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Acupuncture for Anxiety in Respiratory Disorders

By
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2017

Acknowledgements

I would like to thank my supervisors Professor Anne Bruton and Dr Peter White for their continued encouragement and guidance during my PhD studies. I would also like to thank the team at the Wellcome Trust Research team and the Pulmonary Rehabilitation team at University Hospital NHS Foundation Trust for their help and support with recruitment of participants and taking outcome measures.

I would also like to thank my friends and family that have spurred me on through my PhD journey.

UNIVERSITYOF SOUTHAMPTON

ABSTRACT

FACULTY OF HEALTH SCIENCES

Physiotherapy

Doctor of Philosophy

ACUPUNCTURE FOR RESPIRATORY DISORDERS

By Denise Gibson

Anxiety is a key component of respiratory disorders, which can exacerbate symptoms as well as impact upon treatment outcomes. This PhD offers an original contribution to knowledge by demonstrating the clinical effects of acupuncture on anxiety related to two chronic respiratory disorders, (hyperventilation syndrome (HVS) and chronic obstructive pulmonary disease (COPD)). This thesis contains findings from two novel trials that have examined the use of body acupuncture and ear acupuncture for the treatment of anxiety associated with respiratory disorders. These studies are linked through one research question: does acupuncture, offered as an adjunctive treatment to physiotherapy, reduce anxiety in patients with common chronic respiratory disorders? Previous research examining acupuncture for the treatment of anxiety has focused on the treatment of generalised anxiety disorder, or anxiety related to exposure to anxiety provoking situations. The research included within this thesis has examined the use of acupuncture in a population of individuals with respiratory disorders to assess the feasibility of using acupuncture for anxiety in this population, and to enhance our understanding of its efficacy and clinical benefits.

No previous respiratory acupuncture studies have been identified that were designed with anxiety as a primary outcome. Study 1 is a three-arm single-blind randomised controlled trial (RCT) of acupuncture for HVS. In this trial acupuncture was used as an adjunct to standard physiotherapy (in the form of breathing retraining (BR)). Study 2 was a trial to examine the feasibility of using ear acupuncture as an adjunct to physiotherapy (in the form of pulmonary rehabilitation for COPD). Hypotheses were tested

using anxiety data from the Hospital Anxiety and Depression Scale. The findings from both studies suggest that it is feasible to use acupuncture as an adjunct to physiotherapy in these patient groups. Within each trial, there were no statistically significant differences in anxiety between groups at outcome. However, following the interventions, there were clinically relevant reductions in anxiety in the acupuncture groups within both studies. In study 1 the reduction in mean anxiety scores in the acupuncture group took them to below the cut-off for clinically relevant anxiety. There were also statistically significant between-group differences in breathlessness associated with HVS.

These findings indicate that both body acupuncture and ear acupuncture are feasible in patients with chronic respiratory disorders, when delivered as an adjunct to physiotherapy. They also suggest that acupuncture may have clinically significant benefits for anxiety associated with respiratory disorders, as well as for symptoms such as breathlessness. This knowledge will provide practitioners with some supportive evidence for the use of acupuncture within their clinical practice.

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Academic Thesis: Declaration of Authorship

I, **Denise Gibson** declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

Thesis Title: **ACUPUNCTURE FOR RESPIRATORY DISORDERS**

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. 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;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. 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;

7. Parts of this work have been published as below:

Gibson DH, Bruton A, White P (2010)" Acupuncture for Hyperventilation syndrome" Poster Presentation, Health, Medicine & Life Sciences Annual PGR conference, UoS Southampton England 9th-10th June.

Gibson DH, Bruton A, White P, Arnold E (2010) "Acupuncture for anxiety related to hyperventilation syndrome" Poster presentation and e- communication session European respiratory society conference, Barcelona, Spain 19th-21st September

Gibson DH, Bruton A, White P (2010) "Acupuncture for Respiratory Disorder: What's the point?" *Expert Rev. Resp. Med*. 4(1) 29-37 (2010).

Gibson DH, Bruton A, White P (2017) "Ear Acupuncture for anxiety in patients with chronic obstructive pulmonary disease" Poster presentation, Association of chartered physiotherapists in respiratory care annual conference, York, England 28th-29th April.

Signed: ……

Abbreviations

AACP- Acupuncture Association of Chartered Physiotherapy

ANOVA- Analysis of Variance

BD- Behavioural Desensitisation

BHT- Breath Hold Time

BN- Borkovec and Nau credibility test

BR- Breathing Retraining

CBT- Cognitive Behavioural Therapy

CO_2- Carbon dioxide

COPD- Chronic Obstructive Pulmonary Disease

ECG-Electrocardiogram

$ETCO_2$ End-Tidal Carbon Dioxide

HAD- Hospital Anxiety and Depression Scale

HAD A- Hospital Anxiety and Depression scale- anxiety rating

HAD D- Hospital Anxiety and Depression scale- depression rating

HVPT- Hyperventilation Provocation Test

Li 4 Large Intestine 4 (acupuncture point)

Lv 3- Liver 3 (acupuncture point)

MARM- Manual Assessment of Respiratory Motion

MRC- Medical Research Council

MYMOP2- Measure Yourself Medical Outcome Profile

NS- Non significant

NRS- Numeric Rating Scale

NQ- Nijmegen Questionnaire

OA- Osteoarthritis

PaO_2- partial pressure of arterial oxygen

$PaCO_2$- partial pressure of arterial carbon dioxide

PCS- Physical Component Summary of Short-Form 36

PD- Panic Disorder

P6- Pericardium 6 (acupuncture point)

RCT- Randomised Controlled Trial

SD- Standard Deviation

SEBQ- Self-evaluation of Breathing Questionnaire

SF-36- Short-Form 36

SG cells- Substantia Gelatinosa cells

SNSQ- Southampton Needle Sensation Questionnaire

SOBQ- Shortness of Breath Questionnaire

STAI- State-Trait Anxiety Inventory

St36- Stomach 36 (acupuncture point)

TCM- Traditional Chinese Medicine

TNS- Transcutaneous electrical stimulation

TENS- Transelectrical nerve stimulation

UHSFT- University Hospitals Southampton NHS Foundation Trust

US- United States of America

VAS- Visual Analogue Scale

VAS-D- Visual Analogue Scale for Dyspnoea

WTCRF- Wellcome Trust Clinical Research Facility

5-HT- 5 Hydroxytryptamine

Chapter 1.

1.1Introduction

A disorder, in medical terms, is an illness that disrupts normal physical or mental functions (OED disorder 2015). There are a variety of conditions that form the known disorders of the respiratory system. They include respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) asthma and cystic fibrosis, as well as conditions where there is no lung pathology but there is disruption of the breathing mechanics or regulation, such as hyperventilation syndrome (HVS) or chest wall disease. The rising prevalence of respiratory disorders is placing increasing pressure upon healthcare resources worldwide, for example the World Health Organisation (WHO) estimates that 65 million people have moderate to severe COPD worldwide. It is also predicted that COPD will become the world's third leading cause of death by 2030 (WHO 2015).

Southampton, England has a particularly high prevalence of COPD compared to the rest of the UK. In March 2010 there were 4,573 people on COPD registers in Southampton (Public Health Southampton 2010). This results in a prevalence rate of 1.7% which is significantly higher than the rate for England as a whole. However, there is some debate around this figure as the British Lung Foundation's (BLF) report "Invisible Lives COPD-Finding the missing millions" (BLF 2009) suggests that there are an estimated 3.7million people with COPD in the UK, but only 900,000 of those have been diagnosed with the disease. Using these figures, the prevalence of COPD in Southampton is estimated to be more like 3.5% (Department of Health 2010).

Unsurprisingly, in 2006 COPD and HVS were two of the most common respiratory disorders presenting to the regional respiratory clinic at University Hospital Southampton NHS Foundation trust (UHSFT). This

author became interested in exploring the use of complementary therapies, as an adjunct to physiotherapy, as many of those affected with respiratory disorders, continued to have significant disability, despite maximum medical therapy.

This author trained as an acupuncturist in 2001 and began using acupuncture for patients with both HVS and COPD with some success. This led to some curiosity around whether acupuncture was efficacious for these disorders and if so, was this because of the commonality both conditions share in their psychological presentation (i.e. high anxiety levels) as well as physical symptoms (e.g. breathlessness)? Anxiety is known to play a key role in both COPD and HVS and evidence suggests it can have a detrimental effect on quality of life, physical function and exacerbations of both conditions (Kim et al 2000, Aydin 2001 & Laurin et al 2009).

Acupuncture is the stimulation of specific points around the body usually but not exclusively by the insertion of fine needles and is a complementary therapy that has been used to treat anxiety (Eich et al 2001, Wang et al (a) 2001, Agarwal et al 2005, Black et al 2011). Its value in the treatment of anxiety for people with respiratory disorders is not yet known,

Hence, this author carried out a pilot study (Gibson et al 2007), initially examining the effect of acupuncture on HVS, compared to conventional physiotherapy (breathing retraining), where the primary outcome was anxiety. The results of this preliminary study are discussed in section1.4 of this chapter and described in more detail in Chapter 5. This small study informed the design of the randomised controlled trial (RCT) presented in this thesis (Study 1). Due to the commonality of some of the associated symptoms between HVS and COPD, the author was keen to investigate whether it was feasible to use acupuncture as a treatment modality for

patients with COPD, which led to the second study presented within this thesis (Study 2).

This chapter aims to briefly describe both HVS and COPD and their symptoms. Its purpose is to also introduce acupuncture as a treatment modality and provide a flavour of what is discussed in the future chapters. It also describes the important preliminary study that has led to this PhD.

1.2 Hyperventilation Syndrome

Hyperventilation is the action of breathing in excess of metabolic requirements and is associated with a reduction of arterial carbon dioxide ($PaCO_2$), leading to respiratory alkalosis (Pfortmueller et al 2015). Changes in $PaCO_2$ and pH induce secondary physiological effects, and if this occurs for some time, unpleasant bodily sensations may occur. Continual and subtle hyperventilation can lead to a chronic condition which has been termed hyperventilation syndrome (HVS), breathing pattern disorder, or medically unexplained dyspnoea (see Chapter 3 section 3.4. for definition of dyspnoea). These terms are often used interchangeably, but describe different aspects of related problems. Patients with HVS are hypothesised to have an increase in sensitivity to levels of $PaCO_2$ (Heistad et al 1972) so that only small changes in $PaCO_2$ caused by trauma, stress or exercise, can produce symptoms (Garssen et al 1986).

The symptoms of HVS such as chest pain, headaches, syncope, breathlessness, blurred vision and paraesthesia often mimic serious disease (Lum et al 1983). Although there is debate about the terminology, the incidence of HVS is believed to be rising as clinicians become more aware of its existence. The prevalence of HVS within the general population is unclear. This author suggests this may be due to the many problems with the terminology used for the condition as well as the assessment and diagnosis of HVS. These issues will be discussed later within this chapter. It has been estimated that up to 10% of the normal population have a form of HVS (Newton 2004). Some investigators have

examined the prevalence of dysfunctional breathing (which is another term used for HVS) in asthma and have found that around a third of men and a fifth of women with asthma also have dysfunctional breathing (Thomas et al 2001). However, these figures must be considered with caution due to the method of screening that was used to detect dysfunctional breathing.

With no clear diagnostic criteria, the cost of HVS to the NHS is unknown, but as symptoms may mimic heart or neurological problems, patients may be subjected to a variety of costly and potentially unnecessary investigations (Chaitow 2002). There is no "gold standard" tool for the diagnosis of HVS and clinicians often resort to excluding all other causes of the symptoms before a diagnosis of HVS is made (Pfortmueller et al 2015). In clinical practice, therefore, it is evident that most HVS patients have been referred to various specialist clinicians before a diagnosis of HVS is made. The Nijmegen questionnaire (NQ) is commonly used as an aid to diagnosis in clinical practice (Van Dixhoorn et al 1985). This is a validated screening tool which has been reported to have 95% effectiveness at distinguishing "hyperventilators" from "non-hyperventilators" (van Dixhoorn et al 1985).

1.3 Chronic obstructive pulmonary disease

COPD is a severe and progressive respiratory disorder that impacts upon an individual's general condition, physical function and quality of life (Kim et al 2000). COPD is characterized by airflow obstruction, which is usually progressive and irreversible. Around 80-90% of COPD patients have smoking as the causative factor (Mikkelsen et al 2004). The main symptoms of COPD are cough, sputum expectoration and progressive breathlessness. There is an estimated 3 million people in the UK who are affected by COPD and around 2 million yet to be diagnosed, as airway obstruction can often be advanced before the diagnosis of COPD is made (NICE Guidelines 2010). COPD is the fifth leading cause of death in the

UK and is characterized by frequent exacerbations of symptoms, which require healthcare interventions and/ or hospital admissions (National COPD Audit 2008). COPD is a disabling condition, which impacts upon quality of life, in that individuals suffering with COPD find it difficult to get out and about or carry out activities that they had previously enjoyed. These issues can lead to anxiety and/ or depression, which can be masked by the symptoms of COPD, making detection difficult in this group of patients.

The association of COPD with anxiety and depression disorders is now well recognised and documented (Mikkelsen et al 2004, von Leupoldt et al 2011). There is a suggested prevalence of anxiety symptoms of between 2% and 50% amongst patients with COPD (Karajgi et al 1990, Dowson et al 2001).

1.4 Anxiety

Anxiety is a major component of both COPD and HVS. The relationship with HVS is complex. At present it remains unclear whether anxiety causes HVS or vice versa (Gardner 1996), or whether the two are associated with no causal relationship. Current treatment for HVS is usually in the form of physiotherapy and /or psychological interventions (Jones et al 2013). It has been claimed that physiotherapy (in the form of BR and relaxation techniques) is now widely accepted as an effective treatment for HVS (Chaitow 2002), however, there is little research evidence to support this claim. There are few studies supporting the use of BR for hyperventilation symptoms and the majority of these studies do not only examine physiotherapy techniques but also techniques used by other practitioners, such as Buteyko (Grossman et al 1985, Han et al 1996, Bowler et al 1998). Although both approaches have been demonstrated to have some efficacy in the treatment of this condition, they may both involve a protracted treatment period with considerable clinician contact

time. Any therapy that augments these approaches could decrease the clinical contact needed and hence potentially reduce the overall cost to health services (Garssen 1986).

Acupuncture is used by many clinical physiotherapists, generally for pain relief. It has been reported to be more efficacious than a placebo control in the treatment of painful conditions (Manheimer et al 2005). A more recent systematic review and individual patient data meta-analysis of acupuncture for pain, was carried out by Vickers et al (2012). Vickers et al aimed to evaluate the effect size of acupuncture for four types of chronic pain; back and neck pain, osteoarthritis (OA), headache and shoulder pain. They combined individual patient data and analysed a total of 17,922 sets of data. Vickers et al (2012) found that there were statistically significant differences between acupuncture and "sham or placebo" acupuncture for chronic pain, although these differences were small. They also found that the "sham" acupuncture was superior to standard treatment which suggests that the therapeutic effects of acupuncture may not be entirely due to the needling of specific acupuncture points. The evidence to support the use of acupuncture for non-painful conditions is less convincing and studies have common methodological flaws. Some of these flaws are evident in the following studies: Wang & Kain 2001a, Wang et al 2001b, Kober 2003, Zhang et al 2003, Wang et al 2004.
The issue of finding an appropriate control for acupuncture trials is controversial. Many studies use a "sham" or placebo acupuncture technique where they insert needles into areas that are not acupuncture points, or place the needles superficially so that deqi or needling sensation is not initiated (deqi is a feeling of heaviness, soreness or numbness that is experienced at the point of needling (Vickers et al 1999)). There is however, debate surrounding the importance of deqi in acupuncture effectiveness (White et al 2010).

The main issue with these placebo techniques is that, because there is still skin stimulation, there may well be a resultant physiological effect (Le Bars 1979). An ideal placebo control should not be distinguishable from "real" acupuncture, and there should not be any resultant physiological or therapeutic effects. It is clear that an ideal acupuncture placebo should compare with the participants expected experience of needling and it should not elicit deqi or needling sensation. A major advance has been the development of the placebo needle (Streitberger & Kleinhenz 1998). This is a blunt needle which is free to move inside the handle. Therefore, when the needle is pressed, it appears to penetrate; but, in fact the handle of the needle telescopes over the shaft (similar to the mechanism within a prop knife/sword used by actors).

Although acupuncture is reported to have been used with some success in patients with respiratory conditions (Jobst 1995), there is little evidence to support its use in the treatment of HVS or COPD. A small study of HVS by Levashov et al (1992) did find reductions in subjective symptoms (such as chest pains and paraesthesia) and in minute volume, but the authors do not discuss possible underlying mechanisms.The author of this thesis suggests that acupuncture may help by reducing the anxiety component of the condition. is well documented that acupuncture influences centres within the brain that may affect anxiety such as the limbic system (Hui et al 2000, Hui et al 2005). There are studies that support the use of acupuncture for anxiety and depression states, but they often have methodological issues such as small sample sizes, and the use of different needling techniques/concepts i.e. "western" *versus* Traditional Chinese Medicine (TCM). Tao 1993, Polyakov 1987 and Zhang 2003 are examples of studies with some of these methodological issues. The basis for the treatment of respiratory conditions such as asthma with acupuncture is well founded in TCM, but there are no clinical trials that confirm that one particular approach is more effective than any other (McCarney et al. 2004).

A small trial, which formed the basis of this author's MSc dissertation, involved an uncontrolled study that used a "western" approach to acupuncture on patients with HVS and resulted in reduced anxiety scores on the Hospital Anxiety and Depression (HAD) scale (Gibson & Bruton 2004). This preliminary study was a single-blind crossover trial where 10 patients diagnosed with HVS received both physiotherapy (in the form of BR) and acupuncture. The participants were randomised into two groups and received both treatments over a 9-week period, with a one-week wash out period between interventions. The results suggest that both standard physiotherapy and acupuncture produce a beneficial effect for people with HVS. However, the effect was greater and longer lasting following acupuncture, than that following breathing control. Although the results from this preliminary study are encouraging, the choice of a crossover design may have been inappropriate. On formal statistical analysis, there was no carryover effect detected from either the acupuncture or the BR. However, when the individual anxiety scores were displayed in graphical form, it suggested that there may have been some carry-over effect, which went undetected due to the small sample size. The data from this preliminary study have been used as the basis for the power calculations to determine sample size for the randomised controlled trial (RCT) described in this thesis.

1.5 Chapter 1 Summary

COPD and HVS are common chronic respiratory conditions with a high prevalence in Southampton UK. Patients with HVS or COPD often require repeated clinical visits which can be protracted. If anxiety coexists with chronic respiratory conditions, it can exacerbate symptoms and/or hinder the outcomes of clinical interventions.

Any treatment that can address the anxiety component of these respiratory conditions may help to improve treatment outcomes and

reduce healthcare costs. Acupuncture has been used for anxiety disorders or situational anxiety with some success and therefore it is hypothesised that it may be of use, in the treatment of anxiety related to respiratory disorder. This author was keen to explore the feasibility and efficacy of acupuncture, in terms of reducing anxiety, in both HVS and COPD, when it's used as an adjunctive modality to standard physiotherapy treatment.

This thesis presents a review of the literature relevant to the research questions (Chapter 2: HVS and COPD; Chapter 3: Anxiety and Breathing; Chapter 4: Non-pharmacological treatments; Chapter 5: Outcome Measures). The first study is described within Chapter 6, and the second study is in Chapter 7. There is a general Discussion of both studies within Chapter 8.

The focus of the next chapter is the respiratory disorders that have been researched during this PhD. It contains a description of the complex nature of these chronic conditions and the dilemmas that clinicians are faced with, when treating individuals with chronic respiratory symptoms.

1.6 Research Questions

The main research question that this PhD aims to answer is:

Does acupuncture offered as an adjunctive treatment to physiotherapy for two common respiratory disorders, enhance treatment outcomes in terms of reducing anxiety?

Secondary research questions are as follows:

1. Does acupuncture, offered as an adjunctive treatment to a physiotherapy BR programme for HVS, enhance patient outcomes in terms of reducing depression and symptom scores?

2. Does acupuncture in the treatment of HVS have any additional effect on increasing End-Tidal Carbon dioxide ($ETCO_2$)(partial pressure of carbon dioxide in exhaled gas) measurements when compared to physiotherapy BR alone?

3.Does acupuncture as an addition to a physiotherapy BR programme for HVS have any specific efficacy over placebo acupuncture treatment?

4. Does acupuncture as an adjunct to a physiotherapy BR programme provide greater improvement in health status when compared to physiotherapy BR alone?

5. Is it feasible to use ear acupuncture as an adjunct to pulmonary rehabilitation, in the treatment of anxiety related to COPD?

Chapter 2.
Respiratory disorders.
Hyperventilation Syndrome and COPD

2.1 Introduction

In order to appreciate the respiratory dysfunction, it is important to have an understanding of respiratory physiology in respiration and breathing. The aim of respiration is to achieve uptake of oxygen and eliminate carbon dioxide (CO_2) (gas exchange). Secondary aims are to facilitate acid-base buffering, hormone regulation and defence against infection.

In order for these aims to be achieved the respiratory system relies upon three functional components (i) mechanical structures (this includes the chest wall, respiratory muscles, and pulmonary circulation), (ii) Thin membrane for gas exchange and (iii) a regulatory or control system (respiratory centres in the brain stem, chemical and mechanical sensors throughout the circulatory and respiratory system). These three components are closely integrated and dysfunction of one can lead to respiratory distress or even failure. The respiratory centres receive and process information from a variety of sources; chemical (central and peripheral chemoreceptors), mechanoreceptors and higher centres (behavioural input) (Altose et al 1999). This information is then transmitted to the upper airways and respiratory muscles, which then contract and generate a negative pressure. This negative pressure is created to overcome chest wall and lung resistance and results in a tidal volume. The tidal volume and respiratory timing determine total ventilation and through mechanoreceptors in the lungs and chest wall modify the activity of the respiratory centres. In the same way, ventilation and gas exchange properties of the lungs, determine the arterial blood gas levels, which through chemoreceptors influence the respiratory centres. The respiratory system is also able to adjust to changing environments and metabolic

conditions to maintain ventilation and preserve oxygen and CO_2 homeostasis. The control of breathing will be discussed later in this chapter.

In both COPD and HVS there is a disruption in the normal physiological processes of respiration, which results in dysfunction. Although the pathophysiological changes with each of these conditions are not identical, there are thought to be some common changes, which will be discussed within this chapter. A literature review of relevant topics associated with two common chronic respiratory disorders, hyperventilation syndrome (HVS) and COPD has been discussed. The varied terminology used to describe HVS have been presented in this chapter, as have the issues around diagnosis for both HVS and COPD. The search strategies for this literature review are documented in Appendix I.

2.2 Hyperventilation

In 1908 a paper described a variety of symptoms associated with over breathing or hyperventilation (Haldane & Poultons 1908).
Hyperventilation occurs where minute ventilation (defined as, the volume of gas that is inhaled or exhaled from the lungs in one minute) exceeds metabolic demands. This can occur acutely and overtly with rapid shallow breathing or can be a consequence of more subtle changes in breathing pattern such as increased yawning or sighing. Acute hyperventilation is considered to be a normal response to stress. It becomes abnormal if the hyperventilation response is excessive or remains present when the stressor is removed (Wilhelm et al 2001).

2.2.2.1 Hyperventilation Syndrome

Patients who have HVS present with a history of chronic symptoms and report acute exacerbations that occur at intermittent periods. It is hypothesised that patients who have chronic hyperventilation have accommodated to lower levels of CO_2. The chemoreceptors in the

medulla, aortic and carotid bodies, regulate breathing by monitoring CO_2 levels. It is possible that these receptors are reset to maintain these lower levels and so hyperventilation becomes a chronic problem (Lum 1983). Small changes in breathing pattern could then further reduce $PaCO_2$ and lead to symptoms (Garssen 1986, Nixon 1993). As far back as the 1930's researchers realised the potential for improvement in hyperventilation symptoms by an increase in the partial pressure of ($PaCO_2$) (Soley & Shock 1938). Subtle and sustained changes in breathing pattern lead to the chronic condition often termed hyperventilation syndrome (HVS) (Kerr et al).

2.2.2 Control of breathing and physiological consequences of hyperventilation

In healthy subjects the main ventilatory drive (80% of the chemical drive) is determined by the level of $PaCO_2$ at the site of the central chemoreceptors which are positioned on the ventral surface of the Medulla Oblongata within the brain stem. A further 20% of the chemical drive to breathe is the level of $PaCO_2$ at the peripheral chemoreceptors within the carotid and aortic bodies. Low arterial oxygen levels (hypoxia) is also a ventilator stimulus via the peripheral chemoreceptors but is barely significant in healthy individuals. This mechanism comes into play only when arterial oxygen levels (PaO_2) are significantly low (5-6kPa) and is only detected by peripheral chemoreceptors. The central and peripheral chemoreceptors provide feedback to the respiratory centers located within the brain stem which also mediates cardiac and vasomotor activity as well as muscular and sympathetic tone, stress and fight or flight activity. The respiratory centres also receive inputs from other neuronal structures such as the cortex, hypothalamus (responsible for temperature control, locomotor and emotional activity) and limbic system (Phillipson et al 1978).

The autonomic control of breathing is determined by impulses from the spinal motor neurones descending (bulbospinal pathway) from the brain

stem (respiratory centres) to the respiratory muscles. Voluntary respiratory manoeuvres are determined by impulses from the motor cortex through the pyramidal tract to the spinal motor neurones supplying the muscles of respiration. This pathway can override the bulbospinal pathway to enable voluntary breathing manoeuvres such as breath holding or breathing exercises. The primary function of breathing is to meet metabolic requirements for the uptake of oxygen and the elimination of CO_2. It also provides behavioural functions such as generating speech. When the behavioural functions of respiration are active normal ventilator responses are often blunted as autonomic pathways are bypassed (Phillipson et al 1978) It is hypothesised that this behavioural aspect to respiration may be a key influence on the dysregulation of breathing experienced within HVS (Folgering 1999).

The action of the respiratory muscles facilitates inspiration and leads to gaseous exchange within the pulmonary parenchyma. This determines the levels of $PaCO_2$ and PaO_2. These levels are then detected by the chemoreceptors and feedback to the respiratory centre to maintain constant levels. This normal control of breathing can be disrupted by the influence of the cortical or hypothalamic systems.

The higher respiratory centre has another characteristic which may explain some physiological responses to hyperventilation. When there is increased activity generated within the respiratory centres, it cannot suddenly reduce activity to a resting level, it continues to fire impulses but decays with time (Fly-wheel phenomena, Eldridge et al 1974). Studies have shown that once stimulated the respiratory centres continue to fire impulses for longer at lower levels of $PaCO_2$. This may explain the delayed recovery period following voluntary hyperventilation or exercise, demonstrated by individuals with HVS (Beumer et al 1971, Warburton et al 2006).

During hyperventilation the lowering of $PaCO_2$ (hypocapnia) makes the blood pH more alkalotic and this causes a left shift in the oxygen-

haemoglobin dissociation curve. (Figure 1a.). This curve shows the relationship between partial pressure of oxygen and the percentage of haemoglobin saturation.

This left shift or Bohr Effect results in a higher affinity of haemoglobin (Hb) for oxygen. This high affinity inhibits adequate oxygen delivery to the tissues and results in several physiological sequelae. There is a constriction of cerebral arteries and oxygen delivery to certain regions of the brain is impaired (Kennealy et al 1980). The resulting cerebral hypoxia can cause some of the most disturbing symptoms such as dizziness, syncope and blurred vision (Lum 1983).

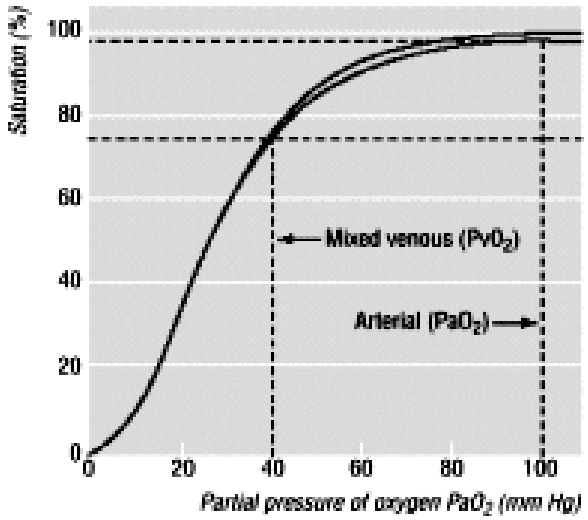

Figure. 1a. Oxygen-Haemoglobin dissociation
(Taken from www.studentbmj.com. Marshall et al (1994))

As a result of the reduced oxygen delivery there is an increase in coronary arterial tone which leads to a decrease in coronary blood flow, producing angina type chest pains, palpitations and arrythmias (Deguire 1992). The increased affinity of Hb for oxygen and alkalosis also leads to changes in serum calcium and a loss of intracellular magnesium levels (George et al 1964). The musculoskeletal consequences of these chemical changes are, predisposition to muscle fatigue, muscle dysfunction and the development of muscular trigger points (Simons et al 1999).

The subsequent lowered calcium ion levels within the plasma also precipitates a hyperexcitability of both motor and sensory neurones, resulting in “increased motor and sensory discharges, muscular tension, spasms, increasing spinal reflexes, heightened perception and other sensory disturbances” (Lum 1994).

The gastrointestinal tract is also affected in that there may be aerophagia and epigastric discomfort which is thought to be caused by the increase in mouth breathing and air gulping in the individual that chronically hyperventilates (Calloway 1985). In addition, there are changes evident within the respiratory tract when $PaCO_2$ is lowered. There is an increase in mast cell stimulation and histamine. These mediators cause local inflammation and oedema within the lungs and lead to an increase in bronchoconstriction (Al-Delaimy 2001, Chaitow 2002). Hence there are some schools of thought that hyperventilation plays a major role in the pathophysiology of asthma (Bowler et al 1998).
There is a school of thought that hyperventilation and the consequential alkalosis can also trigger anxiety and panic when it is interpreted as “representing a danger of suffocation” (Klein 1993).

2.2.3 Symptoms of Hyperventilation Syndrome

The symptoms associated with this condition (such as breathlessness at rest and on exertion, syncope, chest pain or palpitations) are often misattributed to more serious life-threatening conditions (Wilhelm et al 2001). An association between musculoskeletal dysfunction and this condition has also been described (Chaitow 2004). It is suggested that the physiological changes resulting from chronic hyperventilation may be sufficient to modify the normal motor control of skeletal muscle, resulting in musculoskeletal disorders (Table.1 (a) & (b) list of symptoms/conditions associated with HVS (created from information from Newton 2004).

Conditions associated with HVS
Asthma
Chronic Fatigue Syndrome
COPD
Generalised Anxiety
Panic Disorder (PD)
Post-Traumatic Stress Disorder

Table 1a. Common conditions that can be associated with HVS

System	Symptoms
Cardiovascular	Chest pain, palpitations, coronary spasm.
General	Fatigue, exhaustion, reduced exercise tolerance.
Gastric	Dry mouth, abdominal bloating, aerophagia.
General	Fatigue, exhaustion, reduced exercise tolerance.
Musculoskeletal	Muscle spasms, tetany (hands), tremors, muscle tension and muscle soreness
Neurological	Fainting, dizziness, feeling unsteady, loss of consciousness, detachment from reality, Paraesthesia.
Psychological	Anxiety, stress, tension.
Respiratory	Shortness of breath, chest pain, tight chest, excessive yawning.

Table 1b. Summary of the systems affected by HVS and potential symptoms experienced

2.2.4 Hyperventilation and psychological influences

Anxiety was highlighted in the first description of HVS and is thought to be a core component of the syndrome (Lum 1981). It is unclear whether anxiety causes HVS or vice versa. More recent literature highlights not only the association of anxiety with HVS but also the other psychological influences upon the respiratory system, such as emotions, association and conditioned responses. (Gilbert 2002, Jack et al 2004).The symptoms associated with HVS vary in intensity and frequency, in that some patients may be severely disabled and unable to carryout tasks of daily living, while others have more subtle symptoms with minimal impact upon their activities of daily living.

2.2.5 Hyperventilation Syndrome and other associated terms

The term HVS has been used within clinical practice for many years. However, there has been much debate internationally surrounding the definition and terminology used to describe this condition. A definition offered from a consensus conference in 1984 suggests that the somatic symptoms experienced with this condition are induced by the physiological act of hyperventilation. “Hyperventilation syndrome is a syndrome characterised by a variety of somatic symptoms induced by a physiologically inappropriate hyperventilation and usually produced in whole or in part by voluntary hyperventilation” (Howell 1990 page 287). Newton (2004) provided a definition of HVS as being “condition in which minute ventilation exceeds metabolic demands resulting in haemodynamic and chemical changes that produce characteristic symptoms”. In this description of HVS there is no mention of any psychological components to the condition and it relies simply on the theory that hypocapnia (low CO_2) is the causative mechanism for the symptoms experienced.

Alternative definitions have placed a greater emphasis on the dysregulated breathing patterns associated with HVS as opposed to the impact of hypocapnia (Folgering et al 1999). There is also a greater emphasis on HVS being known as a “psychosomatic” disorder, whereby a physical condition is worsened by psychological factors such as anxiety or stress (Levenson 2007). Various authors have used the term “idiopathic hyperventilation” and provide a description of individuals who exhibit symptoms due to profound hypocapnia with no other underlying pathologies, and not associated with fear (Jack et al 2004).

Historically, many authors supported the theory of hypocapnia as the main mechanism for HVS (Lum1983, Garssen1986, Nixon 1993). Conversely, some authors have noted that symptoms can occur without hypocapnia (Ley R 1994, Hornsveld et al 1990, and 1996). Individuals presenting with symptoms and diagnosed with HVS do not always exhibit low arterial CO_2) (Hornsveld et al 1990 and 1996, Garssen et al 1992, Bass 1997 Gardner 2004). Symptoms of HVS have been shown to be reproduced during a voluntary hyperventilation test while CO_2 has been kept stable by the titration of gases, suggesting that hypocapnia is not the only mechanism underlying this condition (Hornsveld et al 1996). This is supported by evidence from individuals that live at high altitudes (who hyperventilate to counteract the lowered barometric pressure), the majority of whom remain symptom free despite lowered arterial CO_2 (Lum 1983). It has been hypothesised that it is fluctuations in CO_2 levels that result in the symptoms of HVS, as opposed to continually subnormal levels (Lum 1983).

The recent debates about the mechanisms underlying HVS have resulted in alternative terminology, being used to describe it. The term medically unexplained dyspnoea (MUD) has been used to describe this type of condition in Eastern literature (Han 2004, Han et al 2008).The use of this term “medically unexplained” can in itself have a negative impact upon

individuals. Studies have reported that when given a diagnosis of medically unexplained symptoms, patients often feel like their symptoms are not taken seriously by medical teams or that their symptoms are misbelieved by clinicians (Edwards et al 2010). This can lead to further anxiety and stress and result in further hospital or GP visits, as the patients' symptoms have not been adequately explained by the healthcare teams (Reid et al 2002, Burton et al 2005). These repeated visits to healthcare practitioners can also have an impact on the clinician themselves as the may feel "frustrated" that they are unable to find a non-functional cause for the symptoms (Warner et al 2011). This could result in over investigation and patients being subjected to tests that are not necessary (Burton et al 2005).

Another reason why MUD may not be the best term to use for HVS is the "dyspnoea" part of MUD, may not apply to all patients with HVS. It is debatable whether HVS is always associated with overt dyspnoea (literally, difficulty with breathing, but used interchangeably with breathlessness) as patients will often present with other symptoms associated with HVS such as, tight feelings across the chest, chest pain or dizziness. It was suggested more than 20 years ago that only a 10% increase in ventilation could more than halve CO_2 levels, but without producing the array of symptoms associated with HVS (Gardner 1996). In a review paper from 1996, Gardner described a poor correlation between $PaCO_2$ levels and symptoms. He reported that respiratory patients could have low $PaCO_2$ levels without exhibiting any symptoms of HVS and vice versa. Han et al (1996) presented supportive data in a comparison study of symptomatic patients with HVS and "normals" where there were no differences in CO_2 levels. This further supports the theory that HVS is not primarily driven by hypocapnia. Experts within the field of respiratory psychophysiology are still unable to provide an adequate, agreed definition of HVS, due to the complex nature of the condition and the multiple components that it involves (Clifton-Smith et al 2011).

Some more recent terms used to describe this syndrome such as "breathing pattern disorder" (Chaitow 2002) or "dysfunctional breathing" (Thomas 2001) may be more appropriate in describing HVS. Neither of these other terms is well described, but Boulding et al (2016 page 287) have recently proposed that dysfunctional breathing is "a term describing a group of breathing disorders in patients where chronic changes in breathing pattern result in dyspnoea and often non-respiratory symptoms in the absence of, or in excess of, organic respiratory disease". They propose that HVS should be considered as just one type of breathing pattern disorder; an idea echoed by others such as Stanton et al (2008), and Courtney (2001). The lack of evidence to support altered CO_2 as a mechanism for HVS suggests other factors such as abnormal breathing patterns, play a key role in the persistence of this condition. Studies of dysfunctional breathing do not include serial/ continuous measures of CO_2 so it is possible that these studies may include participants who hyperventilate or have periods of hypocapnia, who would fit more in the HVS category (Thomas et al 2001, Stanton et al 2008, Thomas et al 2009).

In clinical practice respiratory physicians, neurologists, psychologists and physiotherapists use the terms HVS, breathing pattern disorders and dysfunctional breathing interchangeably. Therefore, for the purpose of this document, the term hyperventilation syndrome (HVS) will continue to be used to describe those individuals who have chronic changes in their breathing pattern, resulting in dyspnoea and other non–respiratory symptoms, either in the absence of an organic respiratory pathology or that are magnified compared to the expected level of symptom with an existing underlying organic respiratory condition.

2.3 Diagnosis of HVS

Acute hyperventilation is considered simple to diagnose as the clinician can observe overt hyperventilation (such as during panic attacks) and can be evidenced by the presence of a lowered arterial CO_2 or $ETCO_2$ (Klein 1993). However, the diagnosis of HVS is more difficult because of its close association with organic respiratory and cardiac diseases. There is, reported evidence that there is a strong link between asthma and HVS (Demeter 1986). Patients with asthma often present with similar symptoms to HVS and there is a physiological link between hyperventilation and bronchoconstriction (Al-Delaimy 2001). Prior to diagnosis patients with HVS have often had a protracted period of investigations and hospital visits to a variety of clinicians. Symptoms such as dyspnoea at rest and during low level exercise, chest tightness, and palpitations may be associated with other more serious respiratory or cardiac conditions which need to be excluded by pulmonary function tests, chest x-ray, cardiac echo and electrocardiogram (ECG).

Once other cardiorespiratory conditions have been excluded, there are a few common tools that can be used to assist in the diagnosis of HVS, described in the next section.

2.4 Diagnostic Tools for HVS

2.4.1Symptom Questionnaires:

The NQ (see Appendix II) is a validated screening tool for the identification of HVS (Van Dixhoorn 1985). It consists of a list of 16 symptoms /sensations associated with hyperventilation. The individuals are asked to report the frequency that they experience these sensations. Examples of the 16 sensations are: shortness of breath, palpitations, cold hands and feet, tight chest. Although it is often used as a diagnostic tool, some sensations may relate to other organic conditions such as anxiety disorders, asthma or chronic lung disease. The original validation study for this questionnaire described it as a useful screening tool, due to its ability to differentiate between those with HVS and non-hyperventilators (Van

Dixhoorn and Duivenvoorden 1985). However, the authors used the reproduction of symptoms on the hyperventilation provocation test (HVPT) to distinguish those with HVS, a test no longer considered useful for the diagnosis of HVS. This will be discussed later within this chapter. The specificity of the NQ (its ability to exclude individuals who do not have HVS) is low and so some authors have stated that it should not be used as a diagnostic tool (Jack et al 2004).

2.4.2 Exercise testing: There is a group of patients with idiopathic hyperventilation who appear to have an abnormal physiological response to exercise. Some individuals with HVS show a delayed recovery of $ETCO_2$ after exercise (>5 minutes) (Jack et al 2004). The mechanisms for this are unclear; however, it seems that individuals display an abnormal ventilatory drive, even at high work rates. An exercise test examining $ETCO_2$ levels before, during and after exercise is therefore used in the battery of tests, to assess for HVS.

2.4.3 Hyperventilation provocation test:

This test was for many years considered the “gold standard” in diagnostic tools for HVS (Howell 1990). The test requires the patient to volitionally hyperventilate either by taking 20 maximally deep breaths or by rapidly breathing for 3 minutes (Hardonk and Beumer 1979). The patient is then asked to report any reproduction of their symptoms. Recent work by many authors has revealed that this test is not sensitive enough to differentiate “normals” from “hyperventilators”. Studies have shown that the reproduction of symptoms was not reliant upon hypocapnia, and when CO_2 levels were maintained, 65% of participants still reported familiar symptoms of HVS. The test-retest reliability is also poor for the HVPT (Lindsay et al 1991). Therefore, this test is no longer routinely used to diagnose HVS (Hornsveld et al 1996, Warburton et al 2006). However, if $ETCO_2$ monitoring is used during the test, it can be a useful discriminatory test.

When challenged by the HVPT, non-hyperventilators often have periods of apnoea (absence of breathing) /hypopnea (reduced breathing rate) during the recovery phase. Individuals with HVS on the other hand, continue to hyperventilate above their baseline for up to 30 minutes after the test (Warburton et al 2006). The mechanisms for this response remain unclear but it is hypothesised that the HVS may in some way blunt the normal ventilatory inhibition that occurs with volitional hyperventilation and subsequent increasing hypocapnia (Folgering 1999, Warburton et al 2006). Therefore, despite the lack of relationship between symptom reproduction and CO_2 levels, the HVPT may still be a useful tool to facilitate a diagnosis of HVS. In clinical practice, however, it may not be the most pragmatic choice in all centres as it requires access to full cardiopulmonary exercise testing equipment and can be time consuming.

2.4.4 Think Test: This test uses the addition of emotional arousal into the HVPT whilst monitoring $ETCO_2$ (Nixon & Freeman 1988). Patients are urged to think about emotional episodes/ topics that may have provoked an altered respiratory pattern during the respiratory assessment. This test is considered positive if the $ETCO_2$ drops by > or equal to 10mmHg. This author was unable to find any validity data on this test.There may also be some ethical issues with using the Think Test. By asking an individual to think about their emotional issues, it is likely as well as potentially provoking a respiratory response, they may also become very emotional. Therefore, it would be prudent to have a psychologist available should the patient require intervention following the Think Test. This may result in a protracted clinic appointment and is not always be possible in a busy respiratory clinic. Therefore, the Think Test is not commonly used in clinical practice for these reasons.

2.4.5 Breathe Hold Time (BHT): Breath holding time is the period of time that individuals can hold their breath, usually from functional residual

capacity (the end of a normal breath out). Studies have shown a reduced BHT in individuals with HVS (Gardner 1996, Jack et al 1998, Jack et al 2004, Warburton et al 2006). Jack et al (2004) found that BHT for participants with HVS could be as little as 20 seconds compared to 60 seconds for a control group.

2.4.6 Assessment of breathing pattern

Breathing pattern relates to the rate or timing, volume and consistency/regularity of breath as well as the movements of the chest wall (Chaitow 2004). Individuals with HVS often display irregularities of breathing pattern (Han et al 1997). The measurement of breathing pattern is not simple as the breathing pattern may be influenced by the fact that the individual is wearing a mask or monitoring device (Han et al 1996). This is true of the "gold standard" for measuring flow, rate and volume, a pneumotachograph.

The gold standard non-invasive measure of breathing pattern is the use of respiratory inductive plethysmography (Carry et al 1997). This involves the placement of sensors on the chest wall and abdomen to assess the balance of abdominal and chest wall movement, respiratory frequency and irregularities. However, there is currently no gold standard measure for chest wall movements. In clinical practice, clinicians often use observatory and/ or palpatory techniques to assess breathing pattern. The MARM (Manual Assessment of Respiratory Motion) developed by Courtney et al (2008) is a method of the clinician using palpatory techniques to assess thoracic and abdominal motion. It also enables the clinician to derive numerical values for the "distribution of breathing motion and area of breathing involvement" (Courtney et al 2008 page 92). Although, there is evidence that the MARM is a valid measure with high inter examiner agreement, these studies were carried out on participants that had simulated breathing patterns rather than on patients (Courtney et al 2009). Therefore, further validation studies are needed to evaluate the use of this technique within clinical practice.

2.5 Treatment strategies for hyperventilation syndrome

Treatment approaches for HVS will be discussed fully in Chapter 3. They are mainly in the form of psychological or breathing rehabilitation and or exercise, rather than pharmacological therapy. Psychological therapies for HVS are often based upon the theory that anxiety is a causal factor of HVS. These psychological treatments usually consist of psychotherapy, cognitive behavioural therapy (CBT) and psychotropic medication (Brashear 1983, Fensterheim et al 1994, Chaitow et al 2014).

A full review of psychological treatments for HVS will not be explored within this document as it is not within the remit of this PhD, however CBT will be described as studies that have included CBT alongside physiotherapy techniques (BR) will be included in this review.

2.5.1 Cognitive Behavioural Therapy

CBT has a basis in the idea of how an individual's thoughts (cognition), feelings (emotions) and actions (behaviour) interact (McLeod 2015). It specifically relates to how thoughts determine what an individual feels and how they act. Therefore, CBT works on thinking errors. When an individual becomes psychologically distressed, they interpret situations differently and in turn this has a negative impact on the actions they take. CBT in HVS is thought to play a key role in helping the client to deal with the often extreme assumptions about the meaning of symptoms (Chaitow et al 2014).

An example of this would be when an individual experiences chest tightness and pain, this could represent an impending heart attack.

CBT aims to support individuals to "reinterpret" these symptoms as symptoms of hyperventilation (Beck 2011). However, CBT has been criticised in that it is not known whether faulty cognition is a cause of psychopathology or as a result of it (Lewinsohn 1981). There is also an argument that some forms of CBT can be forcefully directive in influencing cognition and could be considered unethical (McLeod 2015).

2.5.2 Breathing Rehabilitation Techniques

Treatments that have been used for HVS have traditionally been in the form of BR (BR), relaxation and biofeedback techniques. The literature provides several studies that examine the effects of BR techniques on HVS / breathing pattern disorders, although potential mechanisms for their efficacy remain under debate (Grossman et al 1985, DeGuire et al 1992, Tweedale et al 1994, De Guire et al 1996, Han et al 1996, Han et al 2004). These studies will be discussed in detail in Chapter 4(Acupuncture and Physiotherapy for Anxiety related to Respiratory Disorder).

The use of acupuncture for HVS is not well represented within the literature, with only two small, underpowered studies. However, there is a growing body of evidence for the efficacy of acupuncture in the treatment of anxiety, (Lewis 1987, Uskok 1995, Liu et al 1998, Eich et al 2000, Wang &Kain 2001a, Wang et al 2001b, Kober 2003, Zhang et al 2003, Wang et al 2004, Agarwal et al 2005, Wang et al 2005, Karst et al 2007, Isoyama et al 2011, Wu et al 2011, Black et al; 2011, Michelak-Suaberer et al2012), which as previously noted within this document, is known to play a key role in the pathogenesis of HVS. These studies will be discussed in depth in Chapter 4(Acupuncture and Physiotherapy for Anxiety related to Respiratory Disorder).

2.6 Chronic Obstructive Pulmonary Disease

COPD is a severe and progressive respiratory disorder that impacts upon an individual's general condition, physical function and quality of life (GOLD 2016). COPD is a condition in which symptoms manifest during mid to later life, which may be many years after exposure to a particular causative agent (Salvi 2009). The most important causative factor for COPD is tobacco smoking; however other factors include environmental exposure to pollution, fumes, chemicals, and dust, or genetic susceptibility (MRC 2004, Salvi 2009).

COPD is characterized by airflow obstruction/limitation which produces a progressive and irreversible decline in lung function (NICE 2010) and in 2016 was the fourth leading cause of death in the world (Global initiative for chronic lung disease- GOLD 2016).

