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Chronic cough: An exploration of impact and an evaluation of non-pharmacological
management in adults

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Abstract

Chronic cough is defined as a cough that lasts for greater than 8 weeks in duration and has been estimated to have a prevalence of 11-13% of the population. Limited research has been conducted exploring its impact on the wider community. In up to 42% of chronic cough cases, the cough persists despite medical management, these cases tend to be labelled as refractory chronic cough. Pharmacological treatments are limited often with undesirable side effects. Research into non-pharmacological treatments for refractory chronic cough has been limited.

An internet based European survey explored the impact of chronic cough (January 2012 - April 2013). A systematic review investigated the effectiveness of non-pharmacological interventions for refractory chronic cough. A single blinded multi-centre randomised controlled trial (RCT) investigated the efficacy of a non-pharmacological intervention (Physiotherapy, Speech and Language Therapy Interventions, - PSALTI) on cough related quality of life (QoL), cough frequency, severity, sensitivity, vocal performance, anxiety and depression alongside a control intervention.

In total 1120 responses were collected and analysed from the European survey. Findings identified that cough impacted upon QoL, mood and ability to undertake activities and limited/ no effectiveness of medication; also a wish for more patient information to be available.

PSALTI trial showed statistically significant differences between groups for the outcomes; QoL, cough frequency and urge to cough, improvements were significantly greater in the PSALTI group compared with control. There were no significant changes in outcomes from 4 weeks to 3 months suggesting that observed improvements were maintained.

This thesis has identified the impact of chronic cough in Europe. It identified the need to improve the management of chronic cough and the information available for patients. This

thesis also provides the first evidence within a single blinded multi-centre RCT that PSALTI is an effective treatment option for people with refractory chronic cough.

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Abbreviations

ACCP – American College of Chest Physicians

ACE – Angiotensin Converting Enzyme

BMI – Body Mass Index

BTS – British Thoracic Society

C2 – Concentration of Capsaicin that caused 2 or more coughs

C5 – Concentration of Capsaicin that caused 5 or more coughs

Cu - Concentration of Capsaicin which participants' first rated a perceived urge to cough

CCEI – Crown Crisp Experiential Index

CES-D – Centre for Epidemiological studies depression scale

COPD – Chronic Obstructive Pulmonary Disease

CQLQ – Cough-specific quality-of-life questionnaire

CTU – Clinical trials unit

ELF – European Lung Foundation

EMG - Electromyogram

ERS – European Respiratory Society

FEES- Fibreoptic Endoscopic Evaluation of Swallowing

GORD – Gastro-esophageal Reflux Disease

HADS – Hospital Anxiety and Depression Scale

LCQ – Leicester Cough questionnaire

LCM – Leicester Cough Monitor

MCS – Mental Component Score

MID – Minimal Important Difference

MST – Morphine Sulfate

NHS – National Health Service

PCS – Physical Component Score

PG - Prostaglandin

PP – Per protocol

PPI – Proton pump Inhibitor

PTP – Phonation Threshold Pressure

PSALTI – Physiotherapy, Speech and Language Therapy Intervention

PVFM – Paradoxical Vocal Fold Movement

QoL- Quality of life

RCT – Randomised controlled trial

RSI – Reflux Symptom Index

SF-36 – Short Form 36

STAI – State trait anxiety inventory

TRP – Transient receptor potential

TRPV1 – Transient receptor potential Vanilloid 1

TRPA1 – Transient receptor potential Ankyrin 1

UACS – Upper airways cough syndrome

URTI –Upper Respiratory Tract Infection

VAS – Visual Analogue Scale

VHI – Voice Handicap Index

VPQ – Vocal Performance Questionnaire

The Cougher by Wendy Cope (Cope, 2011)

(A poem given to me by one of my trial participants)

*“ There’s a tickle in my throat
And you’ve hardly heard a note
And you’re wishing you were in some other place
In this silent listening crowd
You’re the one who’ll cough out loud
And you know you’re facing imminent disgrace
Yes, right now you’re in a pickle
And your unmanageable tickle
Is a torment and it’s threatening your poise
Can you hold out any longer
As the urge to cough grows stronger
Any moment you’ll emit a mighty noise
If this bloody piece were shorter
If you had a glass of water
It would help
Oh, if only you could be
At home with a CD
In a armchair free to cough the whole way through
Do you hear a rallentando
Does this mean the end’s at hand
What a mercy! Yes they’re really signing off
They perform the closing bars
And you thank your lucky stars
And its over.
You’ve made it.
You can cough.”*

Overview of thesis

Chronic cough is defined as a cough that lasts for greater than 8 weeks in duration (Morice et al., 2006). Initially chronic cough was only studied and evaluated as a symptom of other respiratory diseases. However this changed in the 1980s when chronic cough began to be studied and explored as a separate condition in its own right (Morice., 2008).

Chronic cough has been shown to cause significant physical and psychological symptoms including chest and abdominal pains, lethargy, incontinence, syncope, vomiting, headaches, voice changes, anxiety and depression. It can also affect societal participation as people with chronic cough have complained their cough interferes with their work, personal relationships and has lead them to avoid societal activities. These physical and psychological symptoms of chronic cough can independently, or act together with the effects on societal participation to interfere with QoL (Birring et al., 2003c, Brignall et al., 2008, French et al., 1998). Studies exploring the impact of chronic cough have tended to focus on patients attending specialist cough clinics (French et al., 1998, Birring et al., 2003c, Brignall et al., 2008) few have looked into the effect of chronic cough in the wider community (Everett et al., 2007, Fujimura., 2012, Adams et al., 2009).

In 1981, in an effort to improve the treatment of chronic cough, Irwin et al (1981) devised an anatomical diagnostic protocol which aimed to help clinicians systematically investigate patients with chronic cough. This protocol has developed over time and has informed the publication of three key chronic cough management guidelines: the European Respiratory Society (ERS) Chronic Cough Taskforce guideline in 2004 (Morice et al., 2004); the British Thoracic Society (BTS) guideline in 2006 (Morice et al., 2006), and the American College of Chest Physicians (ACCP) guideline in 2006 (Irwin et al., 2006). These guidelines identify that the most common causes of chronic cough in adults with a normal chest x-ray are asthma, gastro-oesophageal reflux (GORD) and rhinitis. Despite these diagnostic and

management guidelines, it has been found that in up to 42% of chronic cough cases, the cough continues to persist (Haque et al., 2005). For this group of chronic cough cases various descriptors have been used including: refractory chronic cough (Patel et al., 2011), idiopathic chronic cough (Morice et al., 2006), cough hypersensitivity syndrome (Morice et al., 2014), psychogenic cough (Vertigan et al., 2007a) and habit cough (Vertigan et al., 2007a). One of the most widely used terms is “refractory chronic cough” which is the terminology used throughout this thesis.

The focus for the management of people with refractory chronic cough has largely been in the development of antitussive medications. These have been found to be limited in their efficacy and many have undesirable side effects such as sedation and taste disturbances which affect their tolerability (Chung., 2014).

Non-pharmacological management for refractory chronic cough is an emerging treatment option. These treatment approaches have primarily been delivered by Physiotherapists and Speech and Language therapists and therefore have consequently been named after the healthcare professional involved in treatment; ‘speech language pathology management’ (Ryan et al., 2010, Vertigan et al., 2006) or ‘cough-suppression physiotherapy’ (Patel et al., 2011). There has however been limited evaluation of these non-pharmacological treatments for refractory chronic cough and there had prior to this thesis been no systematic review of the current evidence.

Due to the limited knowledge of the impact of chronic cough in the wider community and the limited research into non-pharmacological treatments for refractory chronic cough this thesis reports the findings from three studies that sought to:

- review the literature for the non-pharmacological management of refractory chronic cough, which is presented as a systematic review in Chapter 2.

- investigate the impact of chronic cough in the community. This investigation was conducted as an internet based survey across Europe in collaboration with the ELF and ERS Chronic Cough taskforce and is presented in Chapter 4.
- explore the effectiveness of a non-pharmacological intervention for refractory chronic cough. This exploration was conducted as a multi-centred randomised controlled trial and is described in Chapter 5.

CHAPTER 1:
INTRODUCTION AND LITERATURE REVIEW

1. Introduction and Literature Review

1.1 Chronic Cough

1.1.2 Definition

Cough is a three phased reflex defence mechanism which protects the airways from risk of aspiration, foreign bodies, infectious organisms and helps to keep the upper airways free from mucus and secretions (Lee and Birring, 2012., Chung and Pavord., 2008). The three phases of this mechanism consist of: an inspiratory phase, followed by a forced expiratory effort against a closed glottis and then a rapid expiration through the mouth after the glottis has reopened and closure of the nasopharynx has occurred (Widdicombe, 2005., Chung and Pavord., 2008). A cough is classified as a chronic cough if it persists for greater than 8 weeks duration (Morice et al., 2006, Morice et al., 2004, Irwin et al., 2006).

1.1.3 Epidemiology

Most surveys (see table 1) that have tried to quantify the epidemiology of chronic cough have aimed to assess the prevalence of cough or phlegm as a symptom of respiratory disorders; mainly asthma, chronic obstructive pulmonary disease (COPD) and bronchitis (Barbee et al., 1991, Montnémy et al., 1998, Lundbäck et al., 1991, Cerveri et al., 2003, Coultas et al., 2001) tending to base their questionnaires on the Medical Research Councils' definition and classification of chronic bronchitis (Medical Research Council, 1965). Thus as Morice (2008) and Kauffmann and Varrasso (2011) highlight these give an indication of the prevalence of cough symptoms but do not clearly identify a true

reflection of the prevalence of chronic cough. These surveys may well have captured acute as well as chronic cough and excluded chronic cough caused by anything other than COPD, asthma or bronchitis. The surveys have also varied in the questions they have asked regarding the prevalence of cough symptoms (see table 2) which may account for the varying prevalence observed in table 1. Despite this, these surveys reported associations between: smoking, increased body mass index (BMI) and chronic cough; and a predominance of females suffering with non-productive and nocturnal chronic cough.

More recent surveys of chronic cough prevalence have focused on chronic cough as a separate condition. Ford et al (2006) surveyed 6416 of the general UK population in Yorkshire and found a prevalence of chronic cough as 12%. Adams et al's (2009) community survey based in Adelaide, Australia found a prevalence of chronic cough as 20.5% in all participants and 18.2% in those with no identified respiratory disease. Adams et al (2009) found for people who had chronic cough without identified respiratory disease, chronic cough was more common for those who currently smoked, were obese, aged less than 40 and greater than 55 years old and had psychological morbidity. In contrast to some of the epidemiology surveys in table 2, and to Ford et al's (2006) survey which found prevalence of chronic cough to be higher in females, Adams et al (2009) found a higher predominance of chronic cough in males. Adams et al (2009) concludes that this difference could be due to men under-reporting their symptoms to clinicians and higher rates of women being treated in specialist cough clinics. This would explain differences in prevalence surveys based in primary and secondary care but does not account for the difference with Ford et al's (2006) survey which was also community based.

Table 1: Prevalence of cough in the community by country (1981-2001)

Year	Country	Cohort	Chronic cough prevalence	Features
1981	Tucson, USA (Barbee et al., 1991)	1109 White Americans >3 years old, of whom 1093 completed smoking questions.	17.9%	29.3% of smokers reported cough, compared to only 11.2% of non-smokers – strong link between smoking and cough.
1985-1986	Norbotten, Sweden (Lundbäck et al., 1991)	6610, 35-36year olds, 50-51 year olds and 65-66 year olds of which 5698 were analysed.	11%	6.8% had symptoms of sputum production and cough simultaneously, strong association between smoking and cough.
1992	Skåne, Sweden (Montnémery et al., 1998)	8469 responses 20-59 year old	12.6%	Higher prevalence of cough in smokers or ex-smokers. Smoking and cough symptoms were higher in females.
1988-1989	South East England (Cullinan., 1992)	9077 responses 5-54 year old, 46% male	14.1% males, 10.6% females	Reported cough every day or half the days of the year.

1988-1994	USA (Coultas et al., 2001)	5743 white Americans ≥45 years old, 52% female	9.3% in responders with no airflow restriction	Reported cough most days for 3 or more consecutive months per year Increasing cough symptoms with airflow restriction, cough present in 49.1% with FEV1<35%.
1990	Uppsala, Sweden (Lúdvíksdóttir et al., 1996) part of the European community respiratory health survey	623 responders 20-44 year olds	11% non productive cough, 8% productive cough, 38% nocturnal cough.	Significantly more female non-productive coughers (p<0.01) and nocturnal coughers (p<0.001). Significantly more smokers suffered with cough (p<0.001). No correlations found between age and cough. Anxiety and depression correlated with productive and non-productive cough.
1998-2000	Italy (Cerveri et al., 2003)	18,645 responses 20-44 year olds	11.9% (95% CI: 11.4-12.4). No significant difference between genders.	Reported cough and phlegm on most days for at least 3 months of the year and for at least 2 successive years. Significantly more current smokers suffered with phlegm and cough (p<0.001). 19.8% reported co-existing asthma.

2001	Europe (Janson et al., 2001)	18,277 responses 20-48 year olds, mean age 34 years old	30.7% nocturnal cough, 10.2% productive and non-productive cough.	Higher prevalence of nocturnal, non-productive and productive cough among smokers. Females are twice as likely to suffer with nocturnal cough and 1.3 times more likely to suffer with non-productive cough than men. Increased BMI also increased prevalence of productive, non-productive and nocturnal cough.
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Table 2: Questionnaires used in epidemiological surveys to assess coughs.

Reprinted from, Pulmonary Pharmacology & Therapeutics, Vol 24, Kauffmann and Varraso, The Epidemiology of Cough, 289-294., Copyright (2011) (Kauffmann and Varraso, 2011), with permission from Elsevier.

Table 1

Questionnaires used in epidemiological surveys to assess coughs.

60's "Classic BMRC/ECSC questions" – Chronic bronchitis

1. Do you usually cough first thing in the morning in the winter?

2. Do you usually cough during the day, or at night, in the winter?

If yes to 1 or 2:

Do you cough like this on most days for as much as three months each year?

90's – "Asthma-like "

(ECRHS) – Adults

ECRHS1 – Have you been woken by an attack of coughing at any time in the last 12 months?

ECRHS 2 – (At the time of lung function tests – acute events) Have you been woken by an attack of coughing in the last 3 days?

(Quality of life AQLQ Item) How much discomfort or distress have you felt over the past 2 weeks as a result of coughing? 1–7 (very great, great, good deal, moderate amount, some, very little, no)

(Isaac) – Children

In the past 12 months, has your child had a dry cough at night apart from a cough associated with a cold or chest infection?

Triggers of cough

(EGEA) Situations which usually induce the following symptoms (... fits of coughing, ...) (last 12 months) : smoky room, contact with cold air, physical effort, hay/cut flowers, animals, dust, occupational exposure, air pollution, weather, emotion, wine/alcohol, aspirin

1.1.4 Patho-physiology of chronic cough

The cough reflex arc consists of three phases: afferent pathway, central pathway and efferent pathway (Polverino et al., 2012). The cough reflex is usually initiated by the stimulation of afferent nerve endings in the mucous membranes of the pharynx and larynx and in the mucosal lining of the upper tracheobronchial airway, (Bickerman and Barach., 1954) which stimulates via the vagus nerve to a 'cough center' in the medulla (Polverino et al., 2012). An efferent signal is then generated and travels down the vagus, phrenic and spinal motor nerves to the respiratory expiratory muscles to produce a cough (Polverino et al., 2012).

