinically relevant, in particular those identified in the intermetatarsal 4/5 space. Characterisation of the remaining FFB using MRI, suggests that some FFB are related to RA disease activity while others are related to biomechanical impairment. Specifically, plantar fluid lesions and intermetatarsal soft tissue lesions appear to be associated with disease activity, while plantar soft tissue lesions appear to be associated with biomechanical impairment. It is also noteworthy that, a trend towards an association between elevated FFB inflammation and patient-reported foot impairment was also observed.

8.2 Summary of advancement of knowledge

This programme of research has utilised novel US and MRI imaging techniques to determine the epidemiology and clinical importance of FFB in patients with RA. The advances in knowledge made by the research studies forming this thesis have been discussed in the corresponding experimental chapters. However, key advances in knowledge may by this programme of research include:

1. US-detectable FFB remain highly prevalent in patients with RA longitudinally
2. The US characteristics of FFB in patients with RA are variable

3. Changes in the presence of US-detectable FFB are associated with changes in RA disease activity
4. US-detectable FFB are identified as a prognostic indicator of patient reported disability and represent a possible novel therapeutic target
5. US-detectable FFB are highly prevalent in patients with RA and medial knee OA compared to healthy volunteers
6. In patients with RA, the presence of US-detectable FFB is associated with inflammation and biomechanical impairment
7. The central distribution pattern of US-detectable FFB, unique to patients with RA, is clinically relevant and associated with metatarsal head erosion
8. The *FFB-score* is reliable and valid for the identification and characterisation of FFB in patients with RA
9. MRI-detectable FFB are highly prevalent in patients with RA, of which 41.7% of MRI-detected FFB were characterised as predominantly fluid & 58.3% as predominantly soft tissue
10. The characterisation of FFB using MRI can identify bursa-like lesions of differing clinical importance:
    - An increased presence of MRI-detected plantar fluid and intermetatarsal soft tissue FFB is associated with increased RA disease activity
    - An increased presence of MRI-detected soft tissue FFB within the plantar fat pad is associated with biomechanical impairment, however these FFB can themselves become inflamed
    - A trend towards those patients with the greatest number of inflamed FFB also reporting the greatest foot impairment was observed

It can be concluded therefore that FFB are highly prevalent and clinically relevant in patients with RA, thus the alternate thesis hypothesis can be accepted and the null hypothesis rejected. Furthermore, clinically relevant FFB can be reliably identified and characterised using the *FFB-score.* The rationale for the clinical importance of subsets of FFB remains unclear however, this thesis has provided support for the hypothesis that both disease mediated inflammation and biomechanical impairment are relevant factors in the genesis of FFB. These findings are summarised figuratively in figure 55.

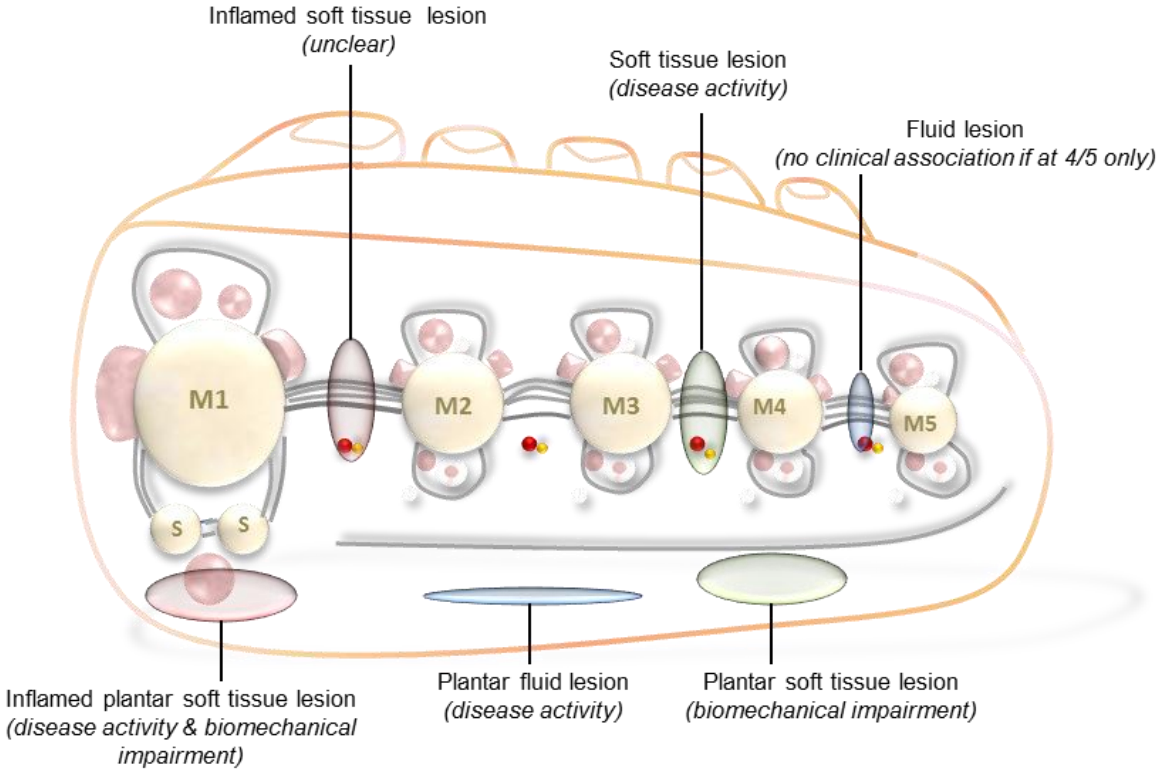


Figure 55: An illustrated summary of the main research findings

8.3 Implications for clinical practice

Overall, the completion of this body of work has led to the identification of a range of FFB characteristics that are evident in patients with RA, the clinical value of which differs. Clear distinction should be drawn however between what can be interpreted as the direct clinical importance of FFB (for example their pathological state) and the clinical value that can be gained from the study of FFB (for example what observing FFB can tell us about our patients).

From the findings of this programme of research it is not possible to conclusively determine to what extent FFB directly contribute to the burden of foot disease in patients with RA. There is however preliminary data that appears to support this hypothesis, for example the number of MRI enhancing FFB observed is new documentation of inflammation within the soft tissues outside of the forefoot joints in patients with RA (Chapter seven). It is possible that selectively targeting therapeutic intervention at inflamed FFB may ease the burden of foot complications in this patient group. Kanbe *et al.* (2006) and Huang *et al.* (2011) have demonstrated significant clinical benefit following the surgical excision of inflamed bursae. However, there is limited additional evidence documented to date advocating the targeted management of inflamed FFB, other than that which is hypothetically proposed (Koski 1998, Harper 2003, Awerbuch *et al.* 1982, Boutry *et al.* 2005). Future research is required to demonstrate the efficacy of selectively treating FFB.

None the less, the findings of this programme of research have highlighted the prognostic clinical value of US-detected FFB for the determination of foot-related disability longitudinally (Chapter four). It is possible to conclude that those patients identified as having four or more US-detectable FFB have greater likelihood of worsening foot-related disability over three years. Thus, the evaluation of US-detectable FFB presence can be used as a clinical adjunct to the assessment of foot health in patients with RA. It is also noteworthy that the study findings suggest that US-detectable FFB presence, as well as foot-related disability, is fluctuant. Therapeutically, this suggests that both factors have potential to be modified and improved. However, additional insight into the mechanisms underpinning this relationship is required before a process of targeted intervention and evaluation can be developed.

The study of MRI-detected FFB suggests that a subset of FFB, (inflamed soft tissue lesions), is associated with disease duration (Chapter seven). The rationale for this is unknown; it is unclear whether this is related to disease chronicity, disease aggression or biomechanical impairment, as suggested by previous authors (Studler *et al.* 2008, Harper 2003, Canoso and Yood 1979b, Awerbuch *et al.* 1982, Koski 1998, Bottger *et al.* 1998). Koski *et al*. (1998), amongst other authors (Awerbuch *et al.* 1982, Bowen *et al.* 2010c, Boutry *et al.* 2003a, OBrien *et al.* 1997, Scutellari and Orzincolo 1998), has suggested that FFB become inflamed as a consequence of RA disease affecting the synovial lining of these lesions. However, the presence of synoviocytes within plantar FFB has not been reported to date. The nature of the plantar tissues identified as inflamed within this study is currently unclear and future histological examination needed. An improved understanding of the mechanisms driving inflammation in this tissue, that was previously considered clinically unimportant or adventitial in healthy volunteers (Studler *et al.* 2008), may improve our understanding of the pathogenesis of RA disease within the forefoot.

Additionally, plantar fluid lesions were determined to be significantly associated with systemic markers of RA disease activity (Chapter seven). Again, this finding appears contradictory to the hypothesis associated with plantar FFB suggested by previous authors; plantar fluid FFB were thought to arise as a consequence of repetitive, excessive linear and torsional biomechanical stress to the fibro-fat pad that resulted in separation of the fibro-collagenous tissue layers and accumulation of slit-like cavities of fluid (Studler *et al.* 2008, Ahmed *et al.* 1994). Perhaps this aetiological assumption is correct, but in patients with RA, the inflammation accompanying this repetitive micro-trauma is poorly regulated, becoming excessive at these sites. Conversely, these lesions may indeed be directly related to RA disease activity; the direct effect of excessive disease-mediated inflammation may not be limited to the synovial tissue of the forefoot. Moreover, RA disease activity may directly affect the structure and proliferation of fibro-collagenous tissue within the plantar forefoot (Mutlu *et al.* 2006, Matsushita *et al.* 2006, Zielaskowski *et al.* 2000, Sanders *et al.* 1998, Oloff-Solomon *et al.* 1984). Future evaluation of the pathogenesis of different FFB characteristics would further inform the understanding of their

clinical value. None the less, the use of the *FFB-score* is demonstrated to be a potentially beneficial clinical adjunct in the evaluation of RA disease activity.

As highlighted by Khan *et al.* (2012) the identification of minimal disease activity is a growing clinical concern. There is a need for improved clinical indicators of continued disease activity because a number of patients continue to report ongoing complications despite up-regulation of pharmacological therapy (Aletaha and Smolen 2011, Aletaha *et al.* 2011, Wells *et al.* 2009). This is evidenced within the RA cohort contributing to this body of research; although not a primary focus of this work, the findings of the study in Chapter six suggest that a number of patients (n=25) continue to have ongoing minimal disease activity within the forefoot (identified using MRI) despite receiving biologic intervention and achieving remission from disease according to DAS 28 evaluation. Arguably, the evaluation of FFB in patients with RA, using the *FFB-score*, is therefore advocated. Use of the *FFB-score* provides clinically relevant information regarding the perpetuation of inflammatory disease within the forefoot in patients with RA beyond that which is detected using current methods of assessment. It is therefore possible that a number of patients who require further up-regulation of treatment, that would otherwise not be reviewed, will be identified with the use of the *FFB-score*. Future work, which cross-validates the findings of the MRI-based *FFB-score* with US-detected FFB, would reduce the time and financial burden of FFB evaluation, potentially improving the clinical utility of an US-based *FFB-score.* The long term economic impact of improved identification of minimal disease activity, via evaluation of FFB, is also warranted.

8.4 Limitations

The specific limitations of each study are explored within the discussion section of the corresponding chapter. However there are a number of limitations that are applicable to all the documented works, which warrant further comment.

A single measure of the impact of FFB was used throughout this programme of research only, the FIS questionnaire (Helliwell *et al.* 2005). At the time of research, this was the only tool that had been previously validated for use in patients with RA and was therefore selected for this reason. However, the FIS questionnaire has not been validated for longitudinal use, although Turner *et al.* (2007) suggested that a score change of three or more, in either direction, was clinically meaningful. As such, these margins of change were adopted in this work. Consequently, the reported estimations of disability impact associated with FFB may be biased by measurement inaccuracy. Such bias is likely to be systematic throughout the reported results, however the direction (e.g. over/under estimation) is unknown. Use of secondary measures, that identify concurrent validity between items, would improve the certainty of an accurate assessment of disability (Silman and Hochberg 2001). Validation of FIS longitudinally would also be of benefit in improving the construct validity of these reported measures. Thus, the variation in disability reported in Chapter four, may be a consequence of measurement error. The

additional use of margins of clinically meaningful change in disability, suggested by Turner *et al.* (2007), potentially increased the stringency of evaluation of change, thereby minimising the effect of measurement error. Conversely, the loss of sensitivity to change, introduced through the grouping of continuous data, may have resulted in an underestimation of clinically meaningful fluctuation in disability (Altman and Bland 1999, Bland and Altman 1996).

The differences in longitudinal disability demonstrated between patients with high/low FFB count are also of interest. Foot impairment improved for both patients with high and low FFB at baseline, with the reported impairment converging between groups at year-three. This may represent an overall regression to the mean disability level for the studied cohort (Bland and Altman 1994b). Alternatively, patients entering the study at baseline were offered podiatric care if required and thus the reduction in impairment may represent a treatment effect (Campbell and Machin 1999). Furthermore, it is possible that those patients with an elevated burden of foot disease, to which FFB presence may be contributing, preferentially sought intervention accounting for the greater reduction in impairment shown in this group. Additional post-hoc analysis of treatment provision would benefit the interpretation of these results (Campbell and Machin 1999). It is also plausible to suggest that those patients with a pre-existing foot complication were more likely to participate within this study and as such the burden of foot disease may be over represented within this cohort. Future inclusion of recruitment analyses may provide further insight into this potential bias. However, the prevalence of reported foot impairment and activity limitation within this study is consistent with those reported by previous authors (Helliwell *et al.* 2005; Turner *et al*. 2007). However it should be noted, that the same preferential bias for recruitment may also be evident within these comparative investigations.

It is interesting, that in contrast to improved foot impairment, reported activity limitation increased. It is plausible that in a treated cohort, patients who feel better and have less foot impairment attempt to undertake more weight-bearing tasks of daily living (Campbell *et al.* 2012, Platto *et al.* 1991). Such patients may become increasingly aware of activity limitations that were otherwise masked by comorbid disease or other social influences/distractions (Bjork *et al.* 2011). Conversely, while foot impairment may be modifiable and can improve, factors contributing to activity limitation perhaps accumulate only (van der Leeden *et al.* 2007, van der Leeden *et al.* 2008). Therefore it may not be possible for improvements in foot impairment to be mirrored with improvements in foot-related activity limitation. In this instance, the assessment of FFB presence may be a useful indicator of potential activity limitation; FFB assessment could be used clinically to identify those patients at greatest risk of worsening activity limitation and to whom management should be targeted.

The degree and impact of pain associated with FFB has not been evaluated in this programme of research. This is a key omission and the potential influence of pain or pain related anxiety, as a confounding or colinear factor, should be considered (Otter *et al.* 2011, Mustafa *et al.* 2012,

McWilliams *et al.* 2012, Campbell *et al.* 2012). Interestingly, Otter *et al.* (2011) note a positive correlation between reported pain and healthcare access. Furthermore, various authors have reported a high incidence of foot specific pain associated with the development of soft tissue lesions of the forefoot (Koski 1998, Iagnocco *et al.* 2001, Ashman *et al.* 2001, Zielaskowski *et al.* 2000). Thus, if longitudinal differences in reported disability are to be considered as a treatment effect, the presence of pain associated with FFB may further confound differences in disability observed between high/low FFB count groups.

A number of investigative techniques have been used to evaluate the mechanical function of the foot. Clinically used static postural measures include navicular height, arch height and valgus index [86, 87]. However, these have been demonstrated to have significantly different inter-rata reliability (p = 0.001- 0.005) even when evaluated in non-pathological populations (Weiner-Ogilvie and Rome 1998; Menz *et al.* 2005). The foot posture index (FPI) was the only clinical static postural tool validated for use for patients with RA.at the time of this study (Redmond *et al.* 2006). The authors acknowledge that the FPI was only able to predict 64% of the variance in static standing position and 41% of the postural variance during the stance phase of gait in this patient group (Redmond *et al.* 2006). None the less, this has been shown to have good internal consistency (Cronbachs alpha=0.83) and allows simple multi-segment, multi-plane evaluation in a clinical setting and as such has clear advantages over the alternative postural tools.