The following is offered as a definition of airflow obstruction related to COPD by the National Institute for Health and care excellence (NICE 2010 page 22) “Airflow obstruction is defined as a reduced FEV_1/FVC ratio (where FEV_1 is forced expired volume in 1 second and FVC is forced vital capacity), such that FEV1/FVC is less than 0.7. If FEV1 is ≥ 80% predicted normal, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough.”

COPD is often described as an “umbrella” term which includes two main diseases (NICE 2010):

(ii) Chronic bronchitis, which is characterized by airway inflammation causing a narrowing of the airways and production of chronic cough and bronchial secretions. Although this term is frequently used in the definition of COPD, it is important to note that this condition can exist independently and may be present before or after the development of airflow limitation, in an individual. Chronic bronchitis can also exist in individuals with normal spirometry (a pulmonary function test that measures volume and flows of air moving in and out of the lungs) (GOLD 2016) which suggests therefore that, if the NICE definition is to be accepted, the presence of this condition alone should not be referred to as COPD.

(ii) Emphysema, which is characterized by a destruction of the alveolar walls resulting in a loss of lung tissue elasticity and enlargement of the lung airspaces. The description of emphysema is often used clinically to describe the structural changes that occur within the lung of a patient with COPD. However, this describes just one of the many structural abnormalities that occur in COPD.

The term COPD is believed to have been initially used in 1965 (Petty 2006) but there have also been many other terms that have been used to

describe this condition in the past such as, chronic obstructive lung disease, chronic obstructive airways disease or chronic airflow obstruction. COPD is now the preferred term to describe this condition (NICE 2010) and therefore will be used for the purpose of this document.

2.7 Prevalence and burden of COPD

According to NICE data there is an estimated 3 million people in the UK who are affected by COPD and approximately 2 million who are yet to be diagnosed (HCC 2006). However the prevalence data, both within the UK and across the globe, is difficult to assess due to the variety of survey methods, criteria for diagnosis and analysis methods used (Halbert et al 2006). In their systematic review and meta-analysis of COPD studies (1990-2004) Halbert et al were able to identify that the prevalence of COPD is higher in men than in women, in those aged ≥ 40 and in smokers / ex-smokers than in non–smokers. The BOLD study of various countries suggested there is a substantial level of COPD in never-smokers (6-11%) (Buist et al 2007). It is hoped that the standardization and improved quality of data collection, diagnostic criteria and analysis will enable a more accurate picture of the global prevalence of this disease in future (see Tables 2 (a) and (b) for the symptoms of COPD and the conditions associated with COPD).

The accuracy of both morbidity and mortality rates for COPD is greatly affected by the lack of reliability of the data collection methods and the diagnostic criteria used (Schirnhofer et al 2007). Morbidity rates are thought to be less reliable due to the range of diagnostic criteria used (Halbert et al 2006) however, unsurprisingly; the data suggest that morbidity associated with COPD increases with age (Schirnhofer et al 2007). This is thought to be compounded by the existence of common chronic co-morbidities associated with COPD (such as heart failure, diabetes, anxiety and depression), which impact upon the management of

COPD and subsequently on the individual's health status (Tsiligianni et al 2011, Panagioti 2014).

Mortality rates associated with COPD are published by the World Health Organisation (WHO) on a regular basis however, due to the variety of terminology used to describe COPD and hence diagnostic codes, interpretation of this data must be considered with a degree of caution (Pena et al 2000). In addition, these rates do not take into account the substantial under diagnosis of COPD which occurs globally, leading to further inaccuracies (Pauwels et al 2001). There are further issues that impact upon the reliability of this data such as whether COPD is used as the primary cause of death when recorded on death certificates (WHO 2015). Some studies suggest that COPD is often added as a contributing factor rather than a direct cause of death (Pena et al 2000). Despite the unreliability of this data, the projected mortality rates for COPD suggest that it is likely to be the third leading cause of death by 2020 (Mathers et al 2006), elevated by the aging population and better medical treatments for co-morbidities associated with COPD.

The economic burden of COPD is significant on a global scale. European data indicate that COPD represents 3% of healthcare costs and global figures estimate total economic costs of $2.1 trillion (Lomborg 2013). Costs of approximately $5.7 billion made COPD amongst the most expensive conditions seen in U.S. hospitals in 2011(Torio 2006).

2.8 Symptoms of COPD

(See Tables 2(a) and 2(b) for a list of symptoms of COPD and associated conditions, created from information in NICE guidelines (NICE 2010).
The airflow limitation that is evident in COPD is as a result of small airway inflammation (resulting in increased mucosal swelling and secretions) and destruction of the lung parenchyma (the functional tissue of the lungs). This causes an increase in lung compliance and the lung is more easily

inflated. This results in an increase in functional residual capacity (the volume of air left within the lungs after a normal tidal breath out) and airflow is reduced during expiration, giving rise to hyperinflation of the lungs. This hyperinflation is thought to affect the length-tension relationship of the respiratory muscles reducing the force they are able to generate causing the accessory muscles of breathing to become activated (Altose et al 1999). The onset of dyspnoea in COPD is thought to be related to the use of the accessory muscles of breathing which also leads to an abnormal upper chest pattern of breathing. There is evidence that this hyperinflation also occurs in individuals with HVS, as a result of "breath stacking" or inadequate time for complete exhalation (Clifton et al 2011).

Symptoms of COPD
Breathlessness (on exertion or at rest) Chronic Cough Regular sputum production Frequent "Exacerbations" of bronchitis (especially in the winter months) Wheeze

Table 2a Symptoms of COPD

Conditions associated with COPD
Asthma Depression PD Generalised Anxiety Hyperventilation syndrome /Dysfunctional breathing

Table 2b Conditions associated with COPD

2.9 Treatment for COPD

There is no cure for COPD, so treatment is based upon alleviating symptoms and optimizing function. The standard pharmacological treatment for COPD is the use of inhaled bronchodilation, steroid therapy, mucolytics and oxygen therapy if appropriate (Pauwels et al 2001). Pulmonary rehabilitation (PR) is also a key strategy in the management of COPD. PR is a multidisciplinary programme providing care for patients with chronic respiratory disease which promotes optimization of individual patient's physical and social performance whilst empowering the patient in self- management strategies (NICE 2010). The recent NICE guidelines for the management of COPD suggest that pulmonary rehabilitation (PR) is the key treatment to improve physical, emotional and social functioning for this group of patients and should be offered to all appropriate patients suffering from COPD (2010) (See Chapter 4 for more detail on PR for COPD). The association of COPD with anxiety and depression disorders is well recognised and documented (Mikkelsen et al 2004, von Leupoldt et al 2011). There is a suggested prevalence of anxiety symptoms of between 2% and 50% amongst patients with COPD (Light et 1985, Karajgi et al 1990, Dowson et al 2001, Panagioti 2014). Evidence suggests that anxiety and depression in COPD often prevent patients from gaining the maximum benefit from a PR programme (von Leupoldt et al 2011). Any therapy that

reduces anxiety and or depression could therefore increase the effectiveness of PR (see Chapter 3 for further debate around anxiety and breathing).

2.10 Chapter 2. Summary

COPD and HVS are common chronic respiratory disorders with very different underlying pathophysiology, but with some commonality in terms of symptoms. Anxiety is a key component of both conditions. The link between anxiety and behavioural influences, and their impact on breathing control will be discussed in Chapter 3. The common non-pharmacological treatments available for the treatment of anxiety related to breathing disorders will be reviewed in Chapter 4.

Chapter 3.

Anxiety and Breathing

3.1Introduction

Anxiety is a general term for several disorders that cause fear apprehension, nervousness and worrying (OED Anxiety 2015). Mild anxiety is a normal response and it plays an adaptive role in human development to indicate when self-protection is required to ensure safety. Anxiety can be present at any age for example anxiety about separation is a normal part of development in young children. It can be difficult to distinguish between what is a normal anxiety response compared to a psychopathology and to determine the point at which pathology begins. The general consensus in determining the threshold for diagnosis of pathological anxiety, is that it is related to the individual's ability to recover from anxiety and remain anxiety free, when the anxiety provoking situation is no longer present(Ref).

The difficulty in separating "normal anxiety" from "pathological anxiety" is reflected in epidemiological studies in which the prevalence of anxiety disorders changes considerably with the variations in definitions of impairment (Klein & Pine 2001). This dilemma gives rise to challenges in terms of timings of treatment. If the diagnostic threshold is set too high, there is a risk that individuals may not receive treatment or is if is set too low, individuals may receive unnecessary intervention. It also gives rise to a difficulty in distinguishing disorder from non-disorder. Wakefield (1992) suggested that having a disorder required both a psychobiological dysfunction which results in maladaptation or suffering or both. An example of this would be if an individual had extreme shyness or behavioural inhibitions but managed to find a comfortable place, which allows them to adapt, without marked distress. Therefore, although there

is some psychobiological dysfunction, these individuals would not be labelled as having a “disorder” as they are not maladapted or suffering.

Anxiety disorder is often classified into several specific types such as(Evans et al 2012): generalised anxiety disorder (GAD)- a pattern of excessive worries on most days for a period of 6 months, Panic Disorder (PD)- the occurrence of spontaneous panic attacks, post-traumatic stress disorder (PTSD)- following exposure to trauma an individual experiences recurrent experiences of the event, obsessive-compulsive disorder(OCD)- recurrent, persistent, intrusive anxiety provoking thoughts or repetitive acts a person is drive to perform and social anxiety disorder- the occurrence of extreme fear in social situations.

In terms of the prevalence of anxiety disorder, the Office of National statistics’ 1-week snap shot UK survey in 2007 revealed a prevalence of 4.4% for GAD, 3.0% for PTSD, 1.1% for PD and 1.1% for OCD. Anxiety disorders are highly prevalent co-morbidities associated with chronic respiratory conditions 54 (Wilgoss & Yohannes 2013) and therefore the literature on the relationship between anxiety and breathing has been reviewed in this chapter. In order to understand this relationship, it is necessary to review the control of breathing in terms of chemical, neural and behavioural factors. Emphasis in this chapter will be placed on the behavioural control of breathing to explore how emotions, including anxiety, interact with breathing mechanisms.

Respiratory disorders that most commonly present with co-existing clinical anxiety are COPD, asthma and hyperventilation syndrome (HVS) (also known as breathing pattern disorder /dysfunctional breathing). A description of HVS can be found in Chapter 2 of this document. The focus of this thesis is on HVS and COPD, so the interaction of anxiety within these conditions and its potential impact on breathing patterns and symptoms, has been reviewed.

3.2 Control of Breathing

3.2.1 Neural control

The central control for breathing is located within the cerebral medulla in the brainstem (Remmers 1999). Neural impulses from the central respiratory pattern generator in the brain stem are transmitted to the respiratory muscles via the spinal cord (Remmers 1999). Various afferent inputs from these complex neural networks within the brain are integrated to produce a respiratory rhythm in response to metabolic demand 54 (Altose 1999). The contraction of the respiratory muscles causes the change in pressures within the thorax that leads to the flow of air (and hence oxygen) into the lungs (Altose 1999).

3.2.2 Chemical control

Oxygen is essential for human metabolism and CO_2 is the end product that needs to be removed from the body. Changes in partial pressures of both CO_2 and oxygen are detected by central chemoreceptor (medulla) and peripheral chemoreceptor (aortic and carotid bodies). The signals from these receptors are relayed back to the brain stem respiratory centres. The breathing rate is then adjusted in response to this to maintain a normal pH and hence homeostasis within the body. This feedback mechanism to create respiratory motor activities is primarily in response to metabolic demand.

This thesis is primarily about anxiety and breathing in chronic respiratory disorders. Therefore, further detail on the physiology of the control of breathing will not be covered. The next section will discuss the behavioural control of breathing.

3.2.3 Behavioural control of breathing

Output from respiratory motor afferents is influenced by external and internal influences over and above metabolic requirements. This has been termed “behavioural breathing” (Homma & Masaoka 2008) . The mechanisms for behavioural breathing are thought to be different to involuntary, metabolic breathing (Homma & Masaoka 2008).

The final motor outputs (muscle activity) for breathing originate in the spinal cord. The descending neural pathways from higher centres, for involuntary and voluntary breathing, are essentially different. The origin for voluntary breathing is in the cerebral cortex, whereas the centre for metabolic breathing is the medulla and pons (Homma and Masaoka (1999).

The limbic system, which provides an important contribution to emotions, also has a significant influence upon breathing patterns. Studies using an electroencephalogram dipole tracing (EEG- DT) method have confirmed activation of the limbic system, when a feeling of anxiety was associated with increases in the respiratory rate (Masaoka & Homma 2001). However, the EEG-DT technique is not without its limitations and can only estimate precise locations of brain activity. The advent of functional magnetic resonance imaging (fMRI) studies of the human brain has enabled more accurate insight into the activities within the limbic system, for example Evans et al (2002) demonstrated in a group, who were mechanically ventilated, that when you induce “air hunger” (uncomfortable urge to breathe), the limbic and paralimbic loci appear to be activated.

Masaoka et al (2003) have shown, in their study whereby patients with lesions of the amygdala (a component of the limbic system) due to epilepsy, that there is a reduction in both anxiety and respiratory rate, when these individuals were subjected to anticipatory anxiety. This provides some support that the limbic system and more precisely the amygdala plays a role in behavioural breathing. The amygdala is known to

play an important role in processing negative emotions such as fear and anxiety (Morris et al 1998, Masaoka & Homma 2001).

Animal and human studies have also confirmed that electrical stimulation of the amygdala complex has resulted in an increase in respiratory rate and a variety of different breathing patterns (Harper et al 1984, Masaoka & Homma 2004). It is thought that the centre for these outputs relating to both anxiety and breathing are located close together and are likely to be within the amygdala. Masoaka & Homma found that stimulation of the amygdala produced a rapid increase in respiratory rate followed by a feeling of fear and anxiety.

Further studies are required in this field of research and understanding the mechanisms for behavioural breathing may help in the development of treatment programmes/approaches. The next section will discuss the relationship between common disorders of breathing and their relationship with anxiety.

3.3 Hyperventilation syndrome and Anxiety

"Hyperventilation syndrome is a syndrome characterised by a variety of somatic symptoms induced by a physiologically inappropriate hyperventilation and usually produced in whole or in part by voluntary hyperventilation" (Howell 1990 page 287). Psychological or emotional influences upon the control of breathing are well documented (Manning et al 1992, Homma et al 2008). As stated earlier, the basic drive to breathe is located within the respiratory centres within the brainstem. There are however, neural pathways that link these centres with the sensory cortex and areas such as the limbic system and hypothalamus that can override the autonomic breathing system and interrupt the normal rhythm and rate of ventilation (Altose 1999). Psychological disturbances, in terms of anxiety, stress, fear or panic, are often the cause of ventilatory and breathing pattern dysregulation, which occurs regardless of input from

chemoreceptor mechanisms (Jack et al 2003). The neural feedback from abnormal lung and respiratory mechanics can perpetuate this dysregulation (Romagnoli et al 2004). Therefore, daily stressful conditions that generate emotional states of hyperarousal result in changes in breathing patterns. Respiration rate and minute ventilation 57 increase and breathing pattern is reported to move from an abdominal to thoracic or chest breathing pattern, resulting in hyperventilation (defined as breathing in excess of metabolic needs) (Timmons et al 1994, Ley 1999).

Emotions such as stress, anxiety and panic have been found to have an association with hyperventilation (Seuss et al 1980, Schleifer et al 2002, Deshmukh et al 2008). There appears to be a reciprocal association between hyperventilation and anxiety whereby changes in emotional arousal can lead to changes in ventilation and vice versa. Hence, there continues to be a "chicken and egg" debate about which factor comes first, the hyperventilation or anxiety. When healthy participants were screened as "likely hyperventilators" (n=18) vs "unlikely hyperventilators" (n=16) using a symptom questionnaire, trait anxiety levels were highly correlated with symptom scores, suggesting a relationship between hyperventilation and anxiety ($r=0.42$ $p<0.001$) (Huey et al 1983). Huey et al screened for "likely hyperventilators" using a non-validated symptom score with listed symptoms that could have been attributable to GAD or other organic disease. Therefore, the results of this small questionnaire study must be considered with caution. Unfortunately, the only validated questionnaire for HVS screening is the NQ which was validated after this study was published (Van Dixhoorn & Duivenvoorden 1985).

Increasing anxiety has been associated with increasing abnormal breathing patterns (Klein 1993, Zvolensky et al 2001). A relationship between hyperventilation and anxiety/stress at work is highlighted by studies from Schleifer et al (1994, 2002) who asked 21 participants to carry out mental tasks both under low and high stress conditions. Although heart rate variability, respiratory rate and self-reports remained

unchanged, $ETCO_2$ was found to differ between task conditions, suggesting there were changes in volumes breathed. They also found that $ETCO_2$ discriminates between high and low mental workload in a computer-based data entry task. Schleifer et al hypothesised that workers hyperventilate under stressful job conditions and that this becomes a chronic conditioned response which impacts upon the musculoskeletal system resulting in increased muscle tension, muscle ischaemia and spasm, which can be the key precursor to the development of work-related musculoskeletal disorders.

A relationship between anxiety and hyperventilation is supported in asthma studies, suggesting hyperventilation is the key pathway for psychosocial stress effects on asthma (Clarke et al 1982, Meuret & Ritz 2010). Ritz et al (2008) found that asthma triggers were associated with hyperventilation symptoms. They demonstrated that asthma patients with more psychological triggers for their condition also reported more frequent hyperventilation symptoms during exacerbations.

3.3.1 Is HVS a trigger for anxiety?

Although anxiety and HVS are believed to be associated, there is a lack of evidence specifically examining any causal relationship between them. One school of thought suggests that hyperventilation is triggered by a stimulus which leads to hypocapnia (low CO_2) and a variety of symptoms and complaints (Klein 1993, Folgering 1999). These symptoms are perceived and often misinterpreted for example: chest pain may be misattributed to a heart attack, or the individual interprets this event as a danger of suffocation. This provokes anxiety and/ or panic which leads to further hyperventilation, resulting in a vicious cycle of hyperventilation – anxiety - hyperventilation. These events may happen in places that stimulate anxiety such as small crowded spaces, and the symptoms are then associated with these environments. When individuals are confronted

with these environments again, they anticipate the unpleasant symptoms, which perpetuates the vicious cycle. Some authors believe that this may be an explanation for panic attacks (Hoes et al 1987, Hibbert et al 1984). It has been suggested that there is a significant overlap between HVS and PD; however, panic does exist without hyperventilation and vice versa (Gardner 1996). There is physiological evidence that patients with anxiety disorders may be exposed to cerebral hypoxia (low oxygen in the brain) which is thought to be secondary to hyperventilation, and may contribute to the pathogenesis of panic and anxiety symptoms (Dratcu 2000).

Hyperventilation is often considered to be a response to danger or fear and prepares the individual to take action. A ventilatory increase, if not followed by activity, will result in further hypocapnia. Healthy participants have exhibited this response with increased anxiety and/or hyperventilation symptoms, when exposed to voluntary hyperventilation (Holloway et al 1987). This supports the theory that hyperventilation itself can influence mood changes and the symptoms experienced in HVS. However, laboratory-based investigations can increase anxiety levels, which may have confounded the results of this study. It has been hypothesised, that individuals who are likely to have HVS are more likely to exhibit a greater vulnerability to increased anxiety levels, when exposed to voluntary hyperventilation (Meuret & Ritz 2010).

3.3.2 Is anxiety a trigger for HVS?

As well as voluntary hyperventilation causing an increase in anxiety there is some evidence from healthy participants that the reverse may be true i.e. that anxiety may cause or trigger hyperventilation and its associated symptoms (Ley & Yelich1998). It is well documented that the anticipation of any impending threat or fearful situation results in an increase in respiratory rate and a change in ventilatory pattern and rhythm (Masoaka et 2001).

Ley & Yelich (1998) examined 32 junior high school students undergoing stressful exam conditions. They allocated the students into one of two groups (16 participants in each group) and classified students as either high or low anxiety according to their scores on an anxiety behaviour scale. They then monitored the students using $ETCO_2$ measurements and subjective symptom scoring, using the NQ during exam conditions. Ley & Yelich (1998) reported that the students with higher levels of anxiety had a larger drop in $ETCO_2$ levels and an increase in NQ scores, during testing. However, this drop in $ETCO_2$ did not reach statistical significance, possibly due to an inadequate sample size. Despite this study not revealing statistically significant results, the authors claim that the $ETCO_2$ levels (which were well matched at baseline), were different between the two groups when measured at outcome. This paper suggests that it was the exposure to the anxiety-provoking exam that promoted the hyperventilation. Therefore, Ley and Yelich suggest that susceptibility to hyperventilation is likely to exist as a "trait" and when challenged by anxiety provoking situations it occurs in healthy participants. However, the data presented in this study reveals that, although there was a greater drop in $ETCO_2$ in the "high anxiety" group, the mean drop was 0.24 %(1.82mmHg). It is unlikely that this drop in $ETCO_2$ would be considered clinically significant but this author is not aware of any studies that examine a minimal clinically significant change in $ETCO_2$ levels. Despite this, the theory proposed by Ley & Yelich (1998) that anxiety is a precursor to HVS and its associated symptoms, has been supported by other studies examining the effect of anxiety on $ETCO_2$, pulmonary function and breathing pattern (Garssen et al 1980, Seuss et al 1980, Ancoli et al 1980, Holloway 1987, Masaoka et al 1999). These trials all examined healthy volunteers and used a variety of stimuli to induce anxiety provoking situations. They all suggest that emotions can affect breathing pattern (either by increasing respiratory rate and minute ventilation or promoting an apical, shallow ventilatory pattern). There was also a significant reduction in $ETCO_2$ levels in three studies (Garssen et al

1980, Seuss et al 1980, Masaoka et al 1999) indicating an element of hyperventilation in participants.

However, these trials are methodologically flawed. The studies were small and two of the studies were non-controlled (Garssen et al 1980, Ancoli et al 1980). The controlled study which did find a statistically significant reduction in $ETCO_2$ during anxiety inducement was carried out at a location of high altitude, which may have affected $ETCO_2$ levels, (see Chapter 1.) (Seuss et al 1980). The trials carried out on healthy participants need to be considered with caution, as although they suggest some changes in ventilatory pattern and lowered levels of $ETCO_2$ with increasing anxiety under laboratory conditions, this may not be generalisable to the those experiencing HVS on a day to day basis. The interconnections between anxiety and respiratory control are very complex and therefore any simple cause/ effect relationship is not evident and has proven difficult to examine.

3.3.3 HVS and Panic disorders

PD is characterised by spontaneous and unpredictable occurrence of panic attacks. The frequency of these attacks can vary from hourly to a few per year. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for PD is that panic attacks must be associated with longer than 1 month of subsequent persistent worry about: (i) having another attack or consequences of the attack, or (ii) significant maladaptive behavioural changes related to the attack. PD is considered to be a specific type of anxiety and is commonly associated with HVS (Gorman et al 1984, Holt &Andrews 1989, De Ruiter 1989, Maddock et al 1991, Rapee et al 1992, Hegel et al 1997 Dratcu 2000). In clinical practice, the symptoms of PD and HVS have considerable overlap, although the two remain distinct conditions. It has been suggested that up to 25% of individuals with HVS also have PD (Kern 2016). This is however, difficult to accurately quantify due to the inconsistencies with and validity of the tools used for the diagnosis of HVS, within the literature. There is also

some evidence that there is also overlap of PD with other respiratory disorders such as Asthma and COPD (Leivseth 2012), so it has been included in this review.

Hyperventilation is often observed during naturally occurring or pharmacologically induced panic attacks and in panic patients between attacks (Gorman et al 1984). There are three main theories relating to the relationship between hyperventilation in itself and panic;

3.3.31 Panic attacks are primarily due to hyperventilation.

Historically hyperventilation was considered to be a means of provoking a panic attack due to the lowering of CO_2 and inducing a respiratory alkalosis (abnormal alkaline condition of body tissues and fluids). At one time a “brown paper bag” CO_2 rebreathing technique was used clinically to curtail panic attacks. Holt & Andrews (1989) in their controlled trial examining 10 patients with agoraphobia/PD/ General anxiety disorder 59(GAD) found that there was a strong relationship between anxiety and hyperventilation in the PD, anxiety groups and normal participants. They found that those with PD had significantly higher HVS symptoms and anxiety during voluntary hyperventilation. It is suggested that these patients exhibit hyperventilation symptoms and that their over-breathing episodes are as a result of their high levels of anxiety (Holt & Andrews 1989). This study had a small sample size resulting in poor generalisability.

Also, this mechanism for panic has been questioned in studies where panic attacks were induced by fearful situations and $PaCO_2$ did not significantly drop in the majority of participants (Garssen et al 1996).

3.3.32 Panic attacks are caused by increasing arterial carbon dioxide levels and hyperventilation results as a compensatory physiological response.

The theory that panic attacks occur as a result of increased CO_2 is supported by trials that have administered inhaled CO_2/oxygen gas mixtures to panic patients and healthy participants (Griez et al 1987, Gorman 1988, Griez et al 1990). Panic attacks were elicited in the majority of patients and ratings for panic symptoms were significantly higher in panic patients, compared to healthy participants. It has been hypothesised that patients with PD have hypersensitive central chemoreceptors, which increase ventilatory responses at lower levels of $PaCO_2$ (Gorman et al 1988). However; it could be that it is the cognitive interpretations of the experiences that the feeling of either high or low CO_2 gives, that cause the panic attacks. A controlled trial was carried out by Rapee et al (1992) with 223 participants. They found that patients with PD responded with greater distress following hyperventilation than those who had generalised anxiety or healthy controls. It has been stated that there is a subgroup of patients with PD who are known to hyperventilate. In a controlled study of PD, Maddock &Carter (1991) examined 24 participants (12 Participants with PD and 12 control participants) and exposed them to eight minutes of voluntary hyperventilation. They found that seven out of the 12 participants in the PD group experienced a panic attack as a result in contrast to the one participant in the control group. Maddock & Carter concluded that PD is closely linked with HVS. These authors also found that those patients that reported greater anxiety levels in the preceding week were more likely to panic during hyperventilation (Maddock and Carter 1991). All of these studies used the relevant DSM criteria to define PD.

Hegel et al (1997), found similar results when they compared patients with PD (n=17), GAD (n=18) and 20 controls. They found that some PD patients had significantly lowered $ETCO_2$ and an increase in respiratory symptoms such as dyspnoea. However, it is important to note that it may have been the experimental conditions that caused the PD group to have

panic attacks as opposed to the hyperventilation. This evidence suggests then that not only can anxiety produce hyperventilation but that there is a reciprocal relationship between the two.

3.3.33 Hyperventilation occurs as a protective mechanism against panic attacks.

Klein (1996) suggested that CO_2 chemoreceptors are linked to a58 specific alarm and escape mechanism sensitive to asphyxiation that is triggered in panic patients. It is thought that secondary hyperventilation symptoms such as, chest pain or dizziness may produce some catastrophic thinking which can intensify the panic.

De Reuiter et al (1989) assessed the relationship between HVS, anxiety and PD in 176 participants with a diagnosis of PD, PA with agoraphobia or GAD with HVS. De Reuiter et al found that HVS was present in 40% of their PD patients and in 82% of their anxiety patients. However, their study used the Hyperventilation Provocation test (HVPT) for diagnosis of HVS and this test has a low specificity i.e. it is not accurate at ruling out those who do not have the condition, making it an invalid tool for the diagnosis of HVS (see chapter 2). The results of this trial (De Ruiter et al 1989) must therefore be considered with caution.

3.3.4 Summary

It is unclear how hyperventilation, PD and GAD are interlinked and whether there are purely physiological or psychological causes for this relationship. Some researchers have found that anxiety can induce hyperventilation (Garssen 1980, Seuss et al 1980) and others have found that hyperventilation can induce anxiety (Maddock & Carter1991, Huey et al 1983). In healthy individuals, hyperventilation increases anxiety levels and reduces cognitive performance (Lishman 1998). It also leads to a systemic alkalosis (over breathing causes excess removal of arterial

CO_2resulting in a rise in blood pH). This causes blood vessels to constrict (vasoconstriction) and therefore reduces oxygen supply to tissues (hypoxia). Cerebral vasoconstriction leads to the symptoms associated with hyperventilation such as light-headedness and fainting. These physiological changes may be implicated in the perpetuation of anxiety.

It is thought that cerebral hypoxia may have a causal link with the anxiety that is commonly a characteristic of COPD (Dratcu 2000). Patients with PD have been found to exhibit EEG changes that indicate cerebral hypoxia when they voluntarily hyperventilate (Dratcu1999). Cerebral hypoxia secondary to chronic hyperventilation could therefore facilitate anxiety and panic symptoms in individuals, which would suggest that hyperventilation, may perpetuate or facilitate anxiety. However, panic attacks are acute episodes of anxiety at the clinical end of the anxiety spectrum and whether the cerebral hypoxia theory would apply at all anxiety levels would need further investigation.

The argument that physiology is the greatest influence on HVS is suggested to be supported by the presence of nocturnal hyperventilation/panic attacks (Ley 1988). There are currently no data available on what proportion of individuals with HVS nocturnal symptoms have, but anecdotal evidence from the clinical environment suggests that they do exist. It has been found that changes in respiratory rate and depth during sleep result in a rise in $PaCO_2$ (Simon et al 2002).

The chronic hyperventilator already has a low bicarbonate buffer level to maintain a normal pH (Chaitow et al 2002). It is hypothesised that the individual with HVS will be more sensitive to small changes in CO_2 levels and their ability to compensate for the rising levels is hindered (Ley 1988). Ley hypothesised that this process then triggers a panic attack and would also explain why HVS sufferers experience attacks, when at rest. However, it could be argued that this theory does not take into account the impact of psychological influences during sleep, such as dreams/negative

thoughts, upon respiratory pattern/ rate. Hence, it is not possible to rule out the psychological effect on HVS.

In summary, there appears to be a relationship between various forms of anxiety and HVS, but the direction and nature of this relationship remains unclear. Nevertheless, it seems logical to conclude that any treatment strategies to tackle HVS should involve methods to address any anxiety component of the condition.

3.4 Chronic Obstructive Pulmonary Disease and Anxiety

There is increasing interest in the role of psychological illness as co-morbidity to COPD. This is due to the emerging evidence that suggests the impact of psychiatric disorders may influence outcomes such as functional ability, health status and hospitals admissions (Cully et al 2006, Eisner et al 2010, Yohannes et al 2000 Panagioti et al 2014). Anxiety alone has been shown to be a predictor of hospitalisations with acute exacerbations of the condition (Dahlen & Janson 2002), associated with reduced health status and impaired functional status (Felker et al 2001, Cully et al 2006).

Historically, COPD research has focused around the impact of co-existing depression on patients with COPD and evidence suggests that clinicians are now better at screening for, recognising, and managing clinical depression in COPD (Yohannes et al 2013). More recently, there has been increasing awareness of the presence of clinical anxiety within the COPD population, which has been of interest to clinicians and researchers, due to the multifaceted relationship between anxiety and the symptoms of respiratory disease, such as breathlessness (Panagioti et al 2014).

Patients with COPD are more likely to exhibit co-existing anxiety and depression than those with other chronic conditions or respiratory

diseases such as pulmonary tuberculosis (Panagioti et al 2014). The factors that determine a predisposition to comorbid anxiety remain unclear but it is hypothesised to be associated with the higher frequency of hospitalisations and the progressive nature of COPD (Wilgoss & Yohannes 2013). However, the precise prevalence of clinical anxiety as a comorbidity to COPD is uncertain, due to factors that will be discussed later within this section.

There are several studies that have examined the prevalence of anxiety in patients with COPD; however, the majority have not included psychiatric interviews to enable formal diagnosis of clinical anxiety. Many studies have used screening measures that can give an indication of clinically relevant anxiety and a measure of psychological distress but should not be used as diagnostic tools (Yohannes et al 2013). The most commonly used screening tool is the HAD scale. This tool has been validated for use in non-psychiatric hospital clinics to detect clinical anxiety (Zigmond & Snaith) however, studies have used a variety of cut off scores to indicate clinical anxiety (Cleland et al 2007) and some items on the scale may also represent symptoms of COPD, itself as well as anxiety. Therefore, using such measures may result in an overestimation of anxiety in many prevalence studies in COPD.

In clinical practice however, it is not practical for all patients with COPD to have formal psychiatric interviews as they are time consuming, costly and require trained healthcare professionals to carry out the interviews (Vogele & Von Leupoldt 2008). The screening tools are used to highlight those patients that are most likely to have clinically significant anxiety levels so that a referral to specialist psychology services can be made (Kuhl et al 2008).

Research studies examining the prevalence of anxiety in COPD have used psychiatric interviews to formally diagnose anxiety in their participants (Dowson et al 2004, Laurin et al 2007, Kuhl et al 2008, Vogele & von Leupoldt 2008). A systematic review of anxiety disorders in patients

with COPD, with formal psychiatric interviews as a diagnosis for clinical anxiety, has suggested that there is a high prevalence of anxiety in patients with COPD (Wilgoss & Yohannes 2013). However, despite this conclusion, the studies included in this systematic review had small sample sizes and the authors describe a wide variation of prevalence across the included studies. The small sample sizes may be related to recruitment issues as individuals may be reluctant to participate in trials that require psychiatric interviews, which are time consuming.

The variation in reported prevalence across these trials may be due to the heterogeneity of the included sample populations. Patients with a range of severity of COPD were included. There is also an issue with the psychiatric classification systems used within the studies reviewed. There were four different diagnostic classification tools used across the studies. This inconsistency across studies makes it difficult to evaluate the prevalence of anxiety in COPD, in terms of the type of clinical anxiety or severity levels of the condition. It is not possible to suggest from this review, any correlation between anxiety prevalence and severity of disease.

The studies included in the systematic review involved predominantly male participants (Wilgoss & Yohannes 2013), but it has been previously documented that the incidence of anxiety is higher in women with COPD (Laurin et al 2007). This would imply that the prevalence data from these studies may not reflect the COPD population as a whole. The heterogeneity of the sample characteristics in this systematic review indicates that the conclusions from this review may therefore not be generalisable to the COPD population.

A controlled study examining the prevalence of anxiety in COPD (Aghanwa & Erhabor 2001) did find that the presence of GAD was significantly higher in a COPD population when compared to age and gender matched, healthy controls ($P<0.05$). This study also had an 83% male population in their sample which would suggest this difference was

underestimated due to the reported increased incidence of anxiety in females. However, this study only examined in-patients and it could be hypothesised that when patients with COPD are hospitalised that they have greater anxiety levels. However, this hypothesis has been refuted by several authors who have found similarly high levels of anxiety in both outpatients and inpatients with COPD (Yohannes et al 2001, Aghanwa & Erhabor 2001, Kuhl et al 2008).

It is not clear from the literature whether there is a higher prevalence of any specific anxiety disorders within COPD than in the healthy population. However, some authors have reported that when they are present, specific anxiety disorders such as PD and phobic anxiety are the most common anxiety disorders evident in patients with COPD (Vogele & von Leupoldt 2008, Wilgoss et al 2013).

Although the precise prevalence of anxiety disorders within both the COPD population and the HVS population remains unquantified, there is consensus that anxiety is a frequent co morbidity in both conditions (Schleifer et al 2002, Deshmukh et al 2008, Wilgoss & Yohannes 2013). One of the most common symptoms in both COPD and HVS is breathlessness (dyspnoea). In the next section, therefore, the relationship between dyspnoea and anxiety will be explored.

3.5 Anxiety and Dyspnoea

Dyspnoea is a term used to describe a range of symptoms related to unpleasant respiratory sensations. A definition offered by the American Thoracic society (ATS 1999), presents dyspnoea as a “subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.” Dyspnoea and anxiety are common symptoms amongst individuals with chronic breathing disorders such as HVS or COPD and it has been suggested that these two components

contribute more to the variation in health status of people with chronic respiratory disease, than reductions in lung function (Leivseth et al 2012).

Dyspnoea is a subjective experience and a well-known feature of chronic respiratory disorders (GOLD 2011). It has been previously discussed within this chapter, that dyspnoea can also be a symptom of anxiety which has been demonstrated by studies in HVS or PD (Smoller et al 1996, Leivseth et al 2012). In chronic respiratory diseases such as COPD, levels of dyspnoea have been found to be independent of severity of the disease (Neuman et al 2006 Giardino 2010), therefore, it could be hypothesised that the variations recorded in dyspnoea amongst the COPD population, are due to anxiety. Leivseth et al (2012) in their epidemiological study of the general population (n=3,369) examined the association between lung function, reported anxiety symptoms and the prevalence of dyspnoea. They found that lung function and anxiety were independently associated with dyspnoea and that reported dyspnoea was more prevalent among people with anxiety symptoms than those without. There have been other studies that have examined the association between anxiety and dyspnoea in the general population or “healthy” volunteers. Dales et al (1989) studied anxiety and dyspnoea ratings in 600 “healthy” participants without any respiratory symptoms and who had never smoked. They reported a strong positive relationship between anxiety and dyspnoea and participants with more psychological symptoms were most likely to report respiratory symptoms such as dyspnoea.

There is debate about whether there is a cause and effect relationship between dyspnoea and anxiety. This is reflective of the debate around the association of HVS and anxiety in that there is uncertainty about whether dyspnoea causes anxiety or vice versa (Giardino et al 2010). Some qualitative research suggests that there is a “dyspnoea-anxiety-dyspnoea” cycle in patients with COPD (Bailey 2004). Bailey proposes that dyspnoea causes anxiety in people with COPD and this anxiety causes further dyspnoea. Allen et al (2012) in their study examining emotion and

breathing (n=71) demonstrated that influencing an individual's emotional state by using positive images, could reduce dyspnoea in healthy volunteers. It is likely that this relationship between dyspnoea and anxiety is reciprocal depending on the situation that the individual is faced with. For example if anxiety is experienced whilst resting, this could precipitate an increase in dyspnoea, whereas during exercise the dyspnoea could exacerbate sensations of anxiety Anxiety often co-exists with depression and therefore any investigations into the relationships between anxiety and dyspnoea need to account for the influence of depression in the analysis.

3.6 Depression and COPD

Depression is a mental condition characterised by severe despondency and dejection as well as feelings of inadequacy and guilt (Katon 2011). Depression and anxiety often co-exist and it has been hypothesised that a "mixed state of depression and anxiety" is more prevalent than depression alone (Tyrer 2001). It is estimated that approximately 50% of those with depression, also have anxiety (Katon 2011). The presence of depression in an individual, with a long-term condition such as COPD, is thought to have a similar negative effect on health status and symptoms as those found with co-existing anxiety and chronic illness.

3.7 Chapter 3. Summary

Breathing is affected by behavioural influences. There is a relationship between anxiety and breathing, but the nature of this relationship in chronic respiratory conditions such as HVS and COPD, is uncertain. A review of the non-pharmacological treatment options that are available for individuals with respiratory disorders is included in the next chapter, with a

discussion about the impact they have upon symptoms and associated conditions such as anxiety.

Chapter 4.
Acupuncture and Physiotherapy for Anxiety related to Respiratory Disorder.

4.1 Introduction

In this chapter, the use of acupuncture for respiratory conditions will be discussed. Two commonly used respiratory physiotherapy treatments will also be discussed as the studies included within this thesis, have evaluated acupuncture as an adjunct to these physiotherapy techniques. The focus of this will be on how the treatments influence outcomes such as symptoms and associated conditions such as anxiety. The treatments presented will be acupuncture, physiotherapy for HVS in the form of breathing retraining and pulmonary rehabilitation used for the treatment of COPD.

4.2 Acupuncture

Acupuncture is defined as the insertion of needles into specific points around the body and is derived from ancient Chinese medicine. However, the Chinese word for acupuncture means “metal, needle, hearing or cauterisation” (Chmielnicki 2017). Therefore, a broader definition of acupuncture involves points also being stimulated via electrical, thermal (moxibustion) or mechanical (acupressure) means. Acupuncture has been used in the Far East for at least 5000 years and it has become increasingly popular within western medicine since the early 1970’s (Filshie et al 2004). In its original form acupuncture was based on the principles of TCM. According to TCM the human wellbeing was reliant upon an energy force “Qi” that circulates around the body. The channels through which this “Qi” flows are known as “meridians”. There are 12 main meridians of the body, each running longitudinally and superficially. They correspond with the main organs of the body and are named accordingly

e.g Liver meridian, gallbladder meridian, kidney meridian. (See appendix III for meridian charts)

The acupuncture points are specific points that lie along these meridians and both TCM and western approaches identify these points by their location on the meridians e.g. Large Intestine 4(Li 4, See Figure (1). (See also appendix III for acupuncture points).

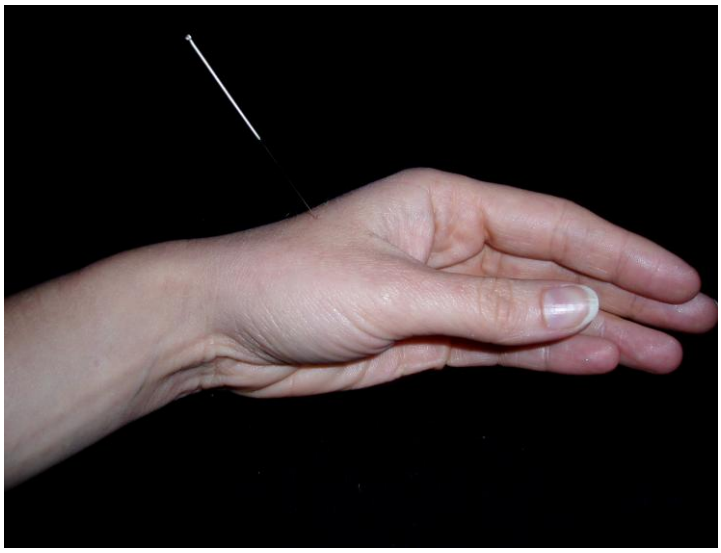

Figure 1b. A picture to show acupuncture at the location of Li 4.

TCM believes that Qi should flow smoothly through each meridian for health to be maintained i.e. if there is a blockage of energy flow then illness will result. The belief is also that the acupuncture points provide a means of altering the flow of Qi through a meridian. Traditional theory is based on the theory of “Yin and Yang”. The Yin and Yang represent opposing forces that are an amalgam of one. TCM regards good health as a balance of Yin and Yang (Gunn1977). In illness or disease, TCM attempts to restore equilibrium within the body and address the balance of Yin and Yang. TCM practitioners take a detailed, case history as well as using observations that are said to reveal information about the patient’s state of health. These involve examination of the shape, coating and colour of the tongue, the colour of the face and the strength, rhythm and quality of the pulse. This system of pulse taking for diagnosis is known as

“pulse diagnosis”. TCM practitioners believe that diagnosis of any systemic disease is possible purely by pulse diagnosis.

Most western acupuncture practitioners have knowledge of TCM but base their point selection according to principles of neurophysiology and anatomy (Filshie et al 2004) and are aware that the peripheral nervous system is best stimulated at certain sites of the body where nerve fibres are more accessible. The Western practitioner will carry out a contemporary examination and medical diagnosis prior to treatment and will often use a combination of traditional points along with trigger point acupuncture.

4.2.1 De qi

” De qi” can be defined as the sensation of heaviness, soreness or numbness that is experienced at the point of needling (Vickers et al1999). It is thought that achieving De qi with acupuncture may provide a better response with treatment (Takeda & Wessel 1994).

Some acupuncturists will always attempt to produce this sensation on needling. Studies have shown that subjects who have experienced de qi during acupuncture had a better response than those that did not, regardless of the placement of the needles (Takeda & Wessel 1994). However, a more recent study of acupuncture for painful conditions suggests that achieving de qi with acupuncture treatment may not be as important in terms of improving outcomes (White et al 2010). There were limitations with this study in that the outcome measure used to assess needling sensation, the Park questionnaire (Park et al 2002). This questionnaire was derived from a pain scale and included descriptors referring to pain and therefore did not include the range of descriptors that could describe needling sensation.

The authors of this study also note that needling sensation was noted at the end of the trial and not at each acupuncture session so they relied upon patients to recall the needling sensations. There are also no trials

examining the effect of de qi on outcome for non-painful conditions and therefore the importance of de qi, in the efficacy of acupuncture, remains unclear. The term efficacy in this document relates to the capacity to produce an effect under ideal “clean” conditions as opposed to effectiveness which refers to pragmatic, real life conditions (Singal et al 2014).

There is a growing body of evidence that supports the use of acupuncture for painful conditions such as neck and back pain (Diener et al 2006, Endres et al 2007, Scharf et al 2006) but there are few robust trials involving acupuncture for respiratory disorders and only 2 examining its effect on HVS.

4.3 Mechanisms of acupuncture

The mechanisms by which acupuncture works remain unclear. Western research on the mechanisms for pain relief has highlighted some potential pathways in acupuncture analgesia. However, this may not provide satisfactory explanations for the application of acupuncture, in other non-painful conditions such as, anxiety or breathlessness. This section will highlight some of the potential mechanisms by which acupuncture is thought to work and will consider the relevance of these mechanisms, in the treatment of HVS.

4.3.1Spinal segmental mechanisms

Studies have shown that acupuncture analgesia can be reversed by naloxone (Cheng et al 1980). This evidence suggests that there is an opoidergic mechanism of the action of acupuncture. Han et al 1984 showed that there were several effects on neurotransmitter substances following acupuncture both within the spinal cord and the brain, for example there is an agonistic effect on 5-HT met-enkephalin and β-endorphin and within the brain and an inhibitory effect on substances such as cholecystokonin octapeptide (CCK-8). CCK-8 is an endogenous opoid

antagonist and therefore works against the effects of opiates such as morphine (Han et al 1994). Acupuncture stimulates the A delta nerves fibres. These afferents terminate in the most superficial zone of the dorsal horn within the spinal cord (Kumazawa et al 1978). In this region of the spinal cord there are also very small cells known as “stalked cells” and there action is to suppress activity in the nearby cells of the “substantia gelatinosa”(SG) on which the unmyelinated pain fibres end (Siugura et al 1986).These stalked cells inhibit the SG cells by releasing the inhibitory opioid transmitter enkephalin (Ruda et al 1984). It has also been found that acupuncture inhibits the action of “Wide dynamic range (WDR) cells”. These cells convey impulses up to the brain where painful stimuli will be consciously interpreted and are highly influenced by the SG cells.

In summary the stimulation of A-delta fibres by an acupuncture needle carries an impulse to stimulate the stalked cells which in turn inhibit the SG via the release of enkephalins which then inhibits the WDR cells and prevents painful stimuli from being consciously interpreted.

4.3.2 Heterosegmental Acupuncture

It is known that the spinoreticular tract carries information generated by nociceptors from the spinal cord up to the reticular formation and the hypothalamus within the brain. The spinothalamic tract on the other hand carries impulses generated by thermal or pinprick stimulation to the ventroposterior thalamus within the brain (Wilis 1985).Evidence suggests that branches of the spinothalamic reach the periaqueductal grey (PAG) matter (Zhang et al 1990).The PAG is thought to be the most effective area in the whole of the nervous system for the inhibition of pain by microinjection of morphine (Tsou & Jang 1964) and is known play a role in the transfer of pain messages up into the cerebral cortex. Therefore, this structure which lies within the midbrain may play a focal role in the non-segmental effects of acupuncture. Mayer et al (1974) found that there was a descending inhibitory pathway from the PAG to the spinal cord and this

was responsible for the inhibition of neural impulses from ascending afferents carrying painful stimuli from the periphery.

This descending pathway connects into the raphe nucleus of the medulla oblongata. From here fibres descend in the dorsolateral funiculus (DLF) f the spinal cord to terminate in the enkephalinergic stalked cells of the dorsal horn (Glazer 1984). The main transmitter substance along these fibres is Serotonin (5-hydroxytryptamine 5-HT). There are also serotonin containing nerve terminals that have free endings within the spinal cord grey matter (Hammond et al 1985). It is hypothesised that this may provide an explanation for the more generalised effect that is achieved from acupuncture. Studies have found increased levels of serotonin within mast cells and platelets following acupuncture therapy (Souvannakitti et al 1993). It has been suggested that it may be via this mechanism that the long-term effects of acupuncture are achieved (Bowsher 2004). However, the evidence for this is lacking and must be considered cautiously. It is also important to mention that the PAG also receives fibres from the hypothalamus that contain the morphine-like substance β-endorphin. The hypothalamus is concerned mainly with the regulation of body functions but also plays a role in emotions. This has been demonstrated by studies that have stimulated the hypothalo-PAG fibres and pain relief has been obtained due to the endorphin release. Noradrenergic systems are also thought to be important and unlike serotonergic fibres they bring about inhibition not through enkephalinergic pathways but by the many types of spinal cell they synapse with. The paragigantocellular reticular nucleus is implicated in the descending noradrenergic system, it does not contain noradrenergic fibres but is thought to relay to a noradrenergic structure which in turn inhibits painful stimuli. Acupuncture is known to stimulate this system (Takeshige et al 1992).