1.1.4.1 Afferent cough pathway

The cough reflex is initiated by a stimulation of c-fibres or subtypes of vagal afferents which respond to mechanical or chemical stimuli. A variety of receptors have been identified to date (Canning 2009):

1. TRP Vanilloid 1 (TRPV1) receptors are stimulated by capsaicin, citric acid, low pH, temperature and bradykinin (Canning et al., 2006; Caterina et al., 1997)
2. TRP Ankyrin 1 (TRPA1) receptors which are stimulated by pollutants as well as bradykinin; nicotine acetylcholine receptors which are stimulated by nicotine
3. E series prostanoid receptors which are stimulated by prostanoids; Bradykinin receptors which are stimulated by bradykinin
4. Ion channels responsive to chemical stimuli which are stimulated by acid from reflux or aspiration of gastric content.

These innervations are found in the airways from the larynx to the large bronchi in humans (Canning 2009).

Chemical stimuli that initiate cough are wide ranging, and clinical and laboratory setting examples include nicotine and other inhaled pollutants, capsaicin and citric acid, bradykinin, inflammatory mediators, as well as acid from reflux or aspiration of gastric content (Canning., 2009). Mechanical stimuli that initiate cough have been identified as mechanical probing of the tracheal, laryngeal and large bronchial mucosa as well as accumulated secretions and aspirate (Canning et al., 2006; Canning., 2009).

1.1.4.2 Central pathways and regulation of cough

Canning et al (2014) reported that currently there are three main parts of the central regulation of cough that have been identified:

1. Central processing of afferent signals in the brainstem;
2. The brainstem control network organisation
3. The involvement of emotions, consciousness and perception of cough in the higher brain areas (subcortical and cortical).

Vagal afferent nerves have been shown to converge at sites of brainstem integration, particularly in the nucleus tractus solitarius (Canning et al., 2006, Canning et al., 2014). The nucleus tractus solitarius is connected to medullary respiratory neuronal network which coordinates efferent motor cough response such as bronchospasm (Shannon et al., 1998, Canning et al., 2014). This neuronal network is commonly referred to in the literature as the cough centre or central cough generator (Chung and Pavord., 2008).

The convergence of the vagal afferent nerves in the nucleus tractus solitaries causes synergistic regulation of the cough reflex. It is thought that this central sensitisation effect is similar to the central sensitisation observed in the study of pain (Mazzone, 2005).

The wider brainstem network that is involved in organising input from afferent nerves includes neurons within the ventrolateral medulla, raphe nuclei, and pons. These neurons have been found to be involved in controlling the duration of all three phases of cough, inspiratory, compressive and expiratory phases as well as the magnitude of the respiratory muscle activation throughout (Canning et al., 2014).

Similarly to swallowing, the cough reflex involves higher brain involvement (cortical and subcortical) which enables humans to voluntarily cough or inhibit cough. It is this cortical

processing of sensory inputs of the cough reflex that creates the perception of the need to cough also known as the perceived urge to cough. Farrell et al (2012) and Mazzone et al (2007) have conducted a number of studies using capsaicin induced cough to establish which areas of the cortex and subcortex are involved during cough reflex and have found a wide distributed network of brain regions activated including “*the prefrontal, motor, somatosensory and cingulate cortices, insula, putamen, thalamus, midbrain, brainstem, and cerebellum*” pg 1328 (Farrell et al., 2012).

1.1.4.3 Efferent Cough Pathway

Impulses are then sent from the cough centre via the vagus, phrenic, spinal motor and superior laryngeal nerves to the intercostal, diaphragm, abdominal wall muscles and glottis (Harsoliya et al., 2011). Resulting in the following stages of the efferent motor response to the cough reflex (Harsoliya et al., 2011, Chung and Pavord., 2008):

1. The diaphragm (supplied by phrenic nerve) and external intercostal muscles (supplied by the segmental intercostal muscles) contract creating a negative pressure within the thorax.
2. Air rushes into the lungs in response to the negative pressure.
3. The glottis (supplied by laryngeal nerve) and vocal cords then close.
4. The abdominal and other expiratory muscles simultaneously contract increasing the pressure within the lungs beneath the closed larynx.
5. The vocal cords and glottis relax and open, causing a sudden quick release of air to remove the cough irritant from the airways.

1.1.5 Impact and Burden of Chronic cough

French et al (1998) were the first to identify that chronic cough is associated with physical and psychosocial deterioration in QoL. When the authors explored which adverse cough

occurrences best explained the deterioration in QoL the following adverse occurrences were identified: patient exhaustion; the need for reassurance that nothing was seriously wrong; the inability to go to the movies due to cough and spouses being unable to tolerate their cough. A number of subsequent studies have further investigated the effects of chronic cough on QoL and have identified a number of frequently reported adverse physical, psychological and social symptoms of chronic cough (see table 3) (Brignall et al., 2008, Birring et al., 2003c, French et al., 2005, French et al., 2004, McGarvey et al., 2006, Dicipinigaitis et al., 2006).

Table 3: Physical, Psychological and Social symptoms related to chronic cough

<u>Physical</u>	<u>Psychological</u>	<u>Social</u>
Chest and stomach pains	Anxiety	Interference with work, communication
Tiredness/ lack of energy	Depression	Interference with personal relationships
Disturbed sleep	Embarrassment	Avoidance of social activities
Voice changes	Frustration	
Incontinence	Worries of serious illness	
Syncope		
Vomiting		
Headaches		

In 2006 two studies: Dicipingaitis et al (2006) and McGarvey et al (2006) highlighted the prevalence of psychological symptoms in people suffering with chronic cough. Dicipingaitis et al (2006), (n=100) found 53% of women and 52% of the men attending a specialist cough clinic with chronic cough scored positively for significant depression symptomatology. They were considered to be at risk of clinical depression at the point of their first clinical appointment. McGarvey et al (2006) (n=57) found that 21% of people with chronic cough attending his specialist cough clinic for their first appointment had borderline anxiety and 12.3% had clinically important anxiety. Borderline symptoms of depression were identified in 10.5% of the cohort and 5% had clinically important symptoms of depression. When assessing trait and state anxiety, 44.5% were found to have moderate trait anxiety and 28% had moderate state anxiety (McGarvey et al., 2006).

Dicipingaitis et al (2006) reported no significant differences in depressive symptoms for people with chronic cough related to age or gender and found no correlation between cough duration and depression. For QoL however French et al (2004) identified a gender disparity, women with chronic cough reporting significantly poorer QoL scores than males (67.1 ± 1.3 vs 59.7 ± 1.8 respectively, $p=0.002$). Women had significantly higher scores for: physical complaints (21.6 ± 0.5 vs 19.0 ± 0.7 respectively, $p=0.004$); psychosocial issues (14.7 ± 0.3 vs 12.9 ± 0.4 respectively, $p=0.002$) and extreme physical complaints (8.9 ± 0.26 vs 6.6 ± 0.26 respectively, $p<0.001$) (French et al., 2004).

All the above studies have served to identify the extent of physical and psycho-social morbidity of chronic cough. They have, however, predominantly focused upon specialist cough clinic attendees without exploring the impact of cough in sufferers within the community.

Everett et al (2007) surveyed 373 community based subjects with self-reported chronic cough in the UK who had responded initially to a radio broadcast request for participants. Everett et al (2007) also found that chronic cough was associated with a significant

adverse impact on the physical, psychological and social wellbeing of the participants. Physical effects of the chronic cough reported by the majority of participants were 'feeling tired/drained' (72%), 'disturbed sleep' (70%), incontinence in women (55% of women), voice problems (67%). Psychological effects of the chronic cough reported by the majority of the participants were 'anger and frustration' (83%), lack of control of their body (76%), participants reported the cough made them worry about their health (69%), made them depressed (55%), upset (80%) and worried about what others thought (76%). Social effects of the chronic cough were also reported by the majority of participants, 67% of participants felt their chronic cough affected their social life and 81% reported their cough affected their ability to make phone calls (81%) (Everett et al., 2007).

Fujimura et al (2012) surveyed 232 participants with self-reported cough registered with a research company via e-mail. This survey captured responses from participants with acute as well as chronic cough, the mean duration of cough reported was 3.8 weeks. Only 23.2% of respondents reported having had a cough for ≥ 8 weeks duration; therefore this survey is less representative of a chronic cough specific population. However the study team did find that 79.3% of women and 68.4% of male respondents found their cough 'troublesome' and affected their activities of daily living (Fujimura., 2012).

Though the above surveys and studies discussed have explored the impact of chronic cough none have explored comprehensively the perspectives of chronic cough sufferers'. The omission of their lived experiences and their views upon the management and treatment received for their chronic cough indicates the absence of the patients' voice. Previous studies and surveys have also been limited in exploring the impact specifically of chronic cough for people in the wider community who have not presented to specialist care.

1.1.6 Differential Diagnosis, Investigations, Treatments and management for main causes of chronic cough

In an aim to help the systematic investigation and diagnosis of people suffering with chronic cough, the anatomical diagnostic protocol was designed by Irwin et al in 1981 (Irwin et al., 1981). Over time this has developed and three key guidelines have been produced on the diagnosis and management of chronic cough: the ERS Chronic Cough Task Force guideline in 2004 (Morice et al., 2004) 'The diagnosis and management of chronic cough'; the BTS guidelines in 2006 (Morice et al., 2006) 'Recommendations for the management of cough in adults'; and the American College of Chest Physicians' (ACCP) guideline in 2006 (Irwin et al., 2006) 'Diagnosis and Management of Cough'.

All of these guidelines agree on an initial approach to the differential diagnosis of chronic cough which consists of: initially discontinuing angiotension converting enzyme (ACE) inhibitor medication; promoting smoking cessation and conducting chest radiology to identify any abnormalities. ACE Inhibitor medication is used to treat hypertension and heart failure but has been shown to cause chronic cough (McEwan et al., 1989). The mechanism by which ACE inhibitor medication causes chronic cough is thought to be due to bradykinin which is usually degraded by ACE sensitising the cough reflex (Fox et al., 1996). Smoking cessation is advocated, as smoking is a common cause of cough and has been shown to be dose related (Morice et al., 2006). Chest radiology enables abnormalities to be detected such as an underlying respiratory disease for many of which cough can be a symptom including chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease and lung cancer. The reasons for respiratory diseases to cause chronic cough are many, but in productive respiratory disorders excessive sputum production is known to trigger the cough reflex (Wilson., 2005) and idiopathic pulmonary fibrosis sufferers have raised inflammatory markers (Hope-Gill et al., 2003).Chest Radiology would also exclude Upper Respiratory Tract Infection (URTI)/ post viral infection which normally causes acute cough but can persistent in some cases

causing chronic cough (Morice et al., 2006, Irwin et al., 2006). URTI is thought to cause chronic cough by inflammatory markers triggering the cough reflex resulting in increased cough hypersensitivity (O'Connell et al., 1996).

Once the above causes of cough have been excluded the consensus of the main clinical guidelines are that there are three main causes of chronic cough in adults who have a normal chest x-ray. These causes are GORD, rhinitis (which is called upper airways cough syndrome (UACS) in the ACCP guideline) and asthma/asthma syndromes (Morice et al., 2004, Morice et al., 2006, Irwin et al., 2006).

GORD is thought to cause chronic cough by a number of mechanisms: by stimulating a esophagotracheobronchial cough reflex - it is hypothesised that cough afferent nerves are present in the distal oesophagus (Harding., 2006, Irwin et al 2000) as the presence of distal esophageal acid has been found to occur simultaneously with coughing (Ing et al., 1992); Micro-aspiration or macro-aspiration of acid can irritate the lower respiratory tract stimulating the afferent limb of cough reflex; or stimulation of the upper respiratory tract (larynx) without aspiration (Harding., 2006); esophageal dysmotility has been found to be present in 67% of GORD related chronic coughers (Kastelik., 2003) and therefore is another mechanism which may cause cough in these individuals; it has also been hypothesised that non-acid reflux may also cause cough (Harding., 2006).

Rhinitis is thought to cause chronic cough by excessive nasal secretions irritating the pharynx and stimulating the afferent cough reflex (Palombini and Araujo., 2005).

The term asthma syndromes has been used when discussing asthma as a common cause of chronic cough as not all chronic cough patients suffering with asthma, present with typical asthma symptoms of airflow obstruction, hyper-responsiveness and inflammation. Some individuals can present with airway hyper-responsiveness but no airway obstruction a situation which has been termed as cough variant asthma (Morice et al., 2006). Others can present with airway inflammation but no airway hyper-

responsiveness which has been termed as eosinophilic bronchitis (Morice et al., 2006, Morice et al., 2004, O'Bryne., 2005, Dicipinigaitis., 2004). Chronic cough sufferers diagnosed with asthma and bronchitis have been shown to have increased levels of prostaglandin E2, D2 and histamine compared to non-coughers (Birring et al., 2004b), which are known to elicit cough and increase cough reflex sensitivity (Choudry et al., 1989).

Despite the consensus in the guidelines (Irwin et al., 2006, Morice et al., 2007a, Morice et al., 2006) for the three main causes of chronic cough for adults with a normal chest x-ray. There is variation in the guidelines as to the order of investigations and treatments for these three main causes as well as the duration and intensity of treatment.

The ACCP guideline (Irwin et al., 2006) promotes that an initial differential diagnosis should start with empirical treatment trials for Rhinitis/UACS; a first-generation antihistamine (no treatment dose or time period suggested) followed by sinus imaging if UACS is suspected but does not respond to the empirical treatment trial. Investigations for asthma should follow (spirometry, bronchodilator reversibility, bronchial provocation challenge) or empirical treatment trials for asthma. These trials should include inhaled bronchodilators and inhaled corticosteroids, and/or 1 to 2 weeks of oral corticosteroids if the patient suffers with severe asthma or has not responded to other asthma treatments but asthma as a cause is suspected. Lastly the ACCP guidelines recommend that people with chronic cough with or without GORD symptoms should complete an empirical treatment trial for GORD for 3 months as well as a pH monitoring test to evaluate acid reflux, and/or barium esophagography for non-acid reflux. If chronic cough persists then further investigations into GORD should be carried out. These include 24 hour oesophageal pH monitoring, endoscopic swallow evaluation, Barium esophagram as well as more in depth investigations for UACS and asthma including CT scan, bronchoscopy. Finally the guidelines advocate investigations into rarer causes of cough such as echocardiograms to assess for premature ventricular causes of cough.

In contrast the ERS chronic cough taskforce (Morice et al., 2004) guidelines advocate for asthma to be investigated and treated first, followed by rhinitis and GORD. The BTS guidelines (Morice et al., 2006) are less formalised regarding the order of treatment of the three main causes. The investigations for asthma in the BTS and ERS Chronic Cough Taskforce guidelines (Morice et al., 2004) are the same as the ACCP, however the empirical treatment trials of oral steroids vary; the BTS guidelines (Morice et al., 2006) are similar to the ACCP and recommend a two week trial whereas the ERS Chronic cough Taskforce guidelines (Morice et al., 2004) recommend a longer 1 month trial.