However, it should be noted that when applied in this work, substantial inter-rater variation was recorded, even after two episodes of dedicated researcher training. As such, and despite moderate agreement subsequently being demonstrated, the findings of this score should be treated with caution; there is likely to be some reporter bias within the recorded results. Furthermore, the clinical relevance of a static measure of alignment is yet to be demonstrated. It has previously been hypothesised that variations in static weight bearing alignment can be related to dynamic biomechanical stress (Hicks 1953; Root *et al*. 1977; Dananberg 2000, Fuller 2000; Kirby 2001). However there is much contention surrounding the theoretical underpinning of this inferred relationship (Wold *et al*.2008). None the less, the results of the work completed as part of this thesis do appear to suggest that, despite these limitations, the FPI score may have clinical relevance when considering the relationship between static foot alignment and FFB prevalence. Further work is required to fully determine the nature of this association.

The provision of ongoing rheumatological care, concurrent to the longitudinal study completed in Chapter four, may introduce treatment effect as a possible confounder within the reported results. Changes in the provision of pharmacological care were not reported or analysed within the scope of this investigation. However, it is plausible that a number of patients will be in receipt of disease modifying anti-rheumatic drugs, such as Methotrexate, which have been previously linked with soft tissue change and nodulosis, or will have had an escalation in drug therapy to include newer biologic therapies, the secondary effects of which remain unknown. As such,

future work which clearly evaluates the potential contributory or colinear effect that differing treatment regimens may have on the soft tissue structures of the foot is warranted.

The *FFB-score* was validated for use in patients with RA against MRI-determined measures of disease activity within the forefoot, adopted from the RAMRIS score (Ostergaard *et al.* 2003). However, these measures have been validated for application to the metacarpophalangeal joints and not the metatarsophalangeal joints (Lassere *et al.* 2003). None the less, there is biological plausibility to the application of this tool to these forefoot joints, although the accuracy of localised disease activity assessment, within the reported validation study in Chapter six, should be considered.

8.4.1 Management of bias

There are a number of potential biases within the reported study findings. The following text therefore summarises such potential sources of bias and considers the methodological adjustments used to manage this where possible. The implications of such biases to the conclusions of this work are considered.

Selection bias, the introduction of error due to systematic differences in the characteristics between those selected or not selected to participate within the study, may be evident within the represented sample population (Silman and Macfarlan 1995). Those patients attending a rheumatology outpatient clinic, within a secondary care setting, were consecutively invited to participate within the baseline study reported in Chapters four and five. As such, the target samples are likely to include those patients with chronic or more active disease and may not be representative of all patients with a rheumatological diagnosis. Indeed, the demographical analysis completed appears to suggest that those patients with more established RA disease are represented within the studied population (Bland and Altman 1994b). The applicability of the study findings to those patients with early disease should therefore be questioned. Future work, that includes an inception cohort, would benefit further study in this area. Post-hoc response analyses were completed for the longitudinal study completed in Chapter four, the findings of which suggest that there may be a systematic difference in those patients willing to return for follow-up assessment and those who withdrew from the study. As such, systematic bias in the inclusion of those patients with the greatest burden of foot or inflammatory disease may result in an over-representation of these or associated characteristics within the study findings. The generalisability of the results of this work the broader population should therefore be considered.

Prevalence bias, the restriction of studied cases to those with only the disease state of interest, was minimised by the recruitment strategy chosen, and is therefore unlikely to be evident within the studied population; Included participants were not recruited based upon the presence or absence of FFB, the primary outcome of interest (Silman and Macfarlan 1997).

Survival bias, the exclusion of cases no longer able to participate within the studied population arising from factors related to the primary outcome of interest, may be evident within the represented sample population (Silman and Macfarlan 1997). It is plausible to suggest that those patients with a greater burden of foot disease and related mobility limitation may be restricted from attending follow-up study visits. Quantification of such bias was attempted via the completion of the response analyses reported in Chapter four (Bland and Altman 1994b). Furthermore, a methodological adjustment to recruitment was introduced subsequent to initial poor response rates at the year three follow-up visit. Eligible participants were offered an option to complete a postal questionnaire only, negating any need for physical attendance at a hospital examination appointment. However, changes to response rates were negligible following this amendment and as such, the likely role of disability as an inhibitor to response can be questioned.

Participant recall bias, differences in a patient's ability to recall information of relevance, may be evident within the represented sample population (Silman and Macfarlan 1994b; Silman and Hochberg 2001). The duration and severity of episodes of poor foot heath may influence the degree of foot-related disability reported by study participants. Similarly, the impact of poor foot health may be more readily recalled if recent life events have been modified as a consequence; the period of time between FIS questionnaire completion and an episode of poor foot health may impact the patient's ability to recall pertinent information. To overcome this, participants were encouraged to consider their responses, and answer based upon their experiences of foot health over the previous week only. Additionally, details of surgical history, previous episodes of poor foot health or related disease activity were cross references and verified by review of the patient's medical notes by the study researcher. However, it remains plausible that FIS scores may be over or underestimated dependent upon a patient's ability to recall related information.

Participant reporting bias, error in response that is dependent upon the willingness of a participant to provide a true response or disclose information of relevance, may be evident within the represented sample population when considering reported foot impairment or activity limitation (Silman and Macfarlan 1994b). However, the primary outcome of interest, FFB, was determined based upon US analysis and is therefore unlikely to be influenced by such reporting bias. To negate potential reporting bias, the researchers were cautious not to demonstrate any preference towards the identification or absence of disability or foot complications.

Researcher observer bias, the systematic error in the researcher's measurement, reporting or documentation of the phenomena of interest, may be evident within the study findings (Silman and Macfarlan 1994b). The identification or FFB using US or MRI may be altered as a consequence of interest or improving familiarity with the image sets. To minimise such bias, all researchers completed assessment skills training prior to the undertaking of data collection. Intra and inter-reader agreement for all methods of FFB identification were completed and the

findings of the study researcher (LH) referenced against the findings of an 'expert' reader (LK/CB). Thus, the relative accuracy of all researchers for the identification and characterisation of FFB has been quantifiably demonstrated to be good, subsequent to agreement analyses. However, it is of note that a learning effect was reported by the main researcher (LH) who was novice to MRI reading at the start of this study. As such, the data reported by LH was not used until consistently high image agreement with an expert reader was achieved, thereby minimising potential reporting inaccuracy. In study two, (Chapter five) there remains however some risk of non-directional misclassification bias when comparing observed phenomena between groups; equal observer bias may occur in both study population. However, the researcher is not blinded to the group from which the participant originates and thus observational bias may potentially be systematic and directional in nature.

It was not feasible to blind the researcher to the patients clinical history in studies one, three and four (Chapters four, six and seven) or patient group in study two (Chapter five). However the comparative expert readers were blinded to the patient's disease status at the time of image acquisition. Thus any potential systematic reporting bias by the main study researcher would be evident within the completed agreement analysis. Thus, there is minimal indication there may be any systematic reporting bias by the main researcher (LH) in the reading of US or MRI images and subsequent FFB prevalence reporting.

8.5 Implications for future research

The completion of this programme of research has led to the identification of a number of areas of future research that warrant further investigation:

1. The assessment of FFB
    a. An investigation of the relative sensitivity and specificity of MRI and US for the detection of FFB subtypes would be of benefit. The use of MRI to identify and characterise FFB has been demonstrated, however application of this new knowledge to inform and direct the use of US would potentially reduce the time and economic burden of FFB evaluation
    b. The inflammatory state of FFB, identified using MRI, has been shown to be clinically relevant. Investigation of the efficacy of Power Doppler use as an adjunct to US evaluation may improve the clinical efficacy of this method of FFB assessment.
    c. The *FFB-score* has been validated for use at a single time point. Longitudinal validation of FFB-score, with assessment of item responsiveness/sensitivity to change and criterion validity would improve the clinical utility of this score.
    d. The content and discriminant of the FFB-score have been demonstrated. The investigation of *FFB-score* construct validity, with concurrent histological examination, would improve our understanding of the clinical relevance of this score.

2. The clinical importance of FFB
    a. Evaluation of FFB size was omitted from the current research programme due to difficulties in reducing measurement error. However, the study completed in Chapter six evidenced strong expert consensus regarding the importance of evaluating FFB size in future research.
    b. Pain associated with FFB or other foot complications has been identified as a potential confounder/collinear factor, which may influence the current understanding of the clinical importance of FFB. Future investigation of the relationship between FFB and pain is therefore warranted.
    c. FFB have been shown to be associated with impaired ankle joint range of motion in patients with medial knee OA, based upon cross section evaluation. Future research investigating the prognostic value of FFB in this patient group may be of clinical benefit. Additionally, the rationale for association between FFB, ankle joint function and medial knee OA remains unclear. There is limited evidence that demonstrates an association between changes in the forefoot and medial knee OA. However the findings of this research suggest that there is efficacy in exploring potential associations between these regions further.

3. Understanding the mechanisms by which FFB may be pathological
    a. Biomechanical impairment has been shown to be significantly related to FFB count. Biomechanical impairment has been assessed using predominantly static measures. However, recent research suggests that static measures are poor indicators of biomechanical impairment compared to dynamic functional measures (Muller *et al.* 2012, Sell 2012, McPoil and Cornwall 1996, Allen *et al.* 2004). Therefore, further evaluation of the relationship between FFB and dynamic measures of biomechanical impairment may provide additional insight into their pathogenesis.
    b. Biomechanical impairment has been determined using estimations of joint biomechanical function. However, direct investigation of biomechanical function and impairment to the tissues of the forefoot would be of greater theoretical efficacy
    c. Evaluation of the local inflammatory infiltrate surrounding and within enhancing FFB tissue would provide addition insight into the cellular mechanisms regulating inflammation within these tissues. An improved understanding of these cellular mechanisms can be used to inform targeted therapeutic intervention.
    d. Patients with medial knee OA were noted as having significantly elevated BMI scores. BMI was therefore identified as a potential confounder within the reported results. The relative contribution of elevated BMI to FFB development in patients with medial knee OA would improve current understanding of the clinical importance of FFB in this patient group.

4. The management of FFB
    a. The findings of this programme of research cannot be used to conclusively advocate the treatment of FFB. However, the preliminary results presented in Chapter seven, suggest that a subset of FFB are related to disease activity or are inflamed. Trials of interventions that seek to reduce the number or inflammatory state of these FFB in particular might demonstrate clinical benefit.
    b. Using the *FFB-score* a number of FFB were identified as associated with RA disease activity. Longitudinal evaluation of these lesions would demonstrate their potential responsiveness to fluctuations in disease state or disease management. Investigation of the value of FFB as an indicator of therapeutic efficacy is warranted and could inform improved timely management of RA disease activity.

5. The assessment of disease activity within the foot
    a. Although not a primary focus of this body of work, a number of patients were identified as having active disease within the forefoot, despite receiving biologic therapy and systemic or composite markers of disease activity suggesting remission (n=25). This has highlighted an unmet need for improved evaluation of disease activity within the forefoot.
    b. There are currently no MRI-based scores that have been validated for use in the evaluation of RA disease activity within the forefoot. As such, the RAMRIS score, validated for use in the hand, was applied to forefoot to allow an evaluation of disease activity within these joints. However development of a validated score, for the evaluation of RA disease activity within the forefoot, is needed.

8.6 Summary

This thesis has uniquely identified the natural history of US-detectable FFB in patients with RA. The presence of FFB at baseline was determined to be a significant prognostic indicator of foot-related disability after three-years. The rationale for this remained unclear at the time of study. Two plausible hypotheses, explaining the relationship between FFB presence and foot-related disability in patients with RA, were extrapolated from the literature: 1. FFB synovium is susceptible to disease-mediated inflammatory processes in a similar manner to joint synovium, and FFB are therefore representative of disease activity (Bossley and Cairney 1980), 2. FFB occur or hypertrophy as a consequence of biomechanical impairment of the forefoot, and are therefore indicative of physical changes in joint and associated tissue function (Studler *et al.* 2008, Ahmed *et al.* 1994). Observed differences in the US characteristics of FFB supported a further hypothesis that subtypes of FFB, related to either inflammation or biomechanical impairment, may co-exist in patients with RA. Subsequently, FFB were determined to be relatively highly prevalent in patients with primary inflammatory or degenerative arthritis compared to healthy volunteers. Furthermore, US-detectable FFB presence was determined to

be associated with both inflammation and biomechanical impairment. The findings of this study appeared to reinforce the hypothesis that subtypes of FFB, related to both inflammation and biomechanical impairment, coexist in patients with RA. However, the need for a user-independent, reliable and valid method of characterising FFB in patients with RA was identified. In response, the MRI-based *FFB-score* was created, evaluated and validated for use in the identification and characterisation of bursa-like lesions of the forefoot in patients with RA. The tool was subsequently applied and the high prevalence of MRI-detectable FFB uniquely reported. The characterisation of MRI-detected FFB has been identified as helpful in identifying those lesions of greatest clinical relevance; there is preliminary evidence to suggest that an increased presence of intermetatarsal soft tissue FFB and plantar fluid FFB is related to increased inflammation. Conversely, an increased presence of soft tissue FFB within the plantar fat pad appears to be related to biomechanical impairment; however these lesions can themselves become inflamed. A trend towards those patients with the greatest number of inflamed FFB also reporting the greatest foot impairment was observed.

The epidemiology & clinical importance of forefoot bursae in patients with rheumatoid arthritis

Key points:

- US-detectable and MRI-detectable FFB are highly prevalent
- US-detectable FFB presence is associated with both inflammation and biomechanical impairment

- FFB can be characterised as predominantly fluid, occurring within the intermetatarsal spaces, or soft tissue, occurring within the plantar fat pad
- An increased presence of intermetatarsal soft tissue FFB and plantar fluid FFB is related to increased inflammation
- An increased presence of soft tissue FFB within the plantar fat pad is related to biomechanical impairment, however these can themselves become inflamed

- US-detectable FFB are prognostic indicators of patient-reported foot-related disability
- A trend towards those patients with the greatest number of inflamed FFB also reporting the greatest foot impairment was observed.

Appendices

A1: Confirmation of sponsorship & insurance

Southampton University Hospitals NHS Trust

Please reply to: Research and Development
Duthie Building (Trust) MP138
Southampton General Hospital
Tremona Road Southampton SO16 6YD

Telephone: 023 8079 5078
Fax: 023 8079 8678
E-mail: kelly.waller@suht.swest.nhs.uk

Miss Lindsay Hooper
Mailpoint 63, Room CG76A
G Level, West Wing
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

21 May 2009

Dear Miss Hooper

ID: RHM MED0871 **A Unique Longitudinal Cohor Study of the Epidemiology, Aetiology and Clinical Importance of Forefoot Bursae in Patients with Rheumatoid Arthritis.**

Re: NHS Research Governance and Identification of Nominated Research Sponsor

I am writing to confirm that Southampton University Hospitals NHS Trust is prepared to act, in principle, as sponsor for this study under the terms of the Department of Health Research Governance Framework for Health and Social Care.

SUHT's final acceptance of sponsorship responsibilities is dependent on full R&D approval, which will incorporate evidence of adequate funding to conduct your study.

SUHT fulfills the role of research sponsor in ensuring management, monitoring and reporting arrangements for research. I understand that you will be acting as the principal investigator responsible for the daily management for this study, and that you will be providing regular reports on the progress of the study to the Trust on this basis.

I would like to take this opportunity to remind you of your responsibilities under the terms of the Research Governance Framework for researchers, principal investigators and research sponsors, that it is a requirement of the terms and conditions of approval that you become fully conversant with the Research Governance Framework on Health and Social Care document which is available from : http://www.dh.gov.uk/en/Policyandguidance/Researchanddevelopment/index.htm

Please do not hesitate to contact us should you require any additional information or support.

May I also take this opportunity to wish you every success with your research.