4.3.3 Diffuse noxious inhibitory controls (DNIC)

DNIC is the term used for a powerful system that is known to have an inhibitory effect Le Bars et al 1979) It has a very short-term effect and is an opoidergic system that acts on the WDR cells. As mentioned earlier these cells convey impulses to the cortex for the perception of pain. Bing et al (1991) has shown that this system is activated by needle stimulation at both acupuncture points and non- acupuncture points.

4.3.4 Oxytocin

Some recent research suggests that there is an increase in oxytocin as a response to non-noxious sensory stimulation. Oxytocin is a hormone and its levels are thought to increase and give rise to an “anti-stress” effect after acupuncture (Uvnas-Moberg et al 1998). It was shown that a five day treatment period with oxytocin gave rise to a long term increase in pain threshold in rats (Petersson et al 1996). More recently oxytocin has been found to have a sedative and anxiolytic effect in rats (Petersson et al 1998). Thus, the increase in oxytocin levels following acupuncture may also provide an explanation for the longer lasting effects of acupuncture. Generalisation of these results to the human population should be considered with caution as the majority of these studies have only yet been carried out in rats.

4.3.5 Placebo effect

Acupuncture may also produce a significant placebo effect. A meta–analysis reviewing placebo versus no treatment suggested that the placebo effects are very small (Hrobjartsson et al 2001). However, some authors have the opposite opinion and describe the non-specific, placebo effects of acupuncture as having powerful and clinically significant influences upon outcomes (Kaptchuk 1998, Kaptchuk 2002). There are several recent controlled trials supporting the theory that acupuncture interventions provide clinically significant placebo effects (Linde at al 2005, Brinkhaus et al 2006, Haake et al 2007, Witt et al 2005, White et al 2012).

All of these trials have observed similar findings whereby outcomes for acupuncture and sham intervention groups were no different. However, substantial improvements in symptoms were evidently greater in the acupuncture and sham acupuncture groups than in control groups, where participants received conventional or no treatment. Linde et al (2007) in a review of four RCTs of acupuncture for various painful conditions suggested that it was in fact the patient's expectation of pain relief that was the most robust predictor of efficacy of acupuncture treatment. This would appear to further support the theory the mechanisms for successful treatment outcomes with acupuncture may be by means of a placebo effect.

Acupuncture often involves several treatment sessions that not only consist of needle insertions but also discussions between patient and clinician re the mechanisms of treatment and the diagnosis. This patient-clinician relationship may well facilitate a form of therapeutic counselling which could play a role in the reduction of anxiety and improved wellbeing. Kaptchuk et al (2008) suggest that both the practitioner-patient relationship and a more supportive consultation processes can highly influence clinical outcomes and can add to the placebo effect observed in many acupuncture trials.

White et al (2012) explored the impact of the practitioner and the patients' belief on the outcomes of acupuncture treatment. This recent RCT of acupuncture for Osteoarthritis (OA) suggests that the patient's perception of the practitioner's experience and authority, affected outcomes. This trial also aimed to examine the effects of manipulating the consultation by randomising some participants to either empathic or non-empathic consultations. However, it appears that the process of consenting the participants for this may well have disguised any differences in outcome as a result. Participants were prepared for non-empathic processes and appeared to draw on others for sources of empathy during their clinic

visits. These authors also discovered that patient's beliefs in the treatment veracity influenced how they would self-report outcomes which could distort interpretation of this type of study.

In summary, several potential pathways for the mechanisms of acupuncture have been presented in this section and evidence to support these mechanisms has been highlighted. However, it is important to note that this evidence has been based on
experimental data from both animal and human studies. The majority of the studies available on the mechanisms of acupuncture are examining its effect on pain. Hence, the evidence for these mechanisms is more convincing, than those that may explain the effects that acupuncture has upon the many non-painful conditions, such as anxiety, depression, nausea, breathlessness.

4.3.6 Is acupuncture safe?

Acupuncture is considered to be a safe treatment modality and surveys of acupuncture treatments support this. White et al (2001) reported on 31,822 acupuncture treatments carried out by members of the British Medical Acupuncture Society or the Acupuncture Association of Chartered Physiotherapists and significant but not serious events, were reported . Minor adverse events occurred in 43 of these treatments. The minor events included fainting, exacerbation of symptoms and lost or forgotten needles. This is the equivalent of 1.4 events per 1000 treatments. A similar survey by MacPherson et al (2001) examined 34,407 acupuncture treatments and similar results were found. These results suggested that 0.12% of acupuncture treatments resulted in minor adverse events. The adverse events included nausea, vomiting, dizziness and bruising. The occurrences of these adverse events are less than those found in other treatments, such as medications, that are considered to be safe.
White et al (2006) carried out further evaluation of the safety of acupuncture by combining the results of the above studies with further

reports. This evaluation of 4,441,103 acupuncture treatments reported 11 serious adverse events, including seven pneumothoraces, two broken needles, one asthma attack and one instance of depression with suicidal thoughts. The minor adverse events were as expected more common and White et al (2006) reported minor events in 3% of cases.

These results are supported by the more recent data from Xu et al (2013) who stated that four surveys of registered, qualified acupuncture practitioners confirmed that serious adverse events after acupuncture were uncommon. These surveys examined greater than 3 million acupuncture treatments and there were no deaths, permanent disabilities and all patients that suffered a serious adverse event, fully recovered.
In summary the literature suggests that acupuncture is an extremely safe treatment modality and the more common adverse events are minor and pose very little risk to the patient.

4.4 Acupuncture for Respiratory Disorders

This section will summarise the limited evidence for the use of acupuncture/ acupressure for symptoms commonly associated with the respiratory conditions of COPD and HVS i.e. breathlessness, bronchoconstriction, retained secretions and hyperventilation. It is important to review this literature as many of the symptoms of respiratory disorders can influence levels of anxiety, which is the main focus of this thesis (Leivseth et al 2012).

4.4.1 Acupuncture and retained secretions

Impaired mucociliary clearance is a feature of several acute and chronic respiratory disorders, resulting in infections and airways obstruction. Three recent systematic reviews conclude that acupuncture for allergic rhinitis is safe, but that results are mixed and inconclusive (Roberts et al 2008, Xiao et al 2009, Lee et al 2009). The only relevant recently published research involving human participants is a study with a misleading title in a nursing

journal (Maa et al 2007). It is misleading on two grounds a) because it is labelled as a pilot study but reads more like a trial that failed to recruit sufficient numbers, and b) the title overstates the findings. Forty-nine patients with bronchiectasis were randomised to receive eight weeks of self-administered acupressure, sham acupressure or standard care. Only 35 completed the study and the authors elected only to analyse these data (i.e. did not use intention-to-treat analysis). Five outcome measures were reported, from three time points, but no primary outcome was identified. The text and tables of presented results are conflicting, as the tables indicate no significant differences among groups for any outcome, but the text claims improvements in self assessed ease of sputum clearance, albeit in the sham group. A systematic review by Passalacqua et al (2006) of the use of CAM for rhinitis and asthma, found few trials for rhinitis, and none of good methodological quality (Passalacqua et al 2006).There is therefore currently no convincing research evidence supporting the hypothesis that acupuncture has a beneficial effect on mucociliary clearance.

4.4.2 Acupuncture and bronchoconstriction

Bronchoconstriction (narrowing of airways) is commonly associated with asthma (a chronic inflammatory disorder of the airways). TCM practitioners have been using acupuncture for the treatment of both acute and chronic asthma for many years. Although there are several published studies examining the efficacy of acupuncture in the treatment of asthma and bronchoconstriction, results are contradictory and have several methodological weaknesses (Tandon et al 1991, Hirsch et al 1994, Martin et al 2002, Najafizadeh et al 2006).

A systematic review and meta-analysis examined acupuncture trials for asthma published between 1970 and 2000 and out of 200 only 12 trials met their inclusion criteria (Martin et al 2002).It was not possible to obtain the data from one trial therefore only data from 11 trials were included.

Seven of the 11 trials used crossover designs, yet only two considered the possibility of period effects and none considered the carry-over effects of acupuncture treatment. The potential carry over effects of acupuncture have been described in a trial by Gibson et al (2007).
Overall analysis revealed there were no statistically significant effects of acupuncture on asthma, in terms of improving lung function or subjective symptoms. However, on analysis of subgroups some significant effects were found in those trials in which bronchoconstriction had been induced. Each of the trials had used various study designs, methods of stimulation, treatment periods and various placebo interventions which may have resulted in stimulation of non-asthma or acupuncture points relevant for other respiratory disorders (Jobst 1995). This may have promoted a physiological response (Le Bars 1979). The authors concluded that there was no evidence of acupuncture efficacy in the treatment of asthma. However, they also acknowledged the shortcomings with their review, e.g. the total integrated sample size was still below the sample size needed to be adequately powered.

A Cochrane review on acupuncture for chronic asthma reached similar conclusions despite using different inclusion criteria (McCarney 2003). The Cochrane review examined chronic asthma, and studies were included if they were randomised trials using acupuncture techniques, including laser/ electrostimulation (Tandon et al 1991, Hirsch et al 1994, Najafizadeh et al 2006). A total of 12 trials (n=350) using both TCM and western approaches were included in the review. The acupuncture treatment strategies differed greatly amongst the studies. Only six out of the nine studies using needle acupuncture, attempted to attain *de qi*. The placebo or sham arms of the needling studies were no different to those included in the Martin et al review (2002), in that they all involved needling either non-acupuncture points or supposedly inactive acupuncture points. The selection of an appropriate inert placebo for acupuncture trials will be discussed in Chapter 8.

The primary outcomes used for the trials included in the Cochrane review were measurements of pulmonary function e.g. Peak Expiratory Flow rate (PEFR) or FEV_1. The trials also monitored medication usage and subjective measures such as global wellbeing. The variability in study design, outcomes and methods of intervention resulted in the data from only two outcomes being pooled (PEFR and global wellbeing). There were no statistically or clinically significant differences between acupuncture and control for either of these outcomes. Although both recent reviews focused on different types of asthma, both reached similar conclusions i.e. that evidence to support the use of acupuncture for asthma was inconclusive, but that some studies do report improvements in medication usage and /or subjective measures. Some patients with asthma may benefit from acupuncture treatment, but identifying this group is not yet possible. A small study by Stockert et al 2007(n=17) carried out subsequent to the last systematic review, suggested a statistically significant improvement in bronchoconstriction, in children with asthma. However, this study was small and acupuncture was used as an adjunct to probiotic therapy and therefore firm conclusions cannot be made based upon these results.

In a controlled study, patients with COPD were stratified into groups according to the extent of their pulmonary hypertension (Buevich et al 2005). The control group received standard medical and physiotherapy care. The treatment groups received acupuncture but this was not standardised in that the number of treatments, the duration of treatments and the number of needles inserted varied according to individuals. The results showed some statistically significant improvements in FEV_1 for the acupuncture group when compared to standard care. However, this study was not sufficiently powered and due to the fact that individuals received different regimens of acupuncture treatment, it is not possible to make generalisations based upon this trial. The many methodological weaknesses in acupuncture research prevent a definitive conclusion as to its efficacy in the treatment of bronchoconstriction.

4.4.3 Acupuncture and breathlessness

A Cochrane review by Bausewein et al (2008) examined non-pharmacological interventions for breathlessness and found 5 studies relating to acupuncture (Jobst et al 1986, Lewith et al 2004, Vickers et al 2005) or acupressure (Maa et al 1997, Wu et al 2004) worthy of including in their review. All of these studies involved COPD participants except the Vickers et al study (2005) which involved only cancer patients. Any comparisons across these studies are made more complex due to the methodological differences between them. Intervention periods ranged from seven days to six weeks. Assessment of breathlessness in these studies varied not only between studies i.e. use of visual analogue scale (VAS)/ numerical rating scale, Borg scale, St George's Respiratory Questionnaire, but also within studies (the Wu et al study was published twice in 2004 with different outcome measures). As with many studies of this nature, although improvements were often seen from pre to post intervention, participants in the placebo groups also improved, thereby giving no significant differences between groups at outcome assessment. All of the studies (except Lewith et al 2004) used sham acupuncture/ acupressure, however sham versions are unlikely to be totally inert and the non-specific effects of any placebo make the ideal trial difficult to design (Birch 2006). Lewith et al (2004) tried to avoid this problem by using mock transcutaneous electrical nerve stimulation (TENS) applied to the same acupressure point. However, there is a chance that some gentle acupressure is applied when attaching the TENS to the skin, which could confound the results.

Suzuki et al (2012) examined a cohort of 68 patients diagnosed with COPD and examined the effect of acupuncture on breathlessness/dyspnoea on exertion. This was a randomised placebo-controlled trial. Participants were randomised into groups to receive either traditional acupuncture or placebo acupuncture (Park sham placebo

needle). Each participant received the intervention once weekly for 12 weeks. This study revealed statistically significant improvements for the traditional acupuncture group in the Borg breathlessness scale after exertion, the six-minute walk test and the SGRDQ when compared to the placebo acupuncture group. This was an interesting study which suggests acupuncture is superior to placebo in terms of breathlessness in COPD. However, the authors do not state whether a power calculation was carried out and did not keep a record of whether the participants had any changes in their COPD medications/ treatment during the 12-week period. The authors state that a larger RCT is required.
Overall, the level of evidence for the use of acupuncture/acupressure for breathlessness is low.

4.4.4 Acupuncture and Hyperventilation Syndrome

There is currently little objective evidence to support or refute the use of acupuncture in the treatment of HVS, either because it has been infrequently researched, or because negative trials have not been published. A small, uncontrolled study conducted by Levashov et al (1992) examined the use of acupuncture in 15 participants previously diagnosed with HVS. They used a combination of both body and ear points and assessed both subjective sensations (breathlessness, air hunger and chest pain) and objective measures such as (ECG changes and minute ventilation), before and after the course of treatment. The results from this study suggested that participants had less heart rate variability and lower minute ventilation, as well as reporting improvements in subjective sensations, following acupuncture treatment. However, this study was not controlled, had a small sample size and provided no statistical analysis. Results must therefore be considered with caution.

This author conducted a single-blind crossover trial comparing acupuncture with BR treatment examined the effects of a 4-week acupuncture treatment, with a 4-week course of BR for patients with HVS

(Gibson et al 2007). In this study both groups received acupuncture and BR with a 1-week washout period. Anxiety was used as the primary outcome measure and was assessed using the HAD scale. The results from this study indicated statistically significant treatment differences (between acupuncture and BR) in favour of acupuncture. There were reductions in both anxiety (p=0.02) and symptoms scores (p=0.03). As this was a crossover trial the potential carryover effect needed to be examined to ensure the first arm of the trial had no effect on the second. The results revealed that there was no carryover effect, however, the sample size (n=10) was very small and may have masked any carryover effect on the results.There were also other methodological issues in that the participants could not be “blinded” to their treatment and the HAD scale is a subjective outcome measure. Further discussion surrounding the issues with “blinding” in acupuncture trials and outcome measure selection will be discussed in Chapter 8.

In clinical practice physiotherapists, would not choose to administer acupuncture for HVS in isolation and it is more often used as an adjunctive treatment to augment the physiotherapy BR programme. Further controlled studies examining these effects are essential to enable firm conclusions regarding the efficacy of acupuncture in the treatment of HVS.

In general, there is a lack of research evidence to suggest any benefit for acupuncture over placebos when treating respiratory symptoms. This contrasts with the considerable longevity of the use of TCM for these conditions, and with the demonstrable popularity for the use of acupuncture by a significant minority of individuals. One of the reasons for this apparent dichotomy relates to the problems with designing robust acupuncture trials which will be discussed in Chapter 8.

4.5 Acupuncture for anxiety and anxiety disorders.

The role of anxiety related disorders in HVS and COPD has previously been outlined within this document. The evidence available for the use of acupuncture for anxiety has been reviewed and will now be discussed (See appendix I for search strategies).

A systematic literature review was published in 2007 which found 12 controlled trials, ten of which were randomised (Pilkington et al 2007). The ten RCTs were Lewis 1987, Uskok 1995, Liu et al 1998, Eich et al 2000, Wang &Kain 2001a, Wang et al 2001b, Kober 2003, Zhang et al 2003, Wang et al 2004. 2 were non-randomised controlled studies (Lanza 1986, Zhou 2003) investigating the effects of acupuncture on anxiety and anxiety disorder over the past 25 years. Two cohort studies were also referred to in the paper but were not included in the systematic review.
A further search revealed a further seven RCTs (Agarwal et al 2005, Wang et al 2005, Karst et al 2007, Isoyama et al 2011, Wu et al 2011, Black et al; 2011, Michelak-Suaberer et al 2012), two cohort studies (Spence et al 2004, Wang et al 2005) and a case series (Rosted et al 2010). Therefore, there were 17 RCTs examining acupuncture for anxiety that were reviewed. Three of these examined anxiety disorders (Liu et al 1998, Eich et al 2000, Zhang et al 2003) one examined anxiety during drug withdrawal (Black et 2011), one looked at anxiety in Women during invitro fertilisation treatment (Isoyama et al 2011) and the remaining 11 examined the effect of acupuncture on certain anxiety provoking situations (Lewis 1987, Uskok 1995, Wang et al (a) 2001, Wang et al (b) 2001, Kober et al 2003, Wang et al 2004, Agarwal et al 2005, Wang et al 2005, Karst et al 2007, Wu et al 2011, Michelak-Sauberer et al 2012) such as pre-operatively or prehospital admission or prior to dental treatment (See Tables.3 a, b & c and 4a & 4b for a summary of all RCTs of acupuncture and anxiety studies). (See appendix I for search strategies).

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All the studies used a variety of acupuncture methods including auricular acupuncture, electroacupuncture and body acupuncture. They all found that acupuncture provided an improvement in anxiety ratings but four revealed non-statistically significant results, when compared to a control (Lewis et al1987, Karst et al 2007, Zhang et al 2003 & Black et al 2011).

When assessing the methodological quality of the studies there were several issues that need to be highlighted. In all of the 17 trials both randomisation and group matching was poorly defined. Therefore, it is not possible to rule out bias in this process. Only two carried out sample size calculations (Wang et al 2001b, Kober et al 2003) and they found statistically significant differences in the acupuncture groups.
The remaining studies were underpowered and this may have resulted in missing statistically significant differences due to small sample sizes (Lewis et al1987, Karst et al 2007, Zhang et al 2003 & Black et al 2011). It may also, due to the insufficient power, have reduced the likelihood that the statistically significant results reflect a true effect.

The studies examining anxiety neurosis or generalised anxiety disorder compared acupuncture to a variety of treatments. Some used sham ("Sham" acupuncture is used in this text to mean any procedure that is pretence of acupuncture) acupuncture/acupressure as controls (Eich et al 2000, Wang et al 2001a), others used anxiolytic drug therapy as a comparison to acupuncture treatment (Lewis 1987, Uskok 1995, Wang et al 2003, Zhang et al 2003, Zhou 2003). In studies where no differences were found between treatments, the control intervention may have been equally as effective as the acupuncture treatment making firm conclusions about the effectiveness of acupuncture difficult (Zhang et al 2003).

In one study, less than half of the participants were diagnosed with anxiety disorder (13) and the remaining participants were diagnosed with minor depression (Eich et al 2000). Therefore, generalisation of these results to

the wider population of anxious patients is difficult. One study examined state anxiety levels in participants recruited from a drug addiction clinic and were undergoing withdrawal from psychoactive drugs (Black et al 2001). This study was an RCT of 101 participants who were randomised into three groups who received ear acupuncture, sham ear acupuncture or standard treatment. Black et al found no statistically significant differences between the three groups and concluded that the ear acupuncture had no specific efficacy over and above sham acupuncture or standard treatment. However, the participants only attended for acupuncture treatment for three consecutive days and this may not have been enough exposure to acupuncture to make these firm conclusions. The studies examining participants during more acute situational anxiety for example immediately prior to a hospital appointment or major surgery (Wang et al 2001, Kober et al 2003), were generally better reported and suggested that ear acupuncture is more effective than sham acupuncture. However, it may be difficult to apply any of these to HVS as it tends to be associated more with chronic anxiety and PD. Each of the studies used very different types and techniques of acupuncture. Those that examined the use of ear acupuncture (- application of needles, electrical stimulation or applied pressure to acupuncture points of the auricle or external ear Oleson 2012) had well defined points for both their intervention and “sham” groups. The controlled trials had different choices of control. Seven of the studies used “sham” acupuncture as a control (Wang et al 2001a, Wang et al 2001b, Kober et al 2003, Wang et al 2005, Agarwal et al 2005, Karst et al 2007, Michelak-Sauberer 2012). In all of these studies a “sham” point was chosen and well defined. The issues regarding choice of placebo controls for acupuncture trials will be discussed later in this chapter and in Chapter 8.

Those anxiety studies that used body acupuncture used either a prescription of well-defined points (Zhang et al 2003) or the points used were individualised for each patient according to the TCM approach. Any

comparison of these studies is difficult due to the very varied nature of both technique and type of acupuncture used. However, a study by Wu et al (2011) compared the use of body acupuncture to ear acupuncture. This was a small randomised trial of 35 participants who were attending a clinic pre-operatively they were randomised and received either body or ear acupuncture. The primary outcome was the Zung self-rating anxiety scale (SAS) and in both the body and ear acupuncture groups there were improvements in mean anxiety levels as measured by the SAS. However, the authors conclude that there were statistically significant differences in anxiety levels in each of the groups, comparing baseline to outcome. These differences need to be considered with caution as these are within-group differences and may relate to regression to the mean rather than a treatment effect.

The technique of acupuncture used was poorly defined in all of the papers. It was not stated whether for example needling occurred until “de qi” or needling sensation, occurred. The duration of treatment and the number of sessions were standard within each of the trials however; it varied from twice weekly to daily sessions and one session to 30 sessions, between the trials. There is no standard accepted number of sessions, time for needling or duration of courses of treatments. However, it is important to note that there is some evidence to suggest the body’s response to acupuncture may change over time (Dyrehag 1997). The evidence to support this is very limited, however, in those studies where there were few acupuncture sessions, the participants may not have gained maximum effect from the acupuncture treatment. Further research is required in this area of acupuncture to determine the optimum duration of a course of acupuncture treatment.

Only two of the trials examined had outcome measurements carried out by blinded assessors. (Kober et al 2003, Wu et al 2011). This may have resulted in some bias within the remaining trials when outcomes were

being measured. Many of the studies used non-validated anxiety scales or subjective symptom reports which can make the results unreliable. There were also a variety of validated anxiety scales used across the studies, which made comparisons of outcome difficult.

Potential mechanisms of how acupuncture works for anxiety disorders is mentioned by most authors in their discussions. There seems to be a consensus that endorphin release, 5-HT (serotonin) and oxytocin are the main mechanisms for acupuncture in these trials. None of the trials attempted to measure any of these substances as outcome measures, so the mechanisms remain unclear. It is also important to note that none of the authors discussed any potential placebo effect of acupuncture.

In summary, there is a paucity of available literature examining acupuncture for the treatment of anxiety disorders. This may be due to the difficulty in the design of a methodologically sound study in this area. Due to the psychological nature of the condition, there may well be a large effect purely from the therapist-patient relationship; there are debates as to which techniques to use, and how often to apply them. There are also difficulties with “blinding” the intervention and the potential physiological effects of sham or placebo procedures makes controlled trials difficult.

The highlighted studies on anxiety show some promising results. However, further methodologically sound trials on the effects of acupuncture are needed.

Study	Design	Acupuncture Type	Control	Outcome Measures	Results
Lewis 1987	RCT n=90 (3-arm)	Auricular acupressure	Diazepam 10mg or Relaxation techniques	Patient reported anxiety	Anxiety between groups NS Reduced sweating (acupuncture p<0.005)
Uskok 1995	RCT n=40	Body and auricular acupuncture (Pericardium 6 and Shenmen)	Diazepam 10mg	STAI	Acupuncture effective (p<0.001)
Wang et al (a) 2001	RCT n=55 (3-arm)	Auricular acupuncture (Shenmen OR relaxation point)	Sham auricular acupuncture	STAI	Acupuncture at relaxation point reduced anxiety significantly (p<0.035)

Table 3a. Summary of controlled trials examining acupuncture for situational anxiety.
Key: RCT: randomised controlled trial, **NS**: not statistically significant, **STAI**: State-Trait Anxiety Inventory, **VAS**: visual analogue scale

Study	Design	Acupuncture type	Control	Outcome Measure	Results
Wang et al (b) 2001	RCT n=91	Auricular acupuncture Group1 TCM points Group 2 Relaxation points	Auricular Sham points	STAI	Relaxation acupuncture group significantly less anxious compared to control (p=0.01)
Kober et al 2003	RCT n=36	Auricular acupuncture At relaxation point	Auricular Sham points	VAS anxiety scale	Acupuncture groups reduced anxiety (p=0.002)
Wang et al 2004 RCT	RCT n=67	Auricular acupuncture at TCM anxiety points	Auricular Sham points	STAI	Acupuncture group had significantly reduced anxiety (p=0.014)

Table 3b. Summary of controlled trials examining acupuncture for situational anxiety.
Key: RCT: randomised controlled trial, **NS**: not statistically significant, **STAI**: State-Trait Anxiety Inventory, **VAS**: visual analogue scale

Study	Design	Acupuncture	Control	Outcome	Results
Agarwal et al 2005	RCT n=76	Acupressure Group1 TCM points Group 2 Relaxation points	Acupressure to "sham point"	VSS	Anxiety on VSS reduced significantly compared to control p<0.001 but not sustained greater than 30 minutes.
Wang et al 2005	RCT n=61	Acupressure at Yintang point	Acupressure to "sham" point	STAI	Anxiety reduced significantly in the acupuncture group compared to control p=0.03
Karst et al 2007	RCT n= 67	Group 1Auricular therapy Group 2 Placebo acupuncture Group 3 sedative (Midazolam)	No treatment	STAI	Auricular therapy and sedative groups less anxious p=0.01 No differences between the acupuncture group and sedative
Wu et al 2011	Randomised/single blind n=35	Group 1 body acupuncture	Group 2 Auricular therapy	SAS	Groups had improved anxiety post intervention. Significant differences within the groups. p=0.00
Michelak-Sauberer et al 2012	RCT n=182	Group 1 Auricular acupuncture Group 2 "sham "auricular points used	No treatment	STAI	Reduction in state anxiety in both auricular acupuncture and sham groups. Significantly greater reduction in auricular acupuncture group compared to sham p=0.008.

Table 3c. Summary of controlled trials examining acupuncture for situational anxiety. Key: RCT: randomised controlled trial, **NS**: not statistically significant, **STAI**: State-Trait Anxiety Inventory, **VAS**: visual analogue scale, SAS Zung self-anxiety rating scale

Study	Design	Acupuncture type	Control	Outcome measures	Results
Liu et al 1998	RCT (3-arm) n=240	Group 1 individualised acupuncture Group 2 Acupuncture & BD	BD only	Clinical symptoms & Zung anxiety rating	Acupuncture and BD had greater improvements in anxiety ($p<0.01$)
Eich et al 2000	RCT n=56	TCM body acupuncture	Sham acupuncture	HAMA HAMD	Acupuncture group greater improvement in anxiety ($p<0.01$) after 10 sessions
Zhang et al 2003	RCT n=296	TCM body acupuncture 4 groups	Doxepin 25mg 3x daily	Clinical symptoms & self rating anxiety scale.	No significant differences between groups($p>0.05$)

Table 4a. Summary of RCTs examining acupuncture for clinical anxiety
Key: RCT: randomised controlled trial, **BD**: behavioural desensitisation, **HAMA**: Hamilton Anxiety scale, **HAMD**: Hamilton Depression scale

Study	Design	Acupuncture type	Control	Outcome measures	Results
Isoyama et al 2011 Anxiety in invitro fertilisation	RCT n=43	Body acupuncture	Sham acupuncture (non-acupuncture points)	HAD	Significant reduction in anxiety scores in the acupuncture group p=0.0008
Black et al 2011 Anxiety in Drug withdrawal	RCT n=101	Auricular therapy	Sham auricular therapy Standard treatment group	STAI	State anxiety improvements within groups but no between group differences.

Table 4b. Summary of RCTs examining acupuncture for anxiety
Key: RCT: randomised controlled trial, **BD**: behavioural desensitisation, **HAMA**: Hamilton Anxiety scale, **HAMD**: Hamilton Depression scale **HAD:** Hospital anxiety and depression scale

4.6 Physiotherapy treatment strategies for hyperventilation syndrome

Physiotherapy treatments that have been used with some success for HVS have traditionally been in the form of BR (BR), relaxation and biofeedback techniques. Although several studies have examined the effects of BR techniques on HVS / breathing pattern disorders, the potential mechanisms for their efficacy remain under debate (Grossman et al 1985, DeGuire et al 1992, Tweedale et al 1994, De Guire et al 1996, Han et al 1996, Han et al 2004).

Acupuncture for HVS has been infrequently studied, with only two small underpowered studies identified (Levashov et al 1992, Gibson et al 2007). However, there is a growing body of evidence for the efficacy of acupuncture in the treatment of anxiety which, is frequently associated with HVS (Uskok 1995, Liu et al 1998, Eich et al 2000, Wang &Kain 2001a, Wang et al 2001b, Kober 2003, Zhang et al 2003, Wang et al 2004, Agarwal et al 2005,Wang et al 2005, Karst et al 2007, Pilkington et al 2007, Isoyama et al 2011, Wu et al 2011, Black et al; 2011, Michelak-Suaberer et al 2012).

4.7 Breathing retraining for hyperventilation

BR techniques have been used successfully in the treatment of HVS by both physiotherapists and clinical psychologists since the late 1960's (Lum 1977, Tweedale et al 1994, Han et al 1996). Both clinical groups use similar techniques focusing on activation of diaphragmatic motion using breathing control, and slow breathing techniques. Relaxation techniques are also generally an integral part of these treatments.

There is a small number of studies carried out within the last 20 years (seven trials) that examine the efficacy of BR in the treatment of HVS or breathing pattern disorders (Grossman et al 1985, DeGuire et al 1992, Tweedale et al 1994, DeGuire et al 1996, Han et al 1996, Han et al 2004, Hagman et al 2011). (See Table 5 for a summary of the BR studies for

HVS). More recent studies investigating BR have examined its efficacy in the treatment of asthma (Thomas et al 2005, Thomas et al 2009). It is well documented that many asthma patients exhibit symptoms of dysfunctional breathing (Bowler 1998, Reddel et al. 2006; Cowie et al. 2008). Breathing techniques such as the Buteyko breathing technique have been examined within the literature (Bowler et al 1998, Cooper et al 2003, McHugh et al 2003, Bruton & Lewith 2005). This technique is based upon the theory that asthma patients hyperventilate, which leads to bronchoconstriction and exacerbates the symptoms of the condition. Buteyko uses periods of "slow breathing" and breath holding strategies to raise CO_2 levels, which in theory encourages bronchodilation. However, these trials have not been reviewed in detail because the focus of this PhD is people with HVS, who do not have other respiratory conditions.

The quality of evidence provided by the seven trials included within this review of BR for HVS is poor (Grossman et al 1985, DeGuire et al 1992, Tweedale et al 1994, De Guire et al 1996, Han et al 1996, Han et al 2004, Hagman et al 2011). There were many methodological issues such as being inadequately powered, non-blinded randomisation (i.e. participants were not blinded to their group allocation), poor standardisation of treatment sessions between participants and poorly defined BR training programmes. Six out of the seven trials used $ETCO_2$ measurements as the primary outcome measure; however, as has previously been discussed there remains a debate about whether hypocapnia is the central mechanism for HVS, so this may not be the most appropriate choice of primary outcome measure. The most recent study examining BR for HVS uses the term "dysfunctional breathing" to describe HVS and focused more on the emotional aspects of the condition, using outcome measures such as the SF-36 (Medical outcomes survey short-form) and the HAD scale. This reflects the shift in thinking in current clinical practice in the treatment of HVS. Greater emphasis is now placed on the psychological

and functional aspects of the condition, as opposed to physiological measures.

All of the seven studies revealed statistically significant results suggesting that BR is effective for the treatment of HVS. These results need to be considered with caution and may reflect some publication bias as no studies are available with negative findings. The close association between anxiety and HVS is highlighted within all of the studies yet only five out of the seven measured the effect of BR on anxiety (Grossman et al 1985, Tweedale et al 1994, Han et al 1996, Han et al 2004, Hagman et al 2011).

The outcome measures used to measure anxiety levels were either a validated State-Trait Anxiety Inventory (Speilberger et al 1970) (STAI) (Grossman et al 1985, Han et al 1996, Han et al 2004), a non-validated self-rating anxiety scale (Tweedale 1994) or the HAD scale (Hagman et al 2011). The study by Tweedale et al (1994) not only prompts doubt over the anxiety outcomes by using a non-validated anxiety scale, it also included patients with co-existing conditions, such as chronic fatigue. It is likely that these participants would describe much higher anxiety and depressions levels when compared to an individual with HVS and no co-existing conditions. This is likely to have influenced the results of this study. Researchers are more aware of these issues and are now beginning to investigate HVS alone, by excluding those with co-existing morbidities or by comparing individuals with HVS alone to HVS as a co-existing condition, such as is found in association with asthma (Hagman et al 2011). This study by Hagman et al (2011) also uniquely examined the long-term effects of BR for HVS by carrying out a five-year follow up of participants. However, these authors used a group of asthma patients who were not given any BR/ physiotherapy intervention as a control arm, which presents a multitude of issues. Patients with asthma often require several visits to healthcare practitioners over a course of five years and these

interactions may well have influenced outcomes. The authors also used a non-validated method of diagnosis of HVS and relied upon the individuals describing five out of ten symptoms listed by the respiratory physicians and physiotherapists. The symptoms list had many symptoms that could be present in many respiratory disorders, not just HVS.

Extrapolation of the results of these trials is further hindered by the lack of acknowledgement of whether participants were on any anxiolytic medication. Only one of the seven trials documented whether any of their participants were currently taking anti-anxiety medication (Han et al 2004). They found that 13% (10) of their participants were on anxiolytic medication before the trial and three of these were able to reduce their doses and stop the medication following BR. Nine of the participants (11%) however, needed to commence medication at the end of the trial, as symptom relief where BR was inadequate. In total, 16 out of the 76 participants in this trial had either commenced or were continuing to take anxiolytic medications such as, Diazepam or Lorazepam. The authors of this study concluded that BR "works on both mind and body, more specifically on anxiety as well as on breathing" (Han et al 2004 page 6). These results were not statistically significant and again must be considered with caution.

A mechanism for the efficacy of BR for HVS remains unclear. BR forms the main component of the treatment packages for HVS however; some treatment packages labelled as BR involve additional techniques such as relaxation methods or biofeedback equipment. The nature of the treatment and the use of techniques that are complex for patients to master, often result in lengthy therapist-patient interaction, which in itself can influence outcomes of therapies. Hence, it is not clear whether it is a single component of the "BR treatment package" or the combined approach that is effective. Future controlled trials addressing these issues

and which account for non-specific treatment effects, are essential in future research within this field.

In summary BR is an accepted therapy used within clinical practice by many clinicians for the treatment of hyperventilation symptoms, and hence for HVS. Robust research evidence to support the clinical use of the technique in HVS is lacking, yet anecdotal evidence from clinical practice suggests BR treatment is successful.

Table 5. to show the main characteristics of the seven studies reviewed to examine the effect of BR in the treatment of HVS

	Study design	No of participants	Type of BR	Control Arm	Outcome measures	Results
Grossman et al 1995	RCT	56	Biofeedback training device	Non-incremental training device	ETCO2 Nijmegen STAI	↑ETCO2 (P<0.001)
DeGuire et al 1992	RCT	41	Biofeedback group sessions	Advice only	ETCO2 Symptom diary, RR	↑ ETCO2 (NS)
Tweedale et al 1994	Cohort	22	Physiotherapy BR	N/A	Nijmegen HAD	↓Anxiety ↑ETCO2,Nijmegen scores(P<0.01)
DeGuire et al 1996	Follow up	10	Single evaluation	N/A	ETCO2 Symptom score RR	↓ETCO2 (P<0.01)
Han et al 1996	Cohort	92	Physiotherapy BR	N/A	ETCO2 Nijmegen STAI	↑Nijmegen (P<0.0001) ↓Anxiety (P<0.05)
Han et al 2004	Cohort	64	Breathing Therapy	N/A	ETCO2 STAI Nijmegen	↑ETCO2(p<0.02) Anxiety &Nijmegen NS
Hagman et al 2011	Controlled trial	45	BR	asthma patients No physiotherapy	SF-36 HAD scale Nijmegen	↑PCS (p<0.04) ↓Nijmegen (p<0.001)

Key: ETCO2 = End Tidal carbon dioxide STAI= State Trait Anxiety Inventory RR = respiratory rate HAD= Hospital Anxiety & Depression scale Nijmegen = Nijmegen Questionnaire. NS= not statistically significant (Where results are statistically significant the P- value is given) PCS= Physical component summary of SF-36.

4.8 Physiotherapy for COPD

Physiotherapy for COPD is most frequently provided within the context of pulmonary rehabilitation (PR) programmes, which are widely viewed as a major component of the treatment of COPD (Nici et al 2006). PR programmes are typically physiotherapy led with multidisciplinary input, and involve the delivery of exercise training, education and psychosocial support, more commonly in outpatient settings. There is good evidence within the literature that a structured PR programme, whereby patients are given education about their condition and self-management strategies as well as an incremental training programme over a period of weeks, can provide statistically and clinically significant improvements in reducing fatigue, dyspnoea and increasing exercise capacity (McCarthy et al 2015). This Cochrane review in 2015 included a total of 65 RCTs (3822 participants) in the meta-analysis. The authors found statistically and clinically significant improvements in quality of life, functional and maximal exercise tolerance, when PR was compared to standard care. McCarthy et al concluded that the evidence was so convincing that further RCTs comparing PR with conventional care were not warranted.

In clinical practice, PR has many different formats depending on where the programmes are being accessed. The PR studies reviewed by McCarthy et al (2015) reflect this, in that there is considerable variety in the types of PR programmes in terms of location, the intervention delivered (exercise alone versus education and exercise) as well as the outcome measures used. McCarthy et al (2015) did carry out some subgroup analysis to examine some of these variables, which revealed no differences between those that received exercise with educational/ psychological interventions compared to those receiving exercise alone. The authors stated “these results could be confounded and should be considered with caution.” Therefore, it is unclear whether it is a single component of PR or the PR itself as a whole that delivers improvements (McCarthy et al 2015).

There is a well-documented body of evidence that COPD is associated with anxiety and depression (Maurer 2008) and that these co-existing psychological conditions can have an impact on reducing quality of life, increasing frequency exacerbations of COPD, reduced self-efficacy and ultimately can increase mortality (Kim et al 2000, Felker et al 2001, Dahlen et al 2002, Crockett et al 2002). There is growing evidence that PR may have a positive impact upon both anxiety and depression, and that this may be providing the clinically significant improvements in quality of life, that is evident within the PR literature (Coventry & Hind 2007). A systematic review in 2011 revealed that anxiety and depression were amongst the main factors that were associated with health-related quality of life (Tsiligianni et al 2011). There is also some suggestion that the presence of anxiety and depression has a greater impact upon functional outcomes and quality of life than either the severity of the disease or the presence of other co morbidities.

Current clinical guidelines make recommendations that patients with severe anxiety and/or depression should be treated with pharmacological intervention (Nici et al 2006). However, the evidence that anxiolytics or antidepressant medication, provide clinically significant improvements, is limited (Usmani 2011). There is also little agreement around the benefits of psychological therapies (e.g.CBT, psycho dynamic psychotherapy, interpersonal psychotherapy) for patients with anxiety relating to COPD. A recent Cochrane review has revealed only 3 RCTs and evidence of a “low quality” for the efficacy of psychological therapies for anxiety in COPD (Usmani et al 2017). PR, however has an increasing evidence base in terms of its benefits for anxiety and depression associated with COPD.

Coventry & Hind (2007) conducted a meta-analysis of PR for the treatment of anxiety and depression. They examined six trials out of a possible 23 RCTS that met their initial criteria. Seventeen studies were then excluded as they either did not use any psychological outcome measures or the

intervention given was not a PR programme. The findings from this meta-analysis revealed that PR was statistically more efficacious that conventional or control treatments in reducing anxiety and depression in people with moderate to severe COPD (Coventry & Hind 2007). The authors found that the largest effect size was associated with levels of depression reducing by a statistically significant amount. Although there was also a significant effect on anxiety levels the effect size was much smaller. There were also no statistically significant differences detected between PR and education alone, in terms of reducing anxiety and depression.

The results of this systematic review and meta-analysis support the efficacy of PR in reducing anxiety and depression associated with COPD. These results do need to be considered with caution for the following reasons:

(i) The degree of anxiety and depression in the participants of the six studies varied to the extent that some had severe clinical levels of anxiety/depression and others had subclinical levels.

(ii) There is a risk that the effect of PR on the physical and psychological outcomes was masked by the fact that some participants had high levels of anxiety/depression which could reduce the efficacy of rehabilitation

(iii) There were methodological problems with the included studies. Some were underpowered (White et al 2002), some resulted in more practitioner contact due to the increased frequency of the PR programmes (Emery et al 1998), and some were not adequately randomised giving imbalances between the treatment and control groups (Guell et al 2006).

(iv) The authors excluded many studies and did not include all that were available. They included those that had the same treatment and control groups

(v) The authors also excluded all non-English language articles due to time constraints. This may have excluded important trials that could have had an impact on outcomes of this analysis.

(vi) As this was a review paper and examined the effect sizes presented by the six studies, these authors were unable to make any conclusions about whether any differences found were indeed clinically significant which this author would argue is most relevant in terms of patient care.

A more recent study by Da Costa et al (2014) included 125 participants with COPD who completed a PR programme, three times per week for 12 weeks. The programme consisted of aerobic and strengthening exercise as well as education sessions and the Beck scales for anxiety and depression and St George's Respiratory Disease Questionnaire (SGRDQ) were used as outcomes. Da Costa et al reported that this PR programme provided statistically significant reductions in both anxiety and depression. This was however not an RCT and therefore a comparison with a "control" group was not possible. The cohort of COPD patients in this study were also not very anxious or depressed as only 17 out of the 125 had moderate anxiety with none being severe. In terms of depression only 19 out of 125 were moderately or severely depressed. The authors also stated that each participant had access to a support group provided by a psychologist which is not always provided in standard PR programmes, and may have confounded the results.

In summary PR is a key component in the treatment of chronic respiratory disease with a sound evidence base in terms of increasing exercise capacity, improving quality of life and reducing dyspnoea. However, any evidence within the literature examining the effect of PR on anxiety and depression should be considered with caution, due to the methodological issues surrounding the available studies.

4.9 Chapter 4. Summary

This chapter contains a review of the treatments commonly used in clinical practice by physiotherapists for HVS and COPD, and the effects that any treatments have on the anxiety components of these conditions.

A review of BR, PR and acupuncture has been presented.The possible mechanisms of acupuncture have also been presented as well as methodological issues surrounding research trials in these fields.

The studies discussed in this chapter, section 4.5 examined the effect of acupuncture on a variety of types of anxiety from situational anxiety to clinical anxiety and the methodological design also varied. The findings from these studies have informed the research design of the two studies included within this thesis. There were potential issues with many aspects of the studies such as in randomisation processes, small sample sizes, inappropriate choice of control, poor definition of the technique, duration and timing of the acupuncture and lack of blinding of the outcome assessors.

The literature around the choice of control for acupuncture studies, the potential nonspecific and therapeutic relationship effects has also influenced the design and methodology of the studies included within this thesis.

The increasing use of acupuncture, as an adjunct to physiotherapy for the treatment of HVS and associated anxiety, has been highlighted in this chapter. The paucity and poor quality of available literature within this area provides a clear rationale for methodologically sound studies examining the efficacy of acupuncture, as an adjunctive treatment to the standard physiotherapy for both HVS and COPD.

The next chapter will go on to discuss the methodological framework and experimental design of the two studies presented within this thesis as well as highlighting and justifying the outcome measures used to evaluate the effect of acupuncture on anxiety related to respiratory disorder.

Chapter 5. Experimental Design and Outcome Measures

5.1 Introduction

In this chapter there is a discussion of the methodological framework for both studies included within this thesis. It highlights the rationale for the choice of experimental design and discusses some of the methodological issues that that this author considered whilst developing the studies.

This chapter will then describe the main outcome measures used within the two studies presented in this thesis. There were many potential measures that could have been used and time was taken to explore all the available tools. The choices made about which measures were selected or rejected have been justified in terms of their suitability, reliability, and ease of administration.

5.2 Experimental Design

The evidence for the use of acupuncture in the treatment of anxiety, related to respiratory disorder, is by no means conclusive and further good quality studies are required to demonstrate its specific efficacy beyond placebo. Therefore, this author explored the options for evaluating acupuncture treatment in order to determine the optimal research design to use. The Medical Research Council (MRC) published a framework (updated 2006) to help researchers to adopt appropriate methods to successfully evaluate complex interventions in healthcare (www.mrc.ac.uk/complexinterventionsguidance). This framework proposed a process of development through to implementation of a complex intervention, in terms of phases of drug development (Craig et al 2008). The MRC guidance proposes the key elements of evaluating complex interventions as follows:

5.2.1. Development (identifying the evidence base, developing theory, modelling process and outcome).

This thesis has highlighted the existing evidence for the use of acupuncture for respiratory disorders and anxiety (see Chapter 4). The review of the evidence has enabled this author to generate the research questions stated in Chapter 1.

5.2.2 Assessing Feasibility (testing procedures, estimating recruitment and retention, determining sample size).

Evaluations are often undermined by issues with acceptability, compliance, delivery of intervention, recruitment and retention and smaller than expected effect sizes that could have been predicted by piloting (Eldridge et al 2004). A pilot study used to inform the design of Study 1 was carried out and published in 2007 (Gibson et al 2007). The data from this pilot study were used to determine the sample size for Study 1 and to assess whether it was feasible to use the placebo needle with a group of patients with HVS. The Pilot study is described in Chapter 6 and was not a scale model of Study 1. It was a cross-over study and findings from this trial suggested that due to the potential carry over effect of acupuncture, it was not appropriate to use this design for the larger trial.

Study 2 was designed as a feasibility study, as the pilot and RCT for Study 1 did not use ear acupuncture and there had been no previous study examining the use of ear acupuncture as an adjunct to PR. It was also essential to establish whether any patient benefits could be detected with the measures that were selected. In terms of level of evidence there are suggestions within the literature that a well conducted RCT can provide a good level of evidence on the feasibility of an intervention (Evans 2002).

5.2.3. Evaluation (assessment of effectiveness)

There are several designs to choose from when evaluating a complex intervention. The MRC guidance suggests that different designs suit different questions and that researchers must be aware of the whole range of experimental and non-experimental approaches in order to facilitate the most appropriate methodological choice. The main research question proposed in this thesis of whether acupuncture as an adjunct to physiotherapy enhances treatment outcomes, in terms of reducing anxiety, is assessing effectiveness and therefore a form of randomised trial was required to eliminate other factors that may influence outcome and selection bias. Also, one of the secondary research questions posed by this author, (Does acupuncture have any specific efficacy over placebo acupuncture treatment?) is attempting to identify specific effects of acupuncture and for this reason an RCT was required.