For the treatment of Rhinitis the ERS Chronic cough Taskforce guidelines (Morice et al., 2004) recommend the same treatment as the ACCP but unlike the ACCP guidelines they recommend a treatment duration of two weeks. The BTS guidelines (Morice et al., 2006) in comparison recommend 1 month of topical corticosteroids, however they explain that this difference is due to first generation sedating antihistamines not being available in the UK. The ERS Chronic Cough Taskforce (Morice et al., 2004) also recommend an alternative Rhinitis treatment option of an oral decongestant for two weeks.

The treatments for GORD also vary between the guidelines; the ERS Chronic Cough Taskforce (Morice et al., 2004) recommend a shorter two month trial of high dose proton pump inhibitors (PPI) or H2 antagonists ± alginates compared to the ACCP three month trial. The BTS guidelines (Morice et al., 2006) recommend at least an 8 week trial of PPI such as omeprazole 20-40mg twice a day before meals.

For the majority of people with chronic cough when thorough investigation and empirical treatment trials have been completed a cause for the cough is found and successfully treated (Morice et al., 2006, Morice et al., 2004). In between 10-42% of cases however, the chronic cough can persist (Haque et al., 2005, Morice., 2002, Vertigan et al., 2006, Vertigan et al., 2007b). Within the literature there is significant variation in the terminology used to define these persistent cases, various terms have been used including: refractory

chronic cough (Patel et al., 2011), idiopathic chronic cough (Morice et al., 2006), cough hypersensitivity (Birring., 2011), psychogenic cough (Vertigan et al., 2007a) and habit cough (Vertigan et al., 2007a). For the purpose of this thesis the term refractory chronic cough will be used.

1.2 Refractory chronic cough

1.2.1 Definition

Refractory chronic cough is defined as a cough greater than 8 weeks in duration that persists despite treatment trials and investigations for the main causes of chronic cough; those being asthma syndromes, GORD and rhinitis (Patel et al., 2011).

1.2.2 Characteristics of refractory chronic cough

Refractory chronic cough predominately affects middle aged women (Birring et al., 2004a, Haque et al., 2005). It has been found to start around the time of the menopause (Mund et al., 2005) or develop after a viral respiratory tract infection (Haque et al., 2005). Organ specific autoimmune disease has also been linked to refractory chronic cough, as it has been found to be present in up to 30% of people; with autoimmune hypothyroidism being particularly common (Birring et al., 2003a).

Most refractory chronic cough patients describe their cough as being dry (62%) and their perceived location of the trigger for their cough to be in their throat (61%) (Vertigan and Gibson., 2011). The majority (94%) also report abnormal laryngeal sensations including

feeling tightness or tickle in throat, feeling like their throat is blocked, itch or dust in throat, feeling like there is something stuck in their throat or that something is pressing on their throat (Vertigan and Gibson., 2011). Numerous triggers have been identified by participants with refractory chronic cough as triggering their cough both tussive and non-tussive triggers. Vertigan and Gibson (2011) identified that most refractory chronic cough patients report predominantly non-tussive cough triggers as their cough triggers. Non-tussive triggers reported include talking, laughing/singing, exercise, change in air temperature or humidity, stress/anxiety, talking on the telephone, eating/drinking, air conditioning. Tussive agents reported include fumes, bleach and aerosols, smoke and shortness of breath.

Poor vocal hygiene and hydration was also identified by Vertigan and Gibson (2011) in people who suffered with chronic cough, 71% had inadequate water intake (<1500ml/day), 39% were mouth breathers, 65% consumed ≥ 3 caffeinated drinks per day. Poor vocal hygiene was found to be related to a greater urge to cough score ($p=0.001$) as rated on a 10 point Borg Scale.

Up to 40% of people with refractory chronic cough also experience significant voice problems (Vertigan et al., 2007d). A number of reasons for these voice changes have been hypothesised; repeated coughing is thought to potentially cause vocal fatigue and people with refractory chronic cough are also thought to have increased laryngeal muscle tension. These changes have been demonstrated by increased breathiness scores for refractory chronic coughers indicating reduced adduction of the vocal folds during phonation shown in Vertigan et al (2007d) and the reduced vocal fold closure phase shown in Vertigan et al (2008b). The authors hypothesised that this reduced vocal fold adduction as well as being due to increased muscle tension could also indicate avoidance of full contact of irritated vocal folds, from repeated coughing, which may trigger cough. A high percentage, 56%, of people with refractory chronic cough have also been found to

suffer with paradoxical vocal fold movement (Ryan et al., 2009), which is the involuntary and episodic adduction of the vocal folds during inspiration (Vertigan et al., 2008b).

1.2.3 Pathophysiology

The pathophysiology of refractory chronic cough is still not fully understood. Several different features have been found in these sufferers including: lymphocytic airway inflammation (Birring et al., 2003a), increased number of mast cells in bronchoalveolar lavage fluid (McGarvey et al., 1999), and increased concentrations of tussive mediators; histamine, prostaglandin (PG) D₂ and PGE₂ in induced sputum (Birring et al., 2004b). PGE₂ has been shown in healthy participants to increase cough reflex sensitivity; healthy participants post inhaling 0.76µmol of PGE₂ were only able to tolerate Geometric mean(95% CI) 4.4 (2.4 to 7.9) nmol of capsaicin before coughing five or more times (C5) whereas at baseline they were able to tolerate 16.2 (14.3 to 18.3) nmol (Choudry et al., 1989). Ho et al (2000) showed in rats that PGE₂ increased excitability of C fibres to capsaicin and lung inflation. Cho et al (Cho et al., 2003) found that people with refractory chronic cough, who had increased cough sensitivity, had increased Substance P in nasal their lavage fluid.

Chung and Pavord (2008) suggested that the effect of repeated coughing on the airway cells in people with chronic cough could cause the release of inflammatory mediators and tissue remodelling. Chung and Pavord (2008) also hypothesised that this could cause a positive feedback process increasing the cough duration and resulting in a change in the cough reflex sensitivity. Increased cough reflex sensitivity in people with refractory chronic cough has been demonstrated in other studies (Prudon et al., 2005, Johansson et al., 2009).

Another cause of refractory chronic cough is thought to be sensitisation of the central cough mechanisms (Chung et al., 2013, Ryan et al., 2012) as refractory chronic cough has been found to share many characteristics to other hypersensitivity syndromes such as chronic pain. As previously described, people with refractory chronic cough have been shown to have an increased sensitivity to tussive triggers that usually cause cough (hypertussia) such as chili and smoke; an increased sensitivity to non-tussive triggers such as talking, laughing and changes in air temperature (allotussia); as well as abnormal throat sensations such as a tickle or lump in throat (laryngeal paraesthesia) (Vertigan and Gibson., 2011).

Immune changes have also been shown in women around menopausal age which has been hypothesised as a possible cause of refractory chronic cough. Mund et al (2001) found an increase in T cells, T helper cells and an increased CD4/CD8 ratio in the lower airways in older females, with the biggest change occurring in women over the age of 43. They hypothesised from this that many women who develop chronic cough post menopause suffer an increase in previously subclinical airway inflammation (Mund et al., 2001).

Autoimmune disease has also been linked as a cause of refractory chronic cough and it has been hypothesised that aberrant homing of inflammatory cells to the lungs from a primary site of autoimmune inflammation could be a potential cause (Birring et al., 2003a, Birring et al., 2004a).

1.2.4 Assessment of refractory chronic cough

The assessment of refractory chronic cough has largely focused on measurement of the impairment; these assessments include cough reflex sensitivity testing, cough frequency and cough severity testing. Other assessments have focused on the measurement of

activity limitations, mood and societal participation restrictions including QoL questionnaires, vocal performance measures and questionnaires to assess mood.

1.2.4.1 Cough reflex sensitivity

In order to test the effectiveness of antitussive medications, agents that evoke a cough response in humans have been investigated. Thus the effectiveness of antitussives on the sensitivity of the cough reflex could be explored. In 1950 the first agent used to evoke a cough response in humans was ammonia vapour (Höglund and Michaëlsson., 1950), other early tussive agents used included ether and peppermint water that, via a endotracheal tube, was sprayed directly onto the larynx in anaesthetised patients (Hillis., 1952). Later studies moved towards less toxic agents and invasive techniques.

Bickerman and Barach (1954) undertook the first study to trial the use of inhaled citric acid and found there to be a dose response reaction to inhaled citric acid in both asthmatics and healthy volunteers. Collier and Fuller in 1984 investigated the use of capsaicin (a chilli extract) and concluded that the capsaicin cough challenge had good repeatability for the number of coughs produced at each capsaicin concentration for each patient, though limited data is provided in their paper on this. The authors also identified that there was a dose-response reaction to capsaicin; the stronger the dose the higher the number of coughs (Collier and Fuller., 1984).

Both citric acid and capsaicin have been recommended by the ERS cough assessment guidelines as tussive agents to be used for cough reflex sensitivity testing (Morice et al., 2007a). To increase standardisation of cough challenge testing the ERS Chronic Cough Taskforce produced recommendations on the equipment to be used, preparation of the solutions used and administration technique of the solutions. The endpoints for both tests

are identified as C2 and C5 which is the concentration at which participants' cough 2 or more times and 5 or more times respectively (Morice et al., 2007a).

Prudon et al (2005) explored the reliability of the capsaicin cough challenge and found for C2, ICC=0.89 and for C5, ICC=0.88 (Prudon et al., 2005). Dicipinigaitis (2003) showed that in healthy participants there is a good long term repeatability of the capsaicin cough challenge. As 83% of the 40 healthy participants who underwent capsaicin cough challenges in his study had C2 and C5 values within 1 doubling dose and 90% within 2 doubling dosages when the capsaicin cough challenges were repeated between 6 to 62 months apart (Dicipinigaitis., 2003). In healthy volunteers cough reflex sensitivity testing has identified that women have a significantly more sensitive cough reflex than males (Dicipinigaitis et al., 2001, Dicipinigaitis and Rauf., 1998a, Prudon et al., 2005). No ethnic or age differences have been identified (Dicipinigaitis et al., 2001, Prudon et al., 2005). Greater cough reflex sensitivity has been shown in people with refractory chronic cough when tested by the Capsaicin cough challenge (Prudon et al., 2005).

1.2.4.2 Urge to cough assessment

Urge to cough assessment has been identified as an important addition to the standard capsaicin cough challenge testing described (1.6.4.2). Urge to cough is defined as “*a measure of the perceptual sensation of a need to cough*” (pg 345) (Davenport et al., 2007). Davenport et al (2007) showed that in healthy adults the concentration required to elicit a reported urge to cough is significantly less than the concentration required to elicit a cough (motor response). Davenport et al (2007) also found a direct relationship between capsaicin concentration and the magnitude of urge to cough. They argued that this indicated that the sensation of the need to cough precedes the motor response of coughing; therefore if patients' perception of the need to cough occurs before they actually

cough, modifying patients' behaviour to the urge to cough may help them to suppress their cough (Davenport et al., 2007).

Dicpinigaitis et al (2012) explored urge to cough response to capsaicin in 100 healthy participants and found similar results to Davenport et al (2007). For the majority of the participants (79 participants, 40 females and 39 males) the capsaicin concentration at which they reported an urge to cough was lower than their motor response (cough) to capsaicin. For most of these participants (77 participants) no more than 3 doubling doses of capsaicin were between their reported first urge to cough and their motor response. For 40 of the 79 participants they coughed on the next doubling dose of capsaicin following the dose they reported their first urge to cough. Dicpinigaitis et al (2012) also found a significantly moderate to strong relationship between urge to cough and C1 (concentration at which they first coughed), C2 and C5 (0.75, 0.74 and 0.57 respectively, $p < 0.0001$).

Dicpinigaitis et al (2012) explored the repeatability of urge to cough assessment and found that when repeating the cough challenge a week later for all participants the concentration at which they reported an urge to cough was reproducible within two doubling doses of capsaicin and for 88% of participants was reproducible within one doubling dose (Kappa 0.70 (95% CI 0.49-0.85)).

In Dicpinigaitis et al's (2012) and Davenport et al's (2007) studies both used a modified Borg scale for participants to rate their urge to cough. Dicpinigaitis et al (2012) asked participants to rate their urge to cough after each concentration of capsaicin that did not result in a cough and Davenport et al (2007) asked their participants to rate their urge to cough after every capsaicin concentration delivered.

Ryan et al (2010) explored urge to cough and cough reflex sensitivity pre and post speech pathology management in people with refractory chronic cough. Similarly to Dicpinigaitis et al's (2012) and Davenport et al's (2007), Ryan et al (2010) also used a modified Borg scale for participants to rate their urge to cough after each concentration of capsaicin

delivered. However they analysed the urge to cough data differently by calculating a median urge to cough score of all the ratings given across the different capsaicin concentrations for a given participant. Therefore this does not allow comparison with previous studies and does not give an indication of the average capsaicin concentration that initiated participants' first urge to cough. Therefore it is not known whether there was a change in the capsaicin concentrations participants were able to tolerate before reporting an urge to cough post treatment.

Young et al (2009) explored urge to cough in people with refractory chronic cough and healthy adults. Young et al (2009) asked the healthy adults to rate their urge to cough after each capsaicin concentration on a 0 to 100mm VAS scale, the refractory chronic cough patients were asked to do the same but to use a modified Borg scale similar to previous studies. At C5 the healthy participants' urge to cough Median (IQR) VAS was 92mm (69 to 99mm), for the refractory chronic cough patients at C5 their urge to cough Median (IQR) Borg was 4 (3 to 6.3). Unfortunately due to different measures being used for both groups the difference in urge to cough cannot be compared, also data is only given in the study as to the urge to cough reported at C5, so the concentration at which both groups reported their first urge to cough is not known.

Urge to cough would appear to be an underexplored assessment method in refractory chronic cough but one with interesting potential. It might offer additional insights into the subtler aspects of the cough reflex; the patients' perceptions and sensations experienced prior to coughing rather than just exploring the motor response.

1.2.4.3 Cough severity assessment

Cough visual analogue scales (VAS); a 0-100mm line with one terminal anchor representing worst cough ever and the other representing no cough, have been widely

used in cough literature to measure patients'/participants' perception of cough severity (Birring et al., 2003c, Abdulqawi et al., 2014). Birring et al (2003c) quantified the reliability of the cough severity VAS for a chronic cough population when repeated two weeks apart as ICC=0.84 (Birring et al., 2003c). These scales are also recommended by the ERS cough assessment guidelines to measure cough severity (Morice et al., 2007a).

The minimal important difference for VAS in chronic cough has not been established yet although for acute cough it is identified as 17mm (Lee et al., 2013).

1.2.4.4 Cough frequency assessment

A variety of subjective scoring systems and diaries have been used to document cough frequency. Due to the psychological effects cough has and the effects it has been shown to have on QoL there is doubt as to whether these subjective scoring systems or diaries are a true representation of cough symptoms and frequency or affected by patients' mood (Smith and Woodcock., 2008). Also, due to the episodic nature of cough, it may be difficult for patients to notice slight changes in cough unless they are extremely vigilant. Currently it is not known exactly how large the change in cough frequency needs to be in order for patients with chronic cough to notice a subjective significant improvement or deterioration benefit (Smith and Woodcock., 2008). In children poor agreement has been found between reported and recorded nocturnal cough (Falconer et al., 1993).

A number of cough monitoring devices have been developed to objectively quantify cough frequency; these vary in their mechanisms of quantifying coughs by either just recording/detecting cough sounds (Matos et al., 2007) or combining this with also detecting chest wall motion or EMG during inspiration or expiration phase of the cough reflex (Coyle et al., 2005). They also vary as to whether the cough monitor software has the facility to automatically count the number of coughs with some user operator input

(Birring et al., 2008) or whether the coughs are manually counted (McGuinness et al., 2012).