Yours sincerely

[redacted]

Kelly Waller
Research Governance Officer

UNIVERSITY OF Southampton

Miss Lindsey Hooper
School of Health Sciences
University of Southampton
University Road
Highfield
Southampton
SO17 1BJ

RGO Ref: 8166
REC No: 09/H0504/93

25 July 2011

Dear Miss Hooper

Project Title The Prevalence and Impact of Forefoot Bursae in Healthy Participants

This is to confirm the University of Southampton is prepared to act as Research Sponsor for this study, and the work detailed in the protocol/study outline will be covered by the University of Southampton insurance programme.

As the sponsor's representative for the University this office is tasked with:

1. Ensuring the researcher has obtained the necessary approvals for the study
2. Monitoring the conduct of the study
3. Registering and resolving any complaints arising from the study

As the researcher you are responsible for the conduct of the study and you are expected to:

1. Ensure the study is conducted as described in the protocol/study outline approved by this office
2. Advise this office of any change to the protocol, methodology, study documents, research team, participant numbers or start/end date of the study
3. Report to this office as soon as possible any concern, complaint or adverse event arising from the study

Failure to do any of the above may invalidate the insurance agreement and/or affect sponsorship of your study i.e. suspension or even withdrawal.

On receipt of this letter you may commence your research but please be aware other approvals may be required by the host organisation if your research takes place outside the University. It is your responsibility to check with the host organisation and obtain the appropriate approvals before recruitment is underway in that location.

May I take this opportunity to wish you every success for your research.

Yours sincerely

[redacted]

Dr Martina Prude
Head of Research Governance

Tel: 023 8059 5058
email: rgoinfo@soton.ac.uk

Corporate Services, University of Southampton, Highfield Campus, Southampton SO17 1BJ United Kingdom
Tel: +44 (0) 23 8059 4684 Fax: +44 (0) 23 8059 5781 www.southampton.ac.uk

UNIVERSITY OF Southampton

TO WHOM IT MAY CONCERN

Insurance for Projects Involving Human Subjects and Requiring Ethics Committee Approval

The University of Southampton holds Professional Indemnity, Clinical Trials and Public Liability Insurance as detailed in the attached confirmation of cover letters.

Cover for participants in research studies undertaken by staff and/or students of the University will be provided under these policies. Insurance for each research study is arranged when the researcher completes the University's Research Governance process.

The University of Southampton and Southampton University Hospitals Trust have procedures and systems in place to ensure that all such projects are notified as required.

[redacted]

Ruth McFadyen
Insurance Office Manager

Finance Department, Insurance Office,
University of Southampton, Highfield Campus, Southampton SO17 1BJ United Kingdom
Tel: +44 (0)23 80 5924790 Fax: +44 (0)23 80592195
http://www.soton.ac.uk/finance/insurance/index.html

A2: Confirmation of ethical approval

AHMCC/STA/hph

10 August 2009

National Research Ethics Service
SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEE (B)
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
Hampshire
SO16 4RJ

Tel: 023 8036 2466
023 8036 3462
Fax: 023 8036 4110

Email: scsha.SWHRECB@nhs.net

Professor Nigel Arden
Reader and Consultant in Rheumatology
Southampton General Hospital
MRC Epidemiology Resource Centre
Tremona Road
Southampton
SO16 6YD

Dear Dr Arden

Study Title: **A unique longitudinal cohort study of the epidemiology, aetiology and clinical importance of forefoot bursae in patients with Rheumatoid Arthritis**
REC reference number: **09/H0504/93**
Protocol number: **3**

The Research Ethics Committee reviewed the above application at the meeting held on 29 July 2009.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Other conditions specified by the REC – optional. Indicate where final versions of documents should be provided to the committee for information, e.g. information sheet

1. **The Committee felt that the reference to non-responders being telephoned should be removed as it is not acceptable to chase this group. .**
2. **The exclusion criteria should make clear that participants with pacemaker and ICDs would be excluded from MRI.**
3. **Both Information Sheet**
   2.1 The reference to 'CERES' should be removed as this organisation no long exists.
4. **Consent Form: Biomechanical Assessment**
   4.1 'Biomechanical' should be changed to 'Walking'.
   4.2 Section 2 "I am free to withdraw at anytime, 'with giving any reason' should be changed to 'without giving any reason'.
5. **Consent Form: Clinical Assessment**
   5.1 Section 2 "I am free to withdraw at any time, 'with giving any reason' should be changed to 'without giving any reason'.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Investigator CV: Catherine Bowen		25 June 2009
Investigator CV: Lindsey Hooper		24 June 2009
Investigator CV: Dr C Edwards		30 June 2009
Alert Sticker	1	24 April 2009
Letter of Invitation to Participant: Walking Assessment	2	20 June 2009
Participant Consent Form: Walking Assessment	2	20 June 2009
Participant Consent Form: Clinical Assessment	2	20 June 2009
Participant Information Sheet: Walking Assessment	2	20 June 2009
Participant Information Sheet: Clinical Assessment	2	20 June 2009
GP/Consultant Information Sheets	1	20 June 2009
Letter of invitation to participant: Clinical Assessment	2	20 June 2009
Questionnaire: Participant Demographic Data	1	24 April 2009
Questionnaire: Participant Ultrasound Data - Left Foot	2	06 May 2009
Questionnaire: Participant Foot Assessment Data	1	24 April 2009
Questionnaire: Leeds Foot Impact Scale	1	24 April 2009
Compensation Arrangements		08 September 2008
Statistician Comments		17 June 2009
Letter from Sponsor		21 May 2009
Summary/Synopsis		
Covering Letter		25 June 2009
Protocol	3	20 June 2009
Investigator CV: Professor N Arden		01 July 2009
Application		29 June 2009

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Reply Slip - Walking Assessment	2	20 June 2009
Reply Slip - Clinical Assessment	2	20 June 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0504/93	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

[redacted]

Dr Helen McCarthy
Chair

Email: scsha.SWHRECB@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers" SL-AR2 for other

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

NHS
National Research Ethics Service

STA

30 September 2009

SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEE (B)
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
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SO16 4RJ

Tel: 023 8036 2466
023 8036 3462
Fax: 023 8036 4110

Email: scsha.SWHRECB@nhs.net

Dr Nigel Arden
Reader and Consultant in Rheumatology
Southampton General Hospital
MRC Epidemiology Resource Centre
Tremona Road
Southampton
SO16 6YD

Dear Dr Arden

Full title of study: **A unique longitudinal cohort study of the epidemiology, aetiology and clinical importance of forefoot bursae in patients with Rheumatoid Arthritis**
REC reference number: **09/H0504/93**
Protocol number: **4**

Thank you for your letter of 20 August 2009. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 29 July 2009. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Protocol	4	15 August 2009
Covering Letter		20 August 2009
Participant Information Sheet: Clinical Assessment	3	15 August 2009
Participant Consent Form: Clinical Assessment	3	15 August 2009
Participant Information Sheet: Biochemical Walking Assessment	3	25 August 2009
Participant Consent Form: Walking Assessment	3	15 August 2009

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

09/H0504/93 **Please quote this number on all correspondence**

Yours sincerely

[redacted]

Mrs Sharon Atwill
Committee Co-ordinator

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within

UNIVERSITY OF Southampton

E04/Aug 2010/ v1.1

Lindsey Hooper
Faculty of Health Sciences
University of Southampton

29 July 2011

Dear Lindsey

Ethics Submission No: - FoHS-ETHICS-2011-040

Title: The prevalence and impact of musculoskeletal ultrasound detectable forefoot bursae in a healthy population

I am pleased to confirm **full approval** for your study has now been given. The approval has been granted by the Faculty of Health Sciences Ethics Committee.

You are required to complete a University Insurance and Research Governance Application Form (IRGA) in order to receive insurance clearance before you begin data collection. The blank form can be found at http://www.soton.ac.uk/corporateservices/rgo/researchgov/whatdocs.html

You need to submit the following documentation in a plastic wallet to Dr Martina Prude in the Research Governance Office (RCO, University of Southampton, Highfield Campus, Bldg. 37, Southampton SO17 1BJ):

- Completed IRGA Research Governance form
- Copy of your research protocol/School Ethics Form (final and approved version)
- Copy of participant information sheet
- Copy of SoHS Risk Assessment form, **signed**
- Copy of your information sheet and consent form
- Copy of this SoHS Ethical approval letter

Continued overleaf

Building 45
Faculty of Health Sciences, University of Southampton, Highfield Campus, Southampton SO17 1BJ United Kingdom
Tel: +44 (0)23 8059 7979 Fax: +44 (0)23 8059 7900 www.southampton.ac.uk/healthsciences

Your project will be registered at the RCO, and then automatically transferred to the Finance Department for insurance cover. **You can not begin recruiting until you have received a letter stating that you have received insurance clearance.**

Please note that you have ethics approval only for the project described in your submission. If you want to change any aspect of your project (e.g. recruitment or data collection) you must request permission from the Ethics Committee and RCO (students should discuss changes with their supervisor before submitting the request to the Ethics Committee).

Yours sincerely

[redacted]

Dr Maggie Donovan-Hall
Vice Chair, FoHS Ethics Committee

t: +44 (0)23 8059 8880
e: mh699@soton.ac.uk
f: +44 (0)23 8059 4792

Building 45
Faculty of Health Sciences, University of Southampton, Highfield Campus, Southampton SO17 1BJ United Kingdom
Tel: +44 (0)23 8059 7979 Fax: +44 (0)23 8059 7900 www.southampton.ac.uk/healthsciences

A3: Confirmation of R & D approval

Southampton University Hospitals NHS Trust

Please reply to: Research and Development
Duthie Building (Trust) MP138
Southampton General Hospital
Tremona Road Southampton SO16 6YD

Telephone: 02380 794901
Fax: 02380 798678
E-mail: danny.pratt@suht.swest.nhs.uk

Miss Lindsay Hooper
Mailpoint 63, Room CG76A
G Level, West Wing
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

22 December 2009

Dear Miss Hooper

ID: RHM MED0871 **A Unique Longitudinal Cohor Study of the Epidemiology, Aetiology and Clinical Importance of Forefoot Bursae in Patients with Rheumatoid Arthritis.**

EudraCT:

Thank you for submitting all the required documentation for Trust R&D approval. I write to inform you that your study has full SUHT R&D approval. Please find attached the Conditions of Trust R&D approval which you are obliged to adhere to.
You are required to keep copies of all your essential documents relating to this study. Please download a copy of the relevant Investigator Site File template from the R&D website: http://tinyurl.com/p8vuek.
Your project is subject to R&D monitoring and you will be contacted by our office to arrange this.
It is a condition of your approval that Chris Edwards and Catherine Bowen have their GCP training updated within six months of starting work on the project.

Please note: A condition of approval is that any changes need to be timeously notified to the R&D office. This includes providing copies of:

. All NRES substantial amendments and favourable opinions;
. All Serious Adverse Events (SAEs);
. NRES Annual Progress Reports;
. Annual MHRA Safety Reports;
. NRES End of Study Declaration;
. Notifications of significant breaches of GCP or protocol

Please quote the above RHM No. on any correspondence with our office.

Should you, or any of your team, require training in any of the policies and procedures required to ensure compliance with the conditions of approval, please refer to the R&D Training website http://tinyurl.com/prkd65 for an up-to-date calendar of training events.

Yours sincerely

[redacted]

Danny Pratt
Research Governance Officer

A4: Participant consent form

Rheumatology Research Unit
Mailpoint 63, Level G, West Wing
Southampton General Hospital,
Tremona Road, Southampton.
SO16 6YD
Tel: 02380 796711/ 5279
Fax: 02380 796711
Email: lindsey.hooper@suht.swest.nhs.uk

NRES code: 09/H0504/93
SUHT Study Number: RHM MED 0871

CONSENT FORM – CLINICAL ASSESSMENT

Project title: The importance of pedal bursae in patients with Rheumatoid Arthritis (FeeTURA^3)

Name of Principal Investigator: Miss Lindsey Hooper

I confirm that I have read and understand the information sheet (V4. 21/10/09-a) provided for the above study and have had the opportunity to ask questions related to this. These questions have been answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

I understand responsible individuals from the University of Southampton, Southampton University Hospitals' NHS Trust (SUHT) or from regulatory authorities where review is relevant to the above research study, may look at sections of my medical notes. I give permission for these individuals to have access to my records. ☐

I agree to blood and urine samples being taken and analysed for the purposes of this study and in potential future studies with ethical approval. ☐

I agree to take part in the above study. ☐

……	……	……
Name of patient	Date	Signature
……	……	……
Name of person taking consent *(If different from researcher)*	Date	Signature
……	……	……
Researcher	Date	Signature

A5: Participant information sheet

Rheumatology Research Unit
Mailpoint 63, Level G, West Wing
Southampton General Hospital,
Tremona Road, Southampton.
SO16 6YD
Tel: 02380 796711/ 5279
Fax: 02380 796711
Email: lindsey.hooper@suht.swest.nhs.uk

NRES Code: 09/H0504/93
SUHT study number: RHM MED0871

PARTICIPANT INFORMATION SHEET – FeeTURA^3 Clinical assessment

You are being invited to take part in a research study. Before you decide if you would like to take part it is important for you to understand why the research is being done and what it will involve. **Please take time to read this information carefully and discuss it with others if you wish.** If you are happy to participate you will be asked to sign a consent form.

Part 1 tells you about the purpose of the study and that will happen to you if you take part
Part 2 gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is unclear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Part 1
1. What is the research about?
This study is a follow-up study to a previous piece of research conducted at Southampton called the FeeTURA study. You may have been a participant in some of this research already. The main purpose of this current study is to investigate swelling (inflammation) in the feet of patients with Rheumatoid Arthritis (RA) or other inflammatory arthritis.

Inflammatory arthritis can cause pain and damage to many joints. The joints most likely to be involved are in the feet and hands. However, most studies have concentrated on problems in the hands, and relatively little is known about the feet. The results from the first FeeTURA study have shown that the swelling in the feet can be very important. In particular, this swelling can be related to increased foot pain and also reduced walking ability. Bursae (small fluid filled sacks), which can become inflamed with these types of arthritis were found to be of particular importance. Being able to see such bursae using ultrasound or MRI and see how they change over time when you attend your rheumatology outpatients or podiatry appointments would help us to decide on the best course of treatment for you and for future patients. For example, this may involve deciding on what medicines and/or doses to use, or providing you with/adjusting existing insoles, to help prevent further pain, deformity or walking disability now or in the future.

2. Why have I been chosen?
You have been chosen either because you took part in the first FeeTURA study and we would like to know how your feet have changed in the 3-years since your taking part or because you have been newly diagnosed with an inflammatory arthritis and we would like to know how your feet are at the moment. You were initially chosen because you have a type of arthritis and attended/ are due to attend The Department of Rheumatology at Southampton General Hospital as part of your usual care.

3. Do I have to take part?
It is your choice if you decide to take part or not. If you do decide to take part you will be asked to sign a consent form. You are still free to stop your involvement in the study at any time and without having to provide any explanation. A decision to withdraw at any time, or decision not to take part, will not affect any care that you will normally receive.

4. What will happen to me if I take part?
If you agree to participate in this study you will be asked to attend a clinical assessment appointment at Southampton General Hospital. During your appointment we will scan the sole of your foot using a diagnostic ultrasound scanner in the same way that unborn babies are scanned within the womb. This will mean that you will be asked to sit on a couch with your feet facing the investigator. The investigator will scan the soles of both your feet and record any areas of swelling (inflammation). A clinical examination of your feet will involve the investigator looking at and feeling the shape, any swelling, lesions or marks on your feet and this information will be noted by the researcher.

Foot pressure measurements will be recorded by a computerised system called the F-Scan. This involves placing specialist insoles into your shoes, which are attached to the computer via a long cable. The insoles are very thin and so fit easily into the shoe without causing rubbing or discomfort. To avoid any possibility of trips you will be guided by the investigator along a walkway away from any free trailing cables that connect the insoles to the computer. The computer automatically records the amount of pressure occurring under the soles of your feet during each footstep.

You will also be asked to complete 2 short questionnaires that ask you about foot pain and walking ability. These questionnaires will take you approximately 10 minutes to complete.