This author also considered that although results from a two-arm randomised controlled trial would inform whether acupuncture was superior to placebo or not, it would not distinguish between whether it was the physiotherapy intervention or the acupuncture that had an effect. Therefore, a three-arm RCT was chosen for the main study. As study 2 was a feasibility study and using a different acupuncture technique (ear acupuncture), three-arm trial was not considered appropriate to test the methodology. The decision about which outcome measures to use is an important one (Craig et al 2008). This author chose anxiety as the primary outcome in order to answer the main research question. Anxiety can be assessed in several ways. Section 5.3 will present all the outcome measures used in both studies with justification for the choices made.

The challenges with acupuncture research are well documented (Lewith et al 2002) such as, the non-specific effects of acupuncture and the influence of the therapeutic relationship on outcomes and these have influenced this author's choice of trial design in terms of which placebo or control to use in each study.

(i)Choice of control for acupuncture trials

The term “sham acupuncture” has been used in several acupuncture studies however, there has been controversy over its meaning. Sham acupuncture is described as an acupuncture control and may relate to various techniques, for example, needling of the non-specific points or superficial needling. There is uncertainty whether the control devices/techniques, used in acupuncture studies, are truly inactive and hence the term “sham acupuncture” is often used.

The issue of finding an appropriate control for acupuncture trials is controversial. A placebo control should be indistinguishable from real acupuncture but without the physiological or therapeutic effect. However, in acupuncture it seems necessary that a placebo touches the skin. This presents a problem because it involves a physiological stimulation which it has been argued produces a DNIC reaction (Bing et al 1991) and this may have clinical effects (Lewith & Vincent 1995). It is possible that sham needling, in terms of deep needling at non-acupuncture points, due its invasive nature, is a more powerful placebo than other procedures. It has also been argued that since nothing that touches the skin can be considered to be “inactive”, the word placebo may be inappropriate to use in acupuncture studies and the term “sham” may be more appropriate as it places emphasis on the psychological effects on the subjects (Park 1999). However, it is impossible to eliminate anything touching the skin and if this was accepted, all acupuncture trial results would be confounded.

The important features of an ideal acupuncture control are: that it should compare with what the subject expects to experience with needling and it should not elicit a specific “de qi” or needling sensation. However, the significance of de qi is not yet clear. There are several sham acupuncture procedures that have been used such as, the insertion of standard needles but in inappropriate or superficial sites (Takeda & Wessel 1994), other devices used to touch or press the skin (White et al 2004), dummy forms of other treatments such as inactivated transcutaneous nerve stimulation (TNS) (Lewith et al 2004). A major advance was the

development of the Streitberger needle (Streitberger & Kleinhenz 1998). This is a blunt needle which is free to move inside the handle, therefore when the needle is pressed on the skin, it appears to penetrate, but the handle of the needle telescopes over the shaft. The needle is held in place with an “o” ring and adhesive tape. The Streitberger needle has been validated for use in acupuncture trials and it has been demonstrated that patients are unable to distinguish between needle acupuncture and this placebo procedure (White et al 2003). There is further discussion on the issue of acupuncture controls, with examples of previous research in Chapter 8 section 8.7.

This author chose to use the Streitberger needle for the trial in Study 1 as it offered a validated sham acupuncture procedure that allows patient-blinding without penetration of the skin. There is also evidence that individuals would not be able to distinguish it from standard acupuncture treatment.

(ii) Non-Specific effects of acupuncture

Acupuncture may also produce a significant placebo (non-specific) effect. A meta– analysis reviewing placebo versus no treatment suggested that the non-specific effects are very small (Hrobjartsson et al 2001). However, some authors have the opposite opinion and describe the non-specific effects of acupuncture as having powerful and clinically significant influences upon outcomes (Kaptchuk 1998, Kaptchuk 2002). There are several recent controlled trials supporting the theory that acupuncture interventions provide clinically significant non-specific effects (Linde at al 2005, Brinkhaus et al 2006, Haake et al 2007, Witt et al 2005, White et al 2012). All of these trials have observed similar findings whereby outcomes for acupuncture and sham intervention groups were no different. However, substantial improvements in symptoms were evidently greater in the acupuncture and sham acupuncture groups than in control groups, where participants received conventional or no treatment. Linde et al (2007) in a review of four RCTs of acupuncture for various painful conditions

suggested that it was in fact the patient's expectation of pain relief that was the most robust predictor of efficacy of acupuncture treatment. This would appear to further support the theory that the mechanism for successful treatment outcomes with acupuncture may be through a non-specific effect.

(iii)Therapeutic Relationships

The influence of the therapeutic relationship on outcomes of acupuncture has previously been discussed in Chapter 4. There is some evidence that the patient-therapist relationship can influence outcomes and therefore in both Study 1 and 2 this author considered that standardisation of the intervention time and interaction with the therapist was important (Kaptchuk et al 2008, White et al 2012). It would help to ensure each participant had similar therapeutic interactions and therefore relationships as this may add to the placebo effect of acupuncture.

5.2.4. Implementation (surveillance and monitoring, Long-term follow up)

A process evaluation was not possible for either of the two studies included within this thesis. This was mainly due to lack of funding. If funding had been available, it may have been possible to explore the way in which the interventions were implemented and could have given insight into the quality of the treatments and identify contextual factors that could have influenced outcomes.

5.3 Outcome Measures:

The outcomes chosen and justification for both studies will be discussed later in the following sections within this chapter.

5.3.1 Tools to assess HVS

The symptoms associated with HVS are complex and varied in nature. They include what would be considered to range from mild intensity paraesthesia to the extreme of severe chest pain, which mimics more serious disease (see Table 1b Chapter 1. for a list of symptoms associated with HVS). Anxiety is also a major component of this condition. There are tools that are symptom scores (e.g.NQ), or that assess levels of breathlessness (Self-evaluation of breathing questionnaire), however, none have been adequately validated or found to be responsive for use as an outcome measure. There is no “gold standard” tool to assess all physical and psychological aspects of this condition, or that is known to be responsive to change, hence the selection of an appropriate outcome measure requires deliberation.

An ideal assessment tool for HVS would include the following:

- Sensitivity to assess small changes in symptoms described by this patient group.
- Ability to exclude other respiratory or psychological conditions as a separate diagnosis, or that may co-exist with HVS.
- Ability to detect physical and psychological symptoms that are present in HVS.

The ideal assessment tool would provide a combination of the symptom scoring provided by the NQ and an anxiety/depression scale. This does not currently exist so a choice had to be made, and as anxiety can be the most disabling symptom of HVS leading to panic attacks and severely limiting symptoms (Han et al 1996), it was chosen as the primary outcome in this trial. Secondary outcomes were a symptom score (NQ) and measurement of health status (MYMOP2).

5.3.2 Tools to assess COPD

COPD is a multi-component disease with effects beyond the respiratory system. The severity of COPD is usually assessed using spirometry (a test of lung function that provides information about airway patency and lung volumes). As previously discussed, the severity of COPD determined through spirometry does not correlate well with the patient experience and symptoms. In clinical physiotherapy practice it is common to use more functional assessments and symptom scores such as: breathlessness scales, tests of exercise tolerance and capacity, or measures of health related quality of life. This author was primarily interested in the impact of interventions on anxiety related to respiratory conditions, and so anxiety was used as the primary outcome measure in this group.

5.4 The primary outcome: Anxiety

5.4.1 Hospital Anxiety and Depression Scale

Identification:

The HAD scale was identified as an appropriate outcome measure as it had been used in published studies of acupuncture for anxiety (Isoyama et al 2011) and HVS (Gibson et al 2007). It is also a tool used in clinical practice in respiratory clinics by physiotherapists (Chaitow et al 2002).

Purpose

The HAD scale (see Appendix VI) was developed by Zigmond & Snaith in 1983 to identify probable/possible anxiety and or depression amongst patients in non-psychiatric hospital clinics. It is divided into an anxiety subscale (HAD-A) and a Depression subscale (HAD-D) both containing seven intermingled items.

Scoring

The two subscales have been found to be independent measures. In its current form the HAD is divided into four ranges: normal (scores 0-7), mild (suggesting a presence of anxiety/ depression (scores 8-10), moderate

(probable presence of anxiety/depression “caseness” scores 11-15) and severe anxiety/depression (scores16-21) (Snaith 2003). In order to prevent any crossover from somatic disorders any sections relating to fatigue, dizziness, headaches, insomnia were excluded. The questionnaire asks the patient to complete it whilst considering how they have been feeling over the past week. It then gives a list of 14 feelings/situations that the patient is required to grade how much concordance their status has with these statements for example Statement 1 “I feel tense or wound up”, the patient is then asked to indicate whether they feel this way “most of the time”, “a lot of the time”, “from time to time”, or “not at all”. These are then graded 3-0 respectively. There are 14 statements in total. The odd numbered questions give a score for depression and the even numbered questions give a score for depression.

The HAD scale is frequently used within physiotherapy practice and has been used for respiratory patients, as an outcome measure following pulmonary rehabilitation. It is quick and easy to complete and has been validated as a tool for use outside of a psychiatric clinic (Zigmond & Snaith 1983). Its major disadvantages are that it does not appear to take into account the different types of anxiety i.e. the individual differences in the intensity and frequency that anxiety presents, or the effect of external stressors upon the individual (Ley & Yelich 1998). The HAD scale also does not have a documented minimal clinically significant difference for its use in HVS. However, it has been suggested that the minimal clinically significant change in the HAD scale for COPD is a change of 1.5 points (Puhan et al 2008). HVS has some similarities with COPD in that it is a chronic condition associated with increased breathlessness and high anxiety levels. Therefore, this level was accepted as a minimal clinically significant change for this study.

There are several other anxiety scales that were available within the literature, however, it was necessary to find a scale that was both

validated in a non-psychiatric environment and that was currently being used within clinical practice.

Validation

The HAD scale is said to be a valid scale for both subscales HAD Anxiety and HAD Depression (Bjelland et al 2001). Both the anxiety and depressions subscales have sensitivity ratings of 0.83 and 0.82 respectively. The sensitivity (how good it is at being able to correctly detect those who do have the condition) and specificity (how good it is at being able to correctly reject healthy individuals without the disease) ratings for both scales was approximately 0.8 which correlates with other well used questionnaires such as the General Health Questionnaire (GHQ).

5.4.2 Other anxiety measures considered

Other anxiety questionnaires were considered as a measurement tool for this study. They were identified as they had been used in published studies of anxiety in respiratory disorders such as the Beck Anxiety Inventory (BAI) (Beck et al 1990). This is a 21-item tool which separates anxiety from depression; however, its item list is very similar to those symptoms listed on the Nijmegen symptom score. Therefore, it has been criticised in the past for not being able to distinguish between GAD and PD.

The STAI Inventory is another well-known tool for the measurement of anxiety (Speilberger et al 1970). It enables the researcher to distinguish between the effects of external stressors and individual differences of the manifestations of anxiety, however, this inventory has been criticised for its reliability issues especially in those who have extreme anxiety states (Barnes et al 2002, Kvaal et al 2005). In Study 2 the STAI is used alongside the HAD scale to account for any external stressors.

Disadvantages of HAD Scale

- It does not take into account any situational anxiety/external stressors

Key features of the HAD Scale

- It is a validated measure which is commonly used by Therapists
- It addresses both anxiety and depression
- It does not overlap with PD which could also be associated with HVS

Therefore, the researcher chose the HAD scale for three main reasons: it had been used in the preliminary study upon which the power calculation was based; the main study (study 1.) presented in this thesis aimed to look primarily at the effects of acupuncture on the anxiety component of HVS; and the HAD scale is commonly used within physiotherapy practice.

5.5 Secondary Outcome measures:

Measures of symptoms of HVS

5.5.1 The Nijmegen Questionnaire

Purpose

The NQ is a validated screening tool for detection of hyperventilation (Van Dixhoorn et al 1985). It has been shown to have 95% effectiveness in discriminating people with symptoms of hyperventilation from “normals” (Van Dixhoorn et al 1985). (See Appendix II)

Scoring

The NQ consists of 16 items of sensations: feelings of tenseness, shortness of breath, accelerated or deeper breathing, inability to deep breathe, palpitations, cold hands or feet, tight chest, chest pain, dizziness, tingling fingers, blurred vision, confusion, stiffness in arms/fingers, abdominal bloating, tightness/tingling around the mouth.

The user is asked to grade each symptom accordingly. The answers are graded as follows: 0= never, = rarely, 2= sometimes, 3= often, 4= very often. Scores of 24 or above are believed to be indicative of HVS. There is no known minimal clinically significant difference for this questionnaire.

Validation

The sensitivity of the NQ in terms of diagnosis of HVS is 0.91 and it has a specificity of 0.95. This questionnaire is the only validated tool that is available for clinicians to assess symptoms of hyperventilation and is commonly used in assessing HVS in clinical practice. The NQ is a validated tool for screening for people with symptoms of hyperventilation; however, it is not validated for diagnosing HVS. Due to the nature of the varied symptoms of HVS there are several other conditions that also may have a combination of these symptoms such as asthma or COPD. Consequently, the difficulty with distinguishing these conditions from the true hyperventilators, using this tool, is well documented within the literature (Jack 2004).

Other measures considered:

At the time that study 1 was first designed there were no other questionnaires that specifically measured the symptoms of HVS. However, in 2009 the Self Evaluation of Breathing Questionnaire (SEBQ Courtney & Greenwood 2009) was published which was developed to measure the respiratory symptoms of dysfunctional breathing. Its reliability has recently been established, and it is said to have a high test-retest reliability (Mitchell et al 2016). It has been suggested that the SEBQ may be a useful screening tool in addition to the NQ, but it was not available at the time.

Disadvantages of the Nijmegen Questionnaire.

The choice of the NQ was made because it has high specificity. Its sensitivity however, is low and it is therefore not good at being able to correctly identify those with the disease. It is therefore not recommended as a diagnostic tool. The listed items on the NQ are symptoms that may be associated with other respiratory or psychological conditions such as asthma, COPD, anxiety disorders. Therefore, in order to reduce potentially unreliable NQ scores in this trial, patients with other co-existing conditions that may present with similar symptoms to HVS, were excluded.

Key features of the Nijmegen Questionnaire

- It is the only validated screening/symptom severity tool for HVS
- It is easy to complete
- It is commonly used in Physiotherapy practice

5.6 Secondary Outcome measures:

Measures of Health Status

5.6.1The Measure Yourself Medical Outcome profile 2 (MYMOP2)

Purpose

The MYMOP2 is a measure of health status (Paterson 1996). It is a patient generated problem specific measure which enables patients to select problems that are most important to them, and that they want addressing from their treatment.

Scoring

The patient is asked to decide which symptom is most problematic for them and they then rate the severity of this symptom e.g. breathlessness on exertion. They are then asked to list an activity that they would like to improve on and that is limited by their symptom e.g. walking distance. The symptom severity (over the past week) is then rated by the patient on a

scale of 0-6 (6 = bad as it can be). The patient is also asked to rate their general health. After the intervention, the patient is asked to complete a follow up form where the same symptom is then rated again on a scale of 0-6.

Validation

The MYMOP2 is reported to have high sensitivity and its index of responsiveness to the minimally clinically important difference (MICD) was also high (Paterson 1996). It has an MICD of 1.

5.6.2 Other measures considered

Other measures of health status were considered such as the SF-36. Health status is defined as "the level of health of an individual, group or population as assessed by that individual or by objective measures" (Medical Dictionary for the Health Professions and Nursing 2012). The SF-36 is a well-known measure of health status that is used in many clinical trials. This questionnaire was considered for this trial because it was used within the researcher's pilot crossover study examining the effect of acupuncture on HVS. The main issue with the SF-36 was that it was very time consuming to complete and participants in the pilot study struggled to complete it. The SF- 12 is a shortened version of the SF-36 but due to the lack of patient generated problem it was decided not to use this.

There are several health status questionnaires designed and validated for use with chronic respiratory diseases. The most commonly known questionnaire St George's Respiratory Questionnaire(SGRDQ) (Jones et al 1991) was considered as another health status measure for study 1. Other researchers examining dysfunctional breathing and HVS have described its use for these conditions (Warburton et al 2006). However, this questionnaire is also very long, and time consuming to complete. It consists of sections that relate to very specific respiratory symptoms such as "how much sputum do you produce per day". Sputum retention is not a symptom associated with HVS. The SGRDQ was used in study 2 as it is

validated for use with COPD patients and was also being used in clinical practice in PR.

Disadvantages of the MYMOP2

- The MYMOP2 requires a research assistant to support the patient to complete it

Key Features of the MYMOP2

- It is practical and applicable for patients.
- It enables people to demonstrate changes in their health status that are important to them
- It allows the individual to highlight the main problems that are affecting quality of life and also includes assessment of general wellbeing.

  It takes into account changes in medication and its importance to the individual. This is very relevant in studies involving complementary therapies as often people seek these therapies to enable them to reduce the required amount of medication (Sharples et al 2003).
- It is brief and simple to administer which makes it easy to apply within clinical practice once the initial questionnaire has been explained.

5.7 Secondary Outcome measures: Measures of Breathlessness

5.7.1 A visual analogue scale of Dyspnoea (VAS-D) (100mm)

Purpose

The VAS-D (Atkin 1969) is a measure of dyspnoea (breathlessness). It is a 100mm line on a page that is anchored at either end with descriptors, for example “No breathlessness” to “Most severe breathlessness”. Respondents are asked to mark a point on the line to represent their symptom experience. Individuals with HVS and COPD commonly complain of breathlessness as their main and most disabling symptom.

The VAS-D was used to assess patients' subjective perceptions of their worst breathlessness during the previous week.

Scoring

Scoring is achieved by measuring from the left end of the scale to the point at which the participant has marked.

Validation

There was no validated measure of breathlessness for use with HVS, but many of the available measures had been validated for chronic respiratory disease. The VAS-D has been demonstrated to have high concurrent validity (r=.97 Gift (1989)) and high construct validity (Gift 1989) in chronic lung disease. The minimal clinically important difference for the VAS-D in respiratory disease is 10-12 units (Ries 2005).

5.7.2 Other measures considered

Two types of breathlessness measures were considered for this study. The researcher debated the use of either an intensity rating scale that would assess the severity of breathlessness (e.g. VAS-D; modified Borg Dyspnoea scale; numeric rating scale (NRS), or a functional assessment of the impact of breathlessness on performance or activity (e.g. Baseline Dyspnoea Index; Medical Research Council Dyspnoea Scale (MRC) (Bestall et al 1999); Shortness of Breath questionnaire (SOBQ) (Eakin et al 1998). The purpose of this outcome measure was to assess the severity of breathlessness and it was felt that the aspects of functional disability would be assessed using the MYMOP2 questionnaire. The preliminary study (Gibson & Bruton 2007) used the MRC Dyspnoea Scale. However, it was clear from the results of this study, that the MRC scale was not sensitive enough to detect changes in breathlessness in HVS patients. Therefore, an intensity rating scale (VAS-D) was chosen for the main RCT described in this thesis.

The MRC dyspnoea scale was used for study 2 as it is a validated measure and was being used within the clinical practice as part of the PR outcomes. The MRC is simple to administer and allows the individual to indicate the extent to which their breathlessness affects their mobility.

The other intensity rating scales considered were the modified Borg Scale (Borg 1982) or the NRS (Gift et al 1998). The Borg scale is a ten-point category ratio scale with descriptive terms prompting responses. It has a high concordance with the VAS-D but is most reliable for post-activity testing (Meek 2003). The NRS is very similar to the VAS-D but has a zero to ten scale that is anchored at each end by descriptors such as “no breathlessness”, moderate breathlessness to “worst possible breathlessness”. VAS-D scores have been shown to be highly correlated with the NRS (Gift 1998).

Disadvantages of the VAS-D

- The VAS-D is purely a rating of intensity of breathlessness. It does not take into account any impact that that breathlessness may have on activities of daily living.
- Patients do not have any descriptions or prompts on the scale to aid the rating of their breathlessness.

Key features of the VAS-D

- It measures the severity of dyspnoea
- It is quick and easy to use
- It is a validated measure of breathlessness intensity.

5.8Tool to assess treatment credibility and expectancy:

The BN credibility scale

Purpose

There is a need in investigational trials to assess therapy credibility and expectancy of outcome (Kazdin 1979). The researcher cannot rule out differential levels of credibility and expectancy (non-specific influences) potentially influencing outcome between conditions. In fact expectancy has been shown in previous studies, examining generalised anxiety disorders, to correlate with therapy outcome (Borkovec &Costello 1993). The Borkovec and Nau credibility scale (BN) was originally developed in 1972 (Borkovec & Nau 1972) within a study of psychological treatments. It has been used extensively within published psychological (Borkovec &Costello 1993) and acupuncture research as a validated tool to assess credibility/expectancy of treatment.

Acupuncture studies have shown that a credibility scale accurately reflects the participants' beliefs surrounding the effectiveness of acupuncture treatment and its authenticity (Vincent & Lewith 1995). It has been suggested that the BN scale is a useful measure of the psychological impact of acupuncture and assessment of the credibility of acupuncture placebo controls (Vincent & Lewith 1995).
The credibility of a treatment is defined as "how convincing and logical a treatment is". The expectancy is defined as "the improvements that clients/patients believe can be achieved".

The questions used in the Borkovec & Nau credibility rating were:
(i) How confident do you feel that this treatment can alleviate your complaint?
(ii) How logical does this treatment seem to you?
(iii) How successful do you think this treatment would be in alleviating other complaints?

(iv) How confident would you be in recommending this treatment to a friend who suffered from similar complaints?

Scoring

Participants are asked to rate their answers to the questions on a 6-point Likert scale ranging from “1 strongly disagree to 5 strongly agree”.

Validation

Studies have demonstrated the validity of this credibility scale (Borkovec & Nau 1972, Vincent 1990). It has high internal consistency (0.84 whole scale). The test-retest reliability was found to be 0.82 (Vincent 1990)

5.8.1 Other measures considered

There is a credibility/expectancy questionnaire (CEQ) (Devilly & Borkovec 2000). This CEQ is based upon the BN scale but includes two further questions that are rated by the participants:

(i) How much do you really feel that therapy will help you reduce your symptoms?

(ii) How much improvements in your symptoms do you really feel will occur?

This researcher felt that although this longer version of the BN scale would provide greater information relating to the expectancy of treatment (Devilly & Borkovec 2000), the main aim of this outcome was to measure the credibility of the treatment conditions. This would ensure that both the treatment and the control or placebo treatments were equally credible.

Disadvantages

- Provides little information relating to expectancy of treatment.

Key features of the Borkovec & Nau credibility Scale

- Provides assessment of the credibility of treatments to ensure both treatment and control are equally credible
- Enables researcher to rule out non-specific influences on the outcomes of investigational studies
- It is simple and easy to use.

5.9 Secondary Outcome Measures:

Exercise Tolerance

5.9.1 Incremental Shuttle Walk Test (ISWT)

The ISWT is used to assess exercise capacity in patients with COPD and is often employed as an outcome measure for PR. This test is a validated field walking test that is used as a pragmatic alternative to a laboratory exercise test for patients with COPD. It has been used in a number of published studies especially trials of PR, as it is similar to a laboratory incremental exercise test being externally paced (Singh et al 2008).
The minimal clinically important change is 48 metres.
The ISWT is used within PR programmes as a clinical outcome and was chosen as a pragmatic choice for Study 2 as the individuals were already carrying out the ISWT as part of their PR clinical outcome measures.

5.10 Secondary Outcome Measures:

Capnography: End-Tidal Carbon Dioxide measurements ($ETCO_2$)

The gold standard tool for measuring carbon dioxide in the blood is an arterial blood gas measurement, which requires an invasive and painful blood test. Capnography ($ETCO_2$) is a non-invasive tool that indicates the amount of expired carbon dioxide (Taghizadieh et al 2015 in the breath. It provides accurate information in terms of ventilation from one breath to the next (Taghizadieh et al 2015).

Capnography was chosen to measure carbon dioxide levels in Study 1 as it is a simple non-invasive tool which has been found to have a close

correlation with the gold standard arterial carbon dioxide measurement (Taghizadieh et al 2016)

5.11 Chapter 5. Summary

Acupuncture has not been shown beyond doubt to be more efficacious than placebo, which is seen as a crucial step before any intervention is recommended to patients. There are two studies included within this PhD programme and this chapter has highlighted the methodological framework for the two studies and justified the different methodological approaches used in both studies. A pilot study for Study 1 had been carried out prior to this PhD and has informed the design of the main RCT described in Study 1. Some of the methodological challenges with acupuncture research has been discussed to highlight how the design of both studies has been influenced to minimise the non-specific effects of acupuncture. All of the methodological issues around acupuncture trial design were carefully considered in the design of the studies, included within this thesis. It was evident that the randomisation process should be stratified to ensure a balance of the degree of anxiety in each group, as well as ensuring that the sample size was large enough to show a true effect. An appropriate inert placebo control was also required with adequate blinding of the outcome assessors and a standardisation of the therapeutic session was necessary, in order to assess the efficacy of acupuncture for respiratory disorders.

This chapter has also justified the main outcome measures selected for the two studies described in this thesis and highlighted the other outcome options, that were explored but rejected. The next two chapters in this document will present the two studies that comprise this PhD programme of study.

Chapter 6. Study 1.

A three-arm randomised controlled trial of acupuncture for the treatment of hyperventilation syndrome

6.1 Research Questions addressed by Study 1

1. Does acupuncture, offered as an adjunctive treatment to a physiotherapy BR programme for HVS, enhance patient outcomes in terms of reducing anxiety, depression and symptom scores?

2. Does acupuncture in the treatment of HVS have any additional effect on increasing $ETCO_2$ measurements when compared to physiotherapy BR alone?

3.Does acupuncture as an addition to a physiotherapy BR programme for HVS have any specific efficacy over placebo acupuncture treatment?

4. Does acupuncture as an adjunct to a physiotherapy BR programme provide greater improvement in health status when compared to physiotherapy BR alone?

6.2 Primary Hypothesis

Null Hypothesis

Acupuncture when used as an adjunct to a conventional physiotherapy BR programme for the treatment of HVS, would have no greater effect in terms of reducing anxiety, when compared to either a placebo adjunct or conventional physiotherapy alone.

Secondary Null Hypotheses

1.Acupuncture used as an adjunct to a physiotherapy BR programme in the treatment of HVS, would have no greater effect in terms of reducing depression, when compared to a placebo adjunct or conventional Physiotherapy BR alone.

2. Acupuncture, when given as an adjunctive treatment to a conventional physiotherapy BR programme for the treatment of HVS, would not have any specific efficacy over a placebo acupuncture treatment in terms of reducing symptoms of hyperventilation syndrome

3. $ETCO_2$ levels would not be affected by the addition of acupuncture treatment to a conventional physiotherapy BR programme in the treatment of HVS

4. Acupuncture, when given as an adjunctive treatment to a conventional physiotherapy BR programme for the treatment of HVS, would not have any specific efficacy over a placebo acupuncture treatment in terms of improving health status.

6.3Trial summary

This trial was a randomised, placebo-controlled trial examining the effect of acupuncture as an adjunctive therapy to physiotherapy in the treatment of hyperventilation syndrome (HVS). Physiotherapy was given in the form of BR and relaxation techniques. The placebo intervention was carried out using the Streitberger needle (Streitberger & Kleinhenz 1998)**.** Participants were recruited via the physiotherapy referrals for the treatment of hyperventilation syndrome and after baseline assessments, were asked to return for treatment four weeks later. Participants were then randomised into one of three groups and asked to attend for 1 hour sessions twice weekly, during a four week interval. All of the groups received physiotherapy in the form of BR and relaxation. One group then also received “real” acupuncture, and one group received placebo acupuncture, as adjunctive treatments. The third group received physiotherapy alone.

HVS presents as a variety of symptoms with anxiety often being cited as a key component. Therefore, the primary outcome used in this study was the HAD scale. Secondary outcomes were in the form of a symptom score (NQ), breathlessness VAS, health related quality of life measures (MYMOP) and credibility rating (Borkovec and Nau credibility test). Cardiorespiratory measurements were taken at every visit pre and post treatment. Figure 2 (page 143) shows the flow of the participants through the study. Data analysis explored changes in outcomes (anxiety and depression, symptom severity, physiological parameters, breathlessness and health related quality of life).

6.4 Aims

The aims of this study were to:
(i) Evaluate whether the use of “real” acupuncture enhances conventional physiotherapy, in terms of reducing anxiety and improving symptoms of hyperventilation, when used as an adjunctive therapy, in the management of HVS,
(ii) Explore whether “real” acupuncture has any specific efficacy over placebo acupuncture in the treatment of HVS.

6.5 Method

The Method will be described in the following sections:

(I) Study design
(ii) Ethics and research governance
(iii) Sample size
(iv) Study Participants
(v) Recruitment
(vi) Randomisation
(vii) Plan of Investigation
(viii) Pilot Study
(x)Trial procedure

(ix)Interventions
(x) Blinding
(xi) Outcome measures
(xii) Data analysis

(i) Study Design

This study was a single blind, three-arm randomised, placebo-controlled trial used to explore the research questions. RCTs are considered to provide the best evidence on the effectiveness of treatment and healthcare interventions (Kirkwood & Sterne 2003). It was hypothesis driven and designed to examine the effects of an intervention and therefore a quantitative, experimental approach was used. There were several potential designs for this study that were considered by the lead investigator.

A preliminary study had previously been carried out by this author examining the effect of acupuncture versus BR for the treatment of HVS (Gibson & Bruton 2007). However, this study had many design faults in that it was a crossover trial as opposed to a parallel design. Although this resulted in a smaller sample size being needed, it presented the investigators with methodological issues such as, the presence of a potential carry-over effect from the acupuncture treatment. As there is no certainty as to when acupuncture effects decay post intervention, it was concluded that a cross-over design was not an appropriate selection when considering the effect of acupuncture interventions.

An RCT requires the participants to be randomly assigned to receive one of two or more interventions (Jadad 1998). The use of an RCT for this study was directed by the primary goal of the study to evaluate the efficacy of 3 interventions (BR and acupuncture, BR and placebo acupuncture and BR alone). This design allowed the researcher to control for any selection bias ensuring that all three groups were as well matched as possible in

terms of baseline data. Randomisation relies upon the statistical power of a study to ensure equal distribution of any key confounding variables (e.g. baseline anxiety levels) (Akobeng 2005). Therefore, this was controlled for by the use of stratified randomisation and the sample size was calculated using the primary outcome measure HAD scale.

The choice of design was also highly influenced by the known powerful non-specific effect of both acupuncture (Carlsson 2002) and BR (De Guire et al 1992 and 1996). Therefore, it was decided that in order to examine potential non-specific effects, a placebo-controlled trial should be carried out. A two-arm placebo-controlled trial was initially considered by this author i.e. the participants would be randomised into two groups, one receiving physiotherapy and "real" acupuncture and the other receiving physiotherapy alongside placebo acupuncture. The weakness with this design is that it does not enable consideration of the potential effects of physiotherapy alone, in the treatment of HVS. Physiotherapy is a widely accepted "standard care" for the treatment of HVS and several studies have highlighted its beneficial treatment effects (Han et al 1996, De Guire et al 1992 and 1996). Hence it was deemed necessary to add in another arm to this trial, whereby a third group received physiotherapy alone. This trial therefore compared a) 'real' acupuncture plus standard care *versus* b) 'placebo' acupuncture plus standard care *versus* 3) standard care. Standard care involved physiotherapy in the form of BR and relaxation techniques. The main disadvantage of this design was that as a three-arm trial, it required a larger sample size to ensure adequate power was given to the study.

To prevent selection bias and to randomly distribute the characteristics of the participants that may influence the outcome, it was decided that participants would be randomised into each group (Akobeng 2005). The primary outcome for this study was anxiety measured by the HAD scale. Therefore, the three groups were also stratified for anxiety levels to ensure

that each was balanced for level of anxiety amongst participants. The investigator could then be confident that the groups were equal for anxiety levels, which would allow comparison of outcomes between the groups without anxiety becoming a confounding factor.

Due to the nature of the interventions, it was not possible to “blind” the clinician to the treatments. Therefore, a single-blind approach was chosen whereby the outcome measurements and questionnaire administration were carried out by a research nurse who was unaware of the intervention that each participant had received. The procedure for the randomisation and “blinding” will be discussed later in this document.

(ii)Ethics

The protocol for this study was submitted to the Southampton and South West Hampshire Research Ethics Committee. Full Ethical approval was granted prior to participants being recruited (see Appendix IV for Ethical approval letter).

During this study, the researcher also worked as a clinical physiotherapist, treating patients with HVS, at the respiratory centre from where participants were to be recruited. Great care was therefore taken to ensure that patients with HVS awaiting physiotherapy treatment did not feel coerced to take part in this trial. The initial information was sent out by post and it was up to each patient to decide whether to contact the researcher or not. The researcher did not contact any patient directly about this trial prior to some interest being shown. It was made clear to all patients that accepting or refusing the invitation to take part in the trial would have no beneficial or adverse effect on their treatment.

All participants were asked to complete a health questionnaire prior to entering the trial to ensure that there were no contraindications to the acupuncture treatment. Eligible participants received both a written and

verbal explanation of the study prior to entering and were advised that they would have the option to withdraw from the trial at any time without affecting their care. Participants were advised that there may be some minor side effects following acupuncture treatment such as skin bruising and minor discomfort.

Participants who were found to have a high level of anxiety and/or depression on the HAD score (i.e.>11) were offered the opportunity to be referred back to their consultant for further treatment at the end of the trial. Those participants who were randomised to groups B or C (placebo acupuncture and BR/ BR alone) were also offered the opportunity to receive acupuncture at the end of the trial.

Only the clinicians that were involved in the initial assessment and treatment arms of the trial had access to the patients' notes.

Research Governance:

This study complied with the research governance framework and was registered with the research and development departments at both University Hospitals Southampton NHS Foundation Trust (UHSFT) and the University of Southampton. Insurance indemnity was obtained from the University of Southampton and the study was registered with the data protection department at SUHT.

(iii) Sample size

Power is defined as "the probability that a statistical test of significance will reject the null hypothesis if a true effect is present" (Moher et al 1994). A power calculation was based on data from the primary outcome measure (HAD Scale – see under Outcome measures for justification) and indicated that a minimum of 24 participants per group were required. The power to detect an effect was set at 80% which is a level most commonly used in health orientated RCTs (Moher et al 1994).

This 80% power would detect a difference in anxiety mean scores of 2.4 assuming the common standard deviation (SD) to be 2.96 using a two-

group t-test with a 0.05 two-sided significance level. To allow for a possible attrition rate of 20% it was planned to recruit 30 participants per group i.e. a total of 90 participants over 2 years. This sample size was deemed to be achievable given the time limits imposed by the PhD programme and the number of referrals of HVS patients to physiotherapy at UHSFT at the time registration of this PhD (2006).

The level of 0.05 was set as the probability of an observed result happening by chance under the null hypothesis (Type I error). There is no published minimal clinically significant change in the HAD scale for HVS patients. However, it has been suggested that the minimal clinically significant change in the HAD scale for COPD is a change of 1.5 points (Puhan et al 2008). HVS is similar to COPD in that it is a chronic condition associated with increased breathlessness and high anxiety levels.

(iv)Study Participants

Patients who were diagnosed with HVS and referred for physiotherapy by the respiratory physicians at SUHT, were considered eligible for the trial. Only newly diagnosed patients were approached, in order to eliminate those who may have already received BR or acupuncture for their condition.

(v) Recruitment

Participants were recruited via the consultant referrals obtained from the Respiratory Centre at UHSFT. There were several advantages to recruiting from there. The Trust is a major teaching hospital on the south coast and has a specialist respiratory service, which accepts tertiary referrals. This results in referrals for consultant clinics being received from both the local Primary Care Trusts but also from other regional areas. As HVS services are not available in many other centres within the region, there was potential for a large cohort of HVS patients to be referred to this centre. However, this meant that potential participants frequently lived some distance from Southampton and were therefore reluctant to take part

in the trial due to the travelling involved. Another advantage to using the Respiratory Centre for access to patients was that the main researcher for this study worked there clinically during the course of the trial. She also worked in close collaboration with the respiratory physicians which resulted in the other clinicians within the unit being made fully aware of the study and receiving frequent reminders to forward referrals to the main researcher. However, this author recognises that being based within the Respiratory Centre and being well known clinically by all the referring clinicians may also have been a potential source of bias. The possibility of recruiting from other larger centres around the region was considered for this study. However, the funding to support time and travel expenses for the researcher was not available; therefore, the Respiratory Centre at UHSFT was chosen as the main recruiting centre for this study.

Once referrals were obtained by the physiotherapists in the Respiratory Centre they were passed onto the main investigator of this study. Section (viii) describes the plan of investigation once the participants were recruited.

Inclusion criteria:

- Over 18 years of age. It was decided that younger patients may well have difficulty attending treatment sessions due to educational requirements and very young may not understand what was required of them.
- Newly diagnosed with HVS
- A Nijmegen score of 23 or above (see Outcome measures).
- Able to attend the WTCRF twice weekly for four weeks.

Exclusion criteria:

- Underlying chronic lung disease;

- Anyone who did not wish to receive acupuncture treatment or for whom it is contraindicated;
- Anyone who was receiving other conventional or alternative therapy for HVS;
-Anyone who had an allergy to sticking plaster;

(vi) Randomisation

The purpose of randomisation within a trial is to ensure that there is no selection bias. This is carried out by distributing the participant characteristics randomly between groups. This ensures that any difference in outcome may be explained by the treatment alone and not by an uneven distribution of characteristics within the groups (Akobeng 2005). Therefore, random allocation of participants enables a balancing of the groups with regards to relevant characteristics such as gender, age, or duration of disease, which may affect the outcomes of the trial. In this study, several methods of randomisation were considered.

The researcher was aware of methods that may be prone to bias such as randomly assigning participants based on characteristics such as their date of birth or hospital number. Therefore, these were not considered. A block randomisation technique was considered whereby participants would be considered in groups and allocated according to a random number sequence (Akobeng 2005). This would ensure an equal number of participants were allocated to each group.
A computer generated random allocation sequence would also help to eliminate selection bias. However, it was necessary to ensure that the groups were balanced for important participant characteristics such as levels of anxiety. Therefore, it was necessary for this study to carry out a stratification of the groups. This eliminated confounding factors and ensured any outcome was due to the treatment process alone.

The primary aim for this trial was to examine the use of acupuncture as an adjunctive treatment to conventional physiotherapy for HVS and it was hypothesised that a greater effect would be seen when “real” acupuncture was used as an adjunctive treatment, in terms of reducing anxiety and hyperventilation symptoms. An anxiety measure was used as the primary outcome and it is noted within clinical practice that there was a noticeable variation in anxiety levels between patients with HVS. In view of the varying levels of anxiety between patients, it was considered necessary by the researcher that the groups needed to be stratified according to baseline anxiety levels. It may have been possible to stratify the groups further for other important factors such as chronicity (Akobeng 2005). However, it was decided that in clinical practice the major factor that determines outcome was anxiety and therefore this alone was used for the stratification process.

In order to minimise selection bias further it was considered appropriate to conceal the assignment of participants from both the main researcher and the research nurses. This prevented the researchers from assigning certain participants to specific intervention groups. An observational study by Schultz et al (2000) revealed that in trials in which randomisation was not concealed, estimated treatment effects were exaggerated by approximately 41% when compared to those that reported allocation concealment. In view of this, the following procedure was carried out for randomisation and participant allocation:

Following full baseline assessments, participants were then randomised into one of three groups. A random allocation sequence was generated by the statistician at the Research and Development Support Unit at UHSFT. The randomisation was stratified using the baseline HAD scale score to achieve between group comparability for anxiety levels. Scores of greater than or equal to 11 are considered to be clinically relevant for anxiety on

the HAD scale. Therefore, a score of 11 was used as the “cut off” point for the stratification.

The three groups were allocated as follows:

- Group A received routine physiotherapy and needle acupuncture.
- Group B received routine physiotherapy and placebo needle acupuncture.
- Group C received routine physiotherapy (See Figure 3).

The Randomisation sequence was held within a locked drawer at the Respiratory Centre, UHSFT and was concealed from the researcher and research nurses. The Baseline HAD Scores were sent to a senior physiotherapist based in this clinic and she calculated the HAD anxiety scores to enable stratification. The physiotherapist then documented the participant number onto the appropriate section of the list. The researcher did not have access to the list and was required to telephone the Respiratory Centre prior to the initial treatment session to enquire as to which group the participant had been allocated.

(vii) Plan of Investigation

(See Figure 2)

All newly diagnosed HVS patients who were referred for physiotherapy at the Respiratory Centre at UHSFT were eligible to participate in this trial (approximately 100 per year).

On referral for physiotherapy, patients were sent an information sheet regarding this trial including written contact details for the researcher (see Appendix V). This information sheet requested that the participants contact the researcher, if they were willing to participate in the trial. The patients were then given two weeks to contact the researcher. If there was no response received from participants within two weeks, they were then telephoned by the WTCRF research nurse to check they had received the

information, and to answer any questions. Those participants who were willing to take part were then asked to contact the researcher directly. The researcher then informed the WTCRF research nurse about the potential participants and the latter then contacted them to arrange a convenient appointment time to attend the WTCRF. On arrival, participants were asked to sign a consent form (See Appendix V) and preliminary baseline assessments were carried out (Baseline 1.), by the research nurse at the WTCRF (see below). Participants who met all the criteria were informed that they had been entered into the trial, but that this would not expedite or delay their treatment appointment time. Patients who did not meet the criteria, or who were unwilling to enter the trial, were reassured that this would not delay their routine treatment appointment time. They were then referred back to the physiotherapy department for conventional treatment. At the time there was generally a 4-week waiting period between initial referral and first treatment appointment time. Therefore, following their initial visit for preliminary measurements, consenting eligible participants were asked to return two to three weeks later for their first trial treatment appointment, when full baseline measures were carried out (Baseline 2) prior to therapy (see below). This provided a brief waiting list control period to a) enable the researchers to examine whether the expectation of receiving treatment has any therapeutic effect (Lewith et al. 2002) and b) provide repeated measures of the primary outcome, against which to compare subsequent measures.

Preliminary baseline assessment (Baseline 1) consisted of medical history and demographic data. A health questionnaire was administered to ensure the participant had no contraindications to acupuncture treatment (see Appendix VI for a copy of the acupuncture health questionnaire and all outcome measure questionnaires. The following baseline measures were also taken:

- HAD scale
- NQ
- A 100mm VAS of breathlessness

Full baseline assessment (Baseline 2) consisted of repeating the HAD, Nijmegen and VAS plus the following:

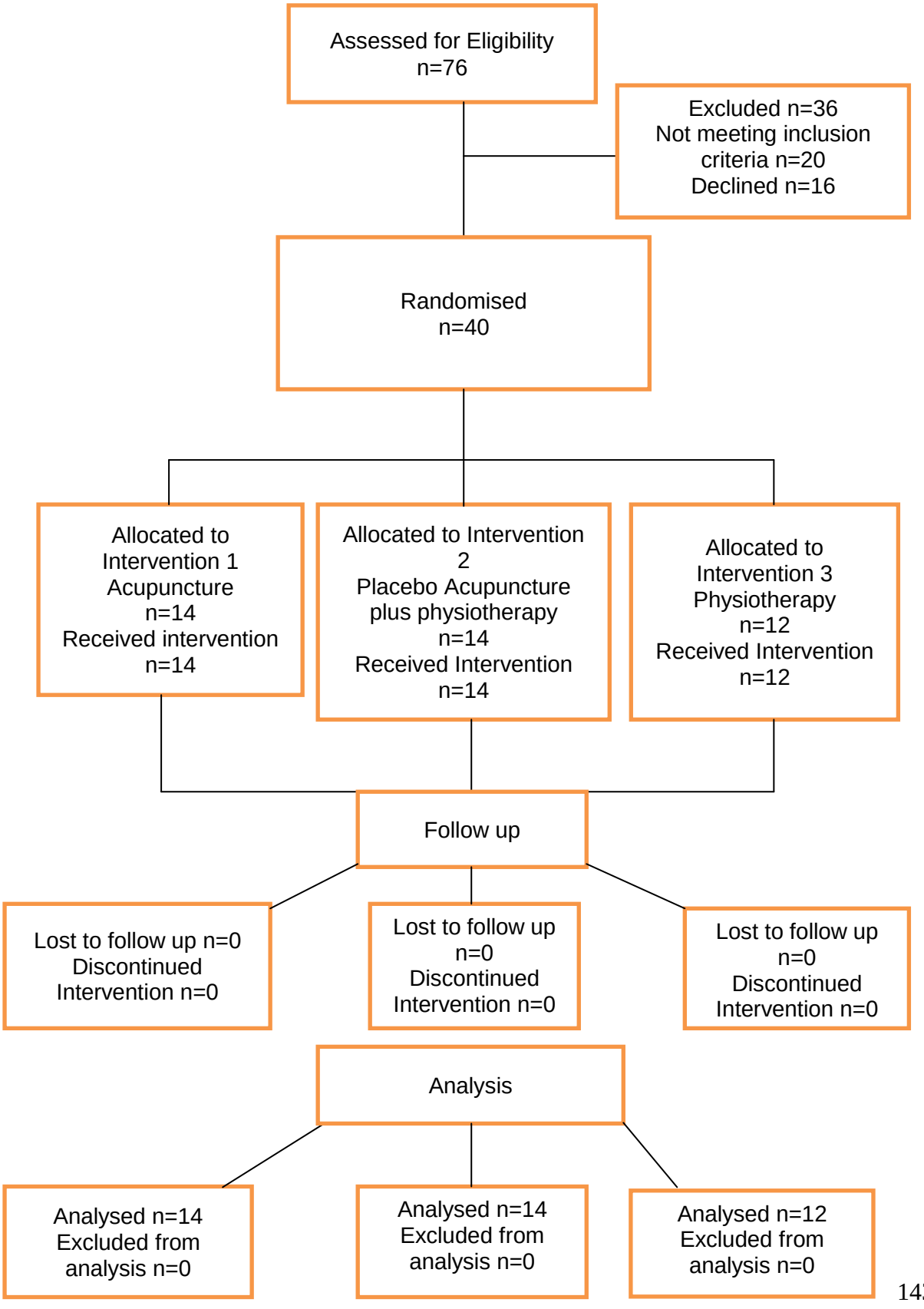
- The Measure Yourself Medical Outcome Profile2 (MYMOP2) questionnaire
- Objective measures of cardiorespiratory performance were also taken, i.e. respiratory rate and pattern, resting $ETCO_2$, oxygen saturation, pulse rate, blood pressure.
- Assessment of treatment credibility (Borkovec & Nau credibility rating)

(viii) Pilot study

Prior to commencing the trial, it was necessary to consider whether some piloting of the methodology was necessary. However, this author had recently completed a study comparing acupuncture treatment with conventional treatment for HVS (Gibson & Bruton et al 2007). This study used a crossover design but had the same interventions for both the conventional physiotherapy and the acupuncture arms of the trial as was planned for this study. Although the crossover design raised many documented methodological issues with the trial, the treatment interventions and their delivery did not present any problems for the researchers. Consequently, the researcher concluded that a pilot was not necessary to test this methodology. It was, however, acknowledged by the researcher that the placebo Streitberger needles were not used in the previous trial. Therefore, the main investigator was trained on the use of these needles by Dr Peter White (Senior Research Fellow, Complementary Medicine Research Unit, University of Southampton). During this preliminary period, the main investigator also tested the

appropriateness of the points chosen to ensure that they were accessible for using the placebo needle.

Figure 2 CONSORT diagram for Study 1



(ix) Trial Procedure

Participants in Group A were asked to attend twice a week for 4 weeks and received standard physiotherapy treatment in the form of BR (BR) and relaxation techniques. They also received acupuncture treatment. After each treatment session, the participant had cardiorespiratory measurements repeated and were asked to complete the VAS for breathlessness. Each participant was also given an advice booklet to take home and follow. At the end of this 4-week period all outcome measures were repeated (see section (xii).

Participants in Group B followed the same protocol as Group A, except for the transposition of placebo needles for 'real' needles. Participants in Group C were asked to attend twice a week for 4 weeks. After the same baseline assessments, they received standard physiotherapy treatment in the form of BR and relaxation techniques only. This enabled the researchers to examine the effects of standard physiotherapy alone, as acupuncture was being used as an adjunctive treatment to physiotherapy. To ensure that each group had the same amount of contact time, this group were also given an extra 30 minutes of relaxation time following the standard physiotherapy intervention. After the intervention, cardiorespiratory measurements were repeated and the participants were asked to complete the VAS-D for breathlessness. They were also given an advice booklet to take home and follow. At the end of this 4-week period all outcome measures were repeated.