Five ambulatory cough monitoring devices have been developed to objectively assess cough frequency: the LifeShirt® System (VivoMetrics, Inc., Ventura, CA, USA)(Coyle et al., 2005); Hull Automatic Cough Counter (Barry et al., 2006); LR102 device (Hsu et al., 1994); Leicester cough monitor (LCM) and VitaloJAK. The use and the validation of the LifeShirt® System, Hull Automatic Cough Counter and LR102 device have been limited compared to the LCM and VitaloJak which are the most widely used cough monitoring devices.

The LifeShirt® System is a portable vest monitoring system which detects cough from a combination of sounds measured via a throat microphone and monitoring of volume and timing ventilatory variables via non-invasive respiratory inductance plethysmography (Coyle et al., 2005, Smith and Woodcock., 2008). The LifeShirt® System's sensitivity, specificity and accuracy have however only been explored in a study of 8 COPD sufferers for whom cough was a predominant symptom (Coyle et al., 2005). In Coyle et al's (2005) study participants were videoed whilst they wore the vest for up to 24 hours and manual counting of coughs was compared to coughs detected by the vest. Sensitivity of the Lifeshirt was found to be 0.781 and specificity 0.996, agreement between the video surveillance and the LifeShirt was kappa = 0.807, (Coyle et al., 2005).

The Hull Automatic Cough Counter uses digital signal processing and a probabilistic neural network to label sounds detected from 24 hour recordings via a lavalier microphone as a cough event or not. User input is then required to determine the number of coughs in each event (Barry et al., 2006). The Hull Automatic Cough Counter has only been explored in thirty-three smokers for their first waking hour. Despite this though the study found the sensitivity was 0.80 (range 0.55 to 100), specificity (0.96 (0.92 to 0.98) and the

repeatability of the analysis software was reported as 100%. The average false positive to true positives was 20% (Barry et al., 2006).

The LR102 device simultaneously records cough sounds via a microphone whilst also recording electromyogram (EMG) signals of the intercostal muscles via 3 surface EMG electrodes (Hsu et al., 1994, Leconte et al., 2011). A study of four hour recordings in 10 participants (4 cystic fibrosis, 5 viral infection and 1 other) found that there was a significant difference between counting coughs from video surveillance compared to the LS107 for single coughs per hour with a difference between the measures of 12.5 coughs ($p < 0.01$) (Leconte et al., 2011).

The most widely used cough monitoring devices are the VitaloJAK and LCM (Spinou and Birring., 2014). The VitaloJAK is a 24 hour recording device with two microphones; a free air condenser microphone and one chest wall air-coupled condenser microphone. Subjects wearing the device initially voluntarily cough at different lung volumes so acoustic parameters can be set to each individual patient (Smith., 2008). With the VitaloJak the 24 hour cough recordings are compressed into shorter recordings lengths and then the coughs are manually counted by the operator, a recent abstract showed that for the VitaloJak compressing the 24 hour recordings to a mean 37.2 minutes still reproduced a 99.3% sensitivity when compared to manual counting of the full recording (McGuinness et al., 2012).

The LCM consists of a MP3 recording device with an external microphone and, similar to the VitaloJak, participants wear the device for 24 hours. Recordings are then analysed using semi-automated cough detection software which is based on the Hidden Markov model (Birring et al., 2008). Validation of the LCM has been completed by comparing automated cough counts with manual cough counts over a 2 hour ($n=9$ chronic cough patients) (Birring et al., 2008), 6 hour ($n=23$, 15 chronic cough patients (Birring et al., 2008), 8 controls) and 24 hour period ($n=12$ respiratory disease patients) (Yousaf et al.,

2013). For the 2 hour comparison the automated cough analysis was found to have a high specificity of 99% and sensitivity of 91%. Median false positive rate was 2.5 coughs per hour. The inter-class correlation between automated and manual cough count was 0.9 ($p < 0.001$). For the 6 hour comparison the interclass correlation between automated and manual cough counts was similar at 0.93 ($p < 0.001$), the specificity was the same at 99% however the sensitivity was less at 86%. The false positive rate decreased with increased time comparison to 1 cough per hour. The automated cough count was found to have a higher repeatability (ICC=0.9).

For the 24 hour recording the interclass correlation was even stronger at 0.98, specificity was higher at 99.9% but sensitivity was lower at 83.8%. Interestingly in this study they found that females coughed more than men, this was true for those with respiratory disease and those who were controls ($p = 0.012$ and $p < 0.001$ respectively) (Yousaf et al., 2013). Though it is advocated by the LCM authors for the device to be worn for 24 hours, a recent study by Lee et al (2012) showed that recordings as short as four hours correlated strongly with 24 hour recordings.

In 2007 the ERS cough assessment guidelines concluded that for objective cough monitors there was no gold standard and there was *'little to commend any particular method of quantifying cough over any other'* pg 1256 (Morice et al., 2007a). Since this guideline there have been significant developments in objective cough monitoring and a number have been used in treatment trials for chronic cough, especially the VitaloJAK and LCM. Today there still is no consensus as to which monitor is the gold standard and there have been no comparison studies between the different devices.

1.2.4.5 Health related QoL measures

The short-form 36 Version 2 questionnaire (SF-36 v2) is a widely used short self-administered health survey which measures eight health domain scales on a 0 -100 point scale (Physical Functioning (PF), Role participation with physical health problems, Bodily Pain, General Health, Vitality, Social Functioning, Role participation with emotional health problems, and Mental Health) (Ware et al., 2000). These domains can then be further summarised into two component summary measures – domains of Physical Component Summary (PCS)/ Physical health and Mental Component Summary (MCS)/ Mental Health. All health domain scales are scored such that higher scores indicate better health (Ware et al., 2000). The SF-36 has been used for many different patient groups, however it has not been validated for use specifically with refractory chronic cough and as the ERS guidelines for assessment of cough (Morice et al., 2007a) state as it is a generic QoL tool it lacks the specificity of disease specific QoL tools. The cough assessment guidelines therefore advocate the use of cough specific QoL measures which have been shown to be more reflective of chronic cough patients' symptoms than generic QoL tools (Kalpaklioglu et al., 2005).

There are two main cough specific quality of life measures that have been developed to evaluate cough related QoL; the cough-specific QoL questionnaire (CQLQ) and the Leicester cough questionnaire (LCQ) (Birring et al., 2003c, French et al., 2002) both of which are recommended by the ERS cough assessment guidelines (Morice et al., 2007a). The CQLQ is a 28-item questionnaire comprised of six domains: physical complaints, extreme physical complaints, psychosocial issues, emotional well-being, personal safety fears and functional abilities (French et al., 2002). It has been shown to have strong test-retest reliability in all six domains ($r > 0.75$ for all domains) and shows significant differences between acute coughers, chronic coughers and smokers (French et al., 2002).

The MID of CQLQ has been established as 13 units in total CQLQ score for chronic cough (Fletcher et al., 2010).

The LCQ is a 19 item questionnaire which measures the effect of cough in three domains: psychological, physical and social, thus it creates four scores: a psychological domain score, physical domain score, social domain score and total score. The LCQ has been showed to have a significantly strong correlation with cough severity VAS ($r_s=-0.72$) and a strong repeatability in all its scores (physical 0.93, psychological 0.90, social 0.88 and total score 0.96). The MID for LCQ has been established as 1.3 in chronic cough (Raj and Birring., 2007). The LCQ has been used in a number of chronic cough and refractory chronic cough clinical trials (Ryan et al., 2012, Yousaf et al., 2010, Patel et al., 2011, Ryan et al., 2010).

1.2.4.6 Mood/ anxiety

A number of different measures have been used in chronic cough to assess anxiety and depression including: the Center for Epidemiologic studies Depression Scale (CES-D) (Dicpinigaitis et al., 2006) which is a 20 item self-reported questionnaire, with a score ≥ 16 indicating significant depressive symptomatology and risk for clinical depression; Hospital anxiety and depression scale (HADS) (Zigmond and Snaith., 1983) a 14 item self-reported questionnaire, with a score of 8-10 indicating a borderline and a score ≥ 11 indicating probable anxiety and depression disorder; State Trait Anxiety Inventory (STAI) (Spielberger et al., 1984) a 40 item questionnaire (20 items for State anxiety, 20 items for trait anxiety but subsets can score between 20-80) which measures the underlying tendency and current state of anxiety, a higher score indicates a greater anxiety (Julian, 2011); and Crown Crisp Experiential Index (CCEI)(Crown and Crisp, 1966) a self-rating

48-item questionnaire which measures 6 scales of free floating anxiety, phobic anxiety, obsessiveness, somatic anxiety, depression and hysteria (McGarvey et al., 2006).

Dicpinigaitis et al (2006) found that of 100 (79% female: 21% male) new chronic cough patients referred to secondary care, 53% had significant depressive symptomatology as rated by CES-D which was not influenced by gender (53% females, 52% male) or duration of cough. McGarvey et al (2006) found that of 57 (70% females) new patients referred to a chronic cough specialist clinic, 21% had borderline anxiety scores, 10.5% had borderline depression score, 12.3% had clinically important anxiety score and 5.3% had clinically important depression scores as rated by HADS. Forty-four percent of participants had moderate trait anxiety scores, 3.8% had high levels of trait anxiety and 28% had moderate state anxiety scores as measured by STAI. Mean phobic anxiety, obsession, somatisation and depression scale scores as part of the CCEI were all higher than values for healthy population. Similarly to Dicpinigaitis et al (2006), McGarvey et al (2006) found no significant gender differences in anxiety or depression scores and only a weak correlation between cough duration and HADS depression scores ($r=0.321$, $p<0.05$).

Vertigan et al (2007c) unlike the previous two studies explored anxiety and depression in participants who had a diagnosis of refractory chronic cough and therefore had undergone extensive medical interventions and treatments and found significantly higher scores for anxiety and depression when compared to healthy controls ($p<0.001$). Vertigan et al (2007c) analysed anxiety and depression in participants with refractory chronic cough, by splitting them into two groups; those who had refractory chronic cough with no signs of PVFM and those who had refractory chronic cough and PVFM. Mean depression scores for both groups were within normal range as scored by HADS. The mean anxiety score for the chronic cough only group was also within normal range for anxiety as scored by HADS. In contrast the participants who had chronic cough and PVFM, the mean anxiety score was identified as borderline for anxiety symptomatology.

Vertigan et al (2007c) may have found lower rates of anxiety and depression compared to Dicipinigaitis (2006) and McGarvey et al (2006) as the participants in their study had undergone multiple investigations and treatment trials for their cough. Participants in Dicipinigaitis et al (2006) and McGarvey et al (2006) studies were assessed for anxiety and depression on their first visit to secondary care. In Dicipinigaitis et al (2006) study they did repeat anxiety and depression assessment and found scores for both significantly reduced following investigations and treatment for cough.

Despite a range of measures being used in the studies of Dicipinigaitis et al (2006) and McGarvey et al (2006) to explore anxiety and depression in chronic cough population, HADS is the only measure that has been used in a refractory chronic cough clinical trial (Ryan et al., 2010). McGarvey et al (2006) found strongly significant concurrent validity when HADS anxiety subscale was compared to STAI state anxiety and trait anxiety ($r=0.621$ and $r=0.607$ respectively, $p<0.01$) as well as CCEI free floating ($r=0.867$, $p<0.01$) and CCEI phobic anxiety ($r=0.603$, $p<0.01$). Strongly significant concurrent validity was also found for HADS depression subscale and CCEI depression score ($r=0.633$, $p<0.01$). Therefore it could be argued that any of these measures could be used to explore mood with people with refractory chronic cough.

1.2.4.7 Voice/vocal related symptoms

A number of outcome measures have been used to assess vocal problems in people with refractory chronic cough. These include: perceptual voice analysis (Vertigan et al., 2007d, Vertigan et al., 2008a), which is a subjective voice assessment undertaken by a trained listener (Vertigan et al., 2007d, Vertigan et al., 2008a); acoustic voice analysis (Vertigan et al., 2008b, Vertigan et al., 2008a), which is an objective electronic measure of vocal function (Dejonckere et al., 2001), and electroglottography (Vertigan et al., 2008b), which

measures vocal fold activity reflecting glottal closure (Bier and Watson., 2012). These measures all require a trained experienced clinician in voice analysis for them to be undertaken; unfortunately this resource is not consistently available in all chronic cough centres.

There are a number of patient self-reporting questionnaires available that have been used to measure patient perceived voice dysfunction of which the following have been studied in depth recently (Carding et al., 2009): The Voice Handicap Index (VHI) a 30 item questionnaire comprising three domains namely, functional, emotional and physical aspects of voice. A total score >33 indicates a mild voice impairment, >44 moderate and >61 severe (Jacobson et al., 1997). The Vocal Performance Questionnaire (VPQ) is a 12 item questionnaire for which a score >12 indicates patient perceived voice dysfunction (Carding and Horsley., 1992); and the Voice Symptom Scale (Dreary et al., 2003) which is a 30 item scale with three domains (impairment, physical symptoms and emotional response), the higher the total score the higher voice impairment.

Carding et al (2009) argues that patient self-reporting scales have the benefit of collecting data on patients' experienced disability from their vocal problems as well as information regarding the quality of their voice. As vocal problems tend to have variable effects over time it enables the patient to report how their voice condition is in general rather than a clinician rating their voice on a single episode in clinic. A single clinical measurement may not be representative of the patient's voice at other times other than during the assessment. All three scales (VHI, VPQ and VSS) have been shown to have excellent internal consistency (Cronbach's coefficient VPQ 0.81, VHI 0.95 and Voice Symptom Scale 0.89) and repeatability (VHI =0.83, VPQ=0.75 and Voice Symptom Scale = 0.63) (Webb et al., 2007). Significantly strong concurrent validity (VHI vs voice symptom scale $r=0.87$, VHI vs VPQ $r=0.76$, VPQ vs voice symptom scale $r=0.78$) (Webb et al., 2007) as well as sensitivity to change post voice therapy (VPQ SD= 1.04, VHI SD=0.62, Voice Symptom Scale SD= 0.78) [128]. Webb et al's (2007) who compared all three scales

concluded they were all reliable and valid patient reported questionnaires for assessing patient's perceived voice dysfunction.

1.2.5 Pharmacological Treatment options

Table 4 shows a number of medications that are discussed in the literature (Cohen and Misono., 2013, Chung., 2007, Morice et al., 2006, Belvisi and Geppetti., 2004) as potentially being effective for refractory chronic cough.