You will also be asked to provide a blood and urine sample. These will be collected by a fully trained research nurse, stored securely and used only for the purposes of research. Some discomfort or a small bruising may occur at the site on your arm from where the blood sample has been taken. However, every effort will be made to minimise this and only fully trained staff will complete collection of this blood sample.

It is expected that this appointment will last approximately 1 hour.

Finally, you will be asked to have an MRI scan of your feet. This will mean walking along the corridor to the radiology department where a radiologist will assist you. You will be asked to lie down and still for approx. 30 minutes while the machine takes pictures of the structures inside your feet.

5. What do I have to do?
Taking part in the study does not alter any of your standards of care. You do not need to alter your lifestyle or diet in any way.

6. What are the benefits of taking part?
The information that we get from this study may help us to treat patients with foot problems associated with Rheumatoid or Inflammatory Arthritis better in the future. There may not be any direct benefit to you associated with taking part in this study however; your taking part helps us to identify swelling, bursae and other foot complications within the feet which contribute to the development of more targeted and timely treatments.

7. What are the possible disadvantages and risks of taking part?
In laboratory trials some risk of ultrasound exposure damage to tissues has been documented. This risk however, is suggested to be due to levels of exposure that are never used within clinical practice. An excellent safety record for ultrasound use exists and after many years of use there has been no documented instance of related human injury. During clinical assessments with new ultrasound equipment such as that used in this study, the total ultrasound exposure is kept as low as reasonable achievable and this is known as the ALARA principle. Implementing

ALARA within the study has required the investigators to receive training in ultrasound use, and further support is available from the radiology department at Southampton General Hospital.

It is possible that the foot pressure measurements recorded by the FScan® machine may pose some risk of trip or fall as the insoles are connected to the computer via long cables. There is also a minor risk of you walking too far and toppling over the FScan® system. To avoid these hazards, the exact distance of the walkway will be explained and demonstrated to you and you will be supervised by the investigator at all times during this activity.

8. What if there is a problem?
Any complaint about the way you have been treated during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

The contact number for any complaints is: Dr Martina Dorward, Research Support Office, University of Southampton, Building 27, Highfield Campus, Southampton. SO17 1BJ. Telephone: 02380 59 8848

9. Will my taking part in this study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2, however your GP may be informed about your participation in this study.

10. Contact for further information
Further information can be obtained from:

Principal Investigator: Miss Lindsey Hooper, Rheumatology Research Unit, Southampton University Hospitals' Trust, at Southampton General Hospital. Telephone: 02380 777 222 extension 5279.

And/or
Chief Investigator: Professor Nigel Arden, Department of Rheumatology, Southampton University Hospitals' Trust, at Southampton General Hospital. Telephone: 02380 79 8723 / 8523 / 6711.

Thank you for reading this.

This completes Part 1 of the Information Sheet.
If the information in Part 1 has been of interest to you and you are considering taking part please continue to read Part 2 before making any decision.

PARTICIPANT INFORMATION SHEET

Part 2
11. What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time without any need to provide a reason for doing so. Your choice to withdraw will have no effect on the care that you normally receive. If you are in agreement images or information gathered up to the point at which you withdraw might still be used.

12. What if there is a problem or something goes wrong?
It is extremely unlikely that taking part in this research project will harm you. If this did occur however there are no special compensation arrangements. If you are harmed due to someone's' negligence, then you may have grounds for a legal action for compensation against (The University of Southampton or Southampton University Hospitals Trust) but you may have to pay your own legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Regardless of this, if you have a concern about any aspect of this study you should ask to speak with investigator who will do their best to answer your questions (Telephone 02380 777222 extension 5279). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained form the Patient Advice and Liaison Service (PALS) information point within the hospital or you can telephone them on 02380 798498 or email PALS@suht.swest.nhs.uk

Alternatively, the consumers for ethics in research (CERES) website: http://www.ceres.org.uk/ is a recommended third independent participant support body.

13. Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will be coded so that at no time will any of your personal details be revealed. The procedures for handling, processing storage and destruction of any data collected during this study are compliant with the Data Protection Act 1998 and in line with the Southampton University Hospitals NHS Trust Policy.

14. What will happen to the results of the research study?
We hope the results are useful and we intend to publish them in a rheumatological journal and to present them at scientific conferences & meetings. The results will also be utilised by the Principal Investigator as contribution towards her PhD thesis, which will be submitted to the University of Southampton. You will not be identifiable in any publications arising from this work.

15. Who is organising and funding the research?
The study is sponsored by Southampton University Hospitals' Trust (SUHT) and cosponsored by Southampton University. The research is organised by investigators from both SUHT and the School of Health Sciences within Southampton University.

16. Who has reviewed the study?
The study has been peer reviewed by the research division of the School of Health Sciences, Southampton University and the SUHT Research and Development Department. The South West Hampshire Local Research Ethics Committee has also reviewed the study.

If you agree to take part you will be given a copy of this information sheet and a signed consent form to keep. If you have read this information sheet and are happy to participate in the proposed study please sign the reply slip attached to the invitation letter and return it in the stamped address envelope provided or to rheumatology reception at your next outpatient appointment.

Thank you for considering taking part and taking time to tread this information sheet.

A6: Participant letter of invitation & reply slip

Rheumatology Research Unit
Mailpoint 63, Level G, West Wing
Southampton General Hospital,
Tremona Road, Southampton.
SO16 6YD
Tel: 02380 796711/ 5279
Fax: 02380 796711
Email: lindsey.hooper@suht.swest.nhs.uk

NRES code: 09/H0504/93
SUHT Study Number: RHM MED0871

Dear……..

Re: The FeeTURA^3 study – Clinical assessment – 'The importance of foot bursae in patients with RA and UIA'

You are being invited to take part in a research study involving the investigation of foot problems in patients with Rheumatoid Arthritis (RA) or Undifferentiated Inflammatory Arthritis (UIA). This is a follow-up investigation to a previous study (FeeTURA) in which you may have already been involved. Professor Nigel Arden, Consultant Rheumatologist, remains as the main supervisor of this follow-up investigation and Miss Lindsey Hooper is the lead researcher (Principal Investigator).

We know that inflammatory arthritis commonly affects the feet, and have also begun to understand more about the associations of swelling, pain and walking ability with RA, following the initial FeeTURA study.

These results of this study have shown that swelling in the feet can vary greatly and can significantly affect a persons' ability to walk or complete daily living tasks. This follow-up study has therefore been designed to investigate how these swellings might change over a 3 year period in patients with established RA or over a 6-month period in those patients newly diagnosed with UIA. This will be investigated using questionnaires, ultrasound, MRI and pressure-sensitive insoles.

Before you decide if you would like to take part it is important that you fully understand why this research is being done and what it will involve. Please find enclosed a copy of the 'participant information sheet' for this study. Please take time to read this information carefully and discuss it with others if you wish.

If you are interested in taking part in the study please complete the enclosed reply slip and return it in the stamped addressed envelope also provided. If you have any concerns or questions regarding this study please feel free to contact Professor Nigel Arden or myself on the details above at any time.

Thank you for taking time to read this information,

Yours sincerely,

Miss Lindsey Hooper
Principal Investigator for this study.

Rheumatology Research Unit
Mailpoint 63, Level G, West Wing
Southampton General Hospital,
Tremona Road, Southampton.
SO16 6YD
Tel: 02380 796711/ 5279
Fax: 02380 796711
Email: lindsey.hooper@suht.swest.nhs.uk

NRES code: 09/G0504/93
SUHT Study Number: RHM MED0871

Dear Miss Hooper,

I am happy to be contacted to discuss my willingness to be considered for the following study further:

Study: FeeTURA^3 study – Clinical assessment – 'The importance of forefoot bursae in patients with RA and UIA'

…… …….. ……
Name of patient (printed) Signature Date

My contact telephone number is:……..

The date of my next Rheumatology Outpatients Appointment is: ……

Please return this reply slip using the self-addressed envelope provided.

Thank you.

Lead Researcher contact details:
Miss Lindsey Hooper
Address: As above.
Tel: 02380 777 222 extension: 5279

A7: Data collection forms

A7a: Participant demographic data assessment form (1)

Participant Demographic Data

1.

Patient Addressograph	Patient Code: ……..…	Participant no: ……..……
	Year diagnosed: …….	Arthritis duration: ……..

2. Date of visit: ...../...../.....

Main sites affected: ……...
……..……
….....
.....

3. Age:.....yrs Weight:.....kgs Height.....cms

4. Hand dominance: Left ☐ Right ☐

Question		**Yes** (please tick if appropriate)	**No**
5	Does the patient have and ACR diagnosis of Rheumatoid arthritis?		
6	Is Rheumatoid factor present?		
7	Are anti-CCP antibodies present?		
8	Does this patient have a diagnosis of osteoarthritis?		
9	Has this patient received any IV steroid in the last 8 weeks?		
10	Has this patient received any intra-muscular steroid in the last 8 weeks?		
11	Is this patient currently receiving oral steroid therapy?		
11b	If yes, please provide details:		
12	Has this patient received any intra-articular steroid (or other) injections to the foot or ankle within the last 8 weeks?		
12b	If yes, please provide details:		
13	Is this patient receiving anti-TNF therapy currently?		
13b	If yes please provide details:		
14	Is this patient currently taking Methotrexate?		
14b	If yes, please provide details:		

		Yes	No
14c	Has this patient taken Methotrexate previously?		
14d	If yes, please provide details:		
15	Is this patient currently taking Leflunomide?		
16	Is this patient currently taking Sulphasalazine?		
17	Is this patient currently taking Azathioprine?		
18	Is this patient currently taking Amitriptyline?		
19	Is this patient currently taking any other DMARD?		
19b	If yes, please provide details:		
19c	Has this patient taken any of these medications previously?		
19d	If yes, please provide details:		
20	Is this patient currently taking or using any other forms of analgesia?		
20b	If yes, please provide details:		
21	Has this patient ever had lower limb or foot surgery?		
21b	If yes please provide details (including date):		
22	Does this patient currently visit a podiatrist?		
22b	If no has this patient ever visited a podiatrist?		
22c	If yes, please provide details:		
23	Is there any documentation of foot complications in the patients' medical records?		
23b	If yes, please provide details:		

Investigator Signature: .....

Print name: .....

A7b: Participant demographic data collection form (2)

Participant Demographic Data

1.

Participant address details	Participant Code: ……

2. Date of visit: ...../...../.....

3. Age:.....yrs Weight:.....kgs Height.....cms

4. Hand dominance: Left ☐ Right ☐

Question		**Yes** (please tick if appropriate)	**No**
5	Can you confirm this participant has no arthritis?		
6	Has this participant received any IV steroid in the last 8 weeks?		
7	Has this participant received any intra-muscular steroid in the last 8 weeks?		
8	Is this participant currently receiving oral steroid therapy?		
8b	If yes, please provide details:		
9	Has this participant received any intra-articular steroid (or other) injections to the foot or ankle within the last 8 weeks?		
9b	If yes, please provide details:		
10	Is the participant currently using any forms of analgesia?		
10b	If yes, please provide details		
11	Has this participant ever had lower limb or foot surgery?		
11b	If yes, please provide details		
12	Does this participant currently visit a podiatrist/chiropodist?		
12b	If no, has this participant ever visited a podiatrist/chiropodist?		
12c	If yes, please provide details		
13	Does this patient report any foot complications at present or previously?		
13b	If yes, please provide details		

Investigator Signature:.....

Print name:.....

A7c: Musculoskeletal ultrasound assessment form

Participant Ultrasound Assessment – Right Foot

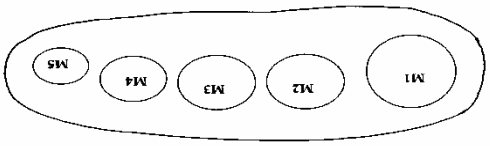
Participant Code: ..... Date: .....

Anatomical location	Synovial hypertrophy present? If yes please specify thickness & grade	Synovial hypertrophy with Doppler Activity? If yes please specify volume	Bone Erosion present? If yes please specify
MTPJ 1			
MTPJ 2			
MTPJ 3			
MTPJ 4			
MTPJ 5			

Anatomical location	Bursae present? *If yes please specify wall thickness & size*	*Bursae present with Doppler Activity? If yes please specify volume*
Sub met 1		
Inter met 1 / 2		
Sub met 2		
Inter met 2 / 3		
Sub met 3		
Inter met 3 / 4		
Sub met 4		
Inter met 4 / 5		
Sub met 5		

Please mark location of bursae

Plantar aspect



Dorsal aspect

Comments:

A7d: Podiatric assessment form

Participant Podiatric Assessment

Participant Code:..... Date: .....

	Component	Score	
		Left (-2 to +2)	Right (-2 to +2)
Rearfoot	Talar head palpation		
	Curves above and below lateral malleoli		
	Inversion/ eversion of Calcaneus		
Midfoot	Bulge in the region of TNJ		
	Congruence of medial longitudinal arch		
Forefoot	Adduction/abduction of the forefoot relative to the rearfoot		
	Total		

Foot Structure Assessment *(Mark as appropriate)*	Right	Left
Hallux Abducto Valgus:	present / absent	present / absent
5th MPJ Exostosis:	present / absent	present / absent
Lesser Toe Deformity:	present / absent	present / absent
MPJ Subluxation:	present / absent	present / absent

Joint Assessment (ROM) *(Mark as appropriate)*	Right	Left
Ankle Joint:	Full / Limited / Rigid	Full / Limited / Rigid
Sub Talar Joint:	Full / Limited / Rigid	Full / Limited / Rigid
Mid Tarsal Joint:	Full / Limited / Rigid	Full / Limited / Rigid
1st MPJ:	Full / Limited / Rigid	Full / Limited / Rigid

Temporal gait parameters	Right	Left
Location of peak pressure (A-F):	……..	……..
Value of peak pressure:	……..	……..
Time of peak pressure:	……..	……..
Total footstep time:	……..	……..
Mean force:		

Other:
Footwear: ……. Orthoses: ……. Ulceration: ……

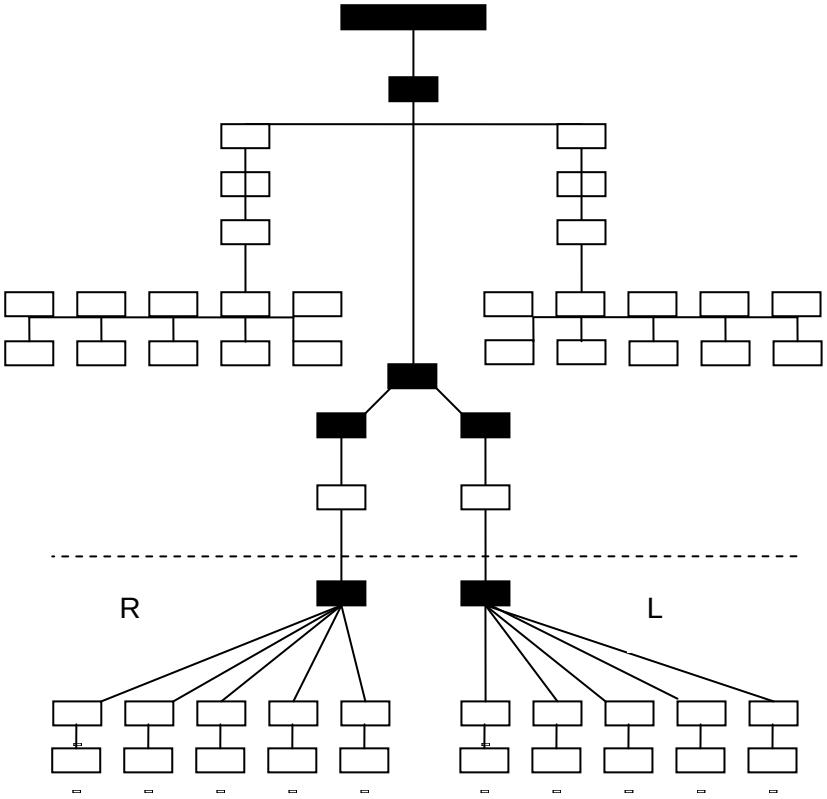
Other comments: ……
Refer for biomechanical assessment? Yes / No
Refer to Consultant / GP? Yes / No
Refer for vascular / neurological assessment? Yes / No
Refer to Orthotist? Yes/ No
Refer for podiatric treatment? Regular Appointment / SR / SOS / Annual Recall / No
Researcher's Signature: ..... Date: ……