Those participants who were randomised to groups B or C were also offered the opportunity to receive acupuncture treatment for four weeks at the end of the trial.

(x) Interventions:

Standard care – Breathing Retraining

Standard physiotherapy in the form of BR is widely accepted as an effective treatment for HVS (Chaitow 2002). There are studies that highlight the efficacy of BR and relaxation techniques for the treatment of HVS (Grossman et al 1985, Han et al 1996, Bowler et al 1998). In this trial, BR consisted of the participant being taught relaxed breathing control whilst being encouraged to nose breathe using a diaphragmatic pattern of breathing. The participants, in a long sitting position (i.e. sitting upright on a plinth/hospital bed, back supported, legs outstretched), were asked to place their hand on their upper abdomen. They were then encouraged to concentrate on breathing in and out through the nose. Once they had mastered this they were asked to facilitate diaphragmatic action by allowing their abdomen to rise when they inhaled and to fall on expiration. The participants were asked to carry out this technique whilst slowing their breathing rate down to approximately six to eight breaths per minute. The clinician advised the participants when they had mastered the technique correctly. They were then asked to sustain this pattern of slow breathing for as long as they could during a 20-30-minute session. The clinician encouraged the participants to continue with the slow breathing during this period, by regularly prompting them during this time. The participants were also advised to carry out this technique at home in the same position, at least three times daily.

Each participant was taught a contract-relax method of relaxation (Mitchell 1988). During this time, the participants were asked to lie down on their backs (bed flat, one pillow) with their eyes closed. The clinician prompted the participant to maximally contract each major muscle group of the body in turn, working from the feet up to the head, over a period of 20-30 minutes. Those in Group C who received physiotherapy alone were asked to continue this technique for a further 30 minutes in order to balance the clinician contact time for each group. The participants were also advised to

practice this technique at home once daily. The BR and relaxation were carried out by the same clinician. This was a physiotherapist with 13 years post qualification experience working in respiratory care.

Acupuncture

A western approach to the acupuncture treatment was used. This was a pragmatic choice, as the practitioner was trained in a western approach. A western approach tends to use a select point prescription for each patient depending on their condition.

A TCM approach to acupuncture would promote an individualised treatment programme for each participant. When examining the literature on acupuncture interventions, for both respiratory and anxiety conditions, there have been a variety of approaches used, and even some that have used a combination of both TCM and western methods (Wang et al 2001, Zhang et al 2003, Jobst et al 1986, Christensen et al 1984). This makes comparison of these studies difficult, but it also seems that the outcomes of these studies do not favour either one of these methods. The author was also aware that the use of a point prescription is a contentious one. However, most physiotherapists are not trained in TCM, so to make this study applicable and generalisable to physiotherapy, a select point prescription was used. The rationale for the points used is that they are reported clinically to be useful for respiratory and hyperventilation disorders and a preliminary study showed good effect when using these points for HVS (Gibson & Bruton 2007). The points used were: Li4, Liver 3 (Lv3), Stomach 36 (St 36) & Pericardium 6 (P6). There is evidence from studies in the anxiety for acupuncture literature that P6 has been used for the treatment of anxiety (Eich et al 2000, Zhang et al 2003). These points are also amenable to the use of placebo needles, due to their accessible anatomical position.

Each participant was treated bilaterally and had a maximum of 8 needles inserted for the duration of each treatment. The needles used were sterile, single-use copper handled needles without guide tubes. They were supplied by Asia-Med GmbH & Co and measured 25mm x 0.25mm. Each needle was inserted until d*e qi* (needling sensation) was obtained. Plastic "O" rings and sticking plaster were used for both intervention and placebo techniques as recommended by Streitberger & Kleinhenz (1998). A draining technique was used, therefore the needles, once inserted, were left for a period of 20-30 minutes. Although many acupuncturists would return to a patient during this time, the need to balance the attention provided in all three groups meant that participants were not routinely checked during this time, unless they requested attention.

The placebo needles used were the Streitberger placebo needle (Streitberger and Kleinhenz 1998). The use of these needles requires a period of training therefore the practitioner (Denise Gibson) was trained in their use, prior to the trial by Dr Peter White (Senior Research Fellow, Complementary Medicine Research Unit, University of Southampton). The placebo needles were applied using the same point prescription (Li4, Lv3, St 36 & P6) using the"O" ring and sticking plaster. The practitioner carrying out the "real" and placebo acupuncture was the author (Denise Gibson) who had been trained in western acupuncture techniques on an Acupuncture Association of Chartered Physiotherapists (AACP) accredited course and had 6 years clinical experience in acupuncture practice.

(xi) Blinding

Due to the nature of both interventions, it was not possible to "blind" the clinician to the treatments. However, the practitioner had minimal interaction with the participants and this was standardised for all. The practitioner avoided any discussion regarding each therapy, or any response to it, with the participant. A research assistant, who was blinded to the group in which participants were receiving treatment, carried out all

outcome measures and administered the questionnaires. There was no acceptable method of measuring participant blinding to the acupuncture treatment. However, at the end of the trial participants in groups A and B were asked if they felt they had received real acupuncture or placebo acupuncture.

(xii) Outcome measures

The null hypothesis stated that there would be no greater effect in treatment outcomes, in terms of a reduction of anxiety and hyperventilation symptoms, following "real" acupuncture when used as an adjunctive to conventional treatment. Therefore, anxiety was chosen as the primary outcome. Secondary outcomes were the varied physiological and subjective symptoms of HVS. The researcher considered many outcome measures and other potential measures are discussed and critiqued in Chapter 4.

The following outcome measures were chosen for this study:

Primary outcome measure:

Hospital Anxiety and Depression Scale

The primary outcome measure was the HAD scale (Zigmond and Snaith 1983). The HAD scale can be viewed in Appendix II of this document.

Secondary outcome measures:

The Nijmegen Questionnaire - The NQ can be viewed in Appendix II of this document. **The Measure yourself Medical Outcome Profile 2 (MYMOP2) -** HVS is often a disabling condition and the symptoms often have a major impact on an individual's quality of life. www.hsrc.ac.uk/mymop. (See Appendix VI).

A breathlessness visual analogue scale (VAS-D) (100mm) - Individuals with HVS commonly complain of breathlessness as their main and most disabling symptom. This was used to assess patients' subjective perceptions of their worst breathlessness during the previous week.

Respiratory physiology measures

Individuals with HVS can have fluctuations in both respiratory pattern and rate resulting in altered CO_2 levels. Therefore, as this trial was examining the effects of treatment on HVS, it was deemed appropriate to assess cardiorespiratory performance in the form of resting $ETCO_2$,

Assessing treatment credibility:

Before and after the trial, participants in groups A and B were asked four questions about treatment credibility using the Borkovec and Nau credibility test (Borkovec & Nau 1972). Before the trial, participants were asked:

(i) How confident do you feel that this treatment can alleviate your complaint?

(ii) How logical does this treatment seem to you?

Following the trial participants were asked:

(i) How successful do you think this treatment would be in alleviating other complaints?

(ii) How confident would you be in recommending this treatment to a friend who suffered from similar complaints?

Responses were then recorded on a 5-point Likert scale with 5 being high credibility. Following the trial, participants who received acupuncture or placebo acupuncture were also asked to predict whether they had received genuine acupuncture or placebo treatment.

(xiii) Data Analysis Process

Patient demographic details were presented in the form of mean and SD The mean, SD and 95% confidence intervals for each intervention group were calculated with respect to primary continuous outcome measure. The outcome measures used provided ordinal data and therefore non-parametric techniques were applied. Comparisons between pre and post intervention within and between each group were performed using non-parametric techniques. Assumptions based on the use of these techniques were also investigated. For data classified as categorical, chi-squared statistics were used. Statistical analysis was performed using SPSS 19.0 and a p-value less than or equal to 0.05 was used to indicate a statistical significant difference.

6.6 Data analysis Plan

Primary Outcome

Anxiety -HADscale

Test 1. Between-group differences at baseline

There are three comparison groups, ordinal data are generated by the HAD, therefore the Kruskal-Wallis Test is appropriate.

Justification: It was assumed that randomisation led to equivalence of baseline scores, but due to small study numbers, this was checked statistically

Test 2. Assessment of within-group differences

Each group is being examined at 2 time points (baseline and post treatment). /Ordinal data are generated therefore Wilcoxon Signed Rank Test is appropriate

Justification: Evidence from previous studies including pilot study that both acupuncture and physiotherapy (BR) can reduce anxiety levels, therefore there is justification for examining the effect of both each therapy alone

Test 3. Between-group comparison

Aim to measure change between all 3 groups/one between group factor (Treatment)/Ordinal data- - non-parametric equivalent of one-way analysis of variance (ANOVA) = Kruskal-Wallis Test

Justification: Evidence from previous studies including pilot study that both acupuncture and physiotherapy (BR) can reduce anxiety levels, therefore there is justification for examining the effect of both each therapy alone and as a combined treatment. The non-specific effect of acupuncture treatment is also well documented

Secondary Outcomes

Symptom Scores -Nijmegen Questionnaire

Test 1. Between-group differences at baseline

There are three comparison groups, ordinal data are generated by the HAD, therefore the Kruskal-Wallis Test is appropriate.

Justification: To determine whether all groups have similar baseline scores.

Test 2. Within Group differences of symptom scores

Each group being examined/looking for change in symptom scores / Ordinal data- non-parametric equivalent to Paired t-Test=Wilcoxon Signed Rank Test

Justification: Evidence from previous studies including pilot study that both acupuncture and physiotherapy (BR) can reduce symptoms of HVS, therefore there is justification for examining the effect of each therapy alone within each group.

Test 3. Between-groups comparison of symptom scores

Aim to measure change between all 3 groups/one between group factor(Treatment)/Ordinal data non-parametric equivalent to ANOVA = Kruskal-Wallis Test.

Justification: Evidence from previous studies including pilot study that both acupuncture and physiotherapy (BR) can reduce symptoms of HVS, therefore there is justification for examining the effect of each therapy alone and as a combined treatment. The non-specific effect of acupuncture treatment is also well documented**.**

Depression HAD scale

Test 1. Between group comparisons at baseline

There are more than two groups/one between group factor (Treatment)/ between group comparison/ Ordinal data-non-parametric equivalent of an ANOVA = Kruskal-Wallis Test.

Justification: To determine whether all groups have similar baseline scores

Test 2. Within-Group differences of Depression scores

Each group is being examined at 2time points (baseline and post treatment). /Ordinal data are generated therefore Wilcoxon Signed Rank Test is appropriate

Justification: Evidence from previous studies including pilot study that both acupuncture and physiotherapy (BR) can reduce depression levels, therefore there is justification for examining the effect of both each therapy

alone and as a combined treatment. The non-specific effect of acupuncture treatment is also well documented.

Test 3. Between-group differences in depression scores

Aim to measure change between all 3 groups/one between group factor (Treatment)/Ordinal data- Non-parametric equivalent to an ANOVA = Kruskal-Wallis Test.

Justification: Evidence from previous studies including pilot study that both acupuncture and physiotherapy (BR) can reduce depression levels, therefore there is justification for examining the effect of both each therapy alone and as a combined treatment. The non-specific effect of acupuncture treatment is also well documented.

Health Status MYMOP2:

Test 1. Within-group differences in health status

Each group is being examined / examining change on a variable at 2 time points/Ordinal data/ - non –parametric equivalent of Paired t- test= Wilcoxon Signed Rank Test.

Test 2. Between-group differences in health status

Aim to measure change between all 3 groups/one between group factor(Treatment)/Ordinal data non-parametric equivalent of an ANOVA = Kruskal-Wallis Test.

Justification: It is well documented within the literature that chronic disease can affect health status and that some treatment modalities which relieve symptoms, may help to improve health status. As HVS is a chronic disease there is justification in assessing the effect of both BR and acupuncture on health status.

Treatment Credibility – Borkovec and Nau

Test 1. Within-group differences in treatment credibility

Each group is being examined / examining change on a variable at 2 time points/Ordinal data/ - non –parametric equivalent of Paired t- test= Wilcoxon Signed Rank Test.

Test 2. Between-group differences in treatment credibility

Examining change in all 3 groups/ two between group factors (treatment credibility & experimental condition)/ Ordinal data- non-parametric equivalent to ANOVA = Kruskal-Wallis Test.

Justification: Acupuncture studies have shown that a credibility scale accurately reflects the participants' beliefs surrounding the effectiveness of acupuncture treatment and its authenticity. It has been suggested that the BN scale is a useful measure of the psychological impact of acupuncture and assessment of the credibility of acupuncture placebo controls (Vincent & Lewith 1995).

End-tidal Carbon dioxide

Test 1. Within-group differences in End-tidal Carbon dioxide

Each group is being examined / examining change on a variable at 2 time points/ interval data- parametric test /paired t-test.

Justification: $ETCO_2$ is known to have a high correlation with $PaCO_2$ which enables the physiological measurement of the level of hyperventilation (Gilbert 2002). There is some debate surrounding the issue of whether $ETCO_2$ levels are a good measure of HVS. It is likely that there is a fluctuation in $PaCO_2$ levels which exacerbates symptoms of this condition (Lum 1981). However, It is a measure frequently used within HVS treatment and research to assess outcomes of treatment (Garssen et al 1992, DeGuire et al 1992, Hornsveld et al 1996 Tweedale et al 1994, De Guire et al 1996, Han et al 1996, Bass 1997, Gardiner 2004, Han et al 2004).

Test 2. Between-group differences in End-tidal carbon dioxide

Aim to measure change between all 3 groups/one between group factor (Treatment)/Interval data- / parametric test ANOVA.

Breathlessness Visual Analogue Scale- Dyspnoea

Test 1. Within-group differences in breathlessness

Each group is being examined / examining change on a variable at 2 time points/ interval data- parametric test /paired t-test.

Justification: Breathlessness or dyspnoea is a common symptom of HVS. Although the NQ examines an aspect of respiratory symptoms it does not enable the recording of the intensity of breathlessness.

Test 2. Between-group differences in breathlessness

Aim to measure change between all 3 groups/one between group factor (Treatment)/Interval data- / ANOVA

6.7 Results Study 1.

6.7.1 The Sample

A total of 76 patients with HVS were referred for physiotherapy, over the data collection period of August 2006-May 2010. A total of 60 patients volunteered to participate in the trial. Twenty were excluded from the trial for the following reasons: body acupuncture was contraindicated (n=8), they had other respiratory co-morbidities such as asthma (n=8) or they had received acupuncture previously for unrelated conditions (n=4). Eligibility for inclusion into this trial was determined prior to consent being obtained, therefore there are no available data on the non-participants. Therefore, a total of 40 participants were included in the trial. All 40 completed the trial and data analysis was carried out on the data derived from these participants. The final study sample of 40 participants was much lower than the anticipated 90, which would have provided 80% power (taking attrition rate into account). This considerably smaller sample size impacts upon the conclusions that can be drawn from this study. The implications of this will be discussed in chapter 8. The smaller than expected sample size was due to an unexpected reduction in HVS referrals received for physiotherapy treatment.

6.7.2 Data Analysis

The results will be presented as follows:

(i) Demographic data and sample characteristics at baseline

(ii) Comparisons of baseline characteristics between groups
(iii) Within groups comparison of HAD anxiety and depression scores pre and post intervention
(iv) Between groups comparison of HAD anxiety and depression scores pre and post intervention

(v) Graphical presentation of the mean anxiety and depressions scores pre and post intervention.
(vi) Two-way analysis of anxiety scores for groups 1 (acupuncture & BR) and 3(BR only).
(v) Results for symptoms, health status, $ETCO_2$ & breathlessness.
(vi) Treatment credibility

(i)Demographic data and sample characteristics at baseline

The demographic and baseline characteristics of the whole sample have been collated and are presented within Table 6. The presented data includes gender, age and baseline anxiety, depression and symptom scores following randomisation into the three treatment groups. There were more females (n=25) than males (n=15) within the whole sample which reflects the prevalence of HVS within the general population. Group 3 (physiotherapy breathing training BR only) however, had more males (n=7) than females (n=5). The ages of the participants ranged from 19 to 75 years. This would seem to reflect the general HVS population where HVS is evident in all age ranges and can be present in young children as well as adults. The mean age in group 3 (46 years SD 13) was lower than in groups 1 or 2, this difference was found to be statistically significant (p=0.02) in this sample (see section (ii). Although randomisation should theoretically even out group characteristics, because of the small sample size, it was decided to conduct statistical tests to compare group means at baseline. The baseline scores for anxiety and depression (as measured by the HAD scale) and the symptom scores (as measured by the NQ) were compared to explore any statistically significant differences among the three groups at baseline. The results of this analysis are presented in section (ii).

	Group 1 n=14	Group 2 n=14	Group 3 n=12
Sex			
Males	4	4	7
Females	10	10	5
Age in years Mean (SD)	62(8.2)	50(18.7)	46(13)
Chronicity of symptoms (years) Mean(SD)	2(1.2)	3(1.9)	3(2)
HAD A **Anxiety** Mean(SD)	9 (3.8)	11(4.5)	10(4.7)
HAD D **Depression** Mean(SD)	5(4.6)	6(4.3)	6(4.2)
Nijmegen	27(10)	29 (9.1)	31(12.3)
Symptom Scores Mean(SD)			

Table.6. Demographic data and baseline scores for the sample after randomisation into 3 groups.

Key: SD: Standard Deviation, HAD A: Hospital Anxiety and Depression Scale (Anxiety): 0=not very anxious, 21-very anxious; HAD D: Hospital Anxiety and Depression Scale (Depression): 0=not very depressed, 21=very depressed; Nijmegen scores: > 23 positive for HVS, group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3= BR only.

(ii)Comparison of the baseline age, anxiety, depression and symptom scores of the three groups.

The baseline ages across all three groups were compared by applying the ANOVA technique. A parametric test was used as this was normally distributed, interval data. Table 7. shows the statistical significance values for each variable.

Variable	**Test statistic and significance value**
Age	One-Way ANOVA F=4.355 p=0.02*****
Chronicity (years)	One-Way ANOVA F=1.11 p=0.338
HAD A (Anxiety)	Kruskal-Wallis H=0.673 p=0.714
HAD D (Depression)	Kruskal-Wallis H=1.144 p=0.564
Nijmegen Questionnaire (symptom scores)	Kruskal-Wallis H=0.563 p=0.755

Table 7. Comparison of the baseline values for the outcome variables between the three groups. Key:***** = statistically significant @p<0.05

This analysis revealed that there were no statistically significant differences in baseline HAD Scale or Nijmegen scores across all three groups.

A one-way between groups analysis of variance was conducted to explore baseline age across the three groups. There was a statistically significant difference at $p<0.05$ level in age (in years) for the three groups. Post-hoc comparisons using the Tukey HSD test indicated the mean score for group one (M=62, SD=8.2) was significantly different from group three (M=46, SD=13). Group two (M=50, 18.7) did not differ significantly from either group one or group three. There were no statistically significant differences between the three groups in terms of chronicity of symptoms (length of time experiencing HVS symptoms).

(iii) Between groups comparison of HAD anxiety and depression scores post treatment

The anxiety and depression data were then analysed to assess for statistical differences among the three groups post treatment (see Table 8).

	Differences between Groups 1, 2 and 3
Anxiety HAD A	H=2.496 df 2 p= .287
Depression HAD D	H=2.178 df 2 p= .336

Table 8. Analysis of between groups differences of treatment outcomes for all three groups using the Kruskal-Wallis Test.Key: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3= BR only.

This analysis revealed that there were no statistically significant differences in the outcomes of treatment comparing all three groups.

(iv)Within groups comparison of HAD anxiety and depression scores pre and post treatment

All three groups were analysed to assess for within-group differences in anxiety and depression, comparing baseline to post treatment scores, on the HAD scale.

The ordinal data provided by the HAD scale determined the use of a non- parametric statistical test. The Wilcoxon Signed Ranks test was applied to these data. Table 9. presents the results of this analysis for all three treatment groups.

	Group 1 n=14	**Group 2** n=14	**Group 3** n=12
Anxiety HAD A	z= -2.587 p= .010*	z= -2.499 p= .012*	z= -2.223 p= .026*
Depression HAD D	z= -2.489 p= .13	z= -1.878 p= .06	z= -1.881 p= .06

Table 9. Analysis of within group differences from baseline to outcome for all three treatment groups.

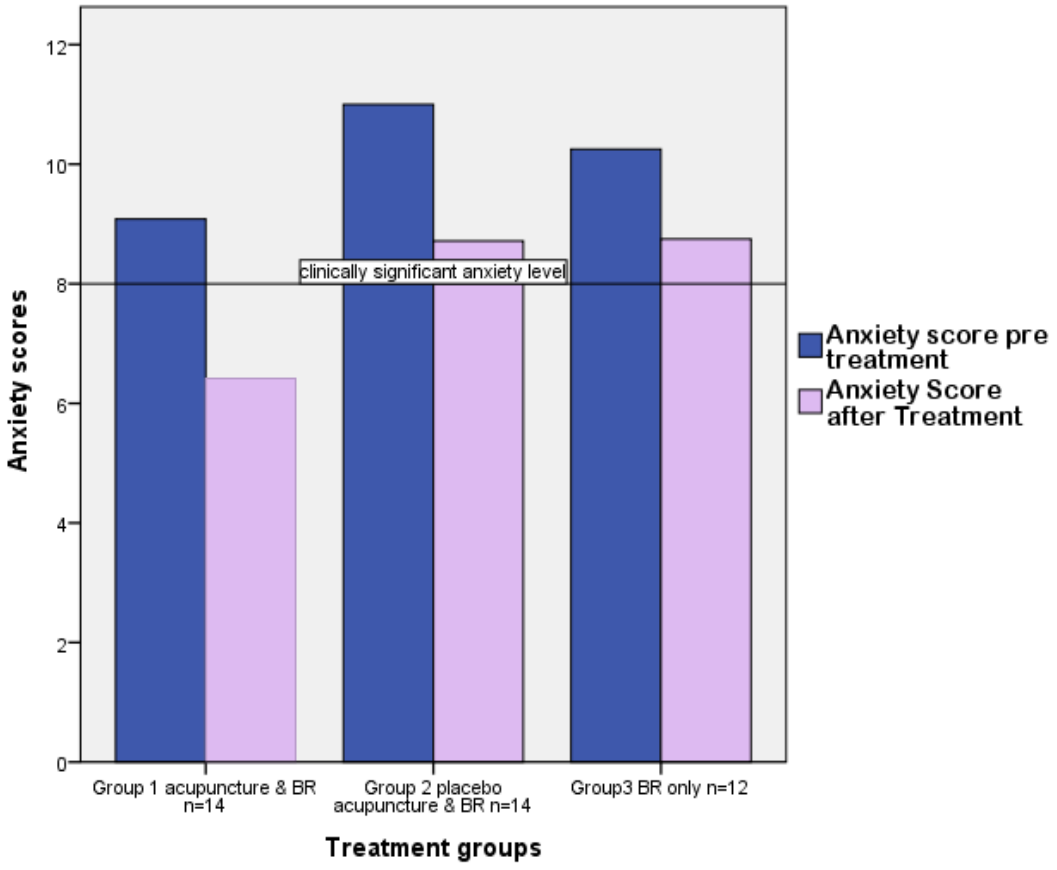
Key: * = statistically significant $p<0.05$ using the Wilcoxon Signed Ranks Test; group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3= BR only.

This analysis reveals that there were statistically significant differences ($p<0.05$) within each treatment group when comparing anxiety scores

(HAD A) at baseline to those following the intervention. This would suggest that all groups improved from baseline for this outcome measure. There were no statistically significant differences in the depression scores (HAD D) within each of the treatment groups, when comparing baseline to outcome.

(v)Graphical presentation of the mean anxiety and depressions scores pre and post treatment

Figure 3. A bar chart to show the mean anxiety (HAD A) scores for each group pre and post treatment.



The bar chart in Figure 3 shows that in all three groups, the baseline anxiety scores were above the level which is considered to be suggestive of the presence of anxiety (clinically significant anxiety - score of 8). The mean score in group 2 was 11 which is the level at which a moderate anxiety state is indicated. There was a reduction in mean anxiety scores following the treatment programme in all three groups. However, in group

1 there was a reduction in mean anxiety levels to below the score considered to be related to the presence of anxiety or clinically significant anxiety(a score of 8).

These results are reflected by the within groups comparisons presented in section (iv) of this chapter.

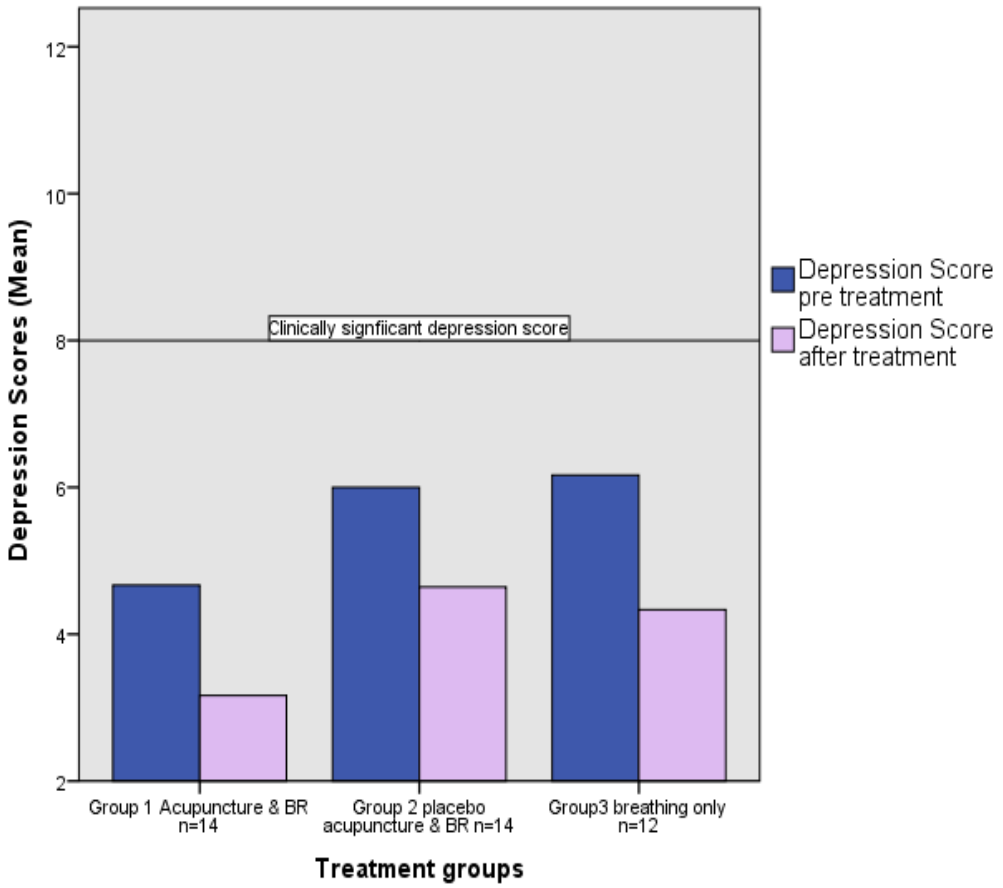


Figure 4. A bar chart to show the mean Depression (HAD D) scores for each group pre and post treatment.

The bar chart (Figure 4.) shows that mean baseline scores were below the level that would be suggestive of the presence of depression (clinically significant level of depression - score of 8). There was a reduction of mean

depression scores following treatment in all three of the groups, however this was not statistically significant (see section (iv).

(vi)Two-way analysis of anxiety scores for groups 1 (acupuncture & BR) and 3 (BR only).

A review of the bar charts (Figures 3&4) revealed that the mean anxiety levels in group 1, who received acupuncture as an adjunct to BR, reduced from a level of mild anxiety (8-10) to below the level considered to represent the presence of clinical anxiety (a score of 8). This change was not evident in either of the other two groups. This prompted the researcher to carry out a Two-way analysis comparing the post treatment anxiety scores of group 1(acupuncture & BR) with group 3 (BR only). The results are displayed in Table10. The analysis was carried out using the Mann-Whitney U Test which is a non-parametric used for comparing 2 independent samples.

	Test statistic Using Mann-Whitney U Test
Differences in anxiety scores between groups 1 & 3	Z= -1.369 p= 0.171

Table 10. Two-way analysis of anxiety scores after treatment between groups 1 and 3.

Key: group 1=acupuncture + physiotherapy n=14 BR, group 3= BR only n=12.

This analysis revealed that there were no statistically significant differences in post treatment anxiety levels between the group that received adjunctive acupuncture (group1) and the group that received BR only (group 3).

(vii)Results for symptoms, health status, end-tidal carbon dioxide & breathlessness

(a) Between group differences for symptoms and Health Status:

	Differences between groups 1,2 & 3
Nijmegen Questionnaire	**H=2.2812**
Symptom score	**Df= 2**
	P=0.320
MYMOP Profile	**H= 5.184**
Health Status	**df= 2**
	p=0.075

Table 11. Analysis of between groups differences of treatment outcomes in terms of symptoms and health status for all three groups using the Kruskal-Wallis Test.

Key: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only.

There were no statistically significant between group differences in treatment outcomes for symptoms or health status, for all three groups (See Table 11). However, the mean symptom scores on the NQ, in both groups 1 and 2 reduced to below the cut-off point that is considered to be the point at which the symptoms are clinically relevant for HVS (a score of 23). See Figure 5.

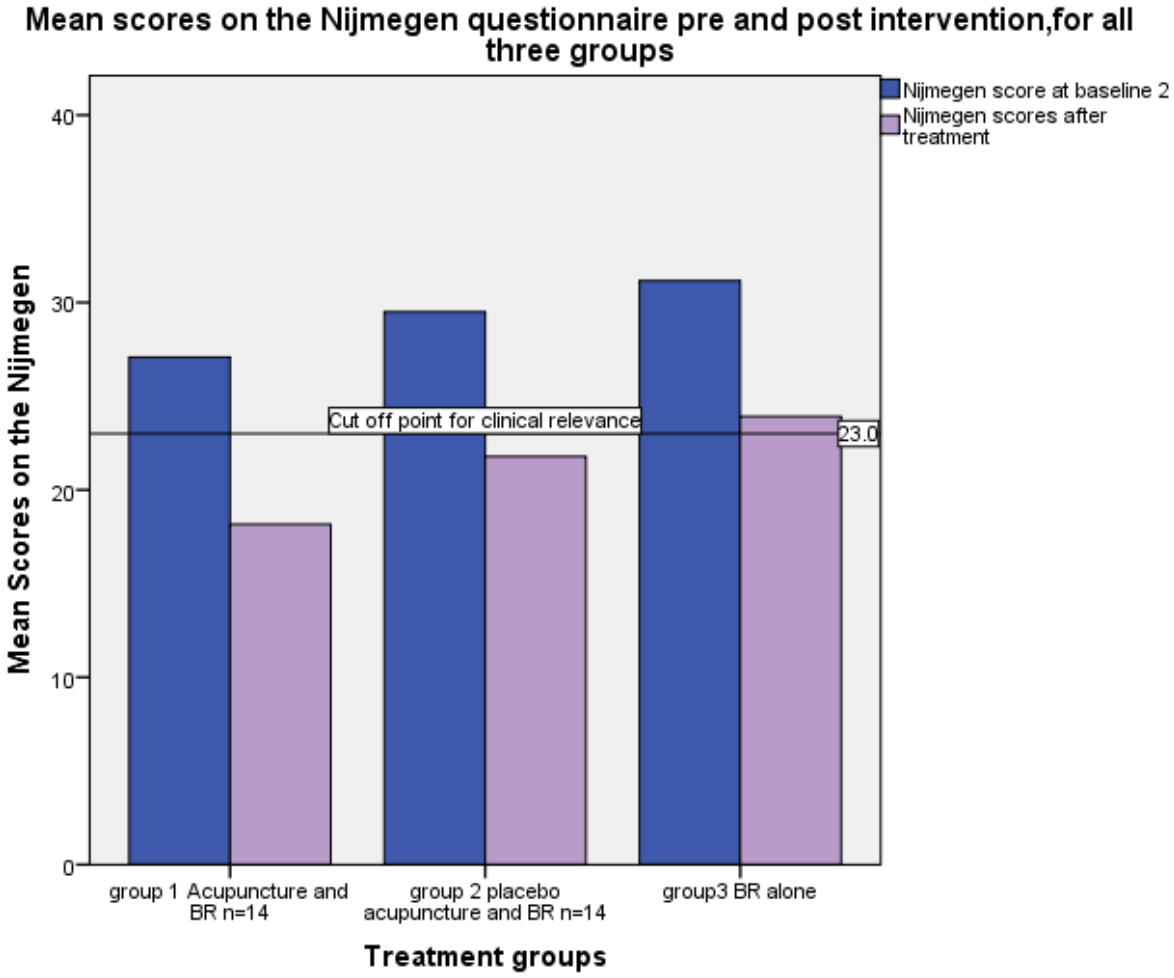


Figure 5. Mean scores of all three groups on the Nijmegen questionnaire before and after treatment

(b) Between group differences $ETCO_2$, and breathlessness

The continuous data for both these variables was examined to assess the assumption that it was derived from a normally distributed population. The results are presented in Table 12 below. A Shapiro-Wilk test show that the p-values are >0.05. Therefore, it was concluded that the data came from a normally distributed population and it can be analysed using parametric tests.

	Shapiro-Wilk Statistic	Df	Sig
End-Tidal Carbon Dioxide	0.955	38	0.128
Breathlessness VAS-D	0.968	40	0.309

Table 12. To show the test of normality for the $ETCO_2$ and breathlessness

A one-way ANOVA test was carried out to explore for any between group differences in outcomes for breathlessness and $ETCO_2$ (see Table 13).

	Differences between groups 1,2 & 3
$ETCO_2$	**F=0.152** **df= 2** **p=0.860**
VAS-D Breathlessness	**F= 8.817** **df= 2** **p=0.001***

Table 13. Analysis of between groups differences of ETCO2 and breathlessness outcomes for all three groups using an ANOVA.

Key: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only. *=statistically significant at $p<0.05$

There was a statistically significant difference in the breathlessness scores measured by the VAS-D, between all three groups. A Tukey's HSD post hoc test revealed Group 1 (acupuncture + BR) had significantly different

scores compared to both Groups 2 (placebo + BR) and 3 (BR only) but groups 2 and 3 were not significantly different from each other. Table 14. Presents the means, SD and 95% confidence intervals for each group.

Group	Mean	SD	CI
1	**3.85**	**1.09**	**3.2-4.4**
2	**5.35**	**1.15**	**4.6-6.0**
3	**5.58**	**1.24**	**4.79-6.37**

Table 14. Mean, Standard deviation and 95%Confidence intervals for breathlessness scores for all three groups post intervention.

Key: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only. CI = 95% Confidence intervals; SD= Standard Deviation

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(c)Within group differences in symptoms and health status

The Kruskall-Wallis test was carried out on the data from the NQ (symptom score) and the profile scores from the MYMOP. Table 15 below shows the results of the analysis.

	Group 1 Acupuncture &BR	Group 2 Placebo Acupuncture & BR	Group 3 BR
Nijmegen Questionnaire	**z=-3.702 p= 0.002***	**z= -2.832 p= 0.005***	**z= -2.710 p=0.007***
MYMOP2 profile	**z= -3.181 p=0.001***	**z= -2.707 p= 0.007***	**z= -3.061 p= 0.002***

Table 15. Analysis of within groups differences of treatment outcomes in terms of symptoms and health status for all three groups using the Kruskal-Wallis Test.

Key: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only.

All three groups had statistically significant within-group differences from baseline to outcome for both symptom scores and health status. The mean MYMOP scores in all domains for all three groups improved from baseline to outcome. Clinically significant improvements were found (>1 increase) in all domains for all groups except for the activity domain in the acupuncture group (group 1.). The largest clinically significant increase in mean health status scores was found in the wellbeing domain of the MYMOP for the acupuncture group (group 1.).

(d)Within-group differences for breathlessness and end-tidal carbon dioxide.

The data from the VAS-D and ETCO2 were analysed using the paired t-test as this was a within group comparison from outcome to baseline. The data was normally distributed and therefore a parametric test was used. (See Tables 16 and 17).

Group	Mean difference	SD	95%CI	df	Sig
1	**0.93**	**0.91**	**0.39- 1.4**	**13**	**0.002***
2	**0.57**	**0.75**	**0.13- 1.00**	**13**	**0.014***
3	**0.25**	**0.45**	**-0.1-0.5**	**13**	**0.08**

Table 16. To show within group analysis baseline to outcome in all three groups for breathlessness scores using the paired samples t-test.

Key: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only. CI = 95% Confidence intervals; SD= Standard Deviation ; * statistically significant $p<0.05$.

There were statistically significant differences in breathlessness scores from baseline to outcome for both groups 1 (acupuncture and BR) and 2 (placebo acupuncture and BR).

Group	Mean Difference	SD	95%CI	df	Sig
1	**-0.5**	**1.7**	**-1.69- 0.5**	**10**	**0.305**
2	**-0.66**	**0.5**	**-0.99- -0.33**	**13**	**0.001***
3	**-0.7**	**1.1**	**-1.47- 0.07**	**10**	**0.72**

Table 17. To show within group analysis baseline to outcome in all three groups for end-tidal carbon dioxide using the paired samples t-test.

Key: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only. CI = 95% Confidence intervals; SD= Standard Deviation; * statistically significant $p<0.05$.

There were statistically significant within-group differences in $ETCO_2$ readings from baseline to outcome for group 2 only (placebo acupuncture and BR). All three groups showed an increase in mean $ETCO_2$, from baseline to outcome.

(vi)Treatment Credibility

The data from the adapted Borkovec and Nau credibility rating was analysed using the Kruskall-Wallis H test to explore any between group differences in the credibility of the treatment they received. Table 18. below shows the results of the between group analysis.

Question on B&N questionnaire	Kruskall-Wallis H test
Q1. How confident do you feel that this treatment can alleviate your complaint?	H= 0.493 df 2 p= 0.781
Q2. How logical does this treatment seem to you?	H= 1.47 df 2 p= 0.478
Q3. How confident would you be in recommending this treatment to a friend who suffered from the same complaint?	H= 6.256 df 2 p= 0.04*
Q4. How successful do you think this treatment would be in alleviating other complaints?	H= 1.026 df 2 p= 0.599

Table 18. Between group differences in treatment credibility.

Key: B&N Borkovec and Nau credibility rating; Groups: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only;* statistically significant $p<0.05$

There was a statistically significant difference between the groups for Q3 which was asked post intervention. It was unclear which groups differed and therefore, a post-hoc analysis was performed using the Dun-Bonferroni post-hoc test. See Table 19 below.

Treatment groups 1-2	Test Statistic	Std Error	Std Test Statistic	Sig	Adj Sig
Grp 1- Grp 2	-2.987	3.972	-0.752	0.452	1.000
Grp 2- Grp 3	-7.195	3.972	-1.811	0.070	0.210
Grp 1-Grp 3	-10.182	4.204	-2.422	0.015	0.046*

Table 19. Post-hoc analysis of treatment credibility Q3.

Significance values have been adjusted by the Bonferroni correction for multiple tests. **Key:** B&N Borkovec and Nau credibility rating; Groups: group 1=acupuncture + physiotherapy BR, group 2= placebo acupuncture + BR, group 3=BR only;* statistically significant $p<0.05$

The post-hoc analysis revealed that the acupuncture group (group1) significantly differed from the group 3 who received BR alone. There was no statistically significant difference between groups 1 and 2 or 2 and 3. The mean scores for both groups 1 and 2 were lower than group 3. The results from this post-hoc analysis suggests that those in groups 1 and 2 were less likely to recommend their treatment to a friend than the BR group and this difference was statistically significant between the acupuncture and the BR groups.

Null Hypothesis	Findings	Accepted/Rejected
Anxiety When used as an adjunct to conventional physiotherapy BR programme for the treatment of HVS, acupuncture would have no greater effect in terms of reducing anxiety, than either a placebo adjunct or conventional physiotherapy alone.	There were no significant between-group differences at outcome. The mean anxiety scores in the acupuncture group reduced to below a clinically positive score for anxiety. In both the acupuncture and placebo acupuncture, the mean anxiety scores reduced by >1.5 which is considered a minimal clinically significant difference. There were statistically significant differences within each of the 3 groups from baseline to outcome, in terms of a reduction in anxiety levels following treatment	**Accepted** However, the mean scores for the acupuncture group reduced to below clinically relevant levels. This was not observed in either of the other groups.
Depression When used as an adjunct to conventional physiotherapy BR programme in the treatment of HVS, acupuncture would have no greater effect in terms of reducing depression, than a placebo adjunct or conventional physiotherapy alone.	There were no statistically significant treatment differences found either within the groups or between the three groups. There was a trend towards a reduction in depression scores in all 3 groups but this was not found to be statistically significant.	**Accepted**
Symptoms When used as an adjunctive treatment to conventional physiotherapy BR programme for the treatment of HVS, acupuncture would have no greater effect in terms of reducing symptoms of hyperventilation than either a placebo adjunct or	There were no statistically significant differences in symptoms between all three groups. However, at outcome, the mean Nijmegen scores in both the acupuncture and placebo acupuncture groups reduced to below the clinically relevant cut off indicating the presence of HVS. This was not the case for the BR group. There were statistically significant within-group	**Accepted** However, the mean scores for both the acupuncture and placebo acupuncture groups reduced to below the clinically relevant cut off point post intervention.

conventional physiotherapy alone.	differences in symptoms from baseline to outcome in all three groups.	
$ETCO_2$ When used as an adjunctive treatment to conventional physiotherapy BR programme for the treatment of HVS, acupuncture would have no greater effect, in terms of increasing $ETCO_2$, than either a placebo adjunct or conventional physiotherapy alone.	There were no statistically Significant between-group differences in $ETCO_2$. There was a statistically significant within group difference in $ETCO_2$ for the placebo acupuncture. All the groups had an increase in $ETCO_2$ from baseline to outcome	**Accepted**.
Health Status When used as an adjunctive treatment to a conventional physiotherapy BR programme for the treatment of HVS, acupuncture would have no greater effect, in terms of improving Health status, than either a placebo adjunct or conventional physiotherapy alone.	There were no statistically significant between-group differences in health status. There were statistically significant within-group differences in the MYMOP profile scores for all three groups. There were clinically significant improvements in all mean scores on the MYMOP domains, comparing baseline to outcome, except for the activity domain for the acupuncture group. The largest clinically relevant increase in health status was found in the wellbeing domain for the acupuncture group.	**Accepted** However, there were clinically relevant improvements in health status for all groups. The greatest improvement in health status was found in the wellbeing domain for the acupuncture group.

Breathlessness When used as an adjunctive treatment to a conventional physiotherapy BR programme for the treatment of HVS, acupuncture would have no greater effect, in terms of improving breathlessness.	There was a statistically significant between-group difference in breathlessness. The breathlessness scores were acupuncture group was significantly different to both the placebo (group 2.) and BR (group 3.) groups. The mean score was significantly lower in the acupuncture group. There were statistically significant within group differences from baseline to outcome for breathlessness in both groups 1 and 2 (acupuncture and placebo acupuncture groups).	**Reject** Acupuncture was found to have a greater effect on reducing breathlessness in HVS when compared to placebo acupuncture and conventional physiotherapy or conventional physiotherapy alone**.**

Table 20. A summary of the main findings in relation to the proposed null hypotheses.

6.8 Chapter Summary

This chapter has presented the analysis of the data derived from Study 1. The findings have been summarised in Table 20 and indicate that all null hypotheses tested to date must be accepted, except for the null hypothesis relating to the impact of acupuncture on breathlessness related to HVS, where the null hypothesis is accepted. There were no statistically significant differences in anxiety between any of the three groups. However, following intervention, there were clinically relevant reductions in anxiety in the acupuncture group and the anxiety scores in the acupuncture group, reduced to below the cut-off for clinically relevant anxiety. There were also statistically significant between-group differences in breathlessness associated with HVS.

The findings from study 1 offered further questions that a second study was warranted. The question of whether acupuncture would offer any clinical benefit for anxiety and breathlessness in other respiratory disorders remained unanswered. Individuals with COPD often have clinical anxiety and disabling breathlessness is a key feature of the condition.

There is also a connection between COPD and HVS in that both conditions can exhibit hyperinflation and patients with COPD can have co-existing HVS as a result.

There were several individuals that were unable to participate in study 1 as “real” body acupuncture was contraindicated either due to skin integrity, anticoagulant use or epilepsy.

The next chapter will present Study 2 of this programme of research and the findings for both studies will be discussed and conclusions made, in Chapter 8.

Chapter 7. Study 2.

A Feasibility study of Ear acupuncture as an adjunct to pulmonary rehabilitation for patients with chronic obstructive pulmonary disease

7.1 Introduction

Ear acupuncture is defined as “a diagnostic and treatment system based on normalising the body’s dysfunction by stimulating acupuncture points on the external ear” (Round et al 2013 page 2). There are also several terms used to describe this treatment such as auricular therapy and auricular acupuncture however, the term ear acupuncture will be used in this thesis. It involves the application of either needles, electrical stimulation or applied pressure to specific areas of the external ear. There are different methods of applying pressure to the ear such as fingers, magnetic or ionic beads or mustard seeds (Round et al 2013). Ear acupuncture is commonly used by clinicians for the treatment of anxiety disorders, chronic pain and disease, obesity and addictions. In this trial, the ear acupuncture consisted of the application of pressure to specific points within the external ear. It was decided not to use needle acupuncture to these points due to the poor blood supply to the ear cartilage and therefore the high risk of infection, which would be difficult to eradicate (Hopwood 2004).

Ear acupuncture was chosen for this study over body acupuncture for several reasons (i) the majority of studies available within the literature that demonstrate some beneficial effects of acupuncture on anxiety have used ear acupuncture (Kober et al 2003, Wang et al 2001 (a),Wang et al 2001 (b), Wang et al 2004), (ii) Patients with COPD are often anxious125 (Yohannes et al 2000) and it is this author’s opinion that the thought of having body acupuncture using needling technique may well have induced greater anxiety prior to treatment and may therefore distort any findings relating to anxiety, (iii)Ear acupuncture used in this study is non-invasive and the small beads of Magrain (Magrain balls are small gold-plated balls

that are on sticking plaster that are used in ear acupuncture to stimulate the ear points) can be left in situ for several days meaning that the participants could continue with their treatment outside of their clinical appointments. This may be particularly helpful for patients with COPD in terms of helping to reduce anxiety/symptoms during activities of daily living.

7.2 Aims

1. To evaluate whether it is feasible to use ear acupuncture as an adjunctive treatment for patients with COPD and anxiety, attending a PR programme and whether this would be acceptable for the participants in a definitive research study.
2. To provide data to enable a power calculation that will inform a definitive trial, examining the effect of ear acupuncture on anxiety related to COPD.