Table 4. Medications for Refractory Chronic Cough

Medication Group	Medications
Opiates	Codeine, Morphine, Diamorphine
Neuro-modulating agents	Baclofen, Gabapentin, Pregablin, Amitriptyline
Local Anaesthetics	Lignocaine
Non-narcotic Antitussive agents	Dextromethorphan, Menthol, ATP gated channel antagonist AF-219 (P2X3 receptor antagonist)

Although these medications are mentioned as potentially being effective for refractory chronic cough, the literature supporting the use of some of these recommended medications in adults with refractory chronic cough is sparse or none existent. Exploration

of the literature failed to identify any studies investigating the use of dextromethorphan or diamorphine with refractory chronic cough adults specifically. Menthol (Morice et al., 1994) and lignocaine (Choudry et al., 1990) have been investigated in healthy volunteers but again no studies were found looking at their effects for people with refractory chronic cough. Only one study was found that explored the effect of Pregablin, this study looked at the effect of Pregablin in 12 patients diagnosed with laryngeal sensitivity dysfunction with or without chronic cough as a chief complaint (Halum et al., 2009). Only 3 participants with chronic cough as a chief complaint were included in the study, two had chronic cough with throat discomfort and 7 had throat discomfort alone. Of those that completed treatment all reported improvements in chronic cough severity on a 0 to 5 rating scale post four weeks of Pregablin which was mostly initially started at 75mg twice a day raised to 150mg twice a day over four weeks (n=1 had to be increased to 150mg three times a day). Of the five participants whose chief complaint was chronic cough two withdrew from the study due to side effects only three completed the study. The side effects for those who withdrew were difficulty thinking and worsening of Charcot-Marie tooth disease leg pain. The other three although they did not withdraw all complained of sedation as a side effect. Limited conclusions can be made about the effect of Pregablin for refractory chronic cough due to the limited sample size.

More evidence was found for the effectiveness of morphine, amitriptyline, gabapentin, baclofen and ATP gated channel antagonist AF-219 (P2X3 receptor antagonist) medications for refractory chronic cough and this has been summarised in table 5.

Only one study has investigated slow release morphine sulfate (MST) for refractory chronic cough, Morice et al (2007b) found 5mg of MST BD for four weeks significantly improved QoL, with the mean improvement in LCQ greater than its MID (Raj et al., 2009) (Mean improvement 3.2, $p < 0.01$). MST also reduced self-reported daily cough counts ($p < 0.01$), but no significant differences in cough reflex sensitivity were found.

Two studies have investigated Amitriptyline for refractory chronic cough; Bastian et al's (2006) cohort study found 92% of their 12 participants reported a reduction in their cough symptoms within 10 days of taking 10mg Amitriptyline daily for 21 days. Jeyakumar et al's (2006) RCT found only 23% of their 13 participants who took Codeine/Guaifenesin for 10 days reported any improvement in their cough and showed any improvement in their QoL scores by Day 10. However in the Amitriptyline group 87% of the 15 participants reported a greater than or equal to a 50% improvement in their cough and 93% reported a greater than or equal to a 10 point decrease in their CQLQ, reflecting an improvement in their cough related QoL.

Two studies have investigated the use of Gabapentin for refractory chronic cough; Mintz and Lee (2006) found 5 of their 6 patient case studies reported significant improvements in their cough symptoms. However the use of Gabapentin in these case studies lacks standardisation as there was a large range in the dosages and duration of the medication used from 100mg BD to 800mg BD; and time period ranged from 3 months to 1 year duration. Ryan et al's (2012) RCT of Gabapentin was more standardised in the duration and dosage of Gabapentin and found significantly greater improvements in QoL (mean change 2.5, $p=0.004$) in the treatment group. This change in QoL was greater than the MID for LCQ (Raj et al., 2009). Ryan et al (2012) also found significant improvements in cough frequency ($p=0.028$) and cough severity ($p=0.029$) in the Gabapentin group compared to placebo.

Dicpinigaitis and Rauf (1998b) was the only study found that has investigated the use of oral Baclofen for refractory chronic cough. They found that for two female case studies following 14 days of oral Baclofen 10mg TDS the participants reported a decrease in their daily reported coughing bouts. Whilst taking placebo medication neither participant had a change in their cough reflex sensitivity however after 14 days of Baclofen participant 1 was able to tolerate 3 doubling dosages more of capsaicin before reaching C5 and

participant 2 was able to tolerate a further 5 doubling dosages of capsaicin before reaching C5.

The latest medication to be investigated for refractory chronic cough has been AF-219 (P2X3 receptor antagonist). When compared to placebo in a dose of 600mg BD over two weeks AF-219 (P2X3 receptor antagonist) was found to significantly reduce cough frequency (daytime and 24 hour), reduce day-time cough severity, urge to cough and improve QoL as measured by CQLQ. There was however, no difference in night time cough frequency (Jeyakumar et al., 2006).

Slow release morphine, amitriptyline, gabapentin and AF-219 (P2X3 receptor antagonist) have all shown beneficial results for refractory chronic cough. Codeine/Guaifenesin was found to be ineffective in the majority of the participants studied in Jeyakumar et al's (2006) study and no other studies investigating the effect of codeine in refractory chronic cough adults could be found.

The mechanism of action of these medications for refractory chronic cough is described by many of the authors of the above studies as poorly or not clearly understood and there is limited discussion of mechanism of action included in their papers (Dickinson et al., 2014, Morice et al., 2007b, Jeyakumar et al., 2006). Of the studies that do discuss mechanism of actions or hypothesised mechanisms of action. Ryan et al's (2012) Gabapentin study discusses that Gabapentin has been shown in chronic pain studies to affect the central calcium channels inhibiting the release of excitatory neurotransmitters such as substance P. However the mechanisms of action for refractory chronic cough are not discussed. Baclofen has been shown to have a centrally acting antitussive effect in guinea pigs and cats, though the mechanism by which this occurs needs further exploration (Bolser et al., 1994). AF-219 (P2X3 receptor antagonist) is thought to work by inhibiting the P2X3 receptors which are ATP-gated ion channels found on vagal afferent C fibres (Abdulqawi et al., 2014).

Despite the promising results found for slow release morphine, amitriptyline, gabapentin and P2X3, there are a number of limitations to the studies investigating these medications. The starting sample sizes for these studies are very small and compounded by attrition; the largest number of participants who completed their treatment trial within one intervention group was 26 in Ryan et al's (2012) study. All the other intervention groups in the other studies had fewer participants complete their treatment trials. There is also (in the context of medication trials) a surprising and disappointing absence of validated objective cough outcome measures in some of the studies. Bastian et al (2006) and Mintz and Lee (2006) used no validated objective outcome measures at all and relied on patient reported improvement in symptoms. The remainder of the studies did use a validated QoL measure; either CQLQ or LCQ. Only Morice et al (2007b) and Ryan et al (Ryan et al., 2012) objectively measured cough reflex sensitivity and only Abdulqawi et al (2014) and Ryan et al (2012) investigated cough frequency and severity objectively. Ryan et al (2012) did however; use their objective cough monitor, the LCM, for a non-validated duration, only recording participants for 1 hour. Lee et al (2012) had previously identified that only cough recordings as short as four hours via the LCM had an acceptable correlation with 24 hour recordings and therefore could be used with confidence.

Another issue related to the pharmacological management of refractory chronic cough are the side effects of medications. Side effects were found for all the medications discussed in table 5 apart from Amitriptyline and Baclofen for which no side effects were reported. Gabapentin and AF-219 (P2X3 receptor antagonist) had a significant number of side effects which were associated with attrition. For AF-219 (P2X3 receptor antagonist) all the participants suffered taste disturbances.

Table 5: Pharmacological treatment options for Refractory Chronic cough

Drug group	Drug Name	Trial methodology	Treatment efficacy	Drop outs and adverse/side effects
Opioids	Morphine Morice et al., 2007b	n= 27 (18 females, mean (SD) age 55(10.6) years) participants with refractory chronic cough. Double blind placebo-controlled crossover study. 4 weeks of slow release morphine sulfate (MST) 5mg twice daily or 4 weeks of matched placebo.	Significant improvement in LCQ at end of treatment in the MST group (Mean improvement 3.2, p<0.01). No significant difference in LCQ score at end of treatment for placebo. Significant difference between groups at end of treatment (p<0.02). Significant reduction in participant daily cough diary scores in MST group (3.4 (1.8), p<0.01). No significant change in placebo group. No significant change in cough reflex sensitivity in either group as measured by citric acid cough challenge testing.	No drop out due to adverse events. Most common side effects: constipation (affected 40% of study group), drowsiness (affected 25% of study group). Other side effect not listed in paper.
Neuro-modulating agents	Amitriptyline Bastian et al., 2006	n=12 (4 females, median (range) age 52 (20 to 75) years) participants with refractory chronic cough. Cohort uncontrolled study 21 days of amitriptyline 10mg OD 2 hours before bedtime.	11 participants self-reported reduction in their cough symptoms within 10 days of starting amitriptyline, median maximum improvement was 5 days (range 1 to 10 days). 4 participants reported 100% improvement	No drop outs or side effects reported.

	<p>Jeyakumar et al., 2006</p>	<p>n=28 (15 females, Amitriptyline group median age 54.6 years, Codeine/Guaifenesin 49.7 years) participants with idiopathic chronic cough</p> <p>Randomised controlled trial</p> <p>10 days of amitriptyline 10mg OD at bedtime or 10 days of 10 to 100 mg/5 mL, 10 mL Codeine/guaifenesin</p>	<p>10 of the 13 participants who took Codeine/Guaifenesin reported 0% improvement by Day 10, 2 reported 25% improvement and only 1 reported 50% improvement.</p> <p>4 of the 15 participants who took Amitriptyline reported 100% improvement, 7 reported 75% improvement, 2 reported 50% improvement, 1 reported 25% improvement and only 1 reported no improvement..</p> <p>10 of the Codeine/Guaifenesin participants reported no improvement in QOL as measured by the CQLQ by Day 10 however 14 of the Amitriptyline participants reported >10 point decrease in CQLQ by Day 10.</p> <p>Amitriptyline was found to be a significant predictor of greater than 50% improvement compared to Codeine/Guaifenesin (p=0.0007).</p>	<p>No drop outs or side effects reported.</p>
	<p>Gabapentin</p> <p>Ryan et al., 2012</p>	<p>n= 62 (40 females, Mean (SD) age 62.7(14) in placebo group, 60.9 (12.9) in Placebo group) participants with refractory chronic cough</p> <p>Randomised, double-blind, placebo-controlled trial</p> <p>Gabapentin gradually increased over 6 initial days to 1800mg dose which was maintained over 10 weeks then was withdrawn gradually over 6 days,</p>	<p>26 participants in the Gabapentin group and 25 participants in the placebo group completed the trial. The Gabapentin group had a significantly greater improvement in QoL (as measured by LCQ, Mean (95%CI) 1.80 (0.56 to 3.04) greater improvement in the Gabapentin group, p=0.004), cough frequency (as measured by LCM, -27.31 (-51.75 to -2.88) greater reduction in the gabapentin group, p=0.028) cough severity (as measured by VAS, -12.23 (-23.22 to -1.25) greater reduction in</p>	<p>There were 11 dropouts in total:</p> <ul style="list-style-type: none"> • 1 did not receive full dose of drug so was withdrawn. • 2 were lost to follow up. • 3 discontinued their intervention due to side effects of

		<p>or 12 weeks of placebo</p>	<p>the Gabapentin group, $p=0.029$) by end of treatment period.</p> <p>No significant difference between groups in cough reflex sensitivity at end of treatment trial ($p=0.72$), urge to cough score (measured during capsaicin cough challenge) ($p=0.30$).</p>	<p>intolerable fatigue, rash, gastroenteritis</p> <ul style="list-style-type: none"> • 1 withdrew as they were concerned with side effects • 1 withdrew as received treatment for comorbidity • 2 withdrew as no perceived efficacy • 1 withdrew to personal reasons <p>Side effects in the treatment group occurred in 10 participants and were:</p> <ul style="list-style-type: none"> • Blurred vision (n=1) • Disorientation, confusion (n=2) • Dizziness (n=3) • Dry/very dry mouth (n=2) • Fatigue (n=3) • Headache (n=1) • Memory Loss (n=1) • Nausea, stomach pain (n=4)
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	Mintz and Lee., 2006	<p>n=6 patients with idiopathic chronic cough.</p> <p>Clinical case studies</p> <p>Up to 1 year duration of Gabapentin 100mg BD increased until improvement or a daily dose of 1600mg is reached.</p>	<p>3 participants reported complete resolution of their cough (however 1 participant's cough only had 3 month resolution then had to double their Gabapentin dose), 1 participant reported their cough greatly decreased, 1 participant reported a decreased cough frequency and intensity and 1 participant reported cough was 10-15% better.</p>	<p>1 participant stopped after 3 weeks due to symptoms of fatigue but restarted Gabapentin and symptoms stopped.</p> <p>1 participant had transient drowsiness that resolved after 1 week.</p>
	<p>Baclofen</p> <p>Dicpinigaitis and Rauf., 1998b</p>	<p>n=2 (69 year old woman and 37 year old woman) patients with refractory chronic cough.</p> <p>Clinical case studies</p> <p>Double blind crossover design</p> <p>14 days 10mg TDS oral Baclofen or placebo, followed by 14 days 10mg TDS oral placebo or Baclofen.</p>	<p>Both participants reported a decrease in cough frequency, participant 1 reported a decrease in daily coughing bouts by 5 after receiving Baclofen compared to no reduction whilst on placebo. Participant 2 reported a decrease in 10 cough bouts a day after receiving Baclofen compared to an increase in daily cough bouts of 6 when on placebo.</p> <p>There was no change in cough reflex sensitivity as measured by C5 after receiving placebo for either participant. However after receiving Baclofen Participant 1 was able to tolerate 3 doubling doses more of capsaicin before reaching C5 and Participant 2 was able to tolerate 5 doubling doses of capsaicin before reaching C5.</p>	<p>None reported</p>

ATP gated channel antagonist	<p>AF-219 (P2X3 receptor antagonist)</p> <p>Abdulqawi et al., 2014</p>	<p>n=24 (18 females, Age Median(IQR) 54.5 (24-70) years old) refractory chronic cough participants</p> <p>Double-blind, placebo-controlled, two-period crossover study</p> <p>Two weeks of either AF-219 (P2X3 receptor antagonist) 600mg BD or placebo then a two week washout period followed by the alternative therapy.</p>	<p>AF-219 (P2X3 receptor antagonist) significantly reduced daytime cough frequency (as measured by VitaloJAK) compared to placebo at end of 2 weeks (Difference between group -75% (-88 to 50), ITT p=0.0003); 24 hour cough frequency (Difference between group -74% (-87 to -46) ITT p=0.001); day-time cough severity (as measured by VAS) (Mean difference between groups -25.6 (-41.5 to -9.6), ITT p=0.003); urge to cough (as measured by VAS) (Mean difference between groups -21.3 (-41.0 to -1.5), ITT p=0.035) and QoL (as measured by CQLQ) (Mean difference between groups -9.2 (-16.8 to -10.7), ITT p=0.0018).</p> <p>However there was no significant difference in night-time cough frequency (ITT p=0.057)</p>	<p>Six participants dropped out of the study due to side effects of AF-219 .</p> <p>Side effects experienced by participants taking AF-219:</p> <ul style="list-style-type: none"> • Dysgeusia (n=21) • Hypogeusia (n=13) • Nausea (n=9) • Oropharyngeal pain (n=5) • Headache (n=3) • Salivary hypersecretion (n=3) • Cough (n=3) • Anosmia (n=2) • Constipation (n=2) • GORD (n=2) • Glossodynia (n=2) • Depressed mood (n=2) • Blurred vision (n=2)
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1.2.6 Non-pharmacological Treatment options

Due to the limited effectiveness and side-effects of many of the antitussive medications (Chung., 2007) non-pharmacological interventions began to be investigated as an alternative treatment for people with refractory chronic cough. A number of terms have been used to describe these interventions usually associating the treatment with the professional group involved in delivery e.g. 'speech pathology management'(Vertigan et al., 2006, Ryan et al., 2010, Ryan et al., 2009), 'cough-suppression physiotherapy' (Patel et al., 2011) or identifying with the treatment intervention e.g. 'respiratory retraining'(Murry et al., 2010) and 'psychotherapy'(Blager et al., 1988). Non-pharmacological treatments for patients with refractory chronic cough have generally been delivered by respiratory physiotherapists or speech and language therapists linked to respiratory, Ear-Nose-Throat, voice and allergy services (Patel et al., 2011, Vertigan et al., 2006).