A7e: Disease activity assessment form

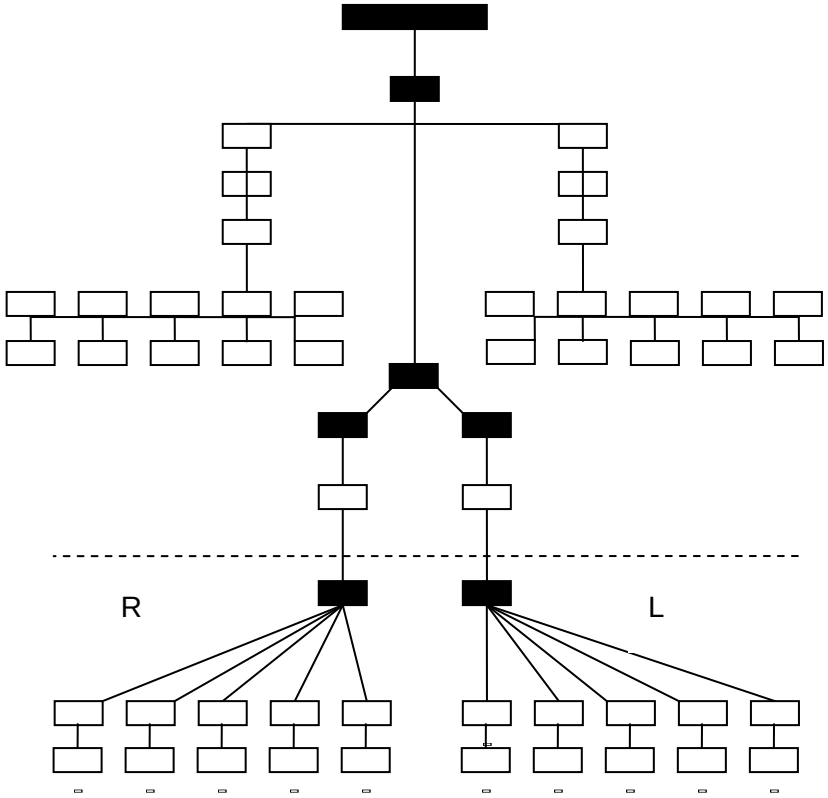
Modified Swollen and Tender Joint Count

Patient ID _____

Which joints are **tender?** (Please tick)



Which joints are **swollen?** (Please tick)



Global VAS: Overall wellbeing: please indicate on the scale below

0 100

Best Imaginable Health State

Worst Imaginable Health State

ESR……Date:……..
CRP……Date:……..
DAS……Date:……..

A7f: Foot Impact Scale – Self completed questionnaire

FOOT IMPACT SCALE

On the following pages you will find some statements that have been made by people who have arthritis in their feet. We would like you to tick **"true"** if the statement applies to you, and tick **"not true"** if it does not.
Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
1.	My feet get painful when I'm standing……	☐	☐
2.	My feet hurt me……	☐	☐
3.	I find the pain in my feet frustrating……	☐	☐
4.	The pain is worse when I've been on my feet all day……	☐	☐
5.	At the end of the day there is pain and tension in my feet…….	☐	☐
	I never get rid of the stiffness in the background…….	☐	☐

Please remember to read each statement thinking about your feet.
Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
7.	My feet throb at night……..	☐	☐
8.	My feet wake me up at night……	☐	☐
9.	I feel as though I've got pebbles in my shoes……	☐	☐
10.	I get pain every time I put my foot down…….	☐	☐
11.	I get a burning sensation all the time……	☐	☐
12.	I cry with pain……	☐	☐

Please check you have ticked a box for every statement on this page

Please remember to read each statement thinking about your feet.
Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
13.	I can only walk in certain shoes……..	☐	☐
14.	I need shoes with plenty of room in them……..	☐	☐
15.	I am limited in my choice of shoes……	☐	☐
16.	I need a wider fit of shoes……..	☐	☐
17.	I feel I need a lot of padding under my feet……..	☐	☐
18.	My footwear always feels heavy……	☐	☐
19.	I have to keep swapping and changing my shoes……	☐	☐
20.	I can't get any shoes on……..	☐	☐
21.	I walk bare foot all the time……	☐	☐

Please remember to read each statement thinking about your feet.
Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
22.	I feel unsafe on my feet……	☐	☐
23.	I have to walk for a bit and sit for a bit……..	☐	☐
24.	I can't run……..	☐	☐
25.	I find I shuffle around……..	☐	☐
26.	I am limping about all the time……	☐	☐
27.	I have to use a walking stick or walking frame…….	☐	☐

Please check you have ticked a box for every statement on this page

Please remember to read each statement thinking about your feet.
Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
28.	It takes me all my time to climb the stairs……	☐	☐
29.	I need help to climb stairs……	☐	☐
30.	I can't walk on cobbles……..	☐	☐
31.	I am unsteady on uneven surfaces……	☐	☐
32.	I can't walk as far as I would like to……	☐	☐
33.	It takes me longer to do things…….	☐	☐
34.	My whole life has been adapted……	☐	☐

Please remember to read each statement thinking about your feet.
Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
35.	My feet restrict my movement……	☐	☐
36.	I get annoyed because I'm slower…….	☐	☐
37.	I get frustrated because I can't do things so quickly….	☐	☐
38.	My whole life has slowed down……	☐	☐
39.	It's reduced the range of things I can do……..	☐	☐
40.	I have to plan everything out……	☐	☐
41.	I can't keep up like I used to…….	☐	☐
42.	Socially it's affected me a lot……	☐	☐
43.	I am ashamed of how I walk…….	☐	☐
44.	I'm nervous of missing a curb edge……..	☐	☐

Please check you have ticked a box for every statement on this page

Please remember to read each statement thinking about your feet.
Please choose the response that applies best to you <u>at the moment</u>.

		TRUE	NOT TRUE
45.	I feel isolated because I can't go very far……	☐	☐
46.	I feel I slow other people down……..	☐	☐
47.	I can't do some of the things I take for granted……	☐	☐
48.	I can't go for walks with the people close to me……..	☐	☐
49.	I'm finding it difficult to be independent…….	☐	☐
50.	I dread finishing up in a wheelchair……..	☐	☐
51.	I get frustrated because I can't do things for myself……	☐	☐

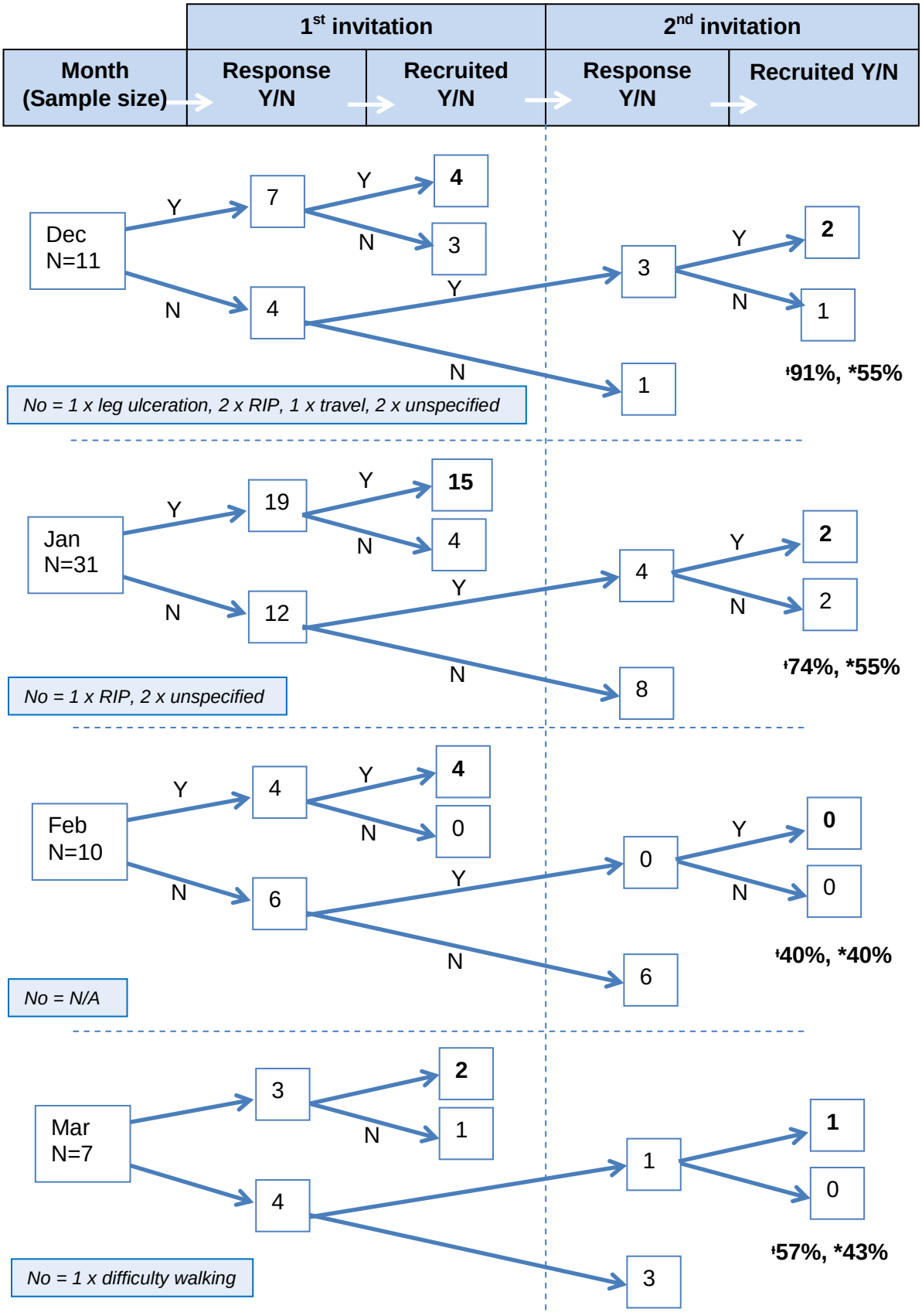
Please check you have ticked a box for every statement on this page

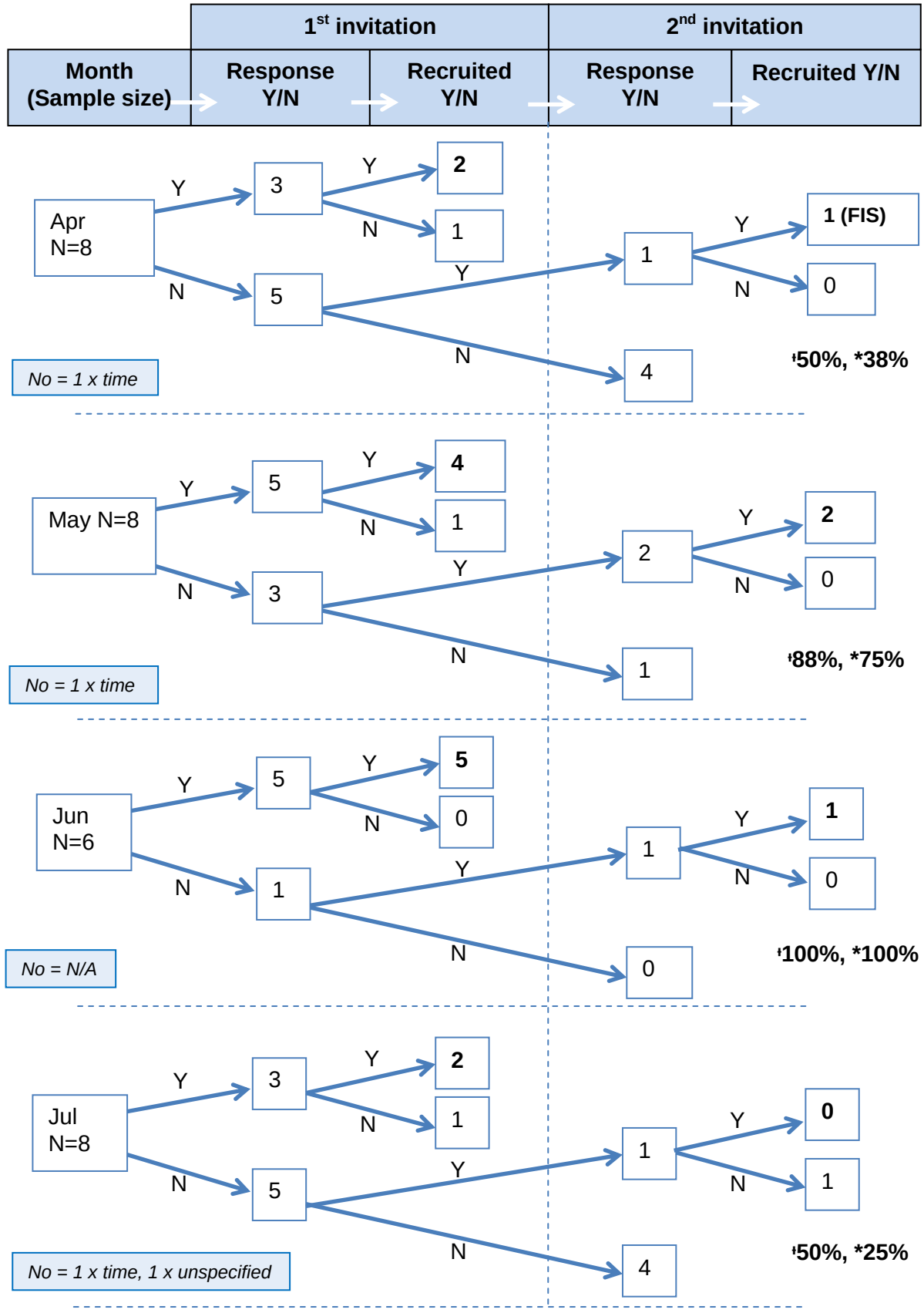
THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