7.3 Research Question

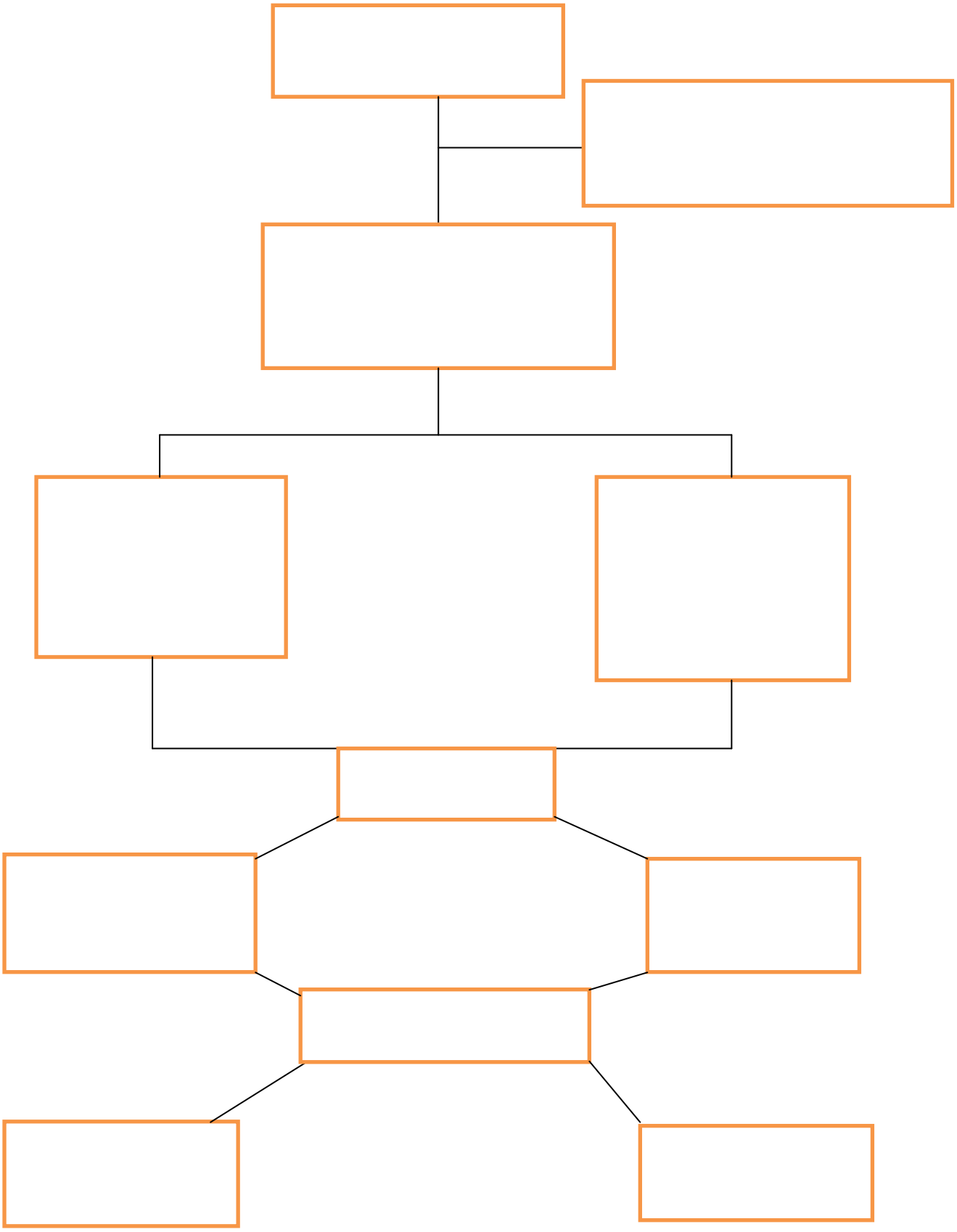
The research question to be answered in a future definitive trial:
Does ear acupuncture have any effect on anxiety levels associated with COPD, when it is used as an adjunct to a PR programme?

7.4 Trial summary

This was a study examining the feasibility of using ear acupuncture as an adjunct to pulmonary rehabilitation (PR) for patients with COPD. PR is a multidisciplinary programme providing care for patients with COPD, which promotes the optimisation of individual patient's physical and soci9al performance, whilst empowering the patient with self-management strategies.
Eligible participants were recruited from those that were referred to PR at University Hospital Southampton NHS Foundation Trust (UHSFT). Baseline assessments were carried out and patients were randomised into

one of two groups. The treatment group received ear acupuncture to recognised ear acupuncture points, whilst the control group received e9ar acupuncture to an area on the ear lobe where there is an absence of acupuncture points. The participants received ear acupuncture twice weekly during their hospitals visits to the six-week PR programme. Anxiety is associated with COPD and is known to have a significant impact upon quality of life as well as a deleterious effect on the efficacy of PR (Tsiligianni et al 2011). Therefore, the primary outcome measure used for this study was the HAD scale (Zigmond & Snaith 1983). Secondary outcomes were in the form of, alternative anxiety and depression measures (STAI) (Spielberger 1970), a respiratory disease questionnaire (St George's Respiratory Disease Questionnaire) (Jones et al 1991), exercise tolerance measure (incremental shuttle walk test (ISWT) (Singh et al 1992) and the MRC breathlessness score (Bestall et al 1999). Figure 6. shows the flow of participants through the study. Data analysis explored changes in outcomes (anxiety, depression, impacts of respiratory symptoms, exercise tolerance and breathlessness scores).

Figure 6 CONSORT diagram for Study 2



7.5 Hypothesis

It is hypothesised that ear acupuncture when used an as adjunct to a PR programme for the treatment of COPD, would have a greater effect in terms of reducing anxiety, when compared to a placebo adjunct.

Null Hypothesis

The Null hypothesis provided here is that which would be used for the definitive RCT. Although significance testing is not necessary in a feasibility study it is acceptable for such studies to include small scale randomised trials to test a methodology. This study was not adequately powered for any firm conclusions to be reached on potential treatment effects. However, in order to lay foundations for the definitive trial and to test the data analysis plan significance testing was carried out for this study.

The null hypothesis states that ear acupuncture, when used as an adjunct to a PR programme for the treatment of COPD, would have no greater effect in terms of reducing anxiety, when compared to a placebo adjunct.

7.6 Method

The method will be described in the following sections:

(I) Study design
(ii) Ethics and research governance
(iii) Sample size
(iv) Study Participants
(v) Recruitment
(vi) Randomisation
(vii) Plan of Investigation
(viii)Trial Procedure
(ix) Interventions
(x) Blinding

(i) Study Design:

A two-arm placebo-controlled feasibility design was used to evaluate the feasibility of using ear acupuncture in COPD patients as an adjunct to PR. Feasibility studies are designed to lay foundations for intervention studies and are often considered critical to the success of an RCT (Shadish et al 2002). There are many aspects of therapy that Feasibility studies can examine (Bowen et al 2009). This study examined the acceptability (how the individuals react to the intervention), expansion of the intervention (an already successful intervention is used in a different population or a different setting including) and practicalities (can an intervention be delivered in a particular way/setting, is recruitment possible? Are the outcomes valid and appropriate?).

This study design was chosen as this author is not aware of any controlled studies within the literature examining the effect of ear acupuncture as an adjunctive therapy to PR, in the treatment of anxiety related to chronic respiratory disease. Therefore, the purpose of this study was to test the method and to inform a power calculation for a larger RCT in this field of research. The National Institute for Health Research Evaluation, Trials and Studies coordination Centre states that “feasibility studies are pieces of research done before a main study in order to answer the question: Can this study be done?” (NETSCC 2012). This supports the choice of a feasibility study for this trial.

This author considers that, an RCT examining the effects of ear acupuncture on anxiety related to COPD, would provide more robust data if designed as a “three-arm” study and this would then take into account not only “real” versus placebo acupuncture but also any anxiolytic effect of a PR programme alone. However, this author wanted to examine the feasibility and acceptability of ear acupuncture as an adjunct to PR prior to embarking upon a three-arm RCT.

The study participants were randomised into one of two groups using stratified randomisation to increase the chances of having equal distribution of key confounding variables (baseline anxiety levels). This author considered it important to test this randomisation process to assess for refusal rates and to examine whether it was possible in a cohort of participants with COPD.

Acupuncture is renowned for its powerful non-specific effect and therefore any future RCT examining the effect of ear acupuncture would require a placebo control (Carlsson 2002). As this feasibility study was considered to be the foundation for a larger RCT in this field, this author considered that it was necessary to include a "placebo-arm" to examine whether both the idea of a placebo treatment and the chosen location for the placebo point, would be acceptable to this cohort of patients.
It was considered necessary to have researchers "blinded" to the interventions. However, due to the nature of ear acupuncture, it was not possible to "blind" the clinician to the treatment. Therefore, a single-blind approach was chosen for the feasibility study, whereby the outcome measurements and questionnaire administration were carried out by a physiotherapist/physiotherapy assistant who was unaware of the intervention that each participant had received. The procedure for the randomisation and "blinding" will be discussed later in section (vi) of this chapter.

(ii) Ethics and Research Governance

This protocol was submitted to the Health Research Authority National Research ethics service (NRES) and was reviewed by the NRES committee- London. Full ethical approval was obtained prior to commencing recruitment of participants (see Appendix IV for ethical approval letter IRAS no: 119521).

Ethical considerations:

During this study, the researcher (this author) worked as a physiotherapist at UHSFT. The participants were given the patient information sheet by another senior physiotherapist (clinical lead for the PR service), at their PR assessment visit, to prevent patients feeling coerced into taking part in this study by someone they knew clinically. The researcher did not contact any patients directly about this trial prior to some interest being shown. It was also made clear to all patients that accepting or refusing to participate in this study would have no beneficial or adverse effect on their treatment.

All participants were asked to complete a health questionnaire prior to entering the trial to screen for contraindications to the acupuncture treatment. Eligible participants received both a written and verbal explanation of the study prior to entering and were advised that they would have the option to withdraw from the trial at any time without affecting their care. Participants were advised that there may be some minor side effects to the ear acupuncture such as redness/discomfort on the ear point. If the discomfort persisted the participants were advised on how to remove the plaster with the Magrain, (small gold-plated balls/beads used to stimulate the auricular point). Participants who were found to have a high level of anxiety and/or depression on the HAD score (i.e.>11) were offered the opportunity to be referred back to their consultant for further treatment at the end of the trial. Those participants who were randomised to the placebo group were offered the opportunity to receive ear acupuncture at the end of the trial. Only the clinicians that were involved in the initial assessment and treatment arms of the trial had access to the patients' notes.

Research Governance:

This study complied with the research governance framework and was registered with the research and development departments at both University Hospitals Southampton NHS Foundation Trust (UHSFT) and

the University of Southampton. Insurance indemnity was obtained from UHSFT.

(iii) Sample size

This study was designed as a feasibility study and therefore a power calculation was not appropriate. Each PR group had a total of 8-10 participants attending a 6-week rolling programme with 2-3 new patients per week. There were 2 PR programmes running each week and therefore a potential of 4-6 new patients per week to recruit. It was anticipated that a sample of 20 patients would be acceptable to assess the feasibility of this research protocol. Therefore, if recruitment was smooth, it was anticipated that these participants could be recruited over a period of 5 weeks. The aim was that there would be 10 participants per group (group A receiving ear acupuncture, group B receiving the control intervention). There is some evidence from PR studies that this number of participants would enable assessment of the key parameters such as drop-out rates and recruitment (Arain et al 2010).

(iv)Study Participants

Patients were adults diagnosed with moderate COPD by a respiratory consultant and spirometry assessment. If they were the referred by the respiratory consultant to attend a PR programme at UHSFT, they were considered to be eligible for the study.

(v) Recruitment

Participants were recruited via the consultant referrals to the PR programme at UHSFT. There were advantages to using this PR programme to recruit participants one of which is that UHSFT is a large teaching hospital on the South coast which has a large respiratory service accepting both primary care and tertiary referrals. A second advantage to

using the UHSFT PR programme, to access patients, was that the primary researcher for this study worked at UHSFT, during the time of this study. Working within the respiratory department resulted in the referring clinicians being fully aware of the study and the researcher was able to provide training sessions on PR and physiotherapy in COPD for the respiratory teams. However, this author recognises that being based within the respiratory services at UHSFT and being well known as a clinician with these services, may have been a source of bias. The possibility of recruiting from other centres around the region was considered for this feasibility study, however, funding for both time and travel expenses was not available for the researcher, therefore UHSFT PR was chosen as the only recruiting centre for this study.

When the potential participants attended for their PR assessment session they were given a patient information sheet about this study by the senior physiotherapist running the PR programme. They were then told to let the physiotherapist know if they wished to participate when they returned for their first PR session. The clinical physiotherapists then in turn informed the researcher about those who wished to participate.

Inclusion criteria

1) Patients with a diagnosis of COPD, confirmed by a consultant physician and for whom a PR programme was appropriate (by the nature of this condition all patients were over 18 years of age).
2) Patients with at least mild clinical anxiety, as measured by a score 8 or more, on the HAD scale.

Exclusion criteria

1) Individuals with allergies to sticking plasters - as the small Magrain balls were attached with sticking plaster.

2) Those for whom PR was contraindicated
3) Those with anxiety scores below 8.
4) Those for whom ear acupuncture was contraindicated i.e. pregnancy, under 18years of age, cardiac pacemaker wearers or immunocompromised.

(vi) Randomisation

The purpose of randomisation in a trial is to eliminate selection bias. This study was a feasibility study and therefore was not required to have participants randomised into groups. However, the plan was to inform a larger RCT and therefore assessment of whether participants would find randomisation acceptable was deemed necessary.

Randomisation in clinical trials aims to distribute participant characteristics randomly between groups. Any difference in outcome may then be explained by the intervention alone and not an uneven distribution of characteristics within the groups. In this feasibility study consideration was given to the different methods of randomisation to determine which method would be most appropriate for the future RCT. This author was aware of simple randomisation techniques such as allocating participants into groups based on characteristics such as date of birth or hospital number. However, these methods are prone to bias and therefore were not appropriate for this trial. The future RCT based upon this feasibility study would examine the use of ear acupuncture, as an adjunctive treatment to PR, in terms of its effect on clinical anxiety. The groups should therefore be balanced at baseline, in terms of the primary outcome (anxiety). A block randomisation method would ensure equal numbers in each group but would not balance for characteristics such as baseline anxiety levels. In clinical practice anxiety levels amongst the population with COPD are known to vary. Therefore, a stratified randomisation technique was used and groups were balanced in terms of baseline anxiety levels, to reduce the effect of any confounding factors and have

more confidence that any outcome would be due to treatment effect alone. It may have been possible to stratify the groups further for other important characteristics, such as severity of COPD, or time since diagnosis, however; this author considered that one level of stratification was adequate to test the randomisation method/acceptability.

In order to minimise selection bias in an RCT it would be considered appropriate to conceal the assignment of participants from both the main researcher and the research physiotherapists. This would prevent the researchers from assigning certain participants to specific intervention groups. An observational study by Schultz et al (2000) revealed that in trials in which randomisation was not concealed, estimated treatment effects were exaggerated by approximately 41% when compared to those that reported allocation concealment.

In view of this, the following procedure was carried out for randomisation and participant allocation:
Following full baseline assessments, participants were randomised into one of two groups. A random allocation sequence was generated by the statistician at the Research and Development Support Unit at UHSFT. The randomisation was stratified using the baseline Hospital Anxiety and Depression (HAD) scale score to achieve between group comparability for anxiety levels. A scores of 8 is considered to be clinically relevant for mild anxiety on the HAD scale. Therefore, a score of 8 was used as the “cut off” point for the stratification.
The two groups were allocated as follows:

- Group A received PR and ear acupuncture
- Group B received PR and placebo ear acupuncture

The randomisation sequence was held within a locked drawer at the Therapy Department reception desk, UHSFT and was concealed from the researcher. The baseline HAD Scores were sent to a senior physiotherapist based in the physiotherapy respiratory team and she

calculated the HAD anxiety scores, to enable stratification. The physiotherapist then documented the participant number onto the appropriate section of the list. The researcher did not have access to the list and was required to ask the respiratory physiotherapist prior to the initial treatment session to enquire as to which group the participant had been allocated.

(vii) Plan of Investigation

All patients diagnosed with COPD and referred to the physiotherapy-led PR programme at UHSFT were eligible to participate in this trial. On the initial assessment appointment for PR, patients were given an information sheet by the senior physiotherapist (clinical lead for PR programme). If they had any questions relating to the trial they were invited to contact the researcher directly. During the initial PR assessment visit, the PR physiotherapist asked willing participants to complete a HAD assessment and those that score 8 or more were eligible for inclusion within the trial. These participants were asked to sign a consent form with the lead investigator for this study and preliminary baseline assessments were taken. Participants who met all the criteria were informed that they had been entered into the trial, but that this would not expedite or delay their PR treatment. Patients who did not wish to take part or who did not meet the criteria were reassured that this would not delay their treatment and they would continue with the planned PR programme.

At the time of this study patients were assessed for PR about 4-6 weeks prior to commencing a PR programme therefore there was a short waiting period prior to attending the programme. On the first day of his or her PR programme each participant was given a time slot to be seen by the researcher for ear acupuncture or placebo treatment. Full baseline measurements were carried out on this visit and on their final PR visit at the end of the six weeks. The HAD scale was carried out every week

during the course of the PR programme. Figure 6. shows the anticipated flow of participants through the study.

(viii) Trial Procedure

In group A participants were invited, on their initial PR session, to commence treatment with the researcher. The researcher provided time slots for the participants to have the intervention, after they had completed their PR session for that day. The researcher located the 2 points on both ears and applied the Magrain with plasters (Magrain- a gold plated ball/bead attached to a small plaster). The participants were advised how to care for the Magrain, when to apply pressure to the points and shown how to remove the Magrain after 2-3 days. This process was repeated at the first PR session each week. The HAD scale was measured once every week after ear acupuncture treatment session. At the end of the six-week period all outcome measures were repeated.

In group B, participants followed the same protocol as group A except the Magrain was applied to one point external to the ear (on the lower medial quadrant of the ear lobe). There are no known acupuncture points around this area. This process was repeated at the first PR session each week. The HAD scale was measured at every week after ear acupuncture treatment session. At the end of the six-week period all outcome measures were repeated and the trial participants were asked whether they felt the treatment they had received was placebo or “real” and whether they thought it was a treatment they would consider accepting again**.**

(ix) Interventions

Treatment arm

The ear points chosen for this study are commonly used points for anxiety (Shenmen and relaxation points (see Figure 7. for point location on the ear) (Kober et al 2003, Wang et al (a) 2001, Wang et al (b) 2001, Wang et al 2004). Each participant on his or her initial visit for the PR programme,

had a short treatment session with the researcher. The ear was cleaned with a sterile wipe and the pressure applied to the two relevant points for 7 seconds. This is the standard treatment time for the application of electrical stimulation (EA) to the ear acupuncture points. This researcher is not aware of any evidence that identifies the optimum time for acupressure to be applied to ear acupuncture points and hence the suggested protocol of 7 seconds for EA, will be used (Hopwood 2004). After this, two tiny ionic beads (Magrain- a gold plated ball attached to a small plaster) was applied to each point within the ear (see Figure 7.for location of ear points). This was repeated for both ears. The participant was advised to keep the Magrain in position for 2-3 days. They were also advised on care of the Magrain (e.g trying not to get them wet) and shown how to apply pressure to the points. They were also instructed to press on the points for 7 seconds three times per day. Participants were allowed to press on the points when they were feeling breathless or anxious throughout the day. They were issued with a diary sheet to allow them to document the number of times they applied pressure to the ear points. The participants were shown how to remove and dispose of the Magrain. The researcher reviewed each participant on the first PR session each week for six weeks, to see how they were and reapply the Magrain.

The practitioner was the lead researcher (Denise Gibson) who has been trained in Western Acupuncture and Ear acupuncture on an AACP accredited course and has 12 years of clinical experience in this field.

Control arm

Each participant randomised to the control arm of this study was seen by the researcher at his or her initial PR session and at their first PR session each week. The placebo treatment involved the application of one Magrain to a point on the lower medial quadrant of the ear lobe. This point has been chosen, as there are no known ear acupuncture points in this region. This process was repeated for both ears and the participants were advised to keep the Magrain in position for 2-3 days. They were given the same

advice regarding applying pressure to this point and in the care of the Magrain. They were also issued with a diary sheet to allow them to document the number of times they applied pressure to this point. The participants were shown how to remove and dispose of the Magrain. The participants were seen by the researcher on the first PR session each week to see how they are and reapply the Magrain.

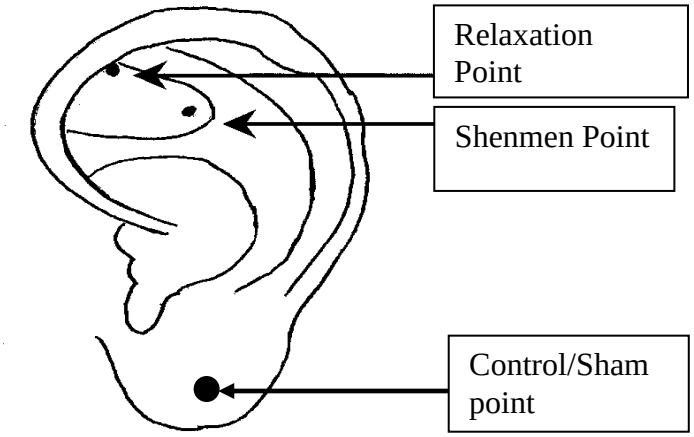


Figure 7. Location of ear acupuncture and placebo points.

(x) Blinding

Due to the nature of the treatments it was not possible to "blind" the researcher to the treatments. However, the researcher had minimal interaction with each participant and this was standardised for all. The researcher avoided any discussions with the participants, relating to the therapy or responses to it. A therapy assistant, who was blinded to the participants' group allocation and usually carries out the outcome measures for PR, carried out the outcome measures for this trial. There are no acceptable methods of assessing participant blinding but at the end

of the trial the participants were asked if they felt they had received “real” or placebo ear acupuncture.

(xi) Outcome measures

The choice of outcome measures reflected those that might be used in a future RCT to answer the question ‘Does ear acupuncture as an adjunct to PR have any effect on anxiety levels in patients with COPD’.

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Therefore, anxiety was chosen as the primary outcome for this study. Secondary outcomes chosen were additional anxiety and depression scales and routine outcomes used following a PR programme.

The researcher considered many outcome measures and the main outcome measures are discussed and critiqued in chapter 5 Outcome Measures.

The following outcome measures were chosen for this study:

Primary Outcome Measure

Hospital anxiety and depression scale (HAD)

The primary outcome measure was the HAD scale (Zigmond and Snaith 1983). Please refer to Chapter 5. For details of the HAD scale. It has been suggested that the minimal clinically significant change in the HAD scale for COPD is a change of 1.5 points (Puhan et al 2008). Therefore, this level was accepted as a minimal clinically significant change for this study.

Secondary Outcome Measures

State-Trait Anxiety Inventory

The STAI measure had not been used in Study 1 but was selected for Study 2 as the STAI is enable assessment of both how anxious an individual when exposed to a situation as well as how anxious an

individual is on a daily basis. Therefore, it might help with distinguishing between changes in anxiety that exists due to attending PR or being in the trial and anxiety that the participants experience on a daily basis. It was of interest to this author whether there may be changes in the state and or trait anxiety following ear acupuncture. Participants in trials may well be anxious simply because they are taking part in a study and being exposed to an intervention. It is also a measure that has been used in many of the previous ear acupuncture trials examining acupuncture for anxiety (Uskok 1995, Wang et al (a) 2001, Wang et al (b) 2001, Wang et al 2004, Karst et al 2007, Black et al 2011, Michelak-Sauberer et al 2012).

This anxiety questionnaire is self-reported and consists of 40 questions that are scored on a 4-point Likert scale (Spielberger et al 1970). These 2 types of anxiety are allocated 20 questions each and individuals are asked to score themselves on these questions using the 4-point likert scale. This is a validated scale that has been found to have a high reliability and is commonly used in many anxiety related research trials (Speilberger et al 1983).

St George's Respiratory Disease Questionnaire (SGRDQ)

This health status measure was selected for this study as it is a measure that is a disease specific questionnaire that is validated for use with COPD patients. It was also being used by the PR team at UHS.

The SGRDQ is commonly used as a health status measurement tool in COPD. It was developed to enable comparative measurements of health amongst patient populations with respiratory disease and to measure changes in health following intervention (Jones et al 1991).

It consists of three main sections and a total score. The sections are:

Symptoms- measuring the severity and frequency of respiratory symptoms.

Activity- measuring activity limitations by breathlessness and activities that cause breathlessness.

Impacts- measures disturbances to psychological and social disturbances due to respiratory disease.
Total Score- measures the impact of the respiratory disease on overall health status. The questionnaire has 50 items with 76 weighted responses and has been validated for use in COPD (Wijkstra et al 1994).

Medical Research Council Breathlessness (dyspnoea) Scale

The MRC dyspnoea scale was selected for this study as it was already being used as an outcome to the PR programme and is a validated scale and has been in use for many years for grading the effect of breathlessness on daily activities (Bestall et al 1999). This scale measures perceived respiratory disability. The MRC dyspnoea scale is simple to administer as it allows the patients to indicate the extent to which their breathlessness affects their mobility.

Incremental shuttle walk test (ISWT)

The ISWT is a validated and sensitive measure of exercise capacity in patients with COPD (Singh et al 1992). It is frequently used as an outcome measure for PR programmes. This measure of exercise tolerance was selected for this study as it is validated for use in COPD and was being measured routinely in the PR programme at UHS.The minimal clinically important difference in the ISWT for individuals is documented as 47.5 Metres (Singh et al 2008).
The MRC breathlessness score, the SGRDQ and the ISWT are all routine clinical outcome measures assessed during the pulmonary rehabilitation programme. The HAD scale and the STAI were additional outcome measures taken entirely for this feasibility study.

(xii) Data Analysis Process

Patient demographic details were presented in the form of mean and SD The mean, SD and 95% confidence intervals for each intervention group were calculated with respect to primary outcome measure. The outcome measures used that provided ordinal data were analysed using non-parametric techniques (HAD Scale, STAI, SGRDQ, MRC breathlessness). Where outcome measures provided continuous data and there was a normal distribution, parametric techniques were applied. Comparisons between pre and post intervention within and between each group were performed using appropriate techniques. Assumptions based on the use of these techniques were also investigated. Statistical analysis was performed using SPSS 21.0 and a p-value less than 0.05 was used to indicate a statistical significant difference. Findings and analysis for this study will be presented in chapter 8.

7.7 Data Analysis Plan

Primary Hypothesis

Ear acupuncture, when used as an adjunct to PR for the treatment of COPD, would have a greater effect in terms of reducing anxiety, when compared to placebo.

Null hypothesis

Ear acupuncture, when used as an adjunct to PR for the treatment of COPD, would give no greater effect in terms of reducing anxiety, when compared to placebo.

Secondary Null hypotheses

(a) Ear acupuncture, when used as an adjunct to PR for the treatment of COPD, would have no greater effect in terms of reducing state anxiety, when compared to placebo.

(b)Ear acupuncture as an adjunctive treatment to PR would have no greater effect in terms of reducing Trait anxiety in participants with COPD, when compared to placebo.
(c)Ear acupuncture, when used as an adjunct to PR for the treatment of COPD would have no greater effect in terms of reducing depression, when compared to placebo.
(d) Ear acupuncture, when used as an adjunct to PR for the treatment of COPD does not have any specific efficacy over a placebo treatment, in terms of improving health status.
(e) Ear acupuncture, when used as an adjunct to PR for the treatment of COPD does not have any specific efficacy over a placebo treatment, in terms of improving breathlessness scores.
(f) Exercise tolerance levels are not affected by the addition of ear acupuncture to a PR programme for the treatment of COPD.

Primary hypothesis analysis

(a) Anxiety HAD Scale: Between-group comparison at baseline

Justification: Baseline anxiety scores will be compared across both groups to ascertain whether randomisation has been effective in ensuring equivalence across both groups.

There are two groups and this is a between group comparison with ordinal data. Therefore, the statistical test used is the Mann-Whitney Test.

(b) Anxiety HAD Scale Within-group analysis baseline to outcome

Justification: There is evidence that ear acupuncture can reduce anxiety levels. There is also well documented evidence on the non-specific effect of acupuncture techniques. Therefore, there is justification in assessing the effect of ear acupuncture on anxiety compared to placebo, when used as an adjunct to PR.

Each group is being examined at two-time points (baseline and outcome) with ordinal data. Therefore, the statistical test used is the Wilcoxon signed rank Test.

(c) Anxiety HAD Scale Between-group analysis at outcome

This is measuring change between both groups with one between group factor (treatment) with ordinal data. Therefore, the statistical test used is the Mann-Whitney Test.

Secondary Outcomes analysis

(a) State Anxiety STAI Within-group analysis baseline to outcome

Justification: There is evidence that individual anxiety levels change according an individual's experience/potential threats/environment. Therefore, it is important to assess effects on "real time" anxiety within the clinical environment**.**

Each group is being examined at two time points (baseline and outcome) with ordinal data. Therefore, the statistical test used is the Wilcoxon signed rank Test.

(b) State Anxiety STAI Between-group analysis at outcome

This is measuring change between both groups with one between group factor (treatment) with ordinal data. Therefore, the statistical test used is the Mann-Whitney Test.

(c) Trait Anxiety STAI Within-group analysis baseline to outcome

Justification: Individuals experience anxiety changes on a day to day basis and it is important when measuring anxiety that the underlying anxiety (Trait) is measured as well as the anxiety levels that may be influenced by the environment.

Each group is being examined at two time points (baseline and outcome) with ordinal data. Therefore, the statistical test used is the Wilcoxon signed rank Test.

(c) Trait Anxiety STAI Between-group analysis at outcome

This is measuring change between both groups with one between group factor (treatment) with ordinal data. Therefore, the statistical test used is the Mann-Whitney Test.

(ii)Depression

(a)Depression HAD Scale Within-group analysis baseline to outcome

Justification: There is evidence within the literature that depression can also be associated with COPD. The presence of depression can also have an impact upon outcomes of therapy, symptoms and exacerbation rates in individuals with COPD.

Each group is being examined at two-time points (baseline and outcome) with ordinal data. Therefore, the statistical test used is the Wilcoxon signed rank Test.

(b)Depression HAD Scale Between-group analysis at outcome

This is measuring change between both groups with one between group factor (treatment) with ordinal data. Therefore, the statistical test used is the Mann-Whitney Test.

(iii)Health Status

Justification: Health related quality of life questionnaires enable clinicians to directly measure the impact of a disease on an individual's daily life and are valuable in research trials to formally examine the effect of an intervention on health status. There is evidence that PR can have a positive impact upon health status for patients with COPD. Therefore, it is important to examine whether ear acupuncture and PR together have any impact upon health status in individuals with COPD

(a) Health status SGRDQ Within-group analysis baseline to outcome

Each group is being examined at two-time points (baseline and outcome) with ordinal data. Therefore, the statistical test used is the Wilcoxon signed rank Test.

(b) Health Status SGRDQ Between-group analysis at outcome

This is measuring change between both groups with one between group factor (treatment) with ordinal data. Therefore, the statistical test used is the Mann-Whitney Test.

(iv) Breathlessness

There is evidence that PR alone can reduce breathlessness scores and individuals are able to carry out more activities of daily living before they have to stop due to breathlessness. Therefore, it is important to examine whether the adjunctive ear acupuncture alongside PR can have any effect on these breathlessness

(a)Breathlessness MRC Within-group analysis baseline to outcome

Each group is being examined at two-time points (baseline and outcome) with ordinal data. Therefore, the statistical test used is the Wilcoxon signed rank Test.

(b) Breathlessness MRC Between-group analysis at outcome

This is measuring change between both groups with one between group factor (treatment) with ordinal data. Therefore, the statistical test used is the Mann-Whitney Test.

(v) Exercise Tolerance

There is strong evidence within the literature that PR programmes can improve exercise tolerance. This can be one of the major benefits of PR, in that patients are able to do more at home and lead a more active life

following PR. If ear acupuncture is used as an adjunctive therapy to PR, it is important to evaluate whether there is any effect on exercise tolerance.

(a) Exercise tolerance Six-Minute Walk test Within-group analysis baseline to outcome

Statistical Analysis: Each group is being examined at two-time points (baseline and outcome) with continuous data. Therefore, the statistical test used is the paired-samples t-Test if the data are normally distributed. If the data were not normally distributed a Wilcoxon Signed-Rank Test was applied.

(b) Exercise tolerance Six-Minute walk between-group analysis at outcome

This is measuring change between both groups with one between group factor (treatment) with continuous data. Therefore, the statistical test used is the Independent samples t-Test unless the data is not normally distributed and in this instance a Mann-Whitney U Test was applied.

7.8 Results Study 2.

7.8.1. The Sample

A total of 20 patients with COPD were referred for PR, over the data collection period of January 2015-September 2015. A total of 17 patients agreed to participate in the trial. Three individuals declined to participate in the trial, two giving reasons that they did not wish to try ear acupuncture and one had a HAD score of <8. One of these three patients reported that he did not like the idea of wearing a bead on his ear as it may look like an earring. These three participants declined prior to consent being obtained, therefore there is no further data on the non-participants. All 17 participants completed the trial and data analysis was carried out on the data derived from these participants. This will be discussed further in Chapter 8.

7.8.2 Feasibility- Acceptability/Practicalities/ Expansion

The protocol for this study was feasible in that it was possible to do the ear acupuncture during the same treatment sessions as the PR programme. The participants had a short break in between the exercise and education components of the PR programme and this was the ideal time for them to receive the ear acupuncture.Two patients did refuse to take part in the trial because they did not wish to try ear acupuncture (one male participant was clear that he did not like the idea of have something in his ear that looked potentially like an “earing”). Therefore, not all patients were receptive to it. The participants that agreed to take part were all receptive to receiving ear acupuncture and all 17 participants tolerated the ear “seeds” well. There were no reported problems with infection or discomfort. There were no reported adverse events during this study. The participants’ ears were checked and the seeds were replaced on a weekly basis by the lead investigator. The seeds had fallen out on 45 of the 187 occasions that the participants had attended PR.

The participants were asked to complete a diary at home of when they pressed the seeds in their ears and what symptom they were experiencing when they did this. Only five of the 17 participants entered any data onto the diary sheets. Two out of the five participants were in group A (acupuncture group) and on average these 2 patients pressed their seeds twice daily when they were experienced breathlessness not anxiety. The remaining three participants that completed the diary sheets, were in group B and pressed the seeds on average twice daily also but did not document the symptoms they were experiencing at the time. Although, not all the participants completed the diaries, they all reported that they did press on the seeds as and when they had symptoms of breathlessness or anxiety.

The participants were required to complete additional questionnaires for the study but they completed the HAD and STAI questionnaires without any issues. It would therefore seem feasible to use additional outcomes in the form of questionnaires for a future trial.

Statistical Analysis

The results of the statistical analysis will be presented as follows:

(i) Demographic data and sample characteristics at baseline

(ii) Comparisons of baseline characteristics between groups

(iii) Between groups comparison at outcome of:

Anxiety and depression scores (HAD and STAI)

Health status (SGRDQ)

Exercise Tolerance

Breathlessness

(iv) Within groups comparison from baseline to outcome of:

Anxiety and depression scores (HAD and STAI)

Health status (SGRDQ)

Exercise Tolerance

Breathlessness

(i)Demographic data and sample characteristics at baseline

The demographic and baseline characteristics of the whole sample have been collated and are presented within Table 21. The presented data includes gender, age and baseline anxiety and depression, following randomisation into the two groups. There was one more female (n=9) than males (n=8) within the whole sample and both groups had both genders roughly equally represented.

The ages of the participants ranged from 58 to 73 years. This reflects the age range of the average COPD population (Buist et al 2007). Although randomisation should theoretically even out group characteristics, because of the small sample size, it was decided to conduct statistical tests to compare group means at baseline. The baseline scores for anxiety and depression (as measured by the HAD scale and STAI) were compared to look for any statistically significant differences. The results of this analysis are presented in section (ii).

	Group A acupuncture n=9	Group B Placebo Acupuncture n=8
Sex		
Males	4	4
Females	5	4
Age in years Mean (SD)	65(5.2)	66(4.3)
HAD A Anxiety Mean(SD)	12(2.2)	9(2.3)
HAD D Depression Mean(SD)	9(3.5)	6(3.0)
STAI State Anxiety Mean(SD)	49(7.4)	41(10.9)
STAI Trait Anxiety Mean(SD)	50(10.2)	42(11.5)

Table 21. to show demographic data and baseline scores for the sample after randomisation into 2 groups.

Key: SD: Standard Deviation, **HAD A:** Hospital Anxiety and Depression Scale (Anxiety)**:** 0=not very anxious, 21-very anxious; **HAD D:** Hospital Anxiety and Depression Scale (Depression)**:** 0=not very depressed, 21=very depressed, **STAI: State Trait Anxiety inventory**, scores range from 20 to 80, higher scores suggest greater anxiety. **Group A:** acupuncture group **Group B:** Placebo acupuncture group

Both groups had clinically significant mean scores for anxiety pre-intervention (i.e. 8 or more) as this was a screening criterion for entry to the trial. However, the mean scores were higher and above the level considered to be clinically relevant for moderate anxiety in group A.

(ii)Comparison of the baseline anxiety and depression scores of the two groups

The primary outcome measures used for this study (HAD scale) and the STAI provide ordinal level data and therefore non-parametric methods were used to analyse these data. The baseline scores for the two groups were compared using a Mann Whitney U test. Table 22 shows the p values for each variable. There were no statistically significant differences at baseline, between the treatment and placebo groups in terms of anxiety or depression.

	Test statistic and significance value
HAD A (Anxiety)	z= ¯2.593 p=0.10
HAD (Depression)	z= ¯1.548 p=0.12
STAI -State	z= ¯1.755 p=0.07
STAI- Trait	z= ¯1.40 p=0.16

Table 22. Comparison of the baseline values for the outcome variables between the two groups using a Mann-Whitney U test.

(iii) Between group comparisons post intervention:

(a) Anxiety and Depression

The anxiety and depression data were analysed to assess for statistical differences between the groups post treatment. A Mann Whitney U test was performed. (see Table 23).

	Differences between Groups A (EA group) and B (placebo group)
Anxiety HAD A	z= -0.478 p= 0.633
Depression HAD D	z= -0.835 p= 0.40
STAI -State	z= -0.355 p= 0.776
STAI- Trait	z= -0.473 p= 0.636

Table 23. Analysis of between groups differences of anxiety and depression treatment outcomes for both groups using the Mann Whitney U Test.
Key: group A = Ear Acupuncture + PR, group B= placebo acupuncture + PR.

This analysis revealed that there were no statistically significant differences in the anxiety and depression outcomes of treatment between both the treatment and placebo groups.

(b) Health status and Breathlessness

The health status data (measured by the SGRDQ) and breathlessness data (measured by the MRC breathlessness score) were analysed to assess for statistical differences in these outcomes post intervention. Both of these outcome measures provide ordinal data and were therefore analysed using the non-parametric test Mann Whitney U (see Table 24.)

Differences between groups A (EA) and B (placebo)	
Heath Status	
SGRDQ	z= -589
Symptoms	p= 0.556
Activity	z= -2.239 p=0.025*
Impact	z= -0.471 p= 0.637
Total	z= -1.179 p=0.239
Breathlessness	z= -0.714 p= 0.475

Table 24. Analysis of between groups differences of Health Status and breathlessness on treatment outcomes for both groups using the Mann Whitney U Test.

Key: SGRDQ: St George's Respiratory Disease Questionnaire **MRC Breathlessness Scale:** Medical Research Council breathlessness scale**, group A** = Ear Acupuncture + PR, **group B**= placebo acupuncture + PR; * statistical significance at p<0.05.

The analysis revealed that there were statistically significant differences between the groups in terms of the activity domain on the SGRDQ. The higher scores on the SGRDQ relate to greater limitations in the domains. The mean activity scores on the SGRDQ for each group revealed that the placebo group had a higher mean score (group A 54 vs group B 87). This suggests that treatment in group A was superior to the placebo treatment.

(c) Exercise tolerance

Exercise tolerance was measured using the six-minute walk test in this study. The data was assessed for normality using the Shapiro-Wilk test (Table 25). The data had a normal distribution as the Shapiro-Wilk test was not significant. The continuous data provided by this test resulted in a t-test being used to assess for statistical differences between the groups at outcome (see Table 26).

	Statistic	Df	Significance
Six Minute Walk	0.904	15	0.109

Table 25. Test of Normality- Exercise Tolerance using the Shapiro-Wilk Test.

	Differences between Groups A (EA) and B (placebo)
Exercise Tolerance Six-Minute walk Test	t= 0.532 df 13 CI (95%) -91-150

Table 26. Analysis of between groups differences in exercise tolerance at outcome using the t-test.
Key: group A = Ear Acupuncture + PR, **group B**= placebo acupuncture + PR.

No statistically significant differences in exercise tolerance were found between groups A and B at outcome.

(iv) Within-group comparisons

(a) Anxiety and depression

Both groups were analysed to assess for within-group differences in anxiety and depression, comparing baseline to post treatment scores, on the HAD scale and the STAI. The Wilcoxon Signed Ranks test was applied to these data. Table 27. presents the results of this analysis for both groups.

	Group A n=9	**Group B** n=8
Anxiety HAD A	z= ˉ2.439 p= 0 .015*	z= ˉ1.289 p= 0.197
Depression HAD D	z= ˉ2.375 p= 0.018*	z= ˉ0.577 p= 0.564
STAI- State	z= ˉ1.719 p= 0.086	z= ˉ0.677 p= 0.498
STAI- Trait	z= ˉ2.549 p= 0.01*	z= ˉ2.032 p= 0.498

Table 27. Analysis of within groups differences in anxiety and depression from baseline to outcome using the Wilcoxon signed ranks test.

Key: group A = Ear Acupuncture + PR, **group B**= placebo acupuncture + PR.* statistical significance at $p<0.05$.

This within-group analysis revealed statistically significant differences for the treatment group (group A) in anxiety and depression (HAD scale) as well as trait anxiety as measured by the STAI.

(b)Health Status and Breathlessness

Both groups were analysed to assess for within-group differences in Health Status and breathlessness, comparing baseline to post treatment scores, on the SGRDQ and the MRC breathlessness scale. The ordinal data provided by both of these outcome measures determined the use of a non-parametric statistical test. The Wilcoxon Signed Ranks test was applied to these data. Table 28. presents the results of this analysis for both groups.

	Group A n=9	**Group B** n=8
Health Status SGRDQ		
Symptoms	z= ¯ 1.125 p= 0.260	z= ¯0.734 p= 0.463
Activity	z= ¯ 0.889 p= 0.374	z= ¯1.992 p=0.046*
Impact	z= ¯1.362 p= 0.173	z= ¯0.943 p= 0.345
Total	z= ¯1.244 p= 0.214	z= ¯1.572 p= 0.116
MRC Breathlessness Scale	z= ¯1.857 p= 0.06	z= ¯1.342 p= 0.180

Table 28. Analysis of within group differences in Health status and breathlessness from baseline to outcome using the Wilcoxon signed ranks test.

Key: SGRDQ: St George's Respiratory Disease questionnaire**, group A** = Ear Acupuncture, **group B**= placebo acupuncture* statistical significance at p<0.05

The analysis revealed a statistically significant within-group difference in group B (placebo acupuncture) for the activity domain of the SGRDQ.

There were no other statistically significant within-group differences for health status or breathlessness.

(c) Exercise Tolerance

Exercise Tolerance was measured by the six-minute walk test. The groups were analysed to assess for within-group differences from baseline to outcome. This outcome measure provides continuous data and therefore was assessed for normality prior to further analysis. The data for both groups was normally distributed as confirmed by the analysis using the Shapiro-Wilk test which was not statistically significant (Group A p=0.715, Group B p=0.259). The parametric test, related samples t-test was therefore applied to the data. Table 29. presents this analysis for both groups.

	Group A n=9	Group B n=8
Exercise Tolerance Six-Minute walk test	t= ˉ3.316 (CI ˉ97- ˉ17) p= 0.01*	t= ˉ0.523 (CI ˉ46-30) p= 0.624

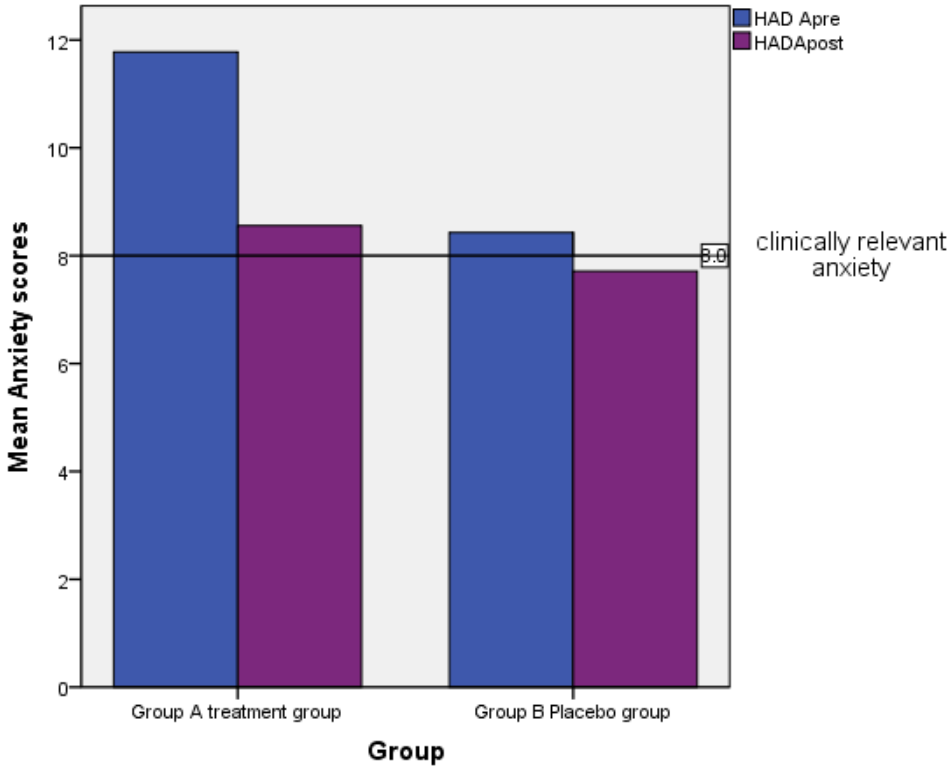
Table 29. Analysis of within groups differences in Exercise Tolerance from baseline to outcome using the t-test.
Key: CI 95% confidence Interval**, group A** = Ear Acupuncture + PR, **group B**= placebo acupuncture + PR.* statistical significance at p<0.05

There was a statistically significant difference in exercise tolerance within group A from baseline to outcome, in this study.

(v) Graphical presentation of the mean anxiety data

The mean anxiety scores from the HAD anxiety scale, pre and post intervention were plotted for both the acupuncture group and the placebo acupuncture group (see Figure 8.)

Figure 8. A Bar Chart to show the mean anxiety scores pre and post treatment for both groups A and B.



The mean anxiety score in group A (acupuncture treatment group) was higher than group B (11.7 vs 8.5 respectively). This difference was not statistically significant. The mean anxiety score in group B was only just clinically significant at 8.5. There was a reduction in mean anxiety scores for both groups. The largest reduction was found in group A. Although the mean score in this group, did not drop below clinical significance, it reduced by 3.3 points which is greater than the level accepted as the minimal clinically significant

improvement in HAD anxiety (1.5), for individuals with COPD (Puhan et al 2008). Group B (placebo acupuncture) also had a reduction in mean anxiety scores which both dropped below the cut off value for clinically relevant anxiety (8) and reduced by the value considered to be the minimal clinically significant improvement for the HAD score in the COPD population.

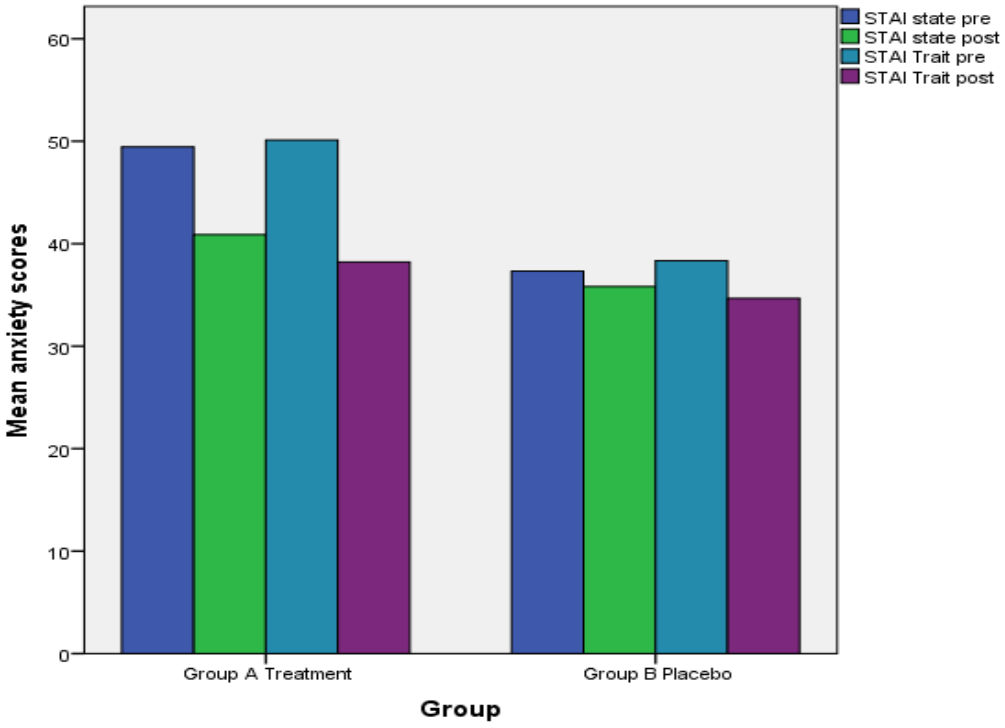


Figure 9. A Bar Chart to show the mean anxiety scores on the STAI pre and post treatment for both groups A and B.