A detailed review of the treatment components and efficacy of non-pharmacological interventions is the focus of chapter 2.

CHAPTER 2

**SYSTEMATIC REVIEW NON-PHARMACOLOGICAL INTERVENTIONS FOR
REFRACTORY CHRONIC COUGH**

2. Systematic Review Non-Pharmacological Interventions for Refractory Chronic Cough

This chapter has been previously published by Springer in Lung Journal, titled 'Nonpharmacological Interventions for refractory chronic cough patients: systematic Review', Volume 192, 2014, pg 75-85, Chamberlain, S., Birring, S.S., Garrod, R, Copyright 13 Oct 2013 (Chamberlain et al., 2014a), with permission from Springer Science+Business Media. Number of figures and tables have been changed for this thesis but no changes to the content have been made.

2.1 Introduction

Chronic cough; defined as a cough present for greater than 8 weeks (Morice et al., 2006) is a common problem with an estimated prevalence of 12% (Ford et al., 2006). Chronic cough is known to cause significant physical and psycho-social morbidity with associated symptoms of vomiting, chest pain, voice changes, sleep deprivation, incontinence, embarrassment, interference with work, relationships and social activities (Brignall et al., 2008).

Most common diagnoses for chronic cough sufferers with a normal chest X-ray are: asthma, gastro-oesophageal reflux (GORD) and rhinitis (also known as upper airway cough syndrome)(Morice et al., 2006). In most, extensive medical management and investigations (Morice et al., 2006, Morice et al., 2004) are effective; however chronic cough can persist in up to 10-42% of cases (Haque et al., 2005, Morice, 2002, Vertigan et al., 2006, Vertigan et al., 2007b). There is significant variation in terminology used to define chronic cough for which there are negative investigations or failed treatments for its main causes. The various terms used include refractory chronic cough (Patel et al., 2011),

idiopathic chronic cough (Morice et al., 2006), cough hypersensitivity (Birring, 2011), psychogenic cough (Vertigan et al., 2007a) and habit cough (Vertigan et al., 2007a, Blager et al., 1988). For this review, we use the term refractory chronic cough, which indicates cough that is persistent for more than 8 weeks, of no known cause, and resistant to medical treatment for the main causes of cough (Morice et al., 2006, Morice et al., 2004).

Refractory chronic cough is more prevalent in females than males, with onset around middle-age (Haque et al., 2005, Birring, 2011). The pathophysiology of cough in this group of patients is unclear; however, changes to both the peripheral and central mechanisms of cough are thought to be contributing factors. People with refractory chronic cough have been shown to have increased cough reflex sensitivity to tussive agents (Prudon et al., 2005, Johansson et al., 2009). In a recent *Lancet* article (Chung et al., 2013) authors hypothesised that changes in afferent neurons' sensitisation could induce spontaneous primary afferent firing (absent of the initial stimuli). Refractory chronic cough shares similarities to other hypersensitivity syndromes such as chronic pain, and central mechanisms are thought to be involved since refractory chronic cough patients have abnormal laryngeal sensations, increased sensation to nontussive stimulus, and a heightened response to tussive stimulus (Vertigan and Gibson, 2011). Similar to the pathophysiology of pain, it has been hypothesised that convergence of central inputs from oesophageal, airway nociceptors, and/or airway afferent nerves could lead to central sensitisation of the cough reflex (Chung et al., 2013). An association between organ-specific autoimmune disease and refractory chronic cough has been identified (Birring et al., 2004a), and there has been a significant increase in people with bronchoalveolar lymphocytosis compared to those with cough and a known pathological cause (Birring et al., 2003a).

Treatments for patients with refractory chronic cough have focused mainly on pharmacological antitussive medications; however, these appear to have limited

effectiveness and side-effects such as sedation have been reported (Chung, 2007). Fortunately, there is now emerging evidence of the benefits of alternative nonpharmacological interventions for people with refractory chronic cough. Depending on the professional group delivering the care, these interventions have been named “speech pathology management” (Vertigan et al., 2006, Ryan et al., 2010, Ryan et al., 2009), “cough-suppression physiotherapy” (Patel et al., 2011), or, after the interventions used, “respiratory retraining” (Murry et al., 2010) and “psychotherapy” (Blager et al., 1988). Most recent studies have included a combination of treatments comprising four key components: education, cough suppression techniques (including breathing exercises), vocal hygiene and hydration and psycho-educational counselling (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009). Older studies (Riegel et al., 1995, Blager et al., 1988) have included some of these treatment techniques or completely different interventions such as biofeedback therapy (Riegel et al., 1995). However, the aims of these treatments have been similar: to reduce laryngeal, neck, and shoulder muscle tension, and reduce laryngeal hypersensitivity and stimulation and cough reflex hypersensitivity.

Up to 40% of people with refractory chronic cough suffer significant voice problems (Vertigan et al., 2007d), and around 56% also have paradoxical vocal fold movement (PVFM), i.e., the adduction of the vocal folds during inspiration and sometimes expiration (Ryan et al., 2009). In these patients the effect of treatment on voice as well as cough has been explored. However, consideration of the literature evaluating the effects of nonpharmacological interventions on voice is outside the scope of this review.

The aim of this review was to critically consider the literature on the effectiveness of nonpharmacological interventions for people with refractory chronic cough using the PRISMA statement (Moher et al., 2009) and the Cochrane handbook for systematic reviews (Higgins and Green, 2011).

2.2 Methods

Search Process

The study population included adults (≥ 18 years old) with refractory chronic cough who either had negative investigations or failed medical management. Intervention was any nonpharmacological treatment or intervention. Neither the frequency nor the duration of the treatments was defined a priori and neither were follow-up times or comparison groups defined. This was done in order to avoid exclusion of too many studies in this new treatment area. Outcomes searched were any subjective or objective measure of cough severity, frequency, sensitivity and cough-related quality of life. We did not define parameters of reliability or sensitivity for outcomes used so as to again not exclude studies in this new treatment area.

Comprehensive searches were conducted using the following electronic databases: EMBASE (1980 to present), AMED (Allied and Complimentary Medicine 1985 to present), Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature 1981 to present) and PsycINFO (1806 to 2012). Bibliographies of all studies and systematic reviews were searched by hand. Figure 1 shows the search strategy used.

Figure 1: Search strategy for systematic review

1= 'chronic cough'
2= 'refractory cough'
3= 'idiopathic cough'
4= 'cough hypersensitivity'
5= 'psychogenic cough'
6= 'habit cough'
7= 1 or 2 or 3 or 4 or 5 or 6
8= 'physiother*'
9= 'speech*'
10= 'behavio*'
11= 'cognitive*'
12= 'psycho'
13= 8 or 9 or 10 or 11 or 12
14= 'cough frequency'
15= 'cough severity'
16= 'cough intensity'
17= 'quality of life'
18= 14 or 15 or 16 or 17
19= 7 and 13 and 18

Eligibility Criteria, Identification and Selection of Studies

Full-text, English language, prospective and retrospective observational studies, experimental studies, and randomised control trials that investigated the effects of nonpharmacological interventions/treatments for chronic cough were included. One reviewer identified and reviewed all titles and abstracts and then the full text of each article.

Exclusion criteria were studies with participants ≤ 18 years old, studies that did not include cough-specific outcome measures, and studies where sample size was ≤ 5 participants.

Critical Appraisal and Summary of Measures

Critical appraisal was carried out by one reviewer using the SIGN appraisal tools (SIGN, 2011) and Cochrane handbook for systematic reviews (Higgins and Green, 2011). Studies were classified using the SIGN (2011) and NICE (2009) study algorithms. Results were collated into a summary using the SIGN evidence tables (SIGN, 2011).

2.3 Data Analysis

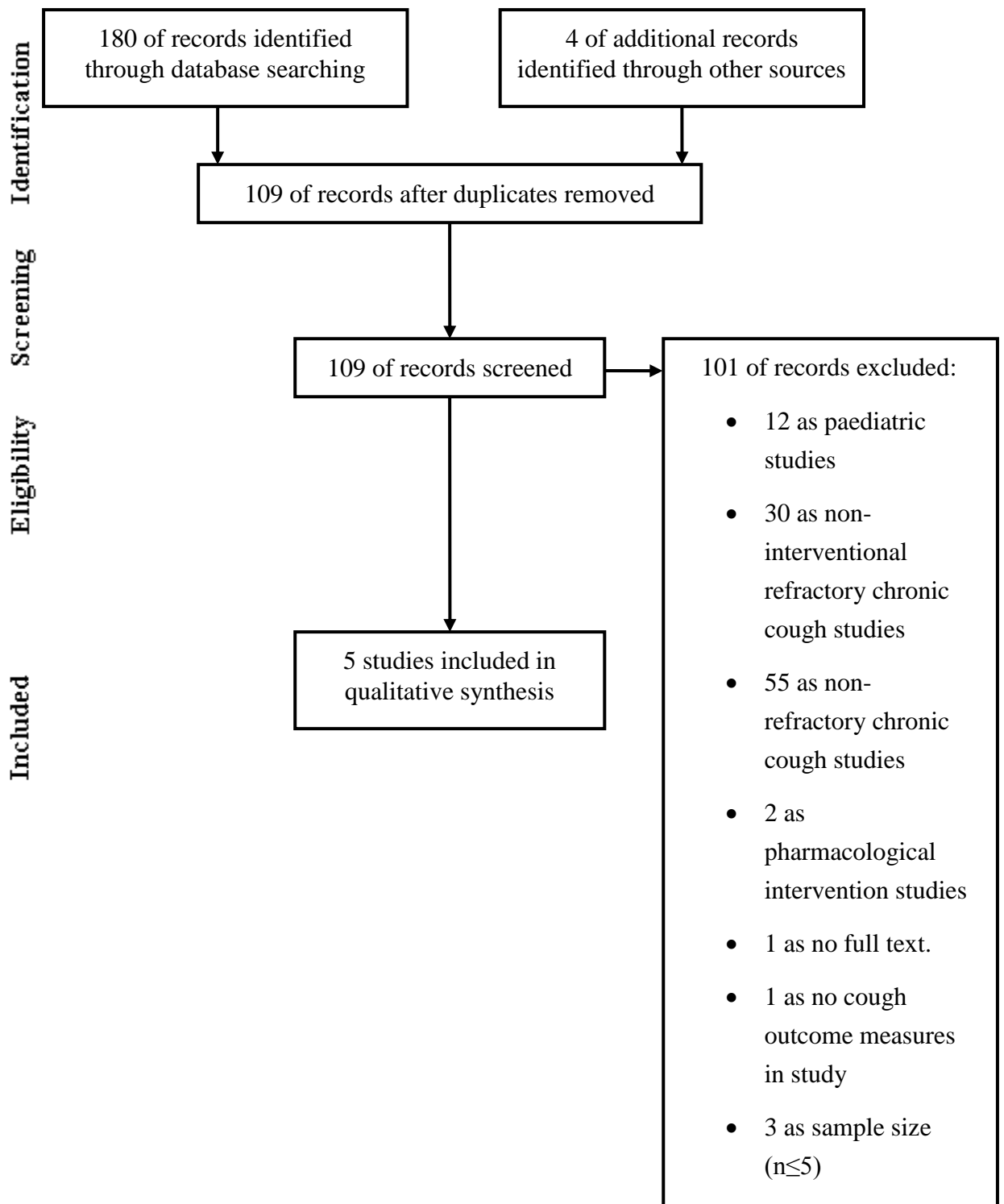
Analysis was carried out by one reviewer. A meta-analysis was not performed because of heterogeneity of study populations, treatment interventions, and outcome measures used in the studies included.

2.4 Results

Study Selection

In total 184 studies were retrieved: 75 were excluded after duplications were removed and 104 were excluded after abstracts were screened (Figure 2). The remaining 5 articles are included in this review.

Figure 2: PRISMA flow diagram of studies screened for systematic review



Study Characteristics of Included Studies

A summary of the studies' characteristics is provided in table 6. The five trials included were conducted in three different countries (Australia, USA and UK) by three different research groups. All of the studies were published in the last 7 years. Only one study was a randomised control trial (Vertigan et al., 2006), three studies were noncomparative prospective studies, and the study by Murry et al (2010) was a noncomparative retrospective study.

Table 6: Evidence table for non-pharmacological interventions for adult refractory chronic

Citation	Study Type	Number of Patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Treatment outcome	Source of funding
Vertigan et al 2006	RCT	n=97, but 10 dropped out (4 in Rx group, 6 in control). Patients studied n=87 (n=43 in Rx arm, 44 in control arm)	<p>Adult refractory chronic cough sufferers (mean(SD) age = 59.4 (13.6), range = 23-84); 64 female, 23 male.</p> <p>No details on participants' cough duration apart from > 2months duration.</p> <p>All had treatment for asthma, post-nasal drip, GORD and had been withdrawn from ACE inhibitors. Participants were excluded if had URTI, untreated allergy, respiratory disease, neurological voice disorders. Two smokers included</p>	<p>Speech pathology evaluation and intervention for chronic cough (SPEICH-C) Consisting of:</p> <ul style="list-style-type: none"> *Education *Strategies to reduce cough *Psycho-educational Counselling *Vocal hygiene education <p>Four 30-min sessions over a 2 month period</p>	<p>Placebo Intervention consisting of healthy lifestyle advice sessions covering:</p> <ul style="list-style-type: none"> *Relaxation *Stress Management *Exercise *Diet <p>Four 30-min sessions over a 2 month period</p>	No follow up post treatment	<p>Patient rated subjective symptom severity and frequency scores on a 5-point Likert scale, 23 in total covering cough, respiratory, voice, and upper airway symptoms. Limitations on daily activities were also rated. Treating clinician also rated patients post treatment as having a successful, partially successful or unsuccessful outcome.</p>	<p>Significant improvement in cough scores for Rx group (95% CI 3-4.9, p<0.001) and placebo groups (95% CI 0.3-2.2, p<0.001).</p> <p>However, improvement was significantly greater in Rx group (95% CI 1.3-4.0, p<0.001)</p> <p>Significant improvements in total symptom score (95% CI 9.0-16.1, p<0.001) and limitation to daily activities (95% CI 0.4-1.0, p<0.001) in treatment group only.</p> <p>88% reported having a successful outcome in the treatment group compared to only 14% in the control treatment.</p>	Grant from Jennifer Thomas through the Hunter Medical Research Institute.