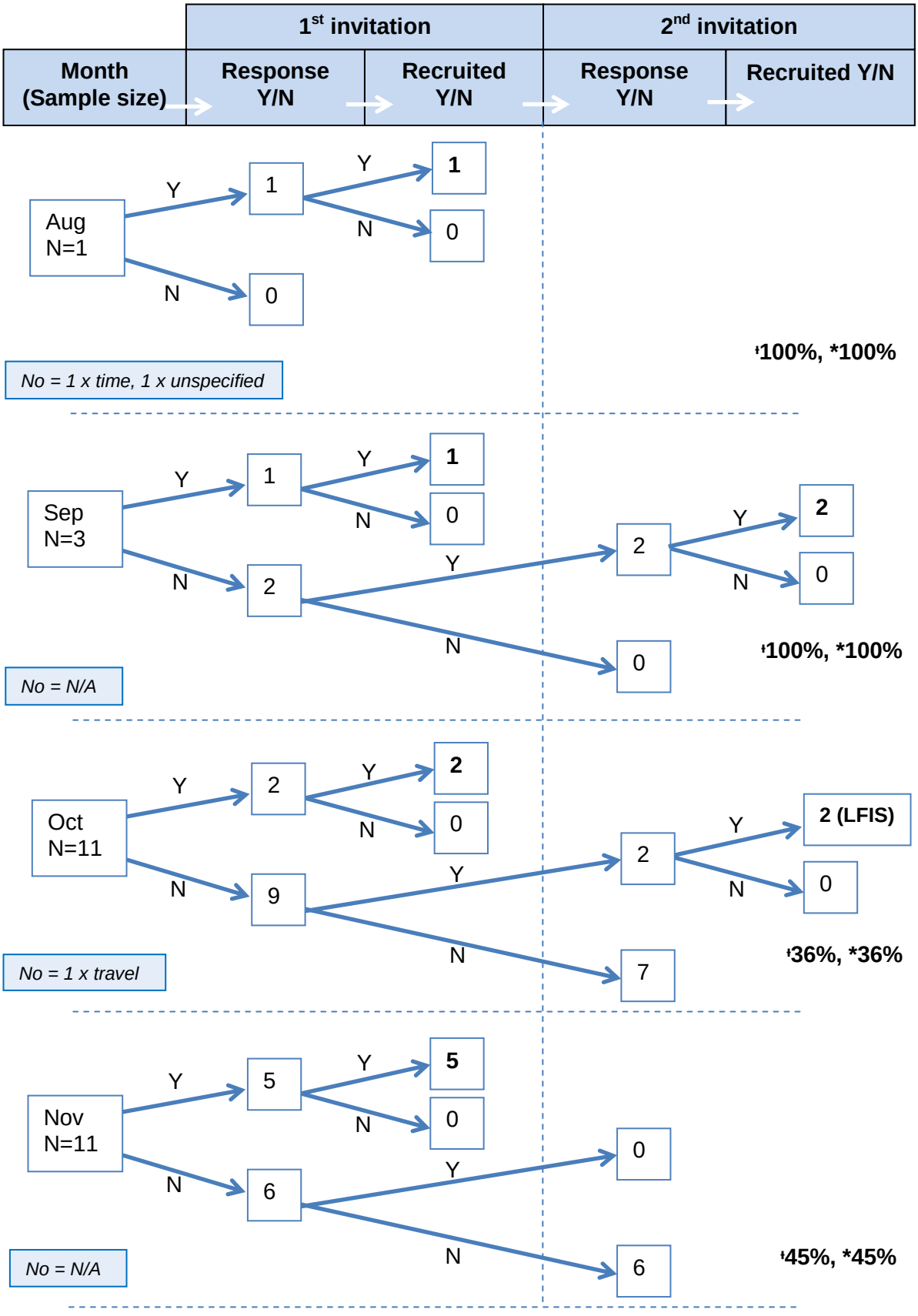
FOR OFFICE USE ONLY

Score 1 =	Score 2 =

A8: Year-three follow-up study response & recruitment rates

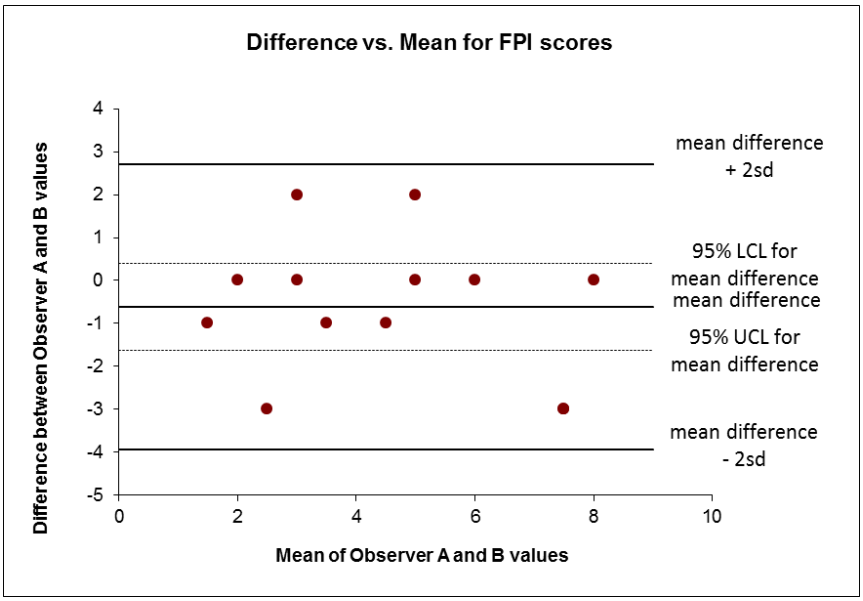



1st invitation
2nd invitation
Month (Sample size)
Response Y/N
Recruited Y/N
Response Y/N
Recruited Y/N
Apr N=8
May N=8
Jun N=6
Jul N=8
Y
N
3
5
2
1
4
0
1 (FIS)
No = 1 x time
No = 1 x time
No = N/A
No = 1 x time, 1 x unspecified
ǂ50%, *38%
ǂ88%, *75%
ǂ100%, *100%
ǂ50%, *25%


1st invitation
2nd invitation
Month (Sample size)
Response Y/N
Recruited Y/N
Response Y/N
Recruited Y/N
Aug N=1
Y
N
1
0
Y
N
1
0
No = 1 x time, 1 x unspecified
ŧ100%, *100%
Sep N=3
Y
N
1
2
Y
N
Y
N
1
0
2
0
Y
N
2
0
No = N/A
ŧ100%, *100%
Oct N=11
Y
N
2
9
Y
N
Y
N
2
0
Y
N
2
0
2 (LFIS)
7
No = 1 x travel
ŧ36%, *36%
Nov N=11
Y
N
5
6
Y
N
Y
N
5
0
Y
N
0
6
No = N/A
ŧ45%, *45%

A9: Calculation of intra-rater FPI reliability – Bland & Altman plots

Intra-rater reliability – demonstration of B-A plots for FPI agreement – Right foot only



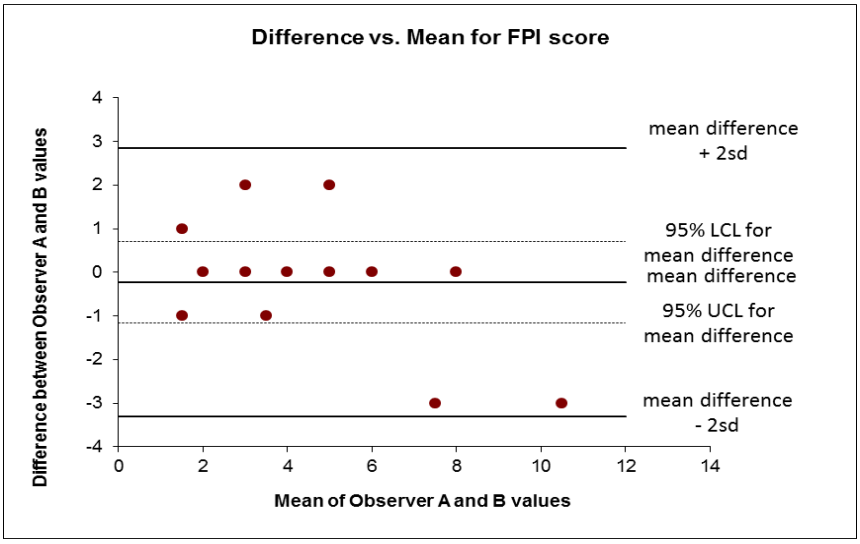
Mean difference: -0.62

Standard error of mean difference: 0.46

95% confidence interval for mean difference: -1.62 → 0.39

Degrees of freedom: 12

Intra-rater reliability – demonstration of B-A plots for FPI agreement – Left foot only



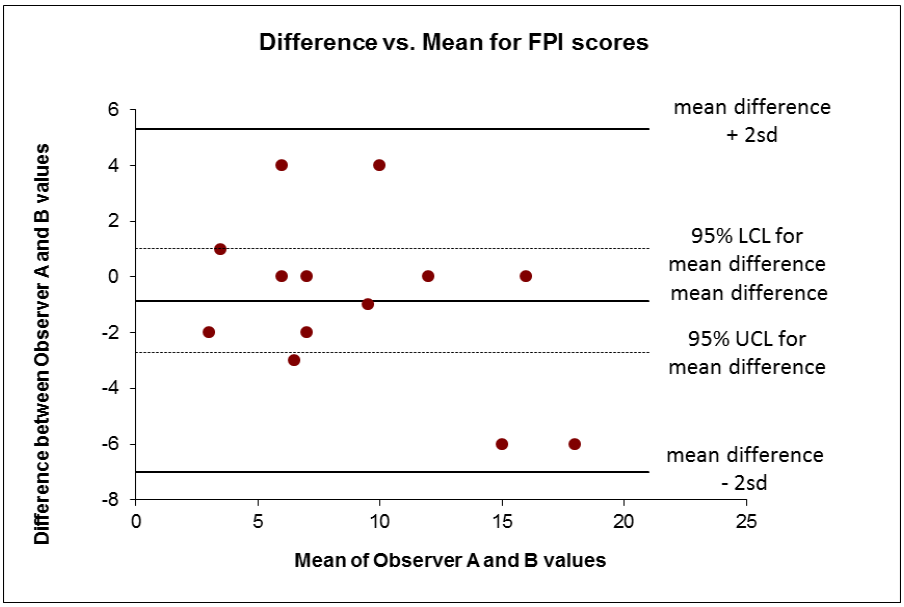
Mean difference: -0.23

Standard error of mean difference: 0.43

95% confidence interval for mean difference: -1.16 → 0.7

Degrees of freedom: 12

Intra-rater reliability – demonstration of B-A plots for FPI agreement – Both feet combined scores



Mean difference: -0.85

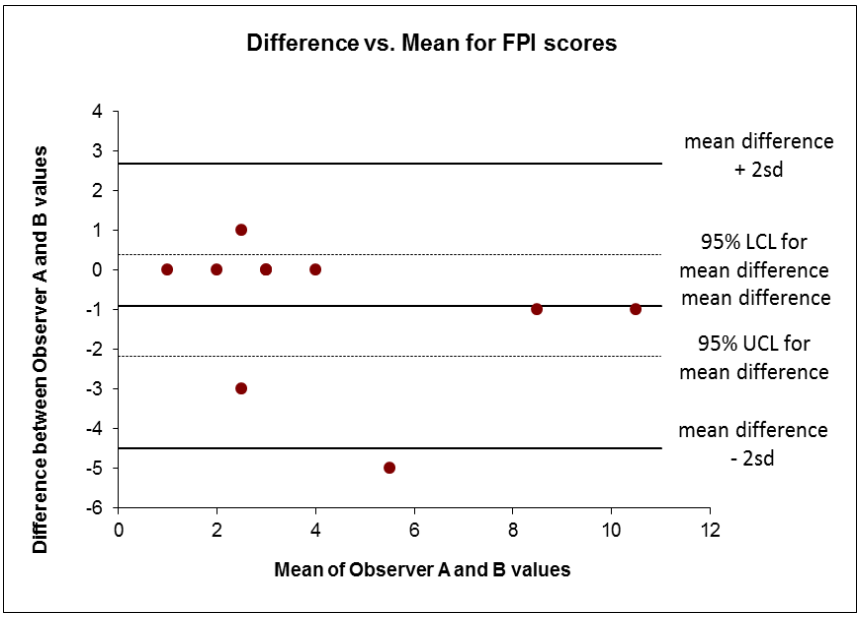
Standard error of mean difference: 0.85

95% confidence interval for mean difference: -2.71 → 1.01

Degrees of freedom: 12

A10: Calculation of inter-rater FPI reliability – Bland & Altman plots

Inter-rater reliability – demonstration of B-A plots for FPI agreement – Right foot only



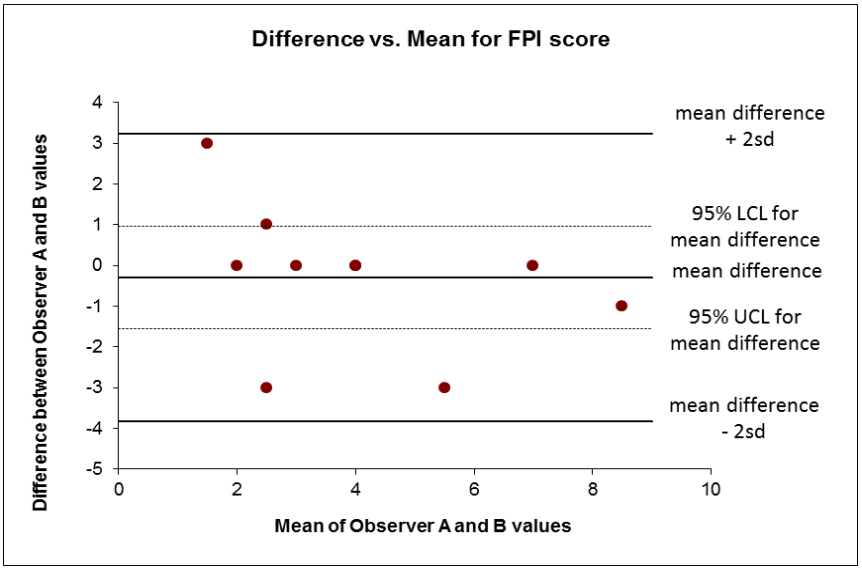
Mean difference: -0.9

Standard error of mean difference: 0.57

95% confidence interval for mean difference: -2.18 → 0.38

Degrees of freedom: 9

Inter-rater reliability – demonstration of B-A plots for FPI agreement – Left foot only



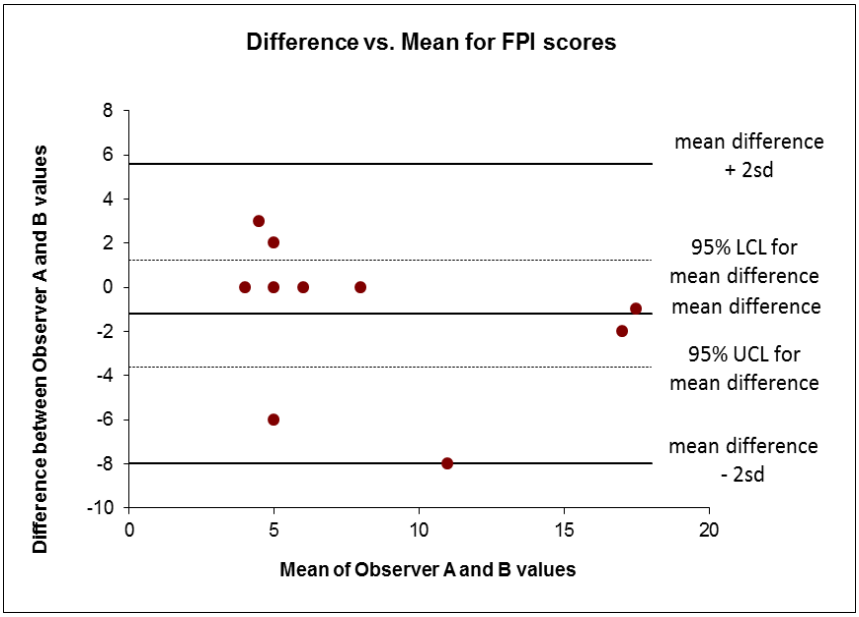
Mean difference: -0.3

Standard error of mean difference: 0.56

95% confidence interval for mean difference: -1.56 → 0.96

Degrees of freedom: 9

Inter-rater reliability – demonstration of B-A plots for FPI agreement – Both feet combined scores



Mean difference: -1.2

Standard error of mean difference: 1.07

95% confidence interval for mean difference: -3.63 → 1.23

Degrees of freedom:

A11: Association analysis

Table A11: FFB count association analysis (RA)
Where ǂ = non-parametric data; *= Significant at the 0.05 level.

	NUMBER OF FFB	
	r	**p-value**
age	-0.150	0.270
BMI	-0.020	0.888
foot posture	0.149	0.272
hallux abducto-valgus	0.230	0.088
lesser digital deformity	0.184	0.174
***ankle jROM**	0.277	0.039
subtalar jROM	0.215	0.111
midfoot jROM	0.228	0.090
metatarsophalangeal jROM	0.238	0.077
disease duration	-0.027	0.843
MTP joint hypertrophy	0.184	0.175
***erosion**	0.419	0.001
ESR	0.015	0.914
CRP	0.050	0.716
DAS 28-ESR	-0.009	0.947
DAS 28-CRP	-0.049	0.718
FIS_{IF}	0.100	0.509
FIS_{AP}	0.161	0.284

A12: Linear regression analysis – FFB as dependent variable

Table A12a: FFB count regression analysis (HV)
i: Results of multiple linear regression analyses for all dependent variables; ii: Results of multivariate regression analysis for previously identified independent predictors of FFB count.
Where CI= confidence interval; BMI=Body mass index; jROM= joint range of motion; DAS= Disease Activity Score. *= Significant at the 0.05 level.

i.