The mean scores for state and trait anxiety for both groups pre-intervention, were above the level considered to be the cut off point for clinically relevant anxiety symptoms (39-40). The bar chart above shows that the mean anxiety scores dropped following intervention in both the treatment and placebo groups. Following intervention, the mean scores for both state and trait anxiety reduced to below the clinically relevant level in both groups, but this reduction was greater in the treatment group (State anxiety 49-40, Trait anxiety 50-38).

7.9 Chapter Summary

Study 2 has been described in this chapter. The results suggest that it is feasible to use ear acupuncture as an adjunct to a PR programme for the treatment of COPD. Chapter 8 will discuss these findings further.

Chapter 8. Discussion

8.1Introduction

The overall aim of this PhD was to examine whether acupuncture is beneficial in the treatment of some common respiratory disorders and whether it is feasible to use it in various forms as adjunctive treatments for individuals with chronic respiratory disorders. This chapter contains a discussion of the findings of the two studies included within this thesis. Although feasibility was not specifically assessed in study 1, there will be some discussion within this chapter around the feasibility of some aspects of the study, when compared to study 2, which directly examined the feasibility of ear acupuncture. It will also raise the debate around acupuncture and its use for the treatment of respiratory disorders as well as discussing the potential limitations of the two included studies and in acupuncture research in general.

Anxiety is well known to co-exist with chronic respiratory disorders. There is some evidence within the literature that acupuncture can have a beneficial effect on some types of anxiety such as preoperative anxiety or GAD. This author was interested in whether acupuncture could have an effect on anxiety associated with chronic respiratory disorders. Therefore, the overall research question for this thesis was as follows:
Does acupuncture offered as an adjunctive treatment to physiotherapy for two common respiratory disorders; enhance treatment outcomes in terms of reducing anxiety?

8.2Main Findings

The main findings from this research are:
In study 1, the were no statistically significant differences in anxiety between the acupuncture, placebo acupuncture or BR groups. However, there were clinically significant reductions in anxiety scores within the acupuncture group which reduced to below the cut-off score for clinically relevant anxiety.

There were also statistically significant reductions in breathlessness following acupuncture when compared to placebo acupuncture or BR alone.

In Study 2, the findings suggest that EA is a feasible intervention as an adjunct to PR, for the treatment of COPD.
Additional findings from the data analysis in Study 2 revealed statistically significant improvements in health status in the EA group, as well as clinically relevant reductions in both anxiety and depression.

8.3 Feasibility Findings:

(a)Recruitment feasibility

In study 1 the recruited sample size of 40 is considerably less than the proposed 90 participants. In order to achieve 80% power a sample size of 90 participants was estimated to be needed (taking into account a 20% attrition rate). This smaller than planned sample size was mainly due to the fact that HVS referral rates during the data collection period were much lower than they had been prior to commencement of this study and more people were ineligible than anticipated. Of the 76 referrals, 20 had to be excluded due to: co-morbidities, contraindications for acupuncture treatment or lack of acupuncture naivety. A post hoc power calculation was not carried out as the initial pilot that generated the power calculation had many methodological flaws and this study is considered a second pilot. There is much debate within the literature regarding the benefit and reliability of post-hoc power calculations and there is a large body of evidence that suggests that post-hoc calculations are not valuable since the effect size is not accurate to determine reliable power (Hoenig and Heisey 2001). This small sample size has an impact on interpretation of the findings of this study. The findings from this
study will need to be considered with caution due to the lack of statistical power achieved. This will be discussed further in this chapter.

In the feasibility study (study 2), the sample was also less than intended (17 rather than 20) due mainly to the reduced number of referrals for PR during the period of time that the study was running. It was estimated that a total of 4-6 new patients would be recruited per week and that recruitment would be completed after a 5-week period. Due to the reduced referral rate for PR during that period, it took 8 months to recruit 17 participants. Recruitment for this was stopped at this point due to the poor referral rate. The PR programme was run at a large acute teaching hospital and due to clinical priorities had to be closed for a period of time which hampered recruitment. However, as study 2 was a feasibility study and a power calculation was not required, the original choice of 20 participants was a pragmatic one based upon previous predicted referral rates and numbers of classes running. Future similar studies could be multi-centre studies which would enable a greater pool of patients attending PR, to recruit from. However, there would need to be some consideration of the difference in PR patients attending the acute hospital PR programme, in that they often have more severe disease and therefore require additional oxygen to exercise.

(b)Patient Acceptability

In study 2 there were two individuals that refused to participate in the trial which suggests that there were some issues with accepting ear acupuncture for some. This may be because the seeds were visible on the external ear and patients felt uncomfortable with this (as suggested by one male participant). The patient diaries were provided to assess whether the participants would be able to record how often they pressed the ear seeds and what symptoms they were experiencing at the time. However, they were only completed in full by two participants out of the 17, both of whom were in the acupuncture group. Only 3 others entered some record into the diary all of whom were in group B and did not record which symptom they were experiencing at the time. Therefore, although all 17 participants completed the trial which suggests most individuals found the

interventions acceptable, there were issues with recording the self treatment (pressing on the ear seeds). Hence, future studies would need to consider other methods/ forms of recording the frequency of application of pressure to the ear points and the symptoms that the participants were experiencing at the time.

(b)Outcomes Feasibility

The outcome measures selected for both studies appear to be feasible to use in acupuncture studies and with these cohorts of participants.
The addition of the STAI, in Study 2, was to distinguish the type of anxiety and aimed to detect changes in trait anxiety versus any anxiety that might have been exacerbated by the trial conditions. It would appear feasible to add these anxiety measure into similar studies as the questionnaire is not onerous and was easily completed by all participants. In Study 2 the participants were also completing other questionnaires as part of their standard PR programme and although none of the participants complained about this, the researcher does acknowledge that there may have been some “questionnaire fatigue” for patients and responses may have been affected by this.

(c)Interventions Feasibility

It appeared that all the interventions used within both studies were feasible interventions, in terms of participant acceptability, and implementation.
The participants in Study 2 were asked to apply pressure to the ear seeds regularly when they were symptomatic. All participants reported that they did remember to press on the ear seeds and they did not experience any adverse effects from the ear seeds. Using EA as an adjunct to PR appeared to be acceptable to the participants and there was an ideal time to apply the intervention whilst the participants were resting from their exercise sessions and prior to the education starting. There were some minor issues in terms of finding a private space to apply the intervention in a busy outpatient department, however these were resolved quickly.

There were no adverse events from any of the interventions. The credibility of the treatments will be discussed later within this chapter.

8.4Outcomes

(a)Primary Outcome- Anxiety

Anxiety co-exists in many chronic respiratory disorders and this is evident from the literature as well as from current clinical practice (Seuss et al 1980, Yohannes et al 2000, Schleifer et al 2002, Deshmukh et al 2008, Panagioti et al 2014). This author selected anxiety as the primary outcome, for both studies included within this thesis, for this reason. It has already been discussed within this document, that the presence of anxiety, as a comorbidity can affect the outcomes of treatment.

In study 1 the analysis revealed that there were statistically significant differences within all three groups in anxiety levels from baseline to outcome. However, there were no statistically significant between-group differences in anxiety following intervention. However, study 2 revealed statistically significant within-group improvements in anxiety (both HADA and State anxiety STAI) only for the group receiving real EA. There were no statistically significant differences between the real EA and placebo EA group at baseline or outcome. These results suggest that acupuncture does not have specific efficacy over placebo acupuncture.

However, there were clinically significant improvements in both the HAD anxiety and the STAI anxiety measures in both studies. When scrutinising the results from both studies all the groups including the placebo groups, had mean HAD anxiety scores that reduced by a score of 1.5 or more which has been recognised as the minimal clinically important change for the HAD anxiety scale in COPD (Puhan et al 2008). This could be due to the fact that just being on a trial could improve symptoms or that there is an element of regression to the mean for the extreme scores. However, there are questions about the level set by Puhan et al as the minimal clinically significant difference and whether this is an appropriate level.

Puhan et al were able to determine this individual minimal clinically significant difference in the HAD scale in a group of 88 patients with COPD who took part in an in-patient rehabilitation programme. However, in their paper they describe the mean HAD anxiety scores at baseline were 7 which is below the level that indicates clinically relevant anxiety and suggests that the cohort was not very anxious or representative of a "normal" COPD population. The authors did say that it is not yet clear whether these results can be generalised to other respiratory conditions. In study 2 the mean scores on both the State and Trait domains of the STAI reduced to below the point considered to be the level for clinically significant anxiety symptoms.

This would suggest that all the interventions examined in this thesis acupuncture, ear acupuncture, BR, pulmonary rehabilitation (PR) had a clinically significant effect on reducing anxiety levels or it may be due to the well documented non-specific effects of acupuncture that are discussed in section 7.8.3 of this chapter. In study 1, all three groups received BR therapy. BR programmes have previously been demonstrated to reduce anxiety levels, in trials involving patients with HVS (Tweedale et al 1994, Han et al 1996, Han et al 2004). In study 2 both groups also took part in a PR programme consisting of physiotherapy-led exercise and education sessions. There is some evidence that aerobic exercise alone can improve anxiety and depression levels (Petruzello et al 2012). However, there is conflicting evidence about the effect PR of PR on psychological health. Diaz et al (2007) in their RCT examining the effect of PR on anxiety and depression in patients with severe COPD, reported statistically significant between-group improvements in both anxiety and depression scores following the PR programme. Two earlier RCTs found no significant improvements in psychological factors following PR (Gayle et al 1988, Ries et al 1995). The impact of PR on psychological health is uncertain.

The reduction in anxiety levels experienced by participants in study 2 could also have been attributed in some way, to the fact that they were exercising in groups. The benefits of group interaction and exercise on anxiety and mood have previously been described within the literature but not in respiratory patient groups (Williams and Lord 1997, Mutrie et al 2006). There is little of evidence to support the theory that exercising in groups reduces anxiety levels, in patients with respiratory disorders. Studies that have examined outpatient group PR versus home individualised PR have found no significant differences in anxiety outcomes. (Maltais et al 2008).

It is also likely that the therapist-patient interaction may have impacted upon these findings. The nature of all interventions across both studies meant that the practitioner spent a substantial amount of time with the patient. In study 1 all groups had the practitioner with them throughout each hour-long treatment session. In study 2 there was a physiotherapist and a support worker present during the PR programme twice weekly and then at each session they were reviewed by the investigator for the research trial. The effect of the therapeutic relationship on treatment outcomes is well documented within the literature (Priebe et al 2011, Joyce et al 1998, Conboy et al 2010, White et al 2011, Macpherson et al 2006). The expectation of relief from symptoms and the patient's beliefs about the acupuncture or physiotherapeutic intervention are also known to affect treatment outcomes (Kong et al 2009). The potential impact of these factors on the outcomes of this study will be discussed later within this chapter.

In both studies, when the groups were examined for between group differences at outcome, it revealed that, despite within-group reductions in anxiety, there were no statistically significant differences between the groups, in terms of anxiety. This supports the suggestion therefore, that all interventions had a similar effect in reducing anxiety. In study 1, this

finding implies that no one individual treatment method was any better than the other for the anxiety element with HVS. This reflects findings documented in some studies examining acupuncture for painful conditions, where acupuncture did not have any specific efficacy over and above the placebo acupuncture treatment (Kaptchuk 2000, 2002, Linde et al 2005,). However, there are a number of large trials for painful conditions that have demonstrated the superiority of acupuncture over usual or conventional treatment (Diener et al 2006, Endres et al 2007, Scharf et al 2006). The results of study 2 (where there were statistically significant improvements within the real EA group compared to placebo), although a feasibility study and underpowered does support a trend towards acupuncture as the superior treatment to placebo. The discrepancy in results across the two studies included within this thesis is also reflected in acupuncture studies within the literature. This continues to be debated within the literature and potential suggestions for these conflicting findings relate to the many methodological issues that surround acupuncture research. Issues such as sourcing an adequate control arm for acupuncture studies as well as trial design, differences in acupuncture technique, blinding and non-specific influences of acupuncture, are thought to have impacted upon the outcomes of many acupuncture trials. These issues will be discussed further later within this chapter.

It is of interest to consider the acupuncture evidence around painful conditions however, the chronic respiratory conditions examined in this programme of research do not predominantly present as painful conditions and the primary outcome for this study was anxiety. Controlled studies that have examined acupuncture for anxiety related disorders have all found verum (genuine) acupuncture to be superior to placebo/sham controls (Liu 1998, Eich et al 2000, Wang et al 2001(a), Wang et al 2001 (b), Kober et al 2003, Wang et al 2004). It should be noted that these studies are not without their methodological flaws. However, many of these used Ear acupuncture and not body acupuncture which might

tentatively support this author's findings in study 2 and could suggest that EA is more efficacious than body acupuncture. Conversely, the many issues around appropriate methodology of acupuncture studies affect the generalisability of the outcomes of these studies within the literature as well as those from study 2 in this thesis.

Another factor that needs consideration for both studies included within this thesis is the anxiety levels at baseline. When the study 1 results for anxiety levels pre and post interventions were plotted graphically (Figure.3.), it was evident that the mean anxiety scores (HAD A) in all three groups, prior to the intervention, were all above the level considered to be the indicator for mild anxiety (a score of 8). The graph shows that the mean anxiety score in group 1, who received the verum acupuncture intervention, dropped to below this level suggesting that on average, participants had mild clinical anxiety prior to the acupuncture treatment which returned to normal following the intervention. A similar reduction of anxiety to within "normal" limits was not evident in the remaining two groups. However, although there were no statistically significant differences in anxiety at baseline between the groups in this study, there were some clinically relevant differences. In group 2 (Placebo acupuncture and BR), the mean anxiety level (HADA) was 11 compared to 9 and 10 in groups 1 and 3 respectively. A score of 11 on the HAD scale relates to a "moderate" anxiety state (Snaith 2003). This suggests that the verum acupuncture group was not as anxious as the placebo acupuncture group, which may have confounded the results of this study.
When the individual cases were examined in each group, it revealed that in group 1 (acupuncture and BR) a total of eight participants were clinically anxious on the HAD scale prior to treatment, and six of those were not clinically anxious following treatment. Groups 2 and 3 had less convincing results in that both groups had high numbers of clinically anxious participants prior to treatment. In group 2 (placebo acupuncture and BR) 10 were clinically anxious; in group 3 (BR only), eight were clinically

anxious. Following treatment, in group 2 two of the 10 anxious participants reduced scores to below clinically anxious levels and only one of the eight anxious participants in group 3 were no longer clinically anxious following treatment. Also, in both the acupuncture group and the placebo acupuncture group, the mean HAD anxiety scores reduced by greater than the minimal clinically significant improvement which has been suggested for chronic respiratory conditions (1.5.). This might suggest some support for the theory that acupuncture had a greater effect on anxiety than standard care (BR). The potential reasons as to why there was also a reduction in anxiety in the placebo acupuncture group will be discussed in section 8.7.3.

In study 2, the converse is evident, in that the EA group at baseline had higher mean anxiety levels than that of the placebo group. In fact, the EA group had a mean HADA value of 12 suggesting moderate anxiety along with higher state and trait anxiety levels (state anxiety 49 and trait anxiety 50), compared to the placebo group (HADA 7, state anxiety 40, trait anxiety 38). In this study, the EA group had within-group statistically significant differences from baseline to outcome on both the HADA and the trait anxiety as well as being close to significance in state anxiety. Although the findings support previous studies within the literature that have found verum acupuncture to be superior to placebo, in the study reported here, this could have been due to regression to the mean (a variable which is extreme on its first measurement will tend to be closer to the average on its second measurement). A larger study with sufficient power and with groups that are equal at baseline is needed to test this hypothesis.

(c)Outcome 2. Depression

In study 1, no statistically significant differences in depression scores(HADD) were seen among the groups at outcome. No baseline between group differences were noted and no statistically significant

differences within each group, when comparing baseline depression to post intervention.

When the mean depression scores pre and post intervention were plotted graphically (Figure 4), it was evident that all three groups had mean baseline scores within the normal range (0-7) suggesting a lack of clinically significant depression amongst this sample population. There are few studies that have examined depression in HVS patients, but those that have done so have also reported low depression prevalence amongst this group.

There was a reduction in mean depression scores in all three groups, which reflects the findings for the anxiety data. However, the reduction in mean depression scores was greater than a score of 1.5 (which is indicative of clinical significance) in only the acupuncture (group1) and BR only (group 2) groups. This suggests that there may be an element of the two interventions that has an effect on depression levels. However, when the individual cases were examined, in each of the groups there were similar numbers of clinically depressed participants at the start of the trial and similar numbers that were not clinically depressed following the treatment. Groups 1 and 2 had three participants and group 3 had four who were clinically depressed before the trial and had below clinical levels of depression after treatment. These results need to be considered with caution. Greater than 50% of the participants in each of the groups had below clinical levels of depression and it is therefore not clear whether any reductions in those scores are clinically meaningful. This study was not designed to treat depression and the participants had low levels of depression which left very little room for improvement in depression. Any change in depression may suggest a link, but the design of the study, the low levels of baseline depression and the lack of statistical power in this study, prevents firm conclusions being made.

Previous studies that have examined the effects of BR on depression have revealed similar results in that the prevalence of depression has been found to be low in an HVS population and treatment with BR produced small reductions in depression levels (Han et al 1996, Tweedale et al 1994). Only one previous study examined the effect of acupuncture and BR on depression levels. This was the author's pilot study for the main study (Gibson et al 2007), which was designed to pilot the methodology, not test the hypothesis.

In Study 2, there were no statistically significant differences found in depression levels between the two groups. Although there were no statistically significant differences in both groups at baseline, group A (real EA) had a mean depression score (HAD D) that was greater than 8 (9) and therefore suggestive of mild depression. Conversely, group B (Placebo EA) had a mean score of 6. It would appear then that as a whole, both groups in study 2 did not have very high levels of depression. However, when the data were scrutinised individually, 53% of participants had clinically relevant depression scores of more than 8. Evidence from a robust meta-analysis examining the prevalence of anxiety and depression in COPD suggests that 25% of patients with COPD had experience of clinically significant depression (Zhang 2011). This would suggest that clinically relevant depression was more prevalent in the COPD cohort participating in study 2, than is estimated within the literature. The PR group that was used for recruitment in study 2, was held at an acute teaching hospital. This type of location for PR is used for patients with complex care needs more severe COPD, due to the high risk of exercising this group of patients.

At outcome, only group A had shown a clinically important reduction in depression mean scores. Group A who received the real EA had a statistically significant reduction in depression scores from baseline to outcome. This reduction in mean scores (9-6) was greater than the

suggested minimal clinically important reduction (Puhan et al 2008) and at outcome the mean score was below the threshold for the presence of clinically relevant depression (8). Therefore, although there were no differences between groups at outcome, this suggests that the real EA was efficacious and superior to placebo EA as an adjunct to PR, in the reduction of depression in this cohort of participants with COPD. Clearly, these results cannot be generalised to the wider population of individuals with COPD, as this was primarily a feasibility study with an inadequate sample. The results from both studies 1 and 2, in terms of the effect of acupuncture on depression, reflect those revealed by the latest Cochrane review of acupuncture for depression (Smith et al 2010). This Cochrane review examined 30 trials and concluded that there was insufficient evidence to support the use of acupuncture for depression due to the high risk of bias evident in many of the trials.

(c) Outcome 3. Symptoms

This section relates to symptoms of HVS evaluated using the NQ (Van Dixhoorn et al 1985) and breathlessness as measured by the VAS-D (Meek 2003) and the MRC dyspnoea Scale (Bestall et al 1999).
The majority of intervention studies to date have used the NQ as an outcome measure to assess the impact of treatments on symptoms of HVS (Grossman et al 1985, Tweedale et al 1994, Han et al 1996, Han et al 2004, Hagman et al 2011). Although the NQ (Van Dixhoorn et al 1985) was originally validated as a screening tool rather than an outcome measure, it is the most commonly used tool for assessment of symptoms associated with HVS, hence it was used as a secondary outcome in study 1. This author is not aware of any previous acupuncture studies that have used the NQ as an outcome measure.

In Study 1, there were no statistically significant differences in the Nijmegen scores between the groups, at outcome. This suggests that

acupuncture as an adjunct to BR is not superior to placebo acupuncture or BR alone.

When the groups were analysed for within group differences from baseline to outcome, all three groups had statistically significant differences in symptoms of HVS. The within-group results need to be considered with caution as although each group improved, this improvement did not reach statistical significance for any one group in the between-group analysis. There is often much debate within the literature about the use of the NQ and although it has a high specificity (the ability to differentiate non-HVS patients from HVS patients), it has low sensitivity and may well not be an appropriate outcome measure to use. The SEBQ is a questionnaire that has been validated for use with individuals with dysfunctional breathing or HVS (Courtney & Greenwood 2009). It was not available when study 1 was designed but future studies in this field should consider using it to complement the NQ as it concentrates purely on the respiratory symptoms of dysfunctional breathing.

However, although the SEBQ appears superior to the NQ as a symptom outcome for HVS or dysfunctional breathing, some of the symptoms it looks for are those that could be experienced due to airway changes that an individua might experience e.g. in Asthma or COPD. For this reason, it may be more appropriate to include both the SEBQ and the Nijmegen as an outcome in HVS studies.

Another symptom related outcome measure used in study 1 was the VAS-D breathlessness measure (Meek 2003). Acupuncture has been found to improve breathlessness/dyspnoea in several studies and for a range of conditions including cancer related breathlessness and in COPD. Breathlessness is a key symptom of HVS which in clinical practice is often described as the most disabling symptom of HVS. The findings from study 1 have shown that the acupuncture group had a statistically significant

improvement in breathlessness scores on a VAS, when compared to placebo acupuncture or BR alone. The change in mean scores however, did not reach the minimal clinically important change (10-12 units) in any of the groups which suggests the improvement in breathlessness was not clinically beneficial (Ries 2005).

In study 2 a dyspnoea scale was used as an outcome to assess for impacts upon symptoms. The MRC dyspnoea scale is used frequently in clinical practice as an outcome measure following PR (Evans et al 2009). It was a pragmatic choice to use the MRC dyspnoea scale as an outcome in this study. This was due to the fact that this scale was being assessed already by the physiotherapists running the PR group and as this was a feasibility study examining EA, this author did not wish to “overload” the participants with many more additional questionnaires.

The beneficial effects of PR on dyspnoea have also been demonstrated within the literature and are evident from the recent Cochrane review of PR for COPD involving 65 RCTs (McCarthy et al 2015). However, there are many measures of dyspnoea used within the field of PR clinically and within research trials. The MRC scale is a grading scale whereby the individual has to rate their dyspnoea that is associated with walking, resulting in a single score. In study 2, there were no differences at baseline in dyspnoea scores between the groups. As expected there was some improvement in mean dyspnoea score for both the real EA and the placebo groups but these changes were not statistically or clinically significant. This suggests that acupuncture does not have any additional statistically significant benefit on dyspnoea over and above PR.

The results from both studies suggest that acupuncture may have statistically significant benefits in terms of reducing dyspnoea but these findings are not clinically significant. Improvements in dyspnoea following acupuncture are evident within the literature. Maa et al (1997) carried out

a cross-over trial examining acupressure as an adjunct to PR and its effect on dyspnoea. They found statistically significant improvements in dyspnoea scores on a VAS but this study was underpowered (n=30), had methodological flaws and the author did not report whether their findings were clinically significant. They used a cross-over design and as has been previously discussed within this thesis, there is evidence that there may be a significant carry-over effect of acupuncture which may have confounded the results (Gibson et al 2007). Suzuki et al (2012) examined the use of body acupuncture in the treatment of COPD in a single-blind randomised controlled study. They found significant improvements in dyspnoea following a 12-week programme of acupuncture treatment. These findings are interesting but this study sadly reflects many of the acupuncture trials in that it was underpowered. The authors used body acupuncture as opposed to EA that was used in this study. It is not possible to make conclusive statements about the effect of acupuncture on dyspnoea for these reasons and the impact of methodological problems within acupuncture research will be discussed later within this chapter.

(d)Outcome 4. Health Status

Both studies included within this thesis examined health status but used 2 different measures. In study 1 the Measure Yourself Medical Outcome Profile (MYMOP2) was used. This questionnaire was designed to score specific measures that are created by the individual patients following treatment interventions. (Patterson 1996) It requires the individual to state 1 or 2 of their main symptoms as well as a daily activity that is hindered by their condition (Patterson 2004). The MYMOP2 profile scores were analysed and there were no statistically significant between-group improvements in health status. There were within-group differences found for both the acupuncture and BR alone groups (from baseline to outcome) ($p=0.007$ & $p=0.01$ respectively).

Although no between-group differences were detected in study 1, there is some evidence that acupuncture interventions have a positive impact upon health status. A randomised placebo-controlled study examining the effect of acupuncture on health status in participants with depression (n=163), found that there were statistically significant improvements in health status using the SF-36 (FanLing 2016). FanLing et al were able to detect statistically significant improvements in all domains of the SF-36 including physical function, social function and emotional function. Unfortunately, this study by FanLing et al (2016) is not comparable with the studies examined within this thesis as they used a TCM approach to acupuncture treatment which included moxibustion and the placement of indwelling needles for 12 weeks.

The MYMOP2 was chosen for study 1 as a health status measure as it is sensitive to change and enables the participant to highlight specific symptoms for which they sought acupuncture treatment (Hull et al 2006). Improvements in scores of greater than 0.5 are considered clinically significant.

When MYMOP2 scores from study 1 were closely scrutinised, they revealed that in all domains, for all three groups, there were clinically significant improvements (domains include symptoms activity and general wellbeing). The trend, which is of interest to this author, is that the greatest mean difference was noted in the general wellbeing domain for the acupuncture treatment group. There was a mean improvement in scores by 1.5 but this was not statistically significant. Further studies, with larger sample sizes, are required to investigate this in more detail.

In Study 2 (feasibility study), the SGRDQ was used as a measure of health status. This was a pragmatic choice as the participants were completing this questionnaire already as a clinical outcome of their PR group. There are many studies that have shown that PR can significantly

improve health status (McCarthy et al 2015). Had this been a definitive, funded RCT this author would have chosen to use MYMOP as well, so that changes in specific symptoms that were important for the participants, could have been examined. Although a feasibility study and underpowered, it is of interest to note that there was a statistically significant improvement in activity scores for the EA (treatment) group suggesting that the real EA group had greater improvements in their activity following treatment than the placebo group. The small sample in both studies included in this thesis, does not enable this author to make firm conclusions around the effect of acupuncture on health status. The trend from both studies would suggest that it may be beneficial, in terms of improving activity levels and general wellbeing.

(e)Outcome 5. Exercise Tolerance

In study 2, the impact of the EA treatment on exercise tolerance was examined. There is a substantial amount of good quality evidence within the literature that PR alone improves exercise tolerance (McCarthy et al 2015). There are very few studies that have examined the effect of acupuncture on exercise tolerance in COPD. Previous studies that have examined the effect of acupuncture on exercise tolerance in COPD have had mixed results. A more recent study has shown some significant improvements on walking distance (Suzuki et al 2012), where as an older study examining acupressure as an adjunctive treatment did not show any statistically significant improvements (Maa et al 1997). These acupuncture studies are not without their methodological flaws and the dilemma with how to design the best methodology for an acupuncture trial will be discussed in the coming sections of this chapter. Analysis of the data from study 2 shows that there were no statistically significant differences in exercise tolerance between both the treatment and placebo group at outcome. However, the minimal clinically important change for the six-minute walk for COPD is 53 metres (Redelmeier 1997) and the EA

treatment group had a mean improvement in walking distance of 57 metres, which is clinically significant.

There were no statistically significant differences between the two groups in study 1 at baseline but there were within-group statistically significant differences from baseline to outcome for the EA treatment group. This suggests that acupuncture, as an adjunct to PR, may have additional benefit in improving exercise tolerance when measured by the six-minute walk. These findings are not generalisable but may be of interest when designing a large controlled trial examining the adjunctive effect of acupuncture to PR for COPD.

8.5 Sample characteristics in Study 1 and 2.

(a)Sex

More females than males participated in study 1 (n=25 i.e. 63%). This partially reflects the higher prevalence of HVS amongst women in the general population, which has been estimated at ratios approaching 7:1 females: males, (Newton 2004). This is thought to be due to the stimulatory effect that the female hormone progesterone has upon the respiratory system, during the menstrual cycle (Ott et al 2006). Women are twice as likely to suffer from PD or social phobias and three times more likely to suffer from agoraphobia when compared to men (Nauert 2006).

The three arms in the first trial had both male and female participants however group 3 (BR only) had more men (n=7) than women (n=5). The randomisation process did not take sex into account because there is no evidence that sex has an impact upon outcomes of acupuncture treatment. There is also no evidence that suggests sex has an influence on treatment outcomes for HVS, but it is possible that sex could affect response to interventions. The mean anxiety, depression and symptom scores for group 3 were not significantly different at baseline when compared to groups 1 and 2 suggesting that, despite there being a

differing balance of males to females, there was no difference in severity of HVS across the three groups, prior to commencing treatment.

In study 2 there was one more female than male (9 vs 8). On statistical analysis, there was no significant difference between anxiety levels on either the HADA or the STAI between males and females at baseline. This is not reflective of the evidence available within the literature that suggests anxiety associated with COPD is more prevalent amongst females with the condition (Aghanwa & Erhabor 2001). However, the sample for this feasibility study is small and therefore is not likely to be representative of the COPD population as a whole. For this reason, it is not possible to make generalisable statements about this second feasibility study.

(b) Age

The mean age of the participants in study 1 was 52 (range 19 to 75 years SD 15.22), this is a higher mean age than has been presented in previous interventional studies for HVS (Grossman et al 1985, DeGuire et al 1992, Tweedale et al 1994, De Guire et al 1996, Han et al 1996, Han et al 2004, Hagman et al 2011). However, the wide age range (19-75 years) is reflected in the most recent study examining BR for dysfunctional breathing (Hagman et al 2011). This five-year follow up study of BR for dysfunctional breathing, described an age range of 25 to 78 years (n=45) and examined BR for asthma compared to BR for dysfunctional breathing. Despite randomisation, when the mean ages for each group were compared at baseline, the analysis revealed statistically significant differences between groups 1(acupuncture & BR) and 3(BR only).
There is no evidence that age has an effect on treatment outcomes for HVS however, this author has found in her clinical practice, that longstanding HVS can be more difficult to treat. It is also likely that the older participants will have had HVS for longer and may have confounded the results. The same can be said for the age of the COPD participants in study 2 in that there is more potential for the older participants to have had

respiratory disorders for longer and therefore the more potential for these individuals to have co-existing morbidities.

The mean age for participants in study 2 was 66 (range 58-73years). The higher mean age for patients with COPD than those with HVS is representative of the patient population where the majority of individuals with COPD are not formally diagnosed until they are over 50 years (NICE 2010).

There is evidence within the literature that the presence of comorbidities with COPD can affect the outcomes of treatment and in particular PR (Kim et al 2000, Kelker et al 2001, Dahlen & Janson 2002). A study by Crisafulli et al (2008) which examined the impact of comorbidities on PR outcomes in 2962 patients with moderate to severe COPD and found that study participants with two or more comorbidities more frequently reached the MCID in MRC dyspnoea scores following PR, although functional assessments were comparable with other participants, with one or no comorbidities. This suggests that COPD patients with comorbidities have greater improvements in some outcomes but not others. Von Leupoldt et al (2011) studied the impact of anxiety and depression on pulmonary rehabilitation outcomes. There were 238 patients with COPD who completed an outpatient pulmonary rehabilitation programme. The presence of anxiety and depression was independently associated with increased dyspnoea, a reduction in health status and walking distance before pulmonary rehabilitation. Although psychological symptoms improved after pulmonary rehabilitation, anxiety and depression were related to poor outcomes after pulmonary rehabilitation.

(c) Chronicity

It is not documented within the literature whether the length of time that an individual has suffered from HVS, has any impact upon the outcomes of treatment. However, it has been found in clinical practice that the more chronic the HVS is, the more intervention the individual requires to

manage the condition. This could be due to the fact that individuals have a learned “habitual” breathing pattern which is more ingrained the longer it continues for, which in turn is more difficult to eradicate with intervention. The mean length of time that the participants had suffered from symptoms of HVS was recorded as a measure of chronicity (this may not have correlated with time of diagnosis as many HVS sufferers have extensive medical investigations before a firm diagnosis is reached). There were no statistically significant differences in the chronicity of individuals amongst the three groups. However, the recording of this characteristic relies upon the participant to report accurately how long they have been experiencing their symptoms. HVS symptoms can initially be subtle and may go unrecognised by some individuals (Chaitow et al 2002). Others will be very sensitive to changes in their breathing pattern and may recognise there is a problem at a much earlier stage. Therefore, this may have had an influence upon outcomes as the groups were not stratified during randomisation, to account for this. However, although age differences were found between the BR group (group 3) and the acupuncture and BR group (group 1), the former being significantly younger than the latter (see section 7.4.2), the former did not have better treatment outcomes for anxiety or depression.

In some respiratory disorders, the length of time that an individual has suffered with the respiratory condition can result in a worsening of symptoms and deterioration of lung function (Celli et al 2004). COPD is a progressive disease which results in a decline in lung function and hence the longer an individual has suffered with COPD, the more likely they are to have progressed to a severe form of the condition. They are also more likely to have developed comorbidities associated with the condition which may influence treatment outcomes, as has been discussed in the previous section (7.4.2).

In terms of the participants in study 2 with COPD, it is also difficult to determine how long the individuals had suffered with the condition. It is like HVS in that there is often a delay between when symptoms arise and when a formal diagnosis is made (NICE 2010). The classification of severity of COPD helps a clinician to determine at what point an individual is, in terms of their disease progression. In study 2 all the participants had moderate to severe COPD, as classified by GOLD (Pauwels et al 2001). Twelve of the participants were classified as having moderate COPD and the remaining five had severe disease. Four out of five of the individuals with severe COPD were in the real EA group where there were statistically and clinically significant improvements in anxiety levels.

8.6 Treatment credibility

In placebo-controlled acupuncture trials, it is important to assess the credibility of the placebo being used. The Borkovec and Nau (B&N) credibility questionnaire was used to assess this in study 1 (Borkovec & Nau 1972). The credibility of the treatments was measured before and after treatment. The B&N scores pre and post treatment in all three groups were high with Mean scores being greater than 4 (5 being the highest possible rating)**.** There were no statistically significant differences in treatment credibility between the three groups. All participants in study 1 that received either real or placebo were asked after the trial whether they thought they had real acupuncture or not. The results showed that all of those in the treatment group (n=14) believed that they had received the real acupuncture versus 9 out of 14, in the placebo group.

This suggests that the placebo had good credibility and but was no different to the real acupuncture treatment. There was equipoise in terms of treatment credibility which means that any treatment expectancy and beliefs are unlikely to have confounded the results. There is evidence that treatment expectancy and beliefs may impact upon physiological

responses during acupuncture treatment and therefore potentially on treatment outcome (Pariente et al 2005).

8.7 Acupuncture Study Design

The design of any study can affect trial outcomes. In this study there were a number of issues commonly encountered in acupuncture studies such as: difficulties with blinding, the acupuncture technique and its quality, non-specific effects and the choice of appropriate acupuncture control. Other design issues relate to the potential impact of external life events that may have influenced anxiety/depression levels. The following sections of this document will discuss each of these issues.

(i)Blinding in acupuncture trials

In order to reduce bias, it is important to explore the possibility of “blinding” interventionists/practitioners to the treatment that participants receive. Bias may be introduced when the investigator is aware of the treatment that an individual will receive. This may influence the way in which outcome data are measured or presented to the participants. This may also occur unintentionally (Kendall 2003). However, in an acupuncture treatment session the practitioner is integral to the intervention, offering a manual treatment. It is not possible to blind the acupuncture practitioner to the intervention and if the practitioner has a strong opinion or a vested interest in the outcome, this may lead to bias. It is not ideal therefore, that in this study the practitioner was also the lead investigator.

In both studies within this thesis, the outcome measures were taken by a research nurse or physiotherapist who was blinded to the treatment that the participants received. However, in study 1, after both real and placebo acupuncture treatment individuals were sometimes left with a small mark, bruise or bleeding which may have indicated the treatment. Therefore, the nurse taking the outcome measures may have been able to distinguish between those who had real acupuncture and placebo acupuncture. This

could have resulted in some bias, however, many of the outcomes including the primary outcome measure, were self-reported and not measured by the research nurse, therefore minimising the potential for bias.

The participants should also be blinded to the treatment arm where placebo treatments are being used. In both studies the participants were blinded to whether they received “real” or placebo acupuncture and at the end of the trial in study 1, they were asked which treatment they felt they had received. This was used to assess for the adequacy of the participants’ blinding. Although all the participants in the “real” thought they received real acupuncture, five participants in the placebo group thought they had placebo treatment. This may be due to the fact that the technique for inserting the placebo needles is different to “real” acupuncture. This trial only included acupuncture naïve participants, but this would not have precluded them from having viewed acupuncture, on the television or internet, for example. As the placebo needle uses a plastic ring and plasters it does appear very different to “real” acupuncture. Although it is important to note that the plastic rings were used in both the acupuncture and placebo acupuncture groups. Therefore, there may not have been adequate “blinding” in this study. However, there is evidence within the literature that the Streitberger placebo needle used in study 1 is a convincing placebo, even with participants that have previously had acupuncture (Chang-Cai Xie et al 2013).

In Study 2, participants were all able to see each other’s EA as they were all exercising twice weekly in groups. However, as both the placebo and the real EA looked the same just in different points on the ear, the placebo treatment may have been less obvious. The participants in study 2 were not asked whether they thought they had “real” or placebo acupuncture as this was a feasibility study examining the feasibility of using EA, not a controlled trial.

(ii)Acupuncture treatment

There are many and very different methods of acupuncture treatment including electroacupuncture, ear acupuncture, acupressure, acupuncture point stimulation with TENS (this is not the same as electroacupuncture), as well as invasive needling. The treatment techniques also vary between practitioners in that some choose to use an individualised treatment where there is a combination of prescribed points, as well as tender local or distal points being stimulated. Other practitioners use a more TCM approach where an individualised diagnosis is made based on the TCM ideas of meridians and energy flow. The studies presented in this thesis, involved invasive needling to body points or ear acupuncture and used a western approach with prescribed points, whereby all participants that received acupuncture treatment had the same points stimulated.

One of the main difficulties with assessing the efficacy of acupuncture from the literature is that there is such a variety of acupuncture techniques and systems used, that many of the studies are not comparable. Many of the existing studies examining acupuncture for anxiety have used a TCM approach and have carried out individualised acupuncture treatments or have used ear acupuncture as opposed to body points (Uskok 1995, Wang et al (a) 2001, Wang et al (b) 2001, Kober et al 2003, Wang et al 2004). The remaining studies have used body acupuncture but have used a TCM approach (Liu et al 1998, Eich et al 2000, Zhang et al 2003). Consequently, it is difficult to compare the findings of study 1 to previous acupuncture and anxiety studies. These findings are also not directly comparable with the Levashov study (1992) which examined acupuncture for HVS, as they used a combination of ear and body points. The results from study 1, however, do appear to mirror those found in the pilot crossover study which suggested that both acupuncture and BR have an effect on anxiety levels in HVS, but acupuncture appears to provide a greater impact on anxiety (Gibson et al 2007). This researcher has not

found any previous studies within the literature examining acupuncture as an adjunct to BR, for hyperventilation or breathing pattern disorders.

Acupuncture techniques used in trials of acupuncture for COPD have also varied from acupressure techniques to acupuncture with moxibustion or electro-acupuncture (Maa et al 1997, Suzuki et al 2012). This makes the body of evidence less robust in that none of the studies are methodologically comparable and hence it is difficult to make generalised statements about the efficacy of acupuncture within a given population. The body of evidence is rising in the field of “pain” but it is still lacking in respiratory acupuncture studies (Gibson et al 2010).

It is not only the approach to acupuncture treatment that can differ between practitioners; it is also the specific acupuncture technique. For example, the importance of achieving deqi with each needle remains unclear. Many experts within the acupuncture field believe it is essential in delivering a good clinical outcome (Filshie et al 2004). Other evidence suggests it is not always important (White 2010). In study 1, the practitioner did aim to achieve deqi with each needle used in the acupuncture group. However, the needling sensation was not documented in any way. It may have been useful to use a needling sensation questionnaire, such as the Southampton Needle Sensation Questionnaire (SNSQ) (White et al 2008), to detect whether deqi was achieved with each session. It has been suggested that individuals may experience an element of deqi with the placebo needles and this may explain the common findings within placebo needle trials, where placebo is as effective as verum acupuncture (White et al 2003) Therefore, within this study it may have been useful to assess this, by also using the SNSQ with the placebo acupuncture group. In study 2 the ear points were stimulated first before placement of the ear seeds however, again no assessment of deqi was made.

The frequency with which individuals receive acupuncture may also impact upon outcomes. In study 1 each participant received their treatment twice weekly for four weeks. Therefore groups 1 and 2 received a total of 8 acupuncture treatments. The number of acupuncture treatment sessions used in controlled trials of acupuncture varies considerably across the available research. However, the frequency of treatment in this study was based upon clinical practice and the pilot crossover study (Gibson et al 2007).
It is possible that a total of eight acupuncture sessions was not adequate in improving anxiety or depression. A study by Eich et al (2000) examining acupuncture for clinical anxiety found that after five sessions of acupuncture there were no statistically significant improvements in anxiety levels but after ten sessions acupuncture was significantly more effective than sham acupuncture ($p<0.01$).

The practitioner carrying out the treatment procedures in this study is an experienced physiotherapist who has been practicing acupuncture for 10 years. However, the practitioner had not used the placebo needle before study 1 and the technique is different to applying a standard acupuncture needle. The practitioner underwent a short training session on the use of the placebo needles but it requires skill to use the Streitberger needle. The practitioner needs to ensure that the needle is concealed from the participant when it is removed as it is somewhat shorter in length. This could affect the “blinding” of the participants. There may therefore have been an element of “unblinding” in study 1 as discussed earlier in this section.

(iii)Non-specific effects and acupuncture controls

The non-specific effects of both BR, PR and acupuncture are well documented (Tweedale et al 1994, De Guire et al 1996, Han et al 1996, Han et al 2004, Hagman et al 2011, Kaptchuk 1998, Kaptchuk 2002). However, there is some debate about whether the process of using a

needle for the intervention is a more powerful placebo (Kaptchuk et al 2000). The active treatment aspect of acupuncture is not yet known, but the non-specific effects are thought to arise from sources such as, practitioner intention and beliefs, patient expectation, patient–practitioner relationship and from the needle puncture itself.

There are several controlled trials of acupuncture where placebo acupuncture provides similar clinically significant outcomes to verum acupuncture (Vickers et al 2012, White et al 2012). These studies and more place the specific efficacy of acupuncture in serious doubt; hence the choice of an appropriate inert acupuncture control is essential. Acupuncture controls such as mock TENS, that do not replicate the procedure of needling have previously been dismissed as “unconvincing” (Vincent & Lewith 1995). Study 1 used a non-penetrating needle (Streitberger needle) as the placebo acupuncture procedure. This has been used in several acupuncture studies. It replicates the procedure of verum acupuncture and therefore can account for the powerful enhanced non-specific effect that comes with needle insertion (Kaptchuk et al 2006, Wayne et al 2009). However, there are limitations to using this method of acupuncture control. It has been demonstrated in several studies that placebo needling can generate a powerful non-specific effect, which is either equivalent to, or outperforms standard conventional care (Haake et al 2007, Scharf et al 2006, White et al 2012).There is evidence that placebo needling can cause micro trauma and local changes in physiology and circulation, as well as a neurochemical response such as diffuse noxious inhibitory control (DNIC), which can promote the healing process (Le Bars et al 1979,Hammerschlag et al 2009).
The Streitberger needle does replicate verum acupuncture but this researcher would argue that an individual who had received acupuncture previously, may be able to detect the difference. Therefore, only acupuncture naïve patients were included within this study and this exacerbated the slow recruitment process. There remains some debate

surrounding this issue as studies have shown that participants with previous acupuncture experience were not able to detect the difference between a non-penetrating sham needle and “real” acupuncture (White et al 2003). However, a more recent study where participants were blindfolded and given both verum acupuncture and placebo acupuncture (using a non-penetrating needle), revealed that participants who had previously received acupuncture were able to distinguish between the two treatments (Chae et al 2011). This study by Chae et al can be criticised for not reflecting clinical practice in that removal of the visual stimulus could have an effect on the outcomes of the treatment. Chang-Cai Xie et al (2013) examined the validity of the placebo needle in a Chinese population, many of whom had received regular acupuncture. They found that the placebo needle was a credible treatment even with those experienced acupuncture patients. The debate continues around whether individuals who are experienced with receiving acupuncture can detect a difference with non-penetrating placebo needles This suggests that future studies, involving non-penetrating sham needle devices, should include some comparison of the credibility of the placebo needle in acupuncture naïve participants versus experienced acupuncture patients.

In study 2 the placebo treatment was the placement of ear seeds in an area on the ear where there are few acupuncture points. However, there is still skin stimulation which could have induced the DNIC response discussed earlier and hence impacted upon the outcomes of the placebo treatment.

The credibility of the placebo control can determine the outcome of the study hence it is important that this is assessed in any controlled acupuncture study. This study used the Borkovec and Nau credibility rating. The findings from this study have been discussed earlier within this chapter but suggest that the placebo was a credible placebo treatment for the majority of the participants.

The impact of having a placebo treatment arm within this trial may also have affected the effectiveness of the verum acupuncture treatment. When participants were consented to the trials they were informed that they may receive a placebo acupuncture treatment which in itself can affect the patient expectancy of receiving an effective treatment. This may have generated a false-negative outcome i.e. a type II error.

There is evidence that expectation can modulate acupuncture outcomes in terms of reducing analgesia (Kong et al 2009). Kong et al used brain imaging techniques to examine this in two verum acupuncture groups. They found that positive expectation can amplify acupuncture analgesia. Pariente et al (2005) found, using similar imaging techniques that treatment expectation resulted in the activation of endorphin rich areas, which may form the basis of the substantial non-specifc effects of acupuncture and placebo acupuncture, in studies for painful conditions. Kaptchuk (2002) suggests that acupuncture may be considered as "placebo-enhancing" providing small specific clinical effects which are reinforced by the patient's expectation of treatment. A more recent study by Foster et al (2010) suggests however, that there was no relationship between patients' treatment preferences or expectations and clinical outcomes in a trial of acupuncture and exercise for knee OA. However, analysis of their secondary outcome, assessing changes in pain and function revealed that participants with a high expectation of the treatment were almost twice as likely to be a positive treatment responder. It must be noted though, that these studies have been assessing pain relief and not non-painful conditions such as anxiety or breathlessness, which have been considered in this thesis. The participants' expectations of treatment outcomes were not examined in these trials but this would be useful in future studies. Further research is required examining the effect of expectancy on anxiety/depression outcomes, following an acupuncture programme.

Other non-specific effects can be related to the practitioner's attitudes and beliefs, therapeutic style and treatment preferences (Feinstein 2002, Foster 2007, White et al 2012). White et al (2012) examined the impact of empathic versus non-empathic consultations in their trial of acupuncture for OA pain. They found that the style of consultation did not seem to affect pain outcomes however; the individual practitioner and the patients' beliefs about treatment veracity had a significant effect on outcome. It must be noted however, that patients were aware from the consenting process of this trial, that they may have a non-empathic "clinical" consultation. The authors hypothesised that participants sought empathy during other aspects of their clinic visits such as the reception staff, which may have confounded the results.