Ryan et al 2009	NCS	n=24 but only 14 had speech pathology treatment (2males, 12females). Four others dropped out of speech pathology treatment	Adult Refractory chronic cough sufferers, non- or ex-smokers with no cardiac or respiratory disease. As part of the study, all had treatment trials for asthma, GORD, rhinosinusitis and sleep apnoea. Then the participants with PVFM and cough had speech pathology management. Median (IQR) age = 56 (40) years old, range 22-78. Cough duration median (IQR) = 18 (48) months	4 weekly sessions of speech pathology management as per Vertigan et al 2006 treatment regime.	No Comparison	Post treatment Ax 8 weeks after speech pathology treatment.	Cough-related quality of life: leicester cough questionnaire (LCQ) at baseline and at follow-up. Generic quality of life measure: SF-36 at baseline and at follow-up. Cough reflex sensitivity: capsaicin cough challenge performed at baseline	Cough-related quality of life significantly improved (LCQ p=0.001) post treatment. Cough reflex sensitivity significantly improvement (C5 p=0.008) post treatment. No information given in article regarding SF-36 scores or changes.	PHD scholarship
Murry et al 2010	NCS	n=16 (no gender details given, age range 29-69)	Adult chronic cough sufferers, who were on twice daily PPI therapy for at least 3 months, had no active sinonasal disease, laryngeal surgery, or documented pulmonary disease.	2-13 sessions of respiratory retraining exercises over a 4-23 week period	No Comparison	Final Ax 3 months after initial visit	Subjective patient report of cough as a problem Question 7 of Reflux Symptom Index (RSI) ("troublesome or annoying	Post Rx only 1 of the 16 participants reported cough as still a problem (p≤0.01). Only 12 of the 16 patients repeated the RSI at end of treatment.	No funding

			Cough duration mean (SD) = 8.4 (5.3) months				cough")	For those who completed it the mean difference was 3.76 (p=0.05).	
Ryan et al 2010	NCS	n=17 (8 male, 9 female). Mean (IQR) age = 61 (20), range = 34-83 Cough duration median (IQR) = 60 (147) months	Refractory chronic cough sufferers (>18years old), all non-smokers.	Up to four 30-min sessions of speech pathology management (same as Vertigan et al 2006) n=1 had 1 session n=3 had 2 sessions n=4 had 3 sessions n=9 had 4 sessions Baseline assessments and four Rx sessions were carried out over 11-15 week period.	No Comparison	Final Ax 2-3 weeks after final treatment session	Cough frequency: ~1 hour Leicester Cough monitor performed at each session and at follow up Cough reflex sensitivity: Capsaicin cough challenge performed at each session and follow up. Cough-related quality of life: LCQ at baseline and follow up.	Significant decrease in cough frequency post treatment (p=0.009). Significance of difference was reached only after treatment session 3 and continued to decrease at treatment session 4 and post-treatment session. Cough reflex sensitivity significantly decreased post treatment (mean ± SD log C5, 1.65 ± 0.88, p<0.0001). Cough reflex sensitivity significantly reduced after each session. Cough threshold and urge to cough also significantly improved post treatment (p=0.001; p=0.01 respectively).	PhD scholarship

								Significant improvement in cough-related quality of life (p=0.002) post treatment.	
Patel et al 2011	NCS	n=23 (13 females, 10 males)	Adult refractory or idiopathic chronic cough sufferers. Nonsmokers at the time of the study, normal chest x-ray and spirometry. Age mean(SD) = 60 (2) years. Cough duration mean (SD) = 42 (10) months.	Up to 3 sessions of cough suppression physiotherapy: Session 1 – education and lifestyle advice; cough control techniques, breathing pattern retraining and vocal hydration. Session 2 – review compliance, holistic advice and reinforcement	No Comparison	Final Ax 2 months after end of treatment.	Cough-related quality of life: LCQ measured at baseline and 2-month follow up. Cough frequency was measured with a 7-point Likert scale.	Cough-related quality of life significantly improved (mean difference 2.7, 95% CI of difference -4.1, -1.3; p<0.001). In all three domains of the LCQ, physical (p=0.001), psychological (p<0.001) and social (p<0.04). Reported cough frequency significantly reduced (mean difference 1.1; 95% CI of difference 0.5-1.8; p=0.002).	No funding

NCS noncomparative study, RCT randomised control trial, ENT ear, nose and throat, PVFM paradoxical vocal fold movement, GORD gastro-oesophageal reflux, Ax assessment, Rx treatment, URTI upper respiratory tract infection

Risk of bias of included studies

The study by Vertigan et al (2006) had the lowest perceived risk of bias as it was the only randomised control trial.

Allocation

Only the Vertigan et al (2006), randomised controlled trial gave full details on the participants who were referred for the study and details on those who were excluded. The randomisation was computer-generated; treating clinicians were not involved in randomisation to reduce possible selection bias.

Blinding

Double-blinding in these types of therapy intervention studies is very difficult because the therapists are involved in the delivery of treatments. Only two of the included studies (Patel et al., 2011, Ryan et al., 2010) clearly mentioned blinding of the administered questionnaires; however, blinding of the other objective measures used in Ryan et al (2010) is unknown. All other studies lacked detail regarding blinding of the therapists providing treatment (Vertigan et al., 2006, Ryan et al., 2009, Murry et al., 2010). In Murry et al (2010), PVFM was verified by two independent raters before and after treatment, but no details were provided concerning verification of the Reflux Symptom Index (RSI) score used to assess cough severity. The Vertigan et al (2006) study was a single-blinded randomised control trial and the only study that kept treatment allocation from the participants until the end of the study. Whether treating therapists were involved with both the intervention group and the control group is not reported. Since clinician judgement regarding improvement was one of the outcome measures used in the study, there may be potential risk of bias. Furthermore, there is no indication of whether the results of patient rating scales were blinded from the treating therapists; performance bias risk is thus difficult to determine.

Incomplete outcome data

In general, all intended outcome measures and details on any drop outs were reported in the prospective studies (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010).

However Ryan et al (2009) despite describing SF-36 in the methodology, provided no results for this outcome.

Selective Reporting

The intended outcome measures were reported in all of the studies.

Other Biases

In three of the five studies (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2009), the treatment interventions were provided in a standardised manner with respect to duration and frequency. However, in Ryan (2010), the number and frequency of sessions varied, making it difficult to compare results.

Study Population

There was significant heterogeneity in the populations studied with respect to age and cough duration. Across most of the studies, mean and median ages were quite similar, ranging from 56 (Ryan et al., 2009) to 61 years old (Ryan et al., 2010). However, a large variation in the age range across the studies was evident (Table 6).

Participants also varied with respect to the duration of their cough, with median cough duration ranging from 18 (IQR 48) months (Ryan et al., 2009) to 60 (IQR 147) months (Ryan et al., 2010). Participants in Vertigan et al (2006) all had cough duration > 2 months.

The studies also varied with respect to inclusion or exclusion of smokers. Patel et al (2011) excluded smokers and ex-smokers, whilst Ryan (2009) included ex-smokers with

less than 10 pack years. Vertigan et al (2006) included two current smokers. Only Ryan et al (2009) provided objective evidence of smoking cessation.

Medical management, including the investigation and treatment regimens trialled before investigating nonpharmacological interventions, also varied across the studies. However, all studies completed investigations for and/or tried medications for asthma, GORD, and rhinitis before starting nonpharmacological interventions. Ryan et al (2009) investigated the presence of PVFM in their participants and investigated only the efficacy of speech pathology management for refractory chronic cough in participants with PVFM.

The dominance of females across four studies was very similar; Murry et al (2010) failed to report gender data.

Intervention

A summary of the interventions used in the different studies is provided in table 7.

Although there were differences among the studies, in general a composite approach was used and consisted of education on cough and/or identification of cough triggers and instruction in cough suppression techniques, breathing exercises, and sometimes vocal hygiene and hydration techniques; interventions also included some form of counselling (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009). The terminology of the breathing exercises varied among the studies, but breathing control/diaphragmatic breathing and relaxed breathing control techniques have all been described as aiming to relax the throat, neck, and shoulder muscles whilst increasing abdominal excursion and reducing upper chest movement (Mathers-Schmidt, 2001, Bruton et al., 2011). Pursed lip breathing has been described as a technique intended to help interrupt coughing (Blager et al., 1988) and reduce some of the adductor activity of the vocal folds during expiration in patients with PVFM (Mathers-Schmidt, 2001).

Treatments in the studies generally ranged from two to four sessions of speech pathology/physiotherapy for cough suppression, and the frequency of the sessions varied

from weekly (Ryan et al., 2009) to completed over 2 months (Vertigan et al., 2006), or within 11 to 16 weeks (Ryan et al., 2010). The Murry et al (2010) study was the only one to investigate breathing exercises as a sole intervention rather than a composite package of care.

Table 7: Different Interventions included in studies investigating non-pharmacological interventions in refractory chronic cough

Interventions		Vertigan et al 2006	Ryan et al 2009	Murray et al 2010	Ryan et al 2010	Patel et al 2011
Education on chronic cough		√	√		√	√
Education on identifying cough triggers		√	√		√	√
Cough suppression techniques		√	√		√	√
Breathing exercises	Pursed Lip breathing	√	√	√	√	√
	Relaxed Throat Breathing	√	√	√	√	√
	Breathing control /diaphragmatic breathing					√
Vocal hygiene and hydration strategies		√	√		√	√
Counselling		√	√		√	√
Throat massage						√

Effects of Interventions

Effectiveness of Nonpharmacological Treatments on Cough Frequency

All three of the studies (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010) that investigated cough frequency reported a decrease in frequency following intervention. Only one study (Ryan et al., 2010) used a validated objective outcome measure; the others used subjective rating scores (Vertigan et al., 2006, Patel et al., 2011). Patel et al (2011) reported a significant reduction in cough frequency, with a mean reduction of 1.1 [CI 0.5-1.8] points on a 7-point Likert scale ($p=0.002$). Ryan et al (2010) used the Leicester Cough Monitor (Matos et al., 2007, Birring et al., 2008) to assess cough frequency and found a significant reduction post treatment ($p=0.009$). However, in the Ryan et al study they used the cough monitor for only 1h despite validation data advising 4- and 24-h use (Lee et al., 2012). Participants were not exposed to their usual cough triggers as they wore only the device during their study visit and a cough provocation test was performed during this hour. Therefore interpretation of these findings as a measure of participants' cough frequency is difficult.

Although cough frequency was recorded in Vertigan et al (2006), individual scores for cough frequency were not reported. Instead, a composite score for cough, derived from scores of cough severity, frequency, throat clearing and nocturnal cough score, was given.

Effectiveness of Nonpharmacological Treatments on Cough Severity

Of the two studies that investigated the effect of non-pharmacological interventions on cough severity (Vertigan et al., 2006, Murry et al., 2010), both reported improvements. These studies varied the outcomes they used to measure cough severity. Murry et al (2010) used question seven of the RSI ("troublesome or annoying cough") as an outcome

of cough severity and found a mean difference in 3.76 points post intervention ($p=0.05$). As mentioned above, Vertigan et al (2006) used a composite score to measure the change in cough symptoms and found a significant improvement in the intervention group (95% CI 3 to 4.9, $p<0.001$) compared with the placebo group (95% CI 1.3 to 4, $p<0.001$). In Murray et al (2010) despite showing statistical improvement in question 7 of the RSI, no significant improvement was found for the overall score and no details on the baseline scores were given, making it difficult to characterise the participants with respect to severity. An 80% improvement, as rated by clinicians, was reported in Vertigan et al (2006) however, these results need to be reviewed with caution due to the potentially high risk of bias of clinician ratings.

Effectiveness of non-pharmacological treatments on cough related quality of life

Four of the included studies (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009) investigated the effect of nonpharmacological interventions on quality of life; all four found there to be beneficial results. Patel et al (2011) and Ryan et al (2010, and Ryan et al (2009) used the Leicester cough questionnaire (LCQ), a validated and reliable cough-related quality-of-life outcome measure (Birring et al., 2003c). All three studies found there to be improvements in the LCQ score greater than the minimal importance difference, which has been reported as 1.3 (Raj et al., 2009). In two studies, the median difference in LCQ was 5.7 ($p=0.001$) (Ryan et al., 2009) and 3.4 ($p=0.002$) (Ryan et al., 2010) and in Patel et al (2011), the mean difference 2.7 (95% CI -4.1 to -1.3). Patel et al (2011) was the only study to report individual domain results and found improvements in all: physical ($p=0.001$), psychological ($p<0.001$), and social domains ($p<0.04$). Vertigan et al (2006) found significant improvements in limitation to daily activities (95% CI 0.4-1, $p<0.001$).

Effectiveness of Non-pharmacological Treatments on Cough Sensitivity

Only Ryan et al (2010) and Ryan et al (2009) explored the effect of nonpharmacological interventions on cough reflex sensitivity, and significant improvements were found in both studies as assessed by capsaicin cough challenge C5 ($p=0.008$) (Ryan et al., 2009) and C5 ($p<0.0001$) (Ryan et al., 2010). Ryan et al (2010) also found cough threshold and urge to cough significantly improved ($p=0.001$ and $p=0.01$ respectively).

2.5 Discussion

This review aimed to assess the effect of nonpharmacological interventions for adults with refractory chronic cough. Results from five studies with 157 active participants were reviewed. Overall, the nonpharmacological interventions investigated yielded improvements in cough frequency (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009), severity (Vertigan et al., 2006, Murry et al., 2010), cough reflex sensitivity (Ryan et al., 2010, Ryan et al., 2009), and quality of life (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009). Vertigan et al (2006) was the only comparative study and found significant improvements in cough symptom scores in the interventional group compared to the control group in which healthy lifestyle advice and education were used.

Improvements in assessing cough need to be made in future studies because of the lack of valid and reliable outcome measures used in the studies reviewed. Only for cough reflex sensitivity and cough-related quality of life, were valid and reliable outcome measures used. Further studies are required to assess these different components of

cough as, for example, only two of the five studies evaluated cough reflex sensitivity (27 participants) (Ryan et al., 2010, Ryan et al., 2009).

The interventions tested in these studies differed in the components included, and the descriptions of techniques were often profession-specific. Generally, the interventions “package” included education, cough suppression techniques, breathing exercises, vocal hygiene and hydration, and counselling, which for the majority of participants was over two to four sessions. This package of treatment significantly reduced cough reflex sensitivity (Ryan et al., 2010, Ryan et al., 2009) and improved cough-related quality of life by a median/mean difference of 2.7-5.7 (Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009) points on the LCQ; which is greater than the minimal important difference score of 1.3 (Raj et al., 2009). The effects of intervention on cough frequency were less consistent across the studies. Patel et al (2011) found a mean decrease of 1.1 points on a 7-point Likert scale for cough frequency; however, the clinical significance of this change is unknown and the study was uncontrolled. Ryan et al (2010) explored cough frequency using a valid objective measure, the Leicester cough monitor; however, this was not used in accordance with developers’ recommendations. Vertigan et al (2006) reported a significant improvement in cough symptom scores compared to healthy lifestyle advice alone.

Murry et al [20] was the only study to investigate one aspect of the other studies’ package of care: respiratory retraining exercises. However, conclusions on the effectiveness of respiratory retraining exercises for chronic cough could not be made from that study because of the small sample size (n=16), the lack of standardisation of intervention duration (2-13 sessions over 4 to 23 weeks) and the lack of valid and objective outcome measures used.

Many of the limitations of the studies were due to risk of bias. Only one randomised control trial was included in this review and therefore risk of selection and allocation bias

was high for many of the studies. Blinding was also a limitation as intervention is delivered by a therapist so it was difficult to double-blind the studies. Only two studies mentioned that the therapists were blinded from the outcome measures (Patel et al., 2011, Ryan et al., 2010).