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**R^2**	**F-value**
age	0.01	0.763 (-0.03-0.04)	0.00	0.092
weight	-0.02	0.175 (-0.06-0.01)	0.04	1.9
BMI	-0.004	0.934 (-0.10-0.09)	0.00	0.01
MTP joint hypertrophy	0.88	0.107 (-0.2-2.0)	0.05	2.7
erosion	0.41	0.072 (-0.04-0.86)	0.07	3.38
***foot posture**	0.17	0.003* (0.06-0.27)	0.17	9.53
***hallux abducto-valgus**	0.88	0.024* (0.12-1.63)	0.10	5.44
***lesser digital deformity**	0.53	0.000* (0.25-0.80)	0.23	14.5
***snkle jROM**	1.09	0.016* (0.22-1.97)	0.12	6.29
***subtalar jROM**	1.27	0.004* (0.42-2.12)	0.16	8.91
***midfoot jROM**	1.27	0.004* (0.42-2.12)	0.16	8.91
metatarsophalangeal jROM	0.61	0.084 (-0.08-1.3)	0.06	3.12

ii.

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**Adjusted R^2**	**F-value**
***foot posture**	0.15	0.022* (0.02-0.27)	0.24	4.16
hallux abducto-valgus	-0.42	0.398 (-1.4-0.57)		
***lesser digital deformity**	0.77	0.026* (0.1-1.43)		
ankle jROM	-0.20	0.742 (-1.4-1.0)		
subtalar jROM				
midfoot jROM	-0.77	0.343 (-2.4-0.85)		

Table A12b: FFB count regression analysis (OA)
i: Results of multiple linear regression analyses for all dependent variables; ii: Results of multivariate regression analysis for previously identified independent predictors of FFB count.

i.

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**R^2**	**F-value**
age	-0.05	0.070 (-0.41-0.004)	0.07	3.43
weight	-0.004	0.786 (-0.04-0.03)	0.00	0.08
BMI	-0.00	0.948 (-0.09-0.09)	0.00	0.00
MTP joint hypertrophy	-0.01	0.979 (-0.48-0.47)	0.00	0.00
erosion	0.03	0.766 (-0.20-0.26)	0.00	0.09
foot posture	-0.04	0.497 (-0.15-0.07)	0.10	0.47

hallux abducto-valgus	-0.22	0.334 (-0.66-0.23)	0.02	0.95
***lesser digital deformity**	0.31	0.057 (-0.01-0.64)	0.07	3.79
***snkle jROM**	-0.44	0.037 (-0.85- -0.03)	0.09	4.62
subtalar jROM	-0.05	0.829 (-0.51-0.41)	0.00	0.05
midfoot jROM	0.09	0.675 (-0.33-0.50)	0.00	0.18
metatarsophalangeal jROM	0.20	0.302 (-0.18-0.58)	0.02	1.09

ii.

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**Adjusted R^2**	**F-value**
***lesser digital deformity**	0.37	0.022 (0.06-0.68)	0.15	5.35
***ankle jROM**	-0.50	0.014 (-0.90- -0.11)		

Table A12c: FFB count regression analysis (RA)
i: Results of multiple linear regression analyses for all dependent variables; ii: Results of multivariate regression analysis for previously identified independent predictors of FFB count.

i.

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**R^2**	**F-value**
age	-0.03	0.270 (-0.07)	0.02	1.24
weight	-0.02	0.269 (-0.07-0.02)	0.02	1.25
BMI	-0.01	0.888 (-0.17-0.14)	0.00	0.02
ESR	0.001	0.933 (-0.03-0.03)	0.00	0.01
CRP	-0.01	0.576 (-0.06-0.03)	0.01	0.32
DAS 28-ESR	-0.02	0.947 (-0.46-0.43)	0.00	0.01
DAS 28-CRP	-0.09	0.718 (-0.59-0.01)	0.00	0.13
MTP joint hypertrophy	0.14	0.175 (-0.06-0.34)	0.03	1.89
***erosion**	0.27	0.001 (0.11-0.43)	0.18	11.49
foot posture	0.04	0.272 (-0.03-0.11)	0.02	1.23
hallux abducto-valgus	0.50	0.088 (-0.08-1.07)	0.05	3.03
lesser digital deformity	0.23	0.174 (-0.10-0.56)	0.03	1.90
***ankle jROM**	0.52	0.039 (0.03-1.01)	0.08	4.47
subtalar jROM	0.41	0.111 (-0.10-0.92)	0.05	2.62
midfoot jROM	0.35	0.090 (-0.06-0.76)	0.05	2.97
metatarsophalangeal jROM	0.40	0.077 (-0.05-0.84)	0.06	3.24

ii.

EXPLANATORY VARIABLE	NUMBER OF FFB			
	Coefficient	**p-value (95% CI)**	**Adjusted R^2**	**F-value**
***erosion**	0.24	0.004 (0.08-0.41)	0.18	7.02
ankle jROM	0.36	0.137 (-0.12-0.83)		

A13: Association analysis

Table 13a: FFB count association analysis (HV)

Where ǂ = non-parametric data; *= Significant at the 0.05 level.

	NUMBER OF FFB	
	r	**p-value**
age	0.046	0.763
BMI	-0.013	0.934
***foot posture**	0.407	0.003
***ǂhallux abducto-valgus**	0.304	0.032
***ǂlesser digital deformity**	0.460	0.001
***ǂankle jROM**	0.344	0.014
***ǂsubtalar jROM**	0.366	0.009
***ǂmidfoot jROM**	0.366	0.009
***ǂmetatarsophalangeal jROM**	0.279	0.050

Table A13b: FFB count association analysis (OA)

	NUMBER OF FFB	
	r	**p-value**
age	-0.261	0.070
BMI	-0.011	0.948
foot posture	-0.098	0.497
hallux abducto-valgus	-0.139	0.334
lesser digital deformity	0.270	0.057
***ankle jROM**	-0.296	0.037
subtalar jROM	-0.031	0.829
ǂmidfoot jROM	0.071	0.625
ǂmetatarsophalangeal jROM	0.117	0.419
disease duration	-0.007	0.962
MTP joint hypertrophy	-0.004	0.979
erosion	0.043	0.766
FIS_{IF}	0.140	0.333
FIS_{AP}	0.055	0.703

Table A13c: FFB count association analysis (RA)

	NUMBER OF FFB	
	r	**p-value**
age	-0.150	0.270
BMI	-0.020	0.888
foot posture	0.149	0.272
hallux abducto-valgus	0.230	0.088
lesser digital deformity	0.184	0.174
***ankle jROM**	0.277	0.039
subtalar jROM	0.215	0.111

midfoot jROM	0.228	0.090
metatarsophalangeal jROM	0.238	0.077
disease duration	-0.027	0.843
MTP joint hypertrophy	0.184	0.175
***erosion**	0.419	0.001
ǂESR	0.015	0.914
ǂCRP	0.050	0.716
DAS 28-ESR	-0.009	0.947
DAS 28-CRP	-0.049	0.718
FIS_{IF}	0.100	0.509
FIS_{AP}	0.161	0.284

A14: Linear regression analysis – FFB as explanatory variable

Table A14a: FFB count regression analysis (HV)
Where HV=healthy volunteer; OA= osteoarthritis; RA= rheumatoid arthritis; FFB= forefoot bursae; FPI= foot posture index; HAV= hallux abducto valgus deformity; LDD= lesser digital deformity; jROM= joint range of motion; FIS_{IF}= foot impact score impairment subscale; FIS_{AP}= foot impact score activity limitation subscale; DAS= disease activity score; CRP= C-reactive protein; ESR= erythrocyte sedimentation rate; JH= joint hypertrophy; ER= erosion; *= Significant at the 0.05 level.

EXPLANATORY VARIABLE: FFB COUNT	DEPENDENT VARIABLE (BIOMECHANICAL)						
	FPI*	**HAV***	**LDD***	**ankle jROM***	**subtalar jROM***	**midfoot jROM***	**MTP jROM**
Coefficient	0.999	0.116	0.442	0.106	0.123	0.123	0.100
p-value	0.003	0.024	0.000	0.016	0.004	0.004	0.084
R^2	0.17	0.10	0.23	0.12	0.16	0.16	0.06
F-value	9.53	5.44	14.50	6.29	8.91	8.91	3.12

Table A14b: FFB count regression analysis (OA)

EXPLANATORY VARIABLE: FFB COUNT	DEPENDENT VARIABLE (BIOMECHANICAL)						
	FPI	**HAV**	**LDD**	**ankle jROM***	**subtalar jROM**	**midfoot jROM**	**MTP jROM**
Coefficient	-0.262	-0.090	0.233	-0.199	-0.020	0.042	0.113
p-value	0.497	0.334	0.057	0.037	0.829	0.675	0.302
R^2	0.01	0.02	0.07	0.09	0.001	0.004	0.02
F-value	0.47	0.95	3.79	4.62	0.05	0.18	1.09

EXPLANATORY VARIABLE: FFB COUNT	DEPENDENT VARIABLE (DISABILITY)	
	FIS_{IF}	**FIS_{AP}**
Coefficient	0.451	0.318
p-value	0.333	0.703
R^2	0.02	0.003
F-value	0.96	0.15

Table A14c: FFB count regression analysis (RA)

EXPLANATORY VARIABLE: FFB COUNT	DEPENDENT VARIABLE (BIOMECHANICAL)						
	FPI	**HAV**	**LDD**	**ankle jROM***	**subtalar jROM**	**midfoot jROM**	**MTP jROM**
Coefficient	0.559	0.106	0.149	0.148	0.113	0.148	0.143
p-value	0.272	0.088	0.174	0.039	0.111	0.090	0.077
R^2	0.02	0.05	0.03	0.08	0.05	0.05	0.06
F-value	1.23	3.03	1.90	4.47	2.62	2.97	3.24

EXPLANATORY VARIABLE: FFB COUNT	DEPENDENT VARIABLE (DISABILITY)	
	FIS_{IF}	**FIS_{AP}**
Coefficient	0.217	0.768
p-value	0.509	0.284
R^2	0.01	0.03
F-value	0.44	1.18

EXPLANATORY VARIABLE: FFB COUNT	DEPENDENT VARIABLE (RA DISEASE)					
	DAS 28-CRP	**DAS 28-ESR**	**CRP**	**ESR**	**JH**	**ER***
Coefficient	-0.027	-0.006	-0.469	0.110	0.244	0.643
p-value	0.718	0.947	0.576	0.933	0.175	0.001
R^2	0.002	0.000	0.01	0.000	0.03	0.18
F-value	0.13	0.005	0.32	0.01	1.89	11.49

A15: Multinomial regression analysis

Table A15a: Multinomial regression analysis (OA)
Where HV=healthy volunteer; OA= osteoarthritis; RA= rheumatoid arthritis; FFB= forefoot bursae; FPI= foot posture index; HAV= hallux abducto valgus deformity; LDD= lesser digital deformity; jROM= joint range of motion; FIS_{IF}= foot impact score impairment subscale; FIS_{AP}= foot impact score activity limitation subscale; DAS= disease activity score; CRP= C-reactive protein; ESR= erythrocyte sedimentation rate; JH= joint hypertrophy; ER= erosion; *= Significant at the 0.05 level.

EXPLANATORY VARIABLE	FFB PATTERN CATEGORY			
	X^2	***df***	**p-value**	**Pseudo-R^2 (Cox & Snell)**
MTP joint hypertrophy	0.31	3	0.957	0.006
erosion	7.24	3	0.065	0.135
FPI	0.51	3	0.915	0.010
LDD	2.03	3	0.567	0.040
FIS_{IF}	1.88	3	0.597	0.037
FIS_{AP}	5.07	3	0.167	0.096

Table A15b: Multinomial regression analysis (RA)

EXPLANATORY VARIABLE	FFB PATTERN CATEGORY			
	X^2	***df***	**p-value**	**Pseudo-R^2 (Cox & Snell)**
MTP joint hypertrophy	8.80	3	0.032	0.145
erosion	15.35	3	0.002	0.240
DAS 28-CRP	4.26	3	0.235	0.073
DAS 28-ESR	0.86	3	0.836	0.015
FPI	1.90	3	0.593	0.033
LDD	3.05	3	0.384	0.053
FIS_{IF}	2.94	3	0.400	0.051
FIS_{AP}	0.84	3	0.841	0.015

A16: *FFB-score* intra-reader & inter-reader agreement analysis

Table A16a: *FFB-score* intra-reader agreement

Lesion type		Factor	PEA	PCA	Kappa (Left: right)
Intermetatarsal	Fluid	Count	50	100	5.5: 5.5
		Shape	50	90	
		Enhancement	20	100	
		MR T1	50	90	
		MR T2	50	50	
	Soft tissue	Count	50	100	7.5: 8
		Shape	40	50	
		Enhancement	50	100	
		MR T1	60	90	
		MR T2	30	80	
Plantar lesion	Fluid	Count	100	100	9: 9
		Shape	100	100	
		Enhancement	100	100	
		MRI T1	100	100	
		MRI T2	100	100	
	Soft tissue	Count	90	100	8: 7
		Shape	90	100	
		Enhancement	90	100	
		MRI T1	90	100	
		MRI T2	90	100	

Table A16b: *FFB-score* inter-reader agreement

Lesion type		Factor	PEA		PCA		Kappa (left: right)
			LK-MT	LK-LH	LK-MT	LK-LH	LK-LH
Intermetatarsal	Fluid	Count	31	50	86	100	4.7: 4.9
		Shape	21	50	79	90	
		Enhancement	71	90	95	100	
		MRI T1	26	50	57	100	
		MRI T2	19	50	55	50	
	Soft tissue	Count	71	100	95	100	7.5: 7.3
		Shape	86	100	90	100	
		Enhancement	81	100	95	100	
		MRI T1	64	100	86	100	
		MRI T2	62	80	74	100	
Plantar lesion	Fluid	Count	93	100	100	100	8.7: 6.6
		Shape	17	100	50	100	
		Enhancement	88	90	98	100	
		MRI T1	90	100	95	100	
		MRI T2	90	100	100	100	

	Soft tissue	Count	19	70	52	100	6.4: 6.4
		Shape	10	40	26	70	
		Enhancement	40	100	88	100	
		MRI T1	10	60	33	100	
		MRI T2	14	40	29	100	

A17: *FFB-score* discriminant validity analysis – localised markers of disease activity

Table A17a: *FFB-score* discriminant validity – MRI-determined disease activity in the forefoot
Where FFB = Forefoot bursae; FL = fluid lesion; ST = soft tissue lesion; Sh = shape; En = enhancement; FIS_{IF} = foot-related impairment; FIS_{AP} foot-related activity limitation.
*Significant at the 0.05 level.