There is strong evidence within the psychiatry literature that suggests the therapeutic style and practitioner-patient relationship can influence psychological treatment outcomes (Preibe et al 2011, Joyce et al 1998).This may therefore be highly relevant in this thesis, as the primary outcome in both studies is anxiety. In study 1, there was one practitioner that provided both the BR and acupuncture treatments to all three groups, which helped to standardise therapeutic style across the groups. Each group was also given a standard intervention time to account for any "attention effect" that could occur. It was however, hard to control for the types of discussions that occurred in some sessions. Often the anxious patients took longer with their outcome measures and hence had a longer amount of time with the research nurse. In study 2, participants received EA from the same practitioner but they took part in the PR programme which was led by a physiotherapist but also involved a programme of multidisciplinary education on COPD. Therefore, there was greater contact with healthcare professionals, which may have positively influenced the patient-practitioner relationship. The PR programme was also a group programme and relationships are built between the participants. As has been discussed earlier in this chapter, there may be psychological benefits

to exercising in groups which may have confounded the results of study 2 (Williams and Lord 1997, Mutrie et al 2006).

8.8 Impact of external life events

As these studies had used anxiety as the primary outcome it may have been prudent to have recorded any major anxiety provoking life events that participants had experienced, during the course of the studies. The researcher anecdotally remembers some participants mentioning stressful life events that occurred during one trial. One participant was referred for a total hip replacement and was on the waiting list for hospital admission and another mentioned that he was made redundant during the course of the trial.

These and other anxiety provoking events that were not taken into account may have impacted upon the findings of this study, in terms of anxiety and depression.

8.9Study limitations

There were some further limitations to the studies presented in this thesis and they will be discussed in the following sections:

(a)The Sample

The sample size for study 1 was substantially smaller than initially planned and could therefore result in type I and type II errors occurring. This was primarily due to a reduction in referrals to physiotherapy for HVS treatment during the data collection period. It is hypothesised that the reduction in referrals coincided with changes within the NHS. Financial constraints have resulted in many conditions now being managed within primary care and only more complex cases are referred to secondary care. Patients with HVS and no co-existing co-morbidities are therefore currently often managed within the primary care setting. The sample size for study 2 was also smaller than planned due to the reduction in referrals for PR during

the study period. Time constraints meant that the study period could not be extended.

Study 1 excluded participants with other co-existing respiratory conditions due the difficulty with separating the respiratory disease symptoms with those of HVS. Studies have shown that due to the close overlap of symptoms between the conditions, it has been difficult to differentiate between HVS and other respiratory conditions such as COPD or asthma (Jack et al 2004). However, this decision is controversial as it could be argued that excluding such patients may not provide a representative sample of an HVS population. It is also important to note when considering COPD and HVS that many of the participants in the study, were either current smokers or ex-smokers and therefore a proportion of these individuals may have had undetected mild COPD, which may have affected outcomes. The lack of a 'gold standard' test to diagnose HVS inevitably leads to potential misclassification. A further issue that may have affected recruitment in study 1 is that the use of acupuncture is becoming more popular, especially for painful conditions. This study excluded individuals who had received acupuncture previously, as it was felt that they may have been able to detect a difference in the placebo acupuncture, which would in turn affect the credibility of the placebo treatment.

In study 2 one participant withdrew from the study once when he was shown where the EA was going to be placed. He reported that he would have felt "uncomfortable" with the seeds (covered by plasters) on his ear lobes. He also stated that they looked like "earrings" and he withdrew for this reason.

In study 1, the differences in age and gender between groups 1 (acupuncture & BR) and 3 (BR only) may have affected treated outcomes in terms of the chronicity of the HVS or intensity of the symptoms.

However, this advantage was not observed in terms of anxiety outcomes for group 3. The randomisation of the groups was stratified for anxiety levels to ensure there were no differences in anxiety levels. There did appear to be a greater mean difference in depression scores for group 3 but this may be explained by the increased relaxation time.

Individuals who were taking prescribed anxiolytic medications were not excluded from the study. This could have affected the anxiety outcomes if the medication dosages changed during the course of the study. Participants were asked to alert the "blinded" research nurse if there were any changes to medications that they were taking during the trial. There were no reports from the participants of any such medication changes, but this relies upon the individual remembering to inform the research team.

(b)Outcome measures

The hospital anxiety and depression scale (HAD)

The primary outcome measure used in both studies was the HAD scale (See Chapter 5)**.** This is a validated questionnaire used to identify anxiety and depression among patients in non-psychiatric clinics (Bjelland et al 2002). The advantage of this scale is that it is quick and easy to complete as well as being validated for use outside of the psychiatric field. It is also frequently used in the field of respiratory therapy practice e.g. following pulmonary rehabilitation. The HAD scale as an outcome measure is not without its flaws. The main disadvantages with the HAD scale is that it does not take into account the different frequency and intensity of anxiety that individuals might experience. It also fails to detect the effect that external influences might have on anxiety. Anxiety is a key component of HVS and it could be argued that the clinical/experimental environment could have caused greater anxiety levels in such patients. The HAD scale is unable to distinguish between what is trait anxiety and that which is brought about by the external influences.

The STAI has been used in many of the BR (Grossman et al 1985, Han et al 1996, Huey 1983, Ley & Yelich 1997) and acupuncture studies for HVS (Uskok et al 1995, Wang et al 2001 (a), Wang et al 2001 (b), Wang et al 2004). Therefore, in study 2 the STAI was used alongside the HAD scale. However, there were no significant differences in state anxiety in either groups which suggests the external influences did not impact upon treatment outcomes.

8.10 Conclusions

The studies presented in this thesis have examined the effect of acupuncture, as an adjunct to physiotherapy, on anxiety related to respiratory disorder.

The findings from both studies suggest that it is feasible to use acupuncture and placebo acupuncture techniques, for trials examining the efficacy of acupuncture for respiratory disorder.

In the sample of people with HVS studied, acupuncture delivered as an adjunct to BR, did not have any specific efficacy over and above placebo acupuncture or BR alone. However, the acupuncture group had the greatest reduction in mean anxiety scores and these scores reduced to below the point considered to be the cut-off for clinical anxiety. These changes did not occur in the other two treatment groups. There were also significant improvements in the symptoms scores for those that received acupuncture. There were statistically significant improvements in breathlessness for the acupuncture group, compared to placebo acupuncture and BR or BR alone. Although these data are inconclusive, they suggest that acupuncture may have some beneficial effects as an adjunct to BR in the treatment of HVS, in terms of reducing anxiety and improving symptoms.

The findings from the second study suggest that it is feasible to use ear acupuncture for patients with COPD as an adjunct to pulmonary rehabilitation. Secondary findings from this study also suggest that there may be a trend towards acupuncture reducing anxiety, depression and

dyspnoea, as well as improving exercise tolerance, when compared to a placebo.

These findings need to be considered with caution as both studies were underpowered and were subject to various methodological limitations. Future studies investigating the efficacy of acupuncture for anxiety associated with respiratory disorders need to be adequately powered RCTs. The choice of placebo control should be carefully considered ensuring that it is credible and is not distinguishable from real acupuncture. The clinician must be skilled at using non-penetrating needle devices, if they are used as a placebo control. The randomisation should be stratified for age and chronicity, as well as anxiety. There should also be some consideration of the expectations/beliefs of acupuncture treatment and an appropriate, validated measure should be used. There should be a primary outcome measure of anxiety that includes assessment of state anxiety to assess the impact of participation in a trial on anxiety levels.

The studies presented in this thesis are novel and the first to examine the use of acupuncture for anxiety associated with respiratory disorders. The studies have also provided original data for the effect of acupuncture on symptoms and health status of individuals with hyperventilation syndrome. The knowledge that acupuncture may give clinically relevant improvements in anxiety, and symptoms for patients with chronic respiratory conditions, will inform practitioners and provide some evidence for them in support of the use of acupuncture, within their clinical practice.

Appendices

I Search Strategies for Literature Review

II Nijmegen Questionnaire

III Meridian charts and acupuncture poin

IV Ethical Approval Study 1 & Study 2

V Patient Information sheets & Consent Forms

VI Outcome Measures

- **Hospital Anxiety and Depression Scale**
- **Measure Yourself Medical Outcome Profile**
- **Acupuncture Health Questionnaire**
- **Sample of State-Trait Anxiety Inventory**

Appendix I

Search Strategies for Literature review

The search strategies included electronic database searching for articles. Search terms were linked to MeSH headings and subheadings to ensure a more comprehensive search. The “related articles” function was also used and related articles were also screened for their relevance to the searches.

The electronic bibliographic databases that were searched were as follows: Medline (including PubMed) Embase, Psych info, CINAHL, AMED, DARE, Cochrane Database of Systematic Reviews.

To ensure difficult to access literature (grey literature) and journals that were not available in the electronic databases were included, a Google search was carried out regularly on all search terms. Also reference lists of all literature found were scanned for relevant articles.

All searches were conducted between October 2007 and January 2017. There were very few studies on HVS after 1990 therefore the search included literature from 1980 to 2017 to ensure literature on HVS was included.

Hyperventilation Syndrome

The search strategy for HVS included the many terms that are used within clinical practice to describe this condition. The following terms were also searched: Breathing Pattern Disorder, Medically unexplained Dyspnoea, Dysfunctional Breathing. The search strategy for anxiety and HVS also included the following terms that are closely associated: General anxiety disorder, Panic disorder.

The following strategies were used:

Hyperventilation syndrome OR breathing pattern disorder OR dysfunctional breathing OR medically unexplained dyspnoea.

Hyperventilation syndrome OR breathing pattern disorder OR dysfunctional breathing OR medically unexplained dyspnoea AND anxiety OR general anxiety disorder OR panic disorder

Breathing Retraining

The search strategy for BR and HVS was not limited by date due to the few recent studies that are available. The search strategy for BR included the many terms that are used interchangeably for this treatment technique. The following terms were included: Breathing retraining, breathing exercises, breathing re-education, yogic breathing, Buteyko breathing techniques, Physiotherapy, physiotherapy breathing techniques.

The search strategy was as follows:
Breathing retraining OR breathing exercises OR breathing re-education OR yogic breathing OR Buteyko breathing techniques OR Physiotherapy OR physiotherapy breathing techniques AND Hyperventilation syndrome OR breathing pattern disorder OR dysfunctional breathing OR medically unexplained dyspnoea

Acupuncture

The search strategy for acupuncture was also not date limited due to the lack of recent studies of acupuncture and HVS.
The variety of terms used to describe acupuncture techniques were also included in the searches such as: auriculartherapy, electroacupuncture, ear acupuncture, meridian therapy, complementary therapy, alternative therapy

The search strategy was as follows:
Acupuncture OR auriculartherapy OR electroacupuncture OR ear acupuncture OR meridian therapy OR complementary therapy, alternative therapy

Acupuncture OR auriculartherapy OR electroacupuncture OR ear acupuncture OR meridian therapy OR complementary therapy, alternative therapy AND Hyperventilation syndrome OR breathing pattern disorder OR dysfunctional breathing OR medically unexplained dyspnoea.

Acupuncture OR auriculartherapy OR electroacupuncture OR ear acupuncture OR meridian therapy OR complementary therapy, alternative therapy AND anxiety OR general anxiety disorder OR panic disorder

Acupuncture OR auriculartherapy OR electroacupuncture OR ear acupuncture OR meridian therapy OR complementary therapy, alternative therapy AND Breathing retraining OR breathing exercises OR breathing re-education OR yogic breathing OR Buteyko breathing techniques OR Physiotherapy OR physiotherapy breathing techniques

Acupuncture OR auriculartherapy OR electroacupuncture OR ear acupuncture OR meridian therapy OR complementary therapy, alternative therapy AND Chronic Obstructive Pulmonary Disease Or COPD.

Acupuncture OR auriculartherapy OR electroacupuncture OR ear acupuncture OR meridian therapy OR complementary therapy, alternative therapy AND Respiratory disorders OR Respiratory conditions.

COPD

Chronic Obstructive Pulmonary Disease OR COPD AND Acupuncture

Chronic Obstructive Pulmonary Disease or COPD AND Anxiety OR Depression

Chronic Obstructive Pulmonary Disease AND Pulmonary Rehabilitation OR Physiotherapy

Chronic Obstructive Pulmonary rehabilitation OR COPD AND ear acupuncture Or Auricular Therapy.

Appendix II

Nijmegen Questionnaire

Nijmegen Questionnaire

Please mark with a tick how often you suffer from the complaints listed

	Never 0	Rare 1	Sometimes 2	Often 3	Very Often 4
Chest Pain					
Feeling Tense					
Blurred Vision					
Dizzy Spells					
Feeling confused					
Faster or deeper breathing					
Short of breath					
Tight feelings in chest					
Bloated in the stomach					
Tingling fingers					
Unable to breathe deeply					
Stiff fingers and arms					
Tight feelings around mouth					
Cold hands and feet					
Heart racing					
Feelings of anxiety					

Total **/64**

Obtained from page 6000 Multidisciplinary Approaches to Breathing Pattern Disorders Second Edition 2014, By Leon Chaitow, Dinah Bradley and Christopher Gilbert.

Appendix III

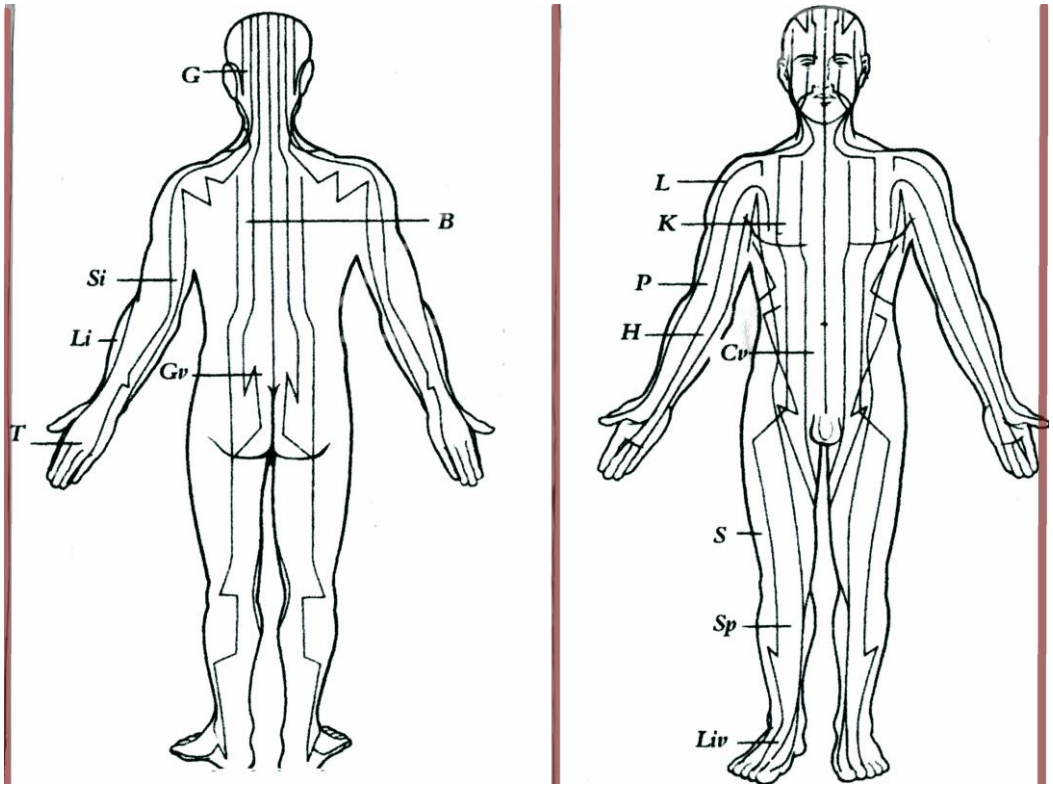
Meridian charts and acupuncture points

Meridians

Each meridian refers to a particular organ of the body. There are standard abbreviations for each meridian as follows (taken with permission from Kenyon .J (2007) " Simply a safer way An Effective Guide to Electro-acupuncture Techniques." Page 11 Dove Alliance)

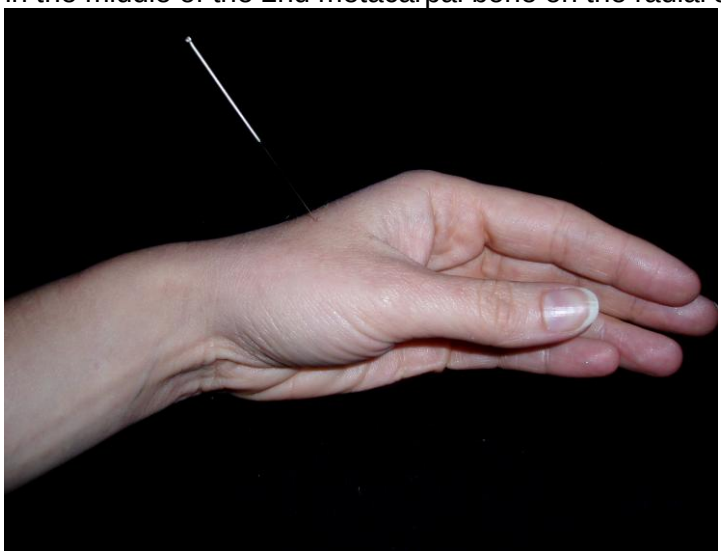
Li – Large Intestine	GB- Gall Bladder
Si-Small Intestine	Lv-Liver
H-Heart	Ki-Kidney
P-Pericardium	St-Stomach-Triple Warmer
Sp-Spleen	
Lu-Lung	CV-Conception Vessel
GV-Governor Vessel	

There are 12 paired meridians, 6 running over the arms and torso and the remaining 6 on the legs and trunk. There are 2 unpaired meridians (GV &CV), they run at midline anteriorly (CV) and posteriorly (GV). (See diagram below- taken with permission (taken with permission from Kenyon.J (2007) "Simply a safer way An Effective Guide to Electro-acupuncture Techniques." Page 11. Dove Alliance)



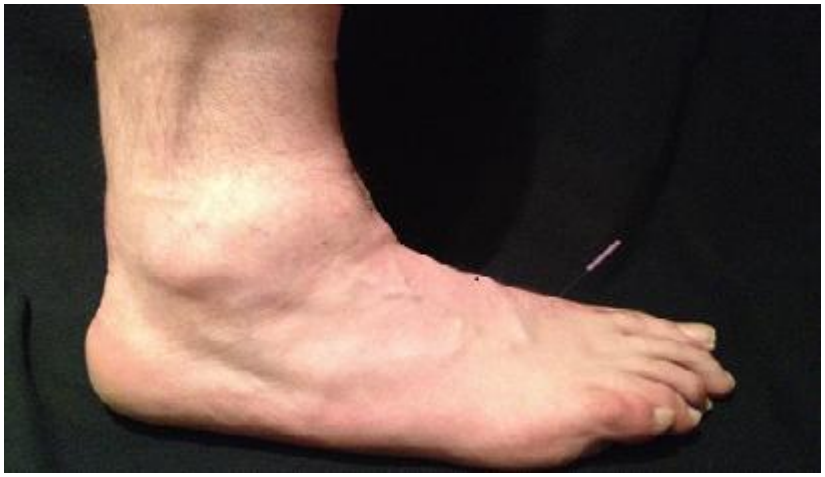
Location of acupuncture points **Large Intestine 4- Li 4**

Located on the dorsum of the hand, between the 1st and 2nd metacarpal bones, in the middle of the 2nd metacarpal bone on the radial side.



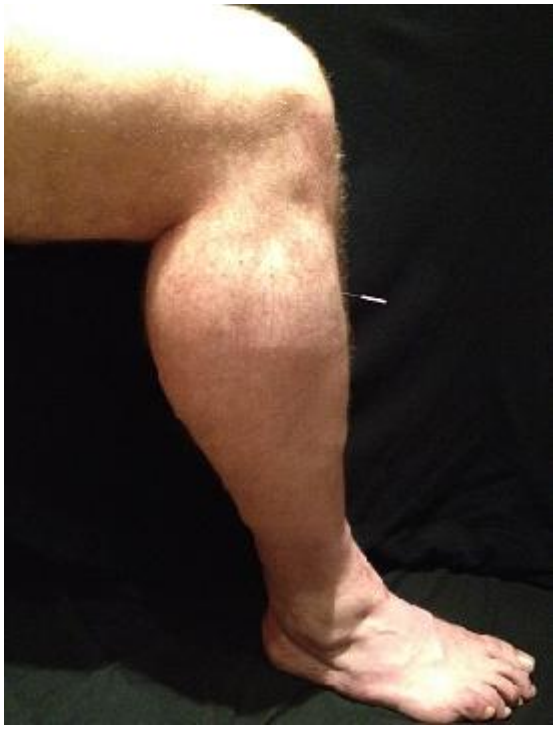
Liver 3-Lv 3

Located on the dorsum of the foot in a depression distal to the junctions of the 1st and 2nd metatarsal bones.



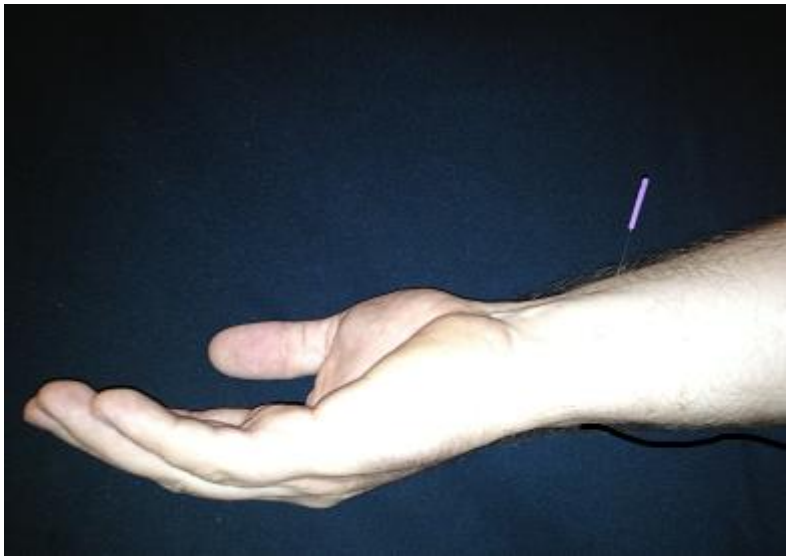
Stomach 36-St 36

Located four fingers width below the patella and one fingers width lateral to the anterior border of the Tibia



Pericardium 6-P6

Located approximately 2.5 fingers widths proximal to the wrist crease on the inside of the forearm. It is between the two main flexor tendons- Palmaris Longus and Flexor Carpi Ulnaris



Appendix IV
Ethical Approval

NHS

SOUTHAMPTON & SOUTH WEST HAMPSHIRE RESEARCH ETHICS COMMITTEES (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: GM.E.hio-au.SWHRECB@nhs.net

STA/cb

03 May 2006

Miss Denise Gibson
Consultant Physiotherapist in Critical Care
Southampton University Hospitals NHS Trust
Tremona Road
Southampton
Hampshire
SO16 6YD

Dear Miss Gibson

Full title of study: **A randomised controlled trial of acupuncture for the treatment of hyperventilation syndrome**

REC reference number: **06/Q1704/28**

Thank you for your letter of 15 April 2006, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		15 February 2006
Investigator CV for Miss D Gibson		22 January 2006
Investigator CV for Dr A Bruton		
Protocol	1	31 January 2006
Covering Letter		22 February 2006
Summary/Synopsis	1	31 January 2006
Letter from Sponsor		18 January 2006
Questionnaire - Acupuncture		02 February 2006

Questionnaire - HAD Scale		
Questionnaire - Nijmegen		
Questionnaire - MYMOP2		
GP/Consultant Information Sheets	1	16 January 2006
Participant Information Sheet	2	12 April 2006
Participant Consent Form	1	21 January 2006
Response to Request for Further Information		15 April 2006
Letter from Funder		21 January 2006
Data Protection		31 January 2006

Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

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.

06/Q1704/28	**Please quote this number on all correspondence**

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

Yours sincerely

Dr Anneke Lucassen
Vice-Chair

Email: GM.E.hio-au.SWHRECB@nhs.net

Enclosures:

Standard approval conditions SL-AC2 for other studies
Site approval form

Copy to:

Professor William M Rosenberg
Southampton University Hospitals NHS Trust
MP 18, Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

NHS
Health Research Authority
National Research Ethics Service
NRES Committee London – Fulham
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7434

11 December 2014

Mrs Denise H Gibson
Therapy department B level West wing
University Hospitals Southampton NHS Foundation Trust
Tremona Road Southampton Hants
SO166YD

Dear Mrs Gibson

Study title:	**A Feasibility study of auricular therapy as an adjunct to pulmonary rehabilitation for Chronic Obstructive Pulmonary Disease.**
REC reference:	**14/LO/2021**
IRAS project ID:	**119521**

Thank you for your submission of 9 December, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Anna Bannister, nrescommittee.london-fulham@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified 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.

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/2021	**Please quote this number on all correspondence**

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

Yours sincerely

Dr Charles Mackworth-Young
Chair

Email:nrescommittee.london-fulham@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mrs Sharon Atwill, University hospital Southampton NHS foundation trust, centre for biomedical research*

Appendix V
Patient Information Sheet
Patient Consent Form

Southampton NHS
University Hospitals NHS Trust

Denise Gibson
Consultant Physiotherapist
Physiotherapy Department
B level, Mailpoint 78
Southampton General Hospital
Tremona Road
Southampton Hants
SO16 6YD
Tel no: 02380 794557

Patient Information sheet

A randomised controlled trial of acupuncture for the treatment of hyperventilation syndrome

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

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

Ask us if there is anything that is not clear or if you would like more information
After reading this information take your time deciding whether or not you wish to take part in this study. This study forms part of the Clinical Doctorate dissertation of Denise Gibson, consultant physiotherapist, Southampton University Hospitals NHS Trust.

Part 1

What is the purpose of this study?

Hyperventilation syndrome is a condition that affects as much as 10% of the population. It can present in a number of symptoms, which can be distressing such as chest pain, breathlessness, headaches and pins and needles. Physiotherapists have been successfully treating patients with hyperventilation syndrome for some time using breathing and relaxation techniques. However, recent interest in alternative or complementary therapies such as acupuncture has prompted its use in the treatment of hyperventilation syndrome. This study aims to examine whether acupuncture is beneficial in treating hyperventilation syndrome when it is used alongside the traditional physiotherapy approach.
We will be using two interventions: 1) Needling to acupuncture points using acupuncture needles, and 2) breathing and relaxation exercises. We

will be particularly interested in how your symptoms react to the treatment and this information may help us to provide more effective treatment in the future for those suffering with a similar condition. This study forms part of the Clinical Doctorate dissertation of Denise Gibson, consultant physiotherapist, Southampton University Hospitals NHS Trust.

Why have I been chosen?
You have been chosen to participate in this study as you have been diagnosed with hyperventilation syndrome and have been referred by your doctor for physiotherapy treatment. There will be many other patients also taking part in this study.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
This study will last for 8 weeks with twice weekly treatment sessions at the Wellcome Trust Clinical Research Facility (WTCRF) at Southampton General Hospital. Your treatment sessions will last approximately 30 minutes per visit. If you require hospital transport for your visit, please ask your physiotherapist.
If you are eligible and agree to take part in the study, you will not receive any treatment on the first visit but we will give you some questionnaires to answer, which will cover several different areas. We will also ask you some questions about your symptoms, general health, and any anxiety or depression you may have had. This sounds like a lot of work but the questionnaires are all quite short and shouldn't take more than a few minutes to fill in. (some of the questionnaires are also repeated at the end). Then you will be given an appointment to commence your treatment in four weeks time. At this time you will be assigned to one of the three treatment groups (you might be assigned to a placebo group). Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. We put people into groups and give each group a different treatment; the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The results are then compared.

One group will receive acupuncture and breathing exercises, the second group will receive dummy or placebo acupuncture and breathing exercises and the third group will receive breathing exercises only. Treatment will then commence. You may find that the treatment will help to reduce your symptoms and any anxiety you may have or you may find it has no effect

at all on you. So that we can standardise the effect of patient/ practitioner interaction, the consultations will have to stick to a pre-determined and very structured formal approach (rather like using a checklist) and this will impose limitations on the practitioner in terms of what he/ she is able to talk about.

Placebo/ dummy treatment
A proportion of patients will receive placebo (dummy) treatment and so the acupuncture points will not be stimulated. i.e. the needle will not penetrate your skin. This will be allocated on a random basis. You will probably not be able to tell and you will not be told if your treatment is placebo or not. After the trial, if you would like to know, we will tell you if your treatment was placebo.

Am I eligible?
We need volunteers aged 18 and above to help us with our research and you have been asked because you have hyperventilation syndrome and have been referred by your consultant for physiotherapy treatment. There are also other conditions, which need to be fulfilled if you are interested in taking part. You must not have any other major or serious illness (if you are not sure about this part, I can discuss it with you). You must not be pregnant or trying to become pregnant. You would need to be able to attend a clinic twice a week for four weeks. You must not be allergic to ordinary sticking plasters or have a needle phobia. If you are a blood donor you may still give blood despite having acupuncture treatment.

What do I have to do?
It is important that you attend the scheduled appointments. However, if they are inconvenient for you please alert your physiotherapist. During the trial you must continue to take your regular medication. If your medication changes during the trial please alert your physiotherapist.

What is the procedure being tested?
The treatment of acupuncture is being tested in this trial.
If you are allocated to either of the two ‘needle’ groups this will involve inserting very thin needles into specific points around your lower leg and hand areas. These will be left in position for up to 30 minutes. The needles usually cause some sensation but this is not painful. Often patients feel nothing at all.
All three of the groups will be given breathing and relaxation exercises. These are abdominal breathing and relaxation techniques that you will need to continue with at home. You will also be given an advice leaflet regarding hyperventilation syndrome to take away and read.

What are the alternatives for diagnosis or treatment?
Alternatives to physiotherapy treatment and acupuncture for hyperventilation syndrome are provided by Clinical psychology in the form of behavioural therapy.

What are the side effects of any treatment received when taking part?
There are very few side effects associated with acupuncture but some patients feel a little tired afterwards and often sleep very well that night. Occasionally a small bruise may appear, but this rarely happens. If you do experience any adverse reaction to the treatment, this will be noted and treatment may be modified accordingly. If you do find that the treatment causes you excessive discomfort we would withdraw you from the trial (or equally you are free to pull out at any time). The breathing and relaxation exercises are not in any way uncomfortable and there are no side effects associated with this treatment. If you experience any adverse reaction this will be noted and your treatment may be modified to cater for this or you can withdraw at any time.

What are the possible disadvantages and risks of taking part?
It is possible that acupuncture if given to a pregnant woman can induce labour. Therefore, pregnant women must not take part in this study neither should women who are planning to become pregnant during the study. Any woman that finds herself pregnant during the course of the study should tell her physiotherapist at the earliest opportunity.
During the study you will be asked to complete a questionnaire, which helps to determine whether you have anxiety or depressive condition. If such a condition is detected you will still be able to continue with the trial and will be offered the opportunity to be referred back to your doctor for further treatment.

What are the possible benefits of taking part ?
Each participant will receive breathing and relaxation exercises, which are known to help your condition. It is hoped that acupuncture will also help your condition although this is not guaranteed. The information from this trial will help us treat future patients with hyperventilation syndrome better.

What happens when the research study stops?
When the study stops you will still be able to continue with treatment from the physiotherapy department if it is still necessary. You will be informed as to whether you received acupuncture or dummy treatment. If acupuncture is found to be beneficial for this condition, those who have not received it will be offered a course of treatment.

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

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.

Contact Details
Miss Denise Gibson
Consultant Physiotherapist
Physiotherapy Department
B level
Southampton University Hospitals NHS Trust
Tremona Road
Southampton
Hants
Contact number: 02380 794557

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.
Part 2

What if relevant new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your physiotherapist will tell you about it and discuss with you whether you want to continue with the study. If you decide to withdraw from the study, your physiotherapist will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.
Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?
It is entirely your choice whether or not you decide to take part in this trial. If you decide to take part you will be given this information sheet and then asked to sign a consent form. If you decide to take part you are also free to withdraw at any time and without giving reason. A decision to withdraw from or not take part in this trial will not affect the standard of care that you will receive. However information collected during the trial may still be used.

What if there is a problem?

If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action against Southampton University Hospitals NHS Trust, but you may have to pay for it. If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Denise Gibson 02380 794557). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Will my taking part be kept strictly confidential?
All information, which is collected, about you during the course of this trial will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. All information will be anonymously coded and held on a computer at Southampton University Hospitals NHS Trust.
Any data that is subsequently published or presented will be in statistical format only and will not include any identifiable personal details.
If you agree, your GP and other medical practitioners involved in your care will be notified of your participation within this trial. Your physiotherapist will gain your consent for this once you have agreed to enter the study.

What will happen to any samples I give?
During this study you will have any blood tests or be asked for any samples.

Will any genetic tests be done?
This study does not require you to have any genetic testing.

What will happen to the results of this study?
The results will be analysed and presented in the Clinical Doctorate Dissertation of Denise Gibson. A summary of the results will be sent to all participants at the end of the study. The results will be published or presented in statistical format at conferences and in journals and will not include any identifiable personal details.

Who is organising and funding the research?
This study is funded by the Physiotherapy Research Foundation (PRF) and all treatment is free to you at the point of contact. This study is also part of a Clinical Doctorate dissertation. The University of Southampton is the academic institution supporting this.

Who has reviewed this study?

The Physiotherapy Research Foundation has reviewed this study.

This study was given a favourable ethical opinion for conduct in the NHS by the

Southampton and South West Hampshire Local research Ethics Committee

If you require any further information please contact:
Denise Gibson
Consultant Physiotherapist, Southampton University Hospitals NHS Trust
Tel no 02380 794557 0r 02380 777222 bleep 1602

Each participant will be given a copy of this information sheet and a signed consent form to keep. Many thanks for taking the time to read this information sheet.

Southampton NHS
University Hospitals NHS Trust

Denise Gibson
Physiotherapy Dept
Level B, Mailpoint 78
Tremona Road
SO16 6YD
Tel. No 02380 794557

Centre Number: :
Study Number:
Patient Identification Number for this trial:

CONSENT FORM

Title of Project: A randomised controlled trial for the treatment of hyperventilation syndrome
Name of Researcher
Please initial box

1. I confirm that I have read and understand the information sheet dated 16/01/06 (Version 2) for the above study.
☐

I have had the opportunity to consider the information ask questions and have had these answered satisfactorily
☐

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

3. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from Southampton University Hospitals NHS Trust or University of Southampton, where it is relevant to my taking part in this research.I give permission for these individuals to have access to my records.
☐

4. I agree to my GP being informed of my participation in the study.
☐

5. I agree to take part in the above study.
☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Participant Information Sheet

Project Title: **A feasibility study of ear acupuncture as an adjunct to pulmonary rehabilitation for patients with Chronic Obstructive Pulmonary Disease**

Introduction:

You are being invited to take part in a research project. This sheet will tell you about the research and why we are doing it. If you don't understand, or want more information, then please ask us. One of our team will go through this information sheet with you and answer any questions you have. . Please ask us if there is anything that is not clear.

What is the purpose of this study?

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder that impacts upon an individual's general condition, physical abilities and quality of life. COPD can present with a number of symptoms such as breathlessness, reduced exercise ability and anxiety. Physiotherapists have been treating COPD for some time using pulmonary rehabilitation sessions for example to give advice on exercise, breathing techniques and coping strategies.

Many Patients with COPD suffer from anxiety, which is known to worsen symptoms such as breathlessness. There is some evidence that ear acupuncture can help to reduce anxiety in individuals with a range of illnesses. This study aims to examine whether the addition of ear acupuncture is beneficial for patients with COPD, when given alongside a pulmonary rehabilitation course. We will be using an ear acupuncture technique that does not involve the use of needles but will involve using a gentle pressure technique applied to specific points on the outer ear.

We will be particularly interested in how your symptoms react to the treatment and this information may help us to provide more effective treatment in the future for those suffering with a similar condition. This study forms part of the PhD thesis of Denise Gibson, consultant physiotherapist, University Hospitals Southampton NHS Foundation Trust.

Why have you been invited?

You have been invited to participate in this study as you have been diagnosed with COPD and have been referred by your doctor for pulmonary rehabilitation.

Do I have to take part?
It is up to you to decide whether or not you wish to take part. If you decide to take part, you will be asked to sign a consent form. Even after you decide to participate, you are still free to withdraw from the study at any time and without giving reason. This will not affect the standard of care that you receive.

What will happen to me if I take part?
This study will last for 6 weeks whilst you are attending for your pulmonary rehabilitation**.** If you are eligible and agree to take part in the study, on your appointment for your pulmonary rehabilitation assessment we will give you some questionnaires to answer, which will cover several different areas. We will also ask you some questions about your symptoms, general health, and any anxiety or depression you may have had. This sounds like a lot of work but the questionnaires are all quite short and shouldn't take more than a few minutes to fill in. (some of the questionnaires are also repeated at the end). At this time you will be assigned to a treatment group (you might be assigned to a placebo group). Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. We put people into groups and give each group a different treatment; the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). This will be similar to "flipping a coin" in order to determine which group an individual will be allocated to. The results are then compared.

One group will recieve ear acupuncture on the specific ear point relating to anxiety, the other group will recieve acupuncture on a point on the ear that does not relate to breathing or anxiety. The practitioner will put a small seed on your ear covered by a small skin coloured plaster. This will remain on your ear and you will be shown how to apply pressure to the plaster. You will be asked to gently press on the plaster three times per day. You may find that the treatment will help to reduce your symptoms and any anxiety you may have or you may find it has no effect at all on you.
In order, that we are sure that the interaction between the patient and the practitioner are the same for each patient, the practitioner will follow a set routine for each appointment (rather like using a checklist). The practitioner will therefore be restricted in terms of what he or she is able to talk about with you.
Placebo/ dummy treatment
A proportion of patients will receive placebo (dummy) treatment and so the points used will not be acupuncture points. This will be allocated on a random basis. You will probably not be able to tell and you will not be told if your treatment is placebo or not. After the trial, if you would like to know, we will tell you if your treatment was placebo.

What are the possible disadvantages and risks of taking part

It is possible that ear acupuncture if given to a pregnant woman can induce labour. Therefore, pregnant women must not take part in this study neither should women who are planning to become pregnant during the study. Any woman that finds herself pregnant during the course of the study should tell her physiotherapist at the earliest opportunity.
During the study you will be asked to complete some questionnaires. One particular questionnaire which helps to determine whether you have an anxiety or depressive condition, will be given to you to complete at 2 weekly intervals, when you attend pulmonary rehabilitation. If such a condition is detected you will still be able to continue with the trial and will be offered the opportunity to be referred back to your doctor for further treatment.

What are the possible side effects of the procedures?
There are very few side effects associated with ear acupuncture but some patients feel a little tired afterwards and often sleep very well that night. Occasionally a small bruise or red mark may appear, but this rarely happens. If you do experience any adverse reaction to the treatment, this will be noted and treatment may be modified accordingly. If you do find that the treatment causes you excessive discomfort we would withdraw you from the trial (or equally you are free to pull out at any time). If you experience any adverse reaction this will be noted and your treatment may be modified to cater for this or you can withdraw at any time.

What are the possible benefits of taking part?
If you do not receive ear acupuncture as part of the trial you will be offered a course of ear acupuncture should you wish to have some. Therefore, each participant will receive ear acupuncture as well as pulmonary rehabilitation. Pulmonary rehabilitation is known to help your condition. It is hoped that the ear acupuncture in addition will also help your condition, although this is not guaranteed. The information from this trial will help us treat future patients with COPD better.

Will my participation in the study be kept confidential?
Yes. Any information about you that leaves the hospital will have your details removed so that they cannot be identified. All samples will be labelled with a number only.

What will happen to the results of the research?
The results will be analysed and presented in the PhD thesis of Denise Gibson. A summary of the results will be sent to all participants at the end of the study. The results will be published or presented in statistical format at conferences and in journals and will not include any identifiable personal details.

Where can I find out more about research in general?

INVOLVE is a national advisory group, funded by the National Institute for Health Research (NIHR). Its role is to support and promote active public involvement in NHS, public health and social care research. http://www.invo.org.uk/ or Wessex House, Upper Market Street, Eastleigh, Hampshire, SO50 9FD, Telephone: 02380 651088 Email admin@invo.org.uk

What if something goes wrong?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Please raise your concerns in the first instance with the Principal Investigator (that is the lead researcher), Denise Gibson and her contact details are at the end of this form. If you wish to make a more formal complaint, please contact the hospital's Patient Advice and Liaison Service (available 9 am to 4.30 pm Monday to Friday, out of hours there is an answer phone).

Patient Support Services
C Level Centre Block
Mailpoint 81
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

Email:
PatientSupportServices@uhs.nhs.uk
Tel: 023 8079 6325

Which insurance provisions are in place?
In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the Sponsor, Southampton University Hospitals NHS Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you.

Principal Investigator Contact details:

Denise Gibson
Consultant physiotherapist
Direct tel: +44 (0)23 81206725
Mobile : 07879432167
email: Denise.Gibson@uhs.nhs.uk

Each participant will be given a copy of this information sheet and a signed consent form to keep. Thank you for taking the time to read this information sheet.

University Hospital Southampton NHS
NHS Foundation Trust

Denise Gibson
Consultant Physiotherapist
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INFORMED CONSENT FORM
ADULT

Title of study: **A feasibility study of ear acupuncture as an adjunct to pulmonary rehabilitation for patients with Chronic Obstructive Pulmonary Disease**

Name of Principal Investigator: Denise Gibson
Centre/Site number:
Study number:
REC approval number:

Participant ID:

Thank you for reading the information about our research project. If you would like to take part, please read and sign this form.

PART A: Consent for the current study
(Samples to be destroyed on study completion unless parts B/C completed)

PLEASE INITIAL THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I have read the information sheet (version 1) dated 03/07/14 for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. 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. ☐

3. I agree fill in a questionnaires and have measurements taken as part of the research in this study. I understand how the questionnaire is filled out and measurements will be taken and that filling in the questionnaire and having measurements taken for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time. ☐

4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University Hospitals Southampton NHS Foundation Trust. I give permission for these individuals to have access to my records. I understand that the information will be kept confidential. ☐

5. I understand that my GP may be informed of my participation and also if any of the results of tests done as part of the research are important for my health. ☐

6. I understand that I will not benefit financially if this research leads to the development of a new treatment or test. ☐

7. I know how to contact the research team if I need to. ☐

8. I agree to participate in this study ☐

Participant:	Date	Signature
Legal Representative (If Applicable):	Date	Signature
Researcher taking consent:	Date	Signature

Original for Investigator Site File, 1 copy for participant, 1 copy for medical record/hospital notes

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Appendix VI
Outcome Measures

Hospital Anxiety and Depression Scale

Measure Yourself Medical Outcome Profile

Acupuncture Health Questionnaire

State Trait Anxiety Inventory

The Hospital Anxiety and Depression Scale- Sample

1	I feel tense or wound up	Most of the time A lot of the time From time to time Not at all	3 2 1 0
2	I still enjoy things I used to enjoy	Definitely as much Not quite so much Only a little Hardly at all	0 1 2 3
3	I get a frightened sort of feeling as if something awful is going to happen	Very definitely Yes but not too badly A little but it doesn't worry me Not at all	3 2 1 0
4	I can laugh and see the funny side of things	As much as I always could Not quite so much now Definitely not so much now Not at all	0 1 2 3
5	Worrying thoughts go through my mind	A great deal of the time A lot of the time From time to time but not too often Only occasionally	3 2 1 0
6	I feel cheerful	Not at all Not often Sometimes Most of the time	3 2 1 0
7	I can sit at ease and feel relaxed	Definitely Usually Not often Not at all	0 1 2 3
8	I feel as if I am slowed down in my thinking	Nearly all the time Very often Sometimes Not at all	3 2 1 0
9	I get a sort of frightened feeling like butterflies in my stomach	Not at all Occassionally Quite often Very often	0 1 2 3

Measure Yourself Medical Outcome Profile

*** MYMOP2 ***

Full name ..... Dateofbirth.....

Today′s date ..... Practitioner seen .....

Choose one or two symptoms (physical or mental) which bother you the most. Write them on the lines. Now consider how bad each symptom is, over the last week, and score it by circling your chosen number.

Symptom 1.....

.....

0 1 2 3 4 5 6

Symptom 2 .....

.....

0 1 2 3 4 5 6

Now choose one activity (physical, social or mental) that is important to you, and that your problem makes difficult or prevents you doing. Score how bad it has been in the last week.

Activity.....

.....

0 1 2 3 4 5 6

Lastly how would you rate your general feeling of wellbeing during the last week?

0 1 2 3 4 5 6

As good as it could be — As bad as it could be

How long have you had Symptom 1, either all the time or on and off? Please circle:

0 - 4 weeks 4 - 12 weeks 3 months - 1 year 1 - 5 years over 5 years

Are you taking any medication FOR THIS PROBLEM ? Please circle:

YES/NO

<u>IF YES:</u>

1. Please write in name of medication, and how much a day/week

.....

.....

2. Is cutting down this medication: Please circle:

Not important a bit important very important not applicable

<u>IF NO:</u>

Is avoiding medication for this problem:

Not important a bit important very important not applicable

Obtained via http://www.bris.ac.uk/primaryhealthcare/resources/mymop/publications/

* MYMOP2 Follow up *

Full name ..... Today's date .....

Please circle the number to show how severe your problem has been IN THE LAST WEEK.

This should be YOUR opinion, no-one else's!

Symptom 1.....

..... 0 1 2 3 4 5 6

As good as it could be — As bad as it could be

Symptom 2.....

..... 0 1 2 3 4 5 6

As good as it could be — As bad as it could be

Activity.....

..... 0 1 2 3 4 5 6

As good as it could be — As bad as it could be

Well-being- how would you rate your general feeling of well-being?.

0 1 2 3 4 5 6

As good as it could be — As bad as it could be

If an important new symptom has appeared please describe it and mark how bad it is below.

Otherwise do not use this line.

SYMPTOM 3: 0 1 2 3 4 5

..... good bad

The treatment you are receiving may not be the only thing affecting your problem. If there is anything else that you think is important, such as changes you have made yourself, or other things happening in your life, please write it here (write overleaf if you need more space):

Are you taking medication FOR THIS PROBLEM ? Please circle: YES/NO

<u>IF YES:</u>

Please write in name of medication, and how much a day / week

.....

.....

.....

.....

Obtained via http://www.bris.ac.uk/primaryhealthcare/resources/mymop/publications/

Acupuncture Health Questionnaire

Below is a list of conditions which may affect your ability to have acupuncture.
Please will you put a tick by any which are known to affect you.

Condition	Yes	No	Comments
Hepatitis			
Diabetes			
HIV			
Epilepsy			
Heart problems			
High blood pressure			
Low blood pressure			
pacemaker			
Oral steroids			
Anticoagulants			
Bruise easily			
Bleed easily			
Fainting			
Fits			
Pregnancy			
Anxious/overfearful			
Altered skin sensation			
Skin conditions			
Allergy to stainless steel			
Under 16 years old			
Unexplained weight loss			
Inability to lie still			
Immunosuppressive disease			

Please ask if you are unsure as to how any of these may affect you.I have read and understood the information sheet and have filled out the healthquestionnaire to the best of my knowledge.I give my consent to receive acupuncture treatment.**Signed……Print……Date…..**

The MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Sample of the State Trait Anxiety Inventory

SELF-EVALUATION QUESTIONNAIRE STAI Form Y-1
Please provide the following information:
Name Date S
Age Gender (*Circle*) **M F** T

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment.* There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

1= not at all, 2= somewhat 3= moderately so 4= very much so.

1. I feel calm **1 2 3 4**
2. I feel secure **1 2 3 4**
3. I am tense **1 2 3 4**
4. I feel strained **1 2 3 4**
5. I feel at ease **1 2 3 4**

Developed by Charles D. Spielberger
in collaboration with R.L. Gorsuch, R. Lushene, P.R. Vagg, and G.A. Jacobs
Published by Mind Garden, Inc.
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www.mindgarden.com

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