	Test item	AUC	Significance	95% Confidence Interval
Erosion	FFB count	0.333	0.081	0.16-0.51
	FFB FL	0.281	0.022*	0.12-0.45
	FFB ST	0.491	0.922	0.31-0.67
	FFB sh	0.384	0.224	0.21-0.56
	FFB en	0.741	0.011*	0.57-0.91
	FFB FL en	0.523	0.812	0.34-0.71
	FFB ST en	0.744	0.011*	0.57-0.92
Oedema	FFB count	0.464	0.691	0.29-0.64
	FFB FL	0.507	0.939	0.33-0.69
	FFB ST	0.462	0.682	0.28-0.64
	FFB sh	0.478	0.808	0.30-0.65
	FFB en	0.718	0.018*	0.56-0.88
	FFB FL en	0.607	0.244	0.43-0.78
	FFB ST en	0.681	0.048*	0.51-0.86
Synovitis	FFB count	0.470	0.741	0.29-0.65
	FFB FL	0.561	0.501	0.39-0.74
	FFB ST	0.410	0.322	0.24-0.59
	FFB sh	0.440	0.509	0.26-0.62
	FFB en	0.759	0.004*	0.61-0.91
	FFB FL en	0.697	0.031*	0.53-0.86
	FFB ST en	0.671	0.060	0.50-0.84

Table A17b: *FFB-score* discriminant validity – patient-reported foot-related disability

	Test item	AUC	Significance	95% Confidence Interval
FIS_{IF}	FFB count	0.195	0.006*	0.06-0.33
	FFB FL	0.301	0.071	0.14-0.47
	FFB ST	0.274	0.040*	0.09-0.45
	FFB sh	0.387	0.304	0.16-0.61
	FFB en	0.527	0.806	0.30-0.76
	FFB FL en	0.490	0.927	0.27-0.72
	FFB ST en	0.502	0.988	0.30-0.70
FIS_{AP}	FFB count	0.288	0.033*	0.12-0.45
	FFB FL	0.260	0.016*	0.11-0.42
	FFB ST	0.385	0.248	0.20-0.57
	FFB sh	0.460	0.686	0.27-0.65
	FFB en	0.472	0.781	0.27-0.68
	FFB FL en	0.338	0.103	0.15-0.53
	FFB ST en	0.576	0.444	0.38-0.77

A18: *FFB-score* discriminant validity – serological/clinical markers of disease activity

Where FFB = Forefoot bursae; FL = fluid lesion; ST = soft tissue lesion; Sh = shape; En = enhancement; CRP = C-Reactive Protein, ESR = Erythrocyte Sedimentation Rate, DAS = Disease Activity Score.

Table A19a. Differentiation between moderate and high disease activity

	Test item	AUC	Significance	95% Confidence Interval
DAS 28-CRP	FFB count	0.404	0.582	0.09-0.72
	FFB FL	0.482	0.920	0.20-0.77
	FFB ST	0.386	0.515	0.06-0.71
	FFB sh	0.228	0.121	0.00-0.47
	FFB en	0.219	0.109	0.04-0.40
	FFB FL en	0.316	0.293	0.08-0.55
	FFB ST en	0.281	0.211	0.06-0.50
DAS 28-ESR	FFB count	0.360	0.277	0.11-0.61
	FFB FL	0.398	0.428	0.18-0.61
	FFB ST	0.376	0.338	0.14-0.61
	FFB sh	0.274	0.08	0.04-0.50
	FFB en	0.338	0.210	0.13-0.55
	FFB FL en	0.376	0.338	0.17-0.59
	FFB ST en	0.398	0.428	0.18-0.62
CRP	FFB count	0.088	0.163	0.00-0.18
	FFB FL	0.075	0.151	0.00-0.19
	FFB ST	0.275	0.447	0.13-0.42
	FFB sh	0.225	0.353	0.09-0.36
	FFB en	0.575	0.800	0.40-0.75
	FFB FL en	0.325	0.554	0.00-0.72
	FFB ST en	0.700	0.499	0.54-0.87
ESR	FFB count	0.487	0.952	0.00-1.00
	FFB FL	0.250	0.238	0.00-0.52
	FFB ST	0.615	0.586	0.14-1.00
	FFB sh	0.577	0.717	0.09-1.00
	FFB en	0.359	0.506	0.04-0.68
	FFB FL en	0.321	0.397	0.04-0.60
	FFB ST en	0.442	0.785	0.06-0.83

A18b. Differentiation between low & moderate disease activity

	Test item	AUC	Significance	95% Confidence Interval
DAS 28-CRP	FFB count	0.482	0.847	0.30-0.67
	FFB FL	0.509	0.923	0.32-0.70
	FFB ST	0.477	0.804	0.29-0.66
	FFB sh	0.451	0.600	0.26-0.64
	FFB en	0.439	0.516	0.25-0.62
	FFB FL en	0.477	0.804	0.29-0.66
	FFB ST en	0.422	0.408	0.24-0.60
DAS 28-ESR	FFB count	0.486	0.881	0.30-0.67
	FFB FL	0.422	0.399	0.24-0.60
	FFB ST	0.548	0.605	0.37-0.73
	FFB sh	0.505	0.957	0.32-0.69
	FFB en	0.378	0.187	0.20-0.56
	FFB FL en	0.422	0.399	0.24-0.60
	FFB ST en	0.380	0.197	0.20-0.56
CRP	FFB count	0.443	0.539	0.26-0.62
	FFB FL	0.373	0.173	0.20-0.55
	FFB ST	0.536	0.698	0.36-0.72
	FFB sh	0.483	0.852	0.29-0.68
	FFB en	0.438	0.504	0.25-0.62
	FFB FL en	0.368	0.157	0.19-0.54
	FFB ST en	0.484	0.862	0.30-0.67
ESR	FFB count	0.385	0.206	0.21-0.56
	FFB FL	0.360	0.124	0.19-0.53
	FFB ST	0.439	0.506	0.26-0.61
	FFB sh	0.421	0.389	0.24-0.60
	FFB en	0.426	0.419	0.25-0.60
	FFB FL en	0.367	0.144	0.19-0.54
	FFB ST en	0.444	0.540	0.27-0.62

A19: The *FFB-score* grading sheet

Intermetatarsal (IM) lesions

Circle as appropriate:
Left foot / Right foot

Factor	IM 1-2	IM 2-3	IM 3-4	IM 4-5
Fluid collection:(y/n)				
Size: (HxWxD, mm)				
Shape: (linear/ reticular/ circular)				
Enhancement: (0-2)				
MR characteristics (T1): (Hypo, Iso, Hyper)				
MR characteristics (T2): (Hypo, Iso, Hyper)				
Soft tissue lesion: (y/n)				
Size: (H x W x D, mm)				
Shape: (linear/ reticular/ circular)				
Enhancement: (0-2)				
MR characteristics (T1): (Hypo,Iso,Hyper)				
MR characteristics (T2): (Hypo,Iso,Hyper)				

Plantar forefoot lesions

Circle as appropriate:
Left foot / Right foot

Factor	Head of metatarsal 1	Head of metatarsal 2	Head of metatarsal 3	Head of metatarsal 4	Head of metatarsal 5
Fluid collection:(y/n)					
Size: (HxWxD, mm)					
Shape: (linear/ reticular/ circular)					
Enhancement: (0-2)					
MR characteristics (T1): (Hypo, Iso, Hyper)					
MR characteristics (T2): (Hypo, Iso, Hyper)					
Soft tissue lesion: (y/n)					
Size: (H x W x D, mm)					
Shape: (linear/ reticular/ circular)					
Enhancement: (0-2)					
MR characteristics (T1): (Hypo,Iso,Hyper)					
MR characteristics (T2): (Hypo,Iso,Hyper)					

A20: Association analysis: the clinical importance of MRI-detectable FFB

Table A20a: Association between systemic disease activity and FFB-subtypes
Where DAS = Disease Activity Score; CRP= C-reactive protein, ESR= Erythrocyte sedimentation rate; FFB= forefoot bursae; IM= intermetatarsal; FL= fluid lesion; EN= enhancement; ST= soft tissue lesion.

	SYSTEMIC DISEASE ACTIVITY r (p-value)				
	DAS 28-CRP	DAS 28-ESR	CRP	ESR	Disease duration
FFB count	-0.10, (0.537)	-0.05, (0.758)	-0.01, (0.949)	-0.00, (0.992)	0.15, (0.339)
IM	-0.03, (0.831)	0.05, (0.754)	0.12, (0.459)	-0.00, (0.993)	0.15, (0.337)
IM_FL	0.01, (0.958)	0.09, (0.583)	0.12, (0.460)	-0.02, (0.901)	0.04, (0.828)
IM_FL_EN	-0.15, (0.338)	-0.12, (0.463)	-0.20, (0.221)	-0.09, (0.557)	-0.22, (0.158)
IM_ST	-0.07, (0.661)	-0.04, (0.797)	0.06, (0.701)	0.00, (0.996)	0.22, (0.166)
IM_ST_EN	-0.23, (0.154)	-0.26, (0.100)	-0.22, (0.163)	-0.08, (0.636)	0.02 (0.913)
IM_EN	0.06, (0.723)	-0.01, (0.966)	0.08, (0.611)	0.12, (0.474)	0.27, (0.079)
PL	-0.13, (0.420)	-0.16, (0.330)	-0.30, (0.055)	-0.01, (0.971)	0.01, (0.934)
PL_FL	0.20, (0.206)	0.08, (0.611)	0.33, (0.035*)	0.25, (0.121)	0.02, (0.885)
PL_FL_EN	-0.01, (0.942)	-0.07, (0.688)	0.01, (0.960)	0.10, (0.526)	-0.07, (0.683)
PL_ST	-0.15, (0.350)	-0.17, (0.285)	-0.34, (0.029*)	-0.03, (0.877)	0.00, (0.984)
PL_ST_EN	-0.15, (0.343)	0.02, (0.923)	-0.03, (0.863)	0.27, (0.083)	0.38, (0.015*)
PL_EN	-0.18, (0.272)	-0.24, (0.139)	-0.24, (0.124)	-0.04, (0.803)	0.23, (0.144)
FL	0.03, (0.847)	0.10, (0.552)	0.08, (0.636)	0.01, (0.932)	0.037, (0.818)
FL_EN	-0.02, (0.894)	0.01, (0.966)	0.09, (0.592)	0.10, (0.531)	0.22, (0.153)
ST	-0.16, (0.307)	-0.15, (0.351)	-0.38, (0.015*)	-0.03, (0.879)	0.23, (0.137)
ST_EN	-0.11, (0.496)	-0.16, (0.328)	-0.21, (0.186)	-0.03, (0.849)	0.13, (0.404)

Table A20b: Association between localised disease activity and FFB-subtypes

	LOCALISED DISEASE ACTIVITY (r (p-value)		
	Synovitis	Bone marrow oedema	Erosion
FFB count	0.23, (0.142)	0.01, (0.951)	0.10, (0.542)
IM	0.22, (0.166)	0.11, (0.501)	0.18, (0.254)
IM_FL	0.12, (0.450)	0.02, (0.908)	0.09, (0.582)
IM_FL_EN	0.30, (0.053)	0.17, (0.271)	0.02, (0.905)
IM_ST	0.37, (0.017*)	0.20, (0.216)	0.20, (0.208)
IM_ST_EN	0.21, (0.188)	0.15, (0.351)	0.14, (0.387)
IM_EN	0.18, (0.251)	0.13, (0.424)	0.12, (0.433)
PL	-0.15, (0.355)	0.01, (0.932)	-0.12, (0.454)
PL_FL	0.20, (0.216)	0.11, (0.492)	0.23, (0.151)
PL_FL_EN	0.06, (0.694)	0.28, (0.077)	0.08, (0.612)
PL_ST	-0.18, (0.259)	0.00, (0.998)	-0.15, (0.349)
PL_ST_EN	0.13, (0.421)	0.10, (0.535)	0.23, (0.145)
PL_EN	-0.12, (0.439)	-0.02, (0.878)	-0.12, (0.443)
FL	0.04, (0.786)	0.13, (0.422)	0.12, (0.469)
FL_EN	0.06, (0.722)	0.02, (0.903)	0.05, (0.750)
ST	-0.08, (0.633)	0.12, (0.452)	-0.05, (0.740)
ST_EN	-0.02, (0.919)	0.22, (0.158)	-0.02, (0.889)

Table A20c: Association between biomechanical impairment and FFB-subtypes

	BIOMECHANICAL IMPAIRMENT r (p-value)						
	FPI	LDD	HAV	Ankle jROM	ST jROM	MF jROM	MTPl jROM
FFB count	-0.11, (0.477)	0.12, (0.441)	0.13, (0.424)	-0.11, (0.477)	-0.12, (0.446)	0.15, (0.366)	0.01, (0.941)
IM	-0.15, (0.363)	0.07, (0.683)	0.06, (0.692)	-0.13, (0.410)	-0.14, (0.381)	0.12, (0.466)	-0.10, (0.518)
IM_FL	0.03, (0.858)	0.03, (0.872)	0.17, (0.288)	0.04, (0.818)	-0.02, (0.917)	0.16, (0.313)	0.03, (0.855)
IM_FL_EN	-0.07, (0.664)	0.01, (0.963)	0.12, (0.443)	-0.28, (0.081)	-0.28, (0.079)	-0.13, (0.411)	-0.12, (0.451)
IM_ST	-0.36, (0.019*)	0.10, (0.550)	-0.16, (0.317)	-0.35, (0.025*)	-0.27, (0.085)	-0.03, (0.848)	-0.28, (0.082)
IM_ST_EN	-0.08, (0.617)	-0.04, (0.783)	0.05, (0.762)	-0.05, (0.738)	0.03, (0.851)	-0.07, (0.646)	-0.20, (0.206)
IM_EN	-0.25, (0.116)	0.13, (0.432)	-0.11, (0.480)	-0.17, (0.303)	-0.11, (0.498)	0.10, (0.548)	-0.16, (0.306)
PL	-0.02, (0.895)	0.14, (0.383)	0.15, (0.347)	-0.04, (0.809)	-0.04, (0.790)	0.11, (0.480)	0.15, (0.340)
PL_FL	-0.09, (0.560)	-0.01, (0.951)	0.27, (0.091)	0.03, (0.837)	0.06, (0.703)	0.25, (0.110)	0.23, (0.146)
PL_FL_EN	-0.03, (0.876)	-0.01, (0.962)	0.06, (0.722)	-0.22, (0.170)	-0.22, (0.170)	-0.02, (0.918)	-0.05, (0.775)
PL_ST	-0.01, (0.951)	0.15, (0.365)	0.12, (0.452)	-0.04, (0.783)	-0.05, (0.746)	0.08, (0.600)	0.13, (0.426)
PL_ST_EN	0.12, (0.442)	0.15, (0.337)	0.30, (0.060)	0.13, (0.403)	0.17, (0.295)	0.31, (0.052)	0.20, (0.221)
PL_EN	-0.12, (0.447)	-0.03, (0.843)	0.01, (0.941)	-0.22, (0.159)	-0.20, (0.221)	-0.08, (0.612)	0.02, (0.890)
FL	0.02, (0.916)	0.02, (0.881)	0.20, (0.216)	0.04, (0.804)	-0.01, (0.955)	0.19, (0.241)	0.06, (0.728)
FL_EN	-0.18, (0.272)	0.04, (0.785)	-0.06, (0.711)	-0.09, (0.570)	-0.06, (0.734)	0.09, (0.574)	-0.12, (0.444)
ST	-0.18, (0.249)	0.13, (0.434)	-0.10, (0.536)	-0.27, (0.084)	-0.17, (0.277)	0.05, (0.745)	-0.03, (0.847)
ST_EN	-0.25, (0.116)	0.16, (0.310)	0.02, (0.907)	-0.20, (0.200)	-0.21, (0.181)	-0.00, (0.996)	-0.10, (0.542)

Table A20d: Association between patient-reported foot-related disability and FFB-subtypes

	DISABILITY r (p-value)	
	FIS_{IF}	FIS_{AP}
FFB count	-0.06, (0.729)	-0.05, (0.764)
IM	-0.04, (0.806)	-0.09, (0.568)
IM_FL	-0.01, (0.937)	-0.01, (0.969)
IM_FL_EN	0.02, (0.912)	-0.05, (0.760)
IM_ST	-0.06, (0.698)	-0.18, (0.246)
IM_ST_EN	-0.11, (0.504)	-0.20, (0.209)
IM_EN	-0.05, (0.742)	-0.04, (0.787)
PL	-0.05, (0.767)	0.02, (0.880)
PL_FL	0.17, (0.270)	0.25, (0.113)
PL_FL_EN	0.01, (0.936)	0.03, (0.832)
PL_ST	-0.07, (0.667)	-0.00, (0.980)
PL_ST_EN	-0.08, (0.630)	0.18, (0.264)
PL_EN	-0.27, (0.089)	-0.06, (0.716)
FL	0.01, (0.958)	0.02, (0.883)
FL_EN	-0.10, (0.533)	-0.03, (0.875)
ST	-0.09, (0.588)	-0.09, (0.580)
ST_EN	-0.12, (0.469)	-0.07, (0.662)

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