Compliance is an interesting limitation of nonpharmacological interventions which was raised in Ryan et al (2010) study. Based on a clinician's opinion, they reported only 53% of their participants were adherent to treatment. As these interventions rely on the participants to practice these treatments over a long period of time, compliance is an important issue for nonpharmacological interventions that may be difficult to measure.

Potential Biases in review process

This review included only studies that looked at the effect of nonpharmacological interventions on cough-related outcome measures. There are other studies that have explored the effect of these interventions on voice but they were not included. Also, for this review only English Language studies were included. The authors of the studies were not contacted to provide further details on the studies; this potentially affected the judgements made regarding risk of bias and study methodology.

2.6 Conclusion

Implications for practice

A package of treatment over three to four sessions and consisting of education on chronic cough; identifying cough triggers; cough suppression techniques; breathing exercises aimed to increase abdominal excursion, relax neck, throat and shoulders and decrease

laryngeal muscular tone; and vocal hygiene and hydration advice, appears to improve cough-related quality of life and decrease cough reflex sensitivity. Further research using valid and reliable outcome measures is needed to more comprehensively establish the treatments' effects on cough frequency and severity. There is currently limited data that compares different components of this package of care to establish the most effective components or the most effective treatment duration or frequency. Ryan et al (2010) commented that in a pilot study they compared supportive counselling to isolated cough suppression therapy and found no change in cough reflex sensitivity after 1 h of intervention. However, more in-depth studies comparing different aspects of nonpharmacological interventions and treatment durations and frequency are needed in order to deliver the most effective care.

Implications for Research

This review points out that more randomised control trials evaluating the effects of nonpharmacological interventions on cough frequency, sensitivity and severity are required. Studies should be rigorously designed with particular attention to blinding of assessors, use of valid and reliable objective outcome measures, and sample sizes that are adequately powered. Standardisation of the use of terms that describe techniques that are multidisciplinary would reduce current confusion in the literature. Studies exploring the optimum treatment frequency, duration and individual components are needed. Future studies should provide comprehensive patient characteristics to determine if different treatment options are required in differing populations, e.g., duration and severity of cough may influence outcomes. Comparisons of nonpharmacological interventions with antitussive medications with cost effectiveness analysis would also help establish this treatment as a mainstream treatment option.

2.7 Summary

Chapters 1 and 2 have identified the need to explore the impact of chronic cough in the wider community; that is to say those individuals with chronic cough, who have not presented to primary or secondary care. There is also a need to explore the impact of chronic cough across countries rather than investigating the impact within a single country and to seek the patient experience or perspective on the management and treatment received for their chronic cough. This is a key perspective that is conspicuously absent from existing research.

Chapters 1 and 2 also identified the current lack of treatment options for refractory chronic cough patients. Current pharmacological treatment options have shown some promising results but are often associated with side effects which are not tolerated by all patients. Emerging non-pharmacological interventions have also shown evidence of potential. It is however noted that studies that have explored the effectiveness of this group of interventions have mostly been limited in sample size, have been cohort studies and used outcome measures of variable rigour. Only one RCT has been conducted in this area which did not include use of validated objective outcome measures. Therefore there is an opportunity to undertake a robust study of the effects of non-pharmacological interventions in a RCT that is adequately powered with the inclusion of validated objective outcome measures.

2.8 Aims of the Study

The main research questions identified from Chapters 1 and 2 were:

1. What is the impact of chronic cough in the wider community across Europe?
2. What are chronic cough sufferer's opinions on the management and treatment they may have received for their cough and what are their perspectives of current treatment options?
3. What is the efficacy of a combined Physiotherapy, Speech and Language Therapy non-pharmacological intervention for refractory chronic cough compared to placebo/ control for cough related QoL, cough reflex sensitivity, cough frequency, cough severity, patients' perceived voice dysfunction, anxiety and depression?

Therefore two aims were identified namely:

1. To explore the impact of chronic cough across Europe as well as explore the opinions of people with chronic cough regarding any management and treatment they may have received for their cough.
2. To evaluate the effectiveness of a combined Physiotherapy, Speech and Language Therapy intervention (PSALTI) for refractory chronic cough compared to control for cough related QoL, cough reflex sensitivity, cough frequency, cough severity, patients' perceived voice dysfunction, anxiety and depression.

CHAPTER 3 METHODOLOGY

3. Methodology

3.1 Overview

The two aims of this thesis were addressed via different methodological approaches in two different studies. This chapter will explore the rationale for the studies' methodological choices. The detailed and specific methodologies related to each of the studies undertaken as part of this thesis will be explored in chapters 4 and 5.

The aim of exploring the impact of chronic cough across Europe as well gaining the opinions of people with chronic cough regarding any management and treatment they may have received for their cough was investigated via a European survey of chronic cough sufferers.

The aim of evaluating the effectiveness of a combined Physiotherapy, Speech and Language Therapy intervention (PSALTI) for refractory chronic cough on cough related QoL, cough reflex sensitivity, cough frequency, cough severity, patients' perceived voice dysfunction, anxiety and depression was investigated via a multi-centred randomised controlled trial (RCT).

3.2 European Chronic Cough Survey

Discussions between the members of the ERS Chronic Cough Taskforce and the ELF identified that there was a need to explore the impact of chronic cough across Europe and to gather the opinions' of people with chronic cough regarding any management and treatment they may have received for their cough. It was decided that the most feasible method for data collection for this study was a survey, as per previous studies that have explored prevalence and the impact of chronic cough discussed in chapter 1. Alternative

models for this research such as multiple interviews were not feasible due to the scale of the study as well as staffing and resource limitations.

Although surveys have been identified as an appropriate approach when gathering information from a large population, Groves (1989) identified four different types of error that survey based research can be at risk of:

- Coverage error - the survey may not reach or capture the sections of the target population;
- Nonresponse error - the survey may not collect sufficient data on the population being investigated;
- Sampling error - the survey selected population may not be a true reflection of the entire population under investigation;
- Measurement error - inaccuracies in responses received from the survey due to inability of the respondents to answer the given questions. This may be due to wording of the survey and/ or inappropriate selection of the mode of data collection.

To help to reduce these errors Check and Schutt (2012) advise careful consideration regarding sampling framework, measurement and questionnaire design including the wording and layout of the survey.

These considerations were thought through during the development of the European chronic cough survey in this thesis. Initially during the survey design previous reviews of chronic cough quality of life literature and published surveys of chronic cough were reviewed so questions included in the new survey built upon the existing literature. This approach is also hoped to avoid crucial questions from being omitted and ensure the relevance of questions included (Check and Schutt., 2012). The survey was designed to include both closed and open questions as both quantitative and qualitative data was intended to be gathered from the survey. Original questions chosen for inclusion in the

survey were discussed within the ERS Chronic Cough taskforce (which included 15 respiratory physicians from nine countries), a multidisciplinary team (respiratory physician and physiotherapists at King's College Hospital) and the ELF. This expert involvement in the question development was undertaken to minimise the measurement error of the survey, members reviewing the survey were asked to check that the proposed questions were not biased in their wording and avoided confusing phrasing which are identified as common errors in surveys by Check and Shutt (2012). The relevance of the questions and omission of questions was also considered during the expert involvement.

Check and Shutt (2012) state that once questions to be included in surveys are identified and have been refined via review and pretesting, it is important to then group the questions into clear categories that will make sense to the potential respondents. For the European chronic cough survey the final survey questions were grouped into 5 broad categories: "About your cough," "How are you affected by your cough?" "Diagnosis of your cough," "Treatment of your cough" and "Support for patients with cough".

There are a number of different strategies to conduct research via a survey including mailed surveys, group-administered surveys, telephone surveys, internet surveys or mixed model surveys (Check and Schutt, 2012). The approach chosen for the European chronic cough survey was an internet based survey. This was chosen as it was an easy method of making the survey available across Europe and additionally enabled responses to be collected from people with chronic cough who may not have sought medical help for their chronic cough symptoms; thus increasing our chance of gathering responses from people with chronic cough within the wider community. Check and Shutt (2012) identify the increasing popularity of internet based surveys as they are easy and cheap to administer, enable data to be analysed quickly and minimise data entry errors as data can be recorded directly into researchers' databases. There are however limitations to their use as they require responders to be computer literate and to have access to a computer

device and the internet. Not all households have this access and those without tend to be from lower socioeconomic backgrounds.

As the survey was intended for a pan European population it was translated into a number of languages to optimise response rates. This translation was undertaken using forward-back translation methodology by native speakers and the back translated surveys were checked by the principal investigator. This methodology of translation has been used in numerous studies to translate questionnaires (Huisman et al., 2007, Han et al., 2014, Felisbino et al., 2014) and with the resource base available for the European cough survey it was the best methodology available to the research team. There are other more in depth translation methodologies e.g. having two separate translators translate the survey which is then reviewed by independent translators, discussed at a team meeting and signed off by an adjudicator. This method is recommended by the Cross-Cultural Survey guidelines (Harkness., 2011). Unfortunately though such an approach was impossible for the European chronic cough survey in this thesis with the study resources available.

3.3 Effectiveness of a combined Physiotherapy, Speech and Language Therapy intervention (PSALTI) for refractory chronic cough study

Chapter 2 identified that investigations into non-pharmacological interventions for refractory chronic cough have mostly been small sample sized cohort studies with only one RCT having been completed that did not include objective outcome measures.

Chapter two concluded “that more randomised control trials evaluating the effects of nonpharmacological interventions on cough frequency, sensitivity and severity are required. Studies should be rigorously designed with particular attention to blinding of assessors, use of valid and reliable objective outcome measures, and sample sizes that are adequately powered” (Chamberlain et al., 2014a). In addressing this need our study

was designed to fit these conclusions and therefore expand on and improve upon previous research in this field.

RCTs are considered to be the most rigorous and stringent way of determining a cause-effect relationship of treatment and determining the cost-effectiveness of that treatment (Sibbald and Roland., 1998). Well-designed RCTs reduce selection bias, observer bias, confounding variables and random errors compared to other study designs (Kendall., 2003). There are four main types of RCT: parallel group trials, crossover trials, cluster randomised trials and delayed start trials for sample sizes $n > 1$.

Parallel group trials consist of two groups for which participants are randomly allocated to, one group receives the treatment being tested and the other receives either a placebo/control or conventional 'usual care' intervention. The outcomes are then compared between the two groups (Tilling et al., 2005, Kendall., 2003). In parallel group RCTs as the two groups are compared to evaluate treatment effectiveness it is essential that the baseline characteristics are similar across both groups to reduce the influence of confounding variables (Kendall., 2003).

In a cross-over designed RCT both groups will experience both treatments but at different times. Therefore one group will receive the placebo/control or conventional care first followed by the intended treatment to be tested; whereas the other group would start with the intended treatment and then receive the placebo/control or conventional care afterwards (Tilling et al., 2005). It is vital therefore in crossover designed studies that an adequate 'washout period' is kept between groups switching from one intervention to the other otherwise residual effects from the group's previous treatment may affect the results of the subsequent treatment received (Jones and Kenward., 2015). This RCT study design has the benefit that participants act as their own controls so it explores within subject changes, rather than comparing changes that occurs in two different groups of participants as in a parallel group RCT design (Jones and Kenward., 2015).

Cluster randomised trials run similar to parallel group RCTs however, instead of participants being randomised individually, they are randomised in clusters. This approach is useful for interventions that may not be individual participant dependant but are looking at groups of patients. For example GP management of conditions or if there is the risk of contamination between participants e.g. different members of the same family being involved in the same study (Kendall., 2003).

Delayed start trials are advocated for use in studies of slowly progressive diseases such as Parkinsons Disease, Alzheimer's Disease, COPD and Rheumatoid Arthritis as it is important in these long term conditions to try to separate the effects of interventions from changes in disease progression (D'Agostino., 2009). These trials run similarly to crossover designed RCTs however instead of the group which has received the active treatment first switching to receive placebo/control or conventional care which the alternative group has received, both groups in the second phase of the trial receive the active treatment. Analysis therefore of the first phase of treatment compares active treatment vs placebo/control or conventional care. However the analysis at the end of the treatment when both groups have received active treatment allows analysis of the disease-modifying effects of the treatment (D'Agostino., 2009). This study design however requires extensive knowledge of the progression of the disease being investigated so that the different phases of the trial are the correct lengths based on the disease progression (D'Agostino., 2009).

For our study into the effectiveness of a combined Physiotherapy and Speech and Language Therapy intervention (PSALTI) for people with refractory chronic cough, a parallel group designed RCT was chosen. A crossover design trial was not chosen as the non-pharmacological interventions are taught therapies and the carry-over of taught treatment cannot be determined as easily as with drug trials. Also the long term effect of non-pharmacological interventions (as discussed in Chapter 2) have not been explored therefore the 'washout period' needed for a crossover design was unknown. In addition a

fundamental principle of RCT studies is for participants to be blinded as to whether the intervention they receive is the active treatment or placebo/control /conventional care treatment. Again this circumstance is different to that of drug trials and it would be difficult with a taught therapy to apply a cross-over design and for participants to remain blinded to their treatment allocation. A cluster RCT design was not appropriate to the study purpose as the group was interested in the experience of individual participants and not groups of participants. A delayed start RCT is an alternative to a parallel group RCT design that could have been chosen for our study however this type of design has not been used in previous chronic cough trials. The progressive nature and/or stability of refractory chronic cough has not been fully explored in the literature and therefore determining the point at which to switch phases of the trial would have been challenging.

Once a parallel group RCT design was decided, strategies were put in place to reduce the errors and biases previously identified. Careful consideration of the randomisation, treatments included, blinding of participants and assessors were all made.

Consideration needs to be given to the randomisation processes included in RCTs to ensure that the randomisation approach chosen does reduce selection and confounding biases (Schulz and Grimes., 2002). Distance randomisation is a randomisation approach which involves investigators contacting a central randomisation service who then issue the patients' treatment allocation. This method of randomisation has been advocated as the most effective method at reducing selection bias when compared to other methods. Methods such as concealment of treatment allocation via sealed envelopes are at a greater risk of being tampered with (Torgerson and Roberts., 1999). Restricted randomisation procedures and stratification are other randomisation processes that can help to reduce the risk of confounding biases. Blocking is a type of restrictive randomisation that can help to ensure sample sizes of different groups in a trial remain similar sizes even at early interim analysis points. Blocking ensures that for every determined number of participants randomised a certain number of participants are

allocated to either group. It is important in trials that are not double blinded that blocking sizes are varied as without varied numbers the allocation of future participants could be anticipated by the treating investigator (Schulz and Grimes., 2002). Stratified randomisation is useful for smaller RCTs when normal randomisation can still produce imbalances in baseline characteristics in groups within the RCT. Stratification helps to create an equal balance in baseline characteristics between the two groups for pre-randomisation determined factors (Schulz and Grimes., 2002).

Considering all these factors regarding randomisation it was decided that for our RCT we would use a distance randomisation process run by the clinical trials unit (CTU) at King's College London. That process required participants' baseline characteristics to be entered anonymously into the CTU's online service who then emailed the participants' treatment allocation to the treating therapist only. It was also decided that in order to avoid selection biases randomisation would only be conducted once the participants' baseline measurements had been completed. The randomisation process was discussed with the study statistician and it was determined that block sizes of 2 and 4 would be used (as our sample size was relatively small and not double-blinded). The randomisation would also be stratified according to age (< 50 and >50 years old) and gender as, as identified in Chapter 1, refractory chronic cough is more common in older females.

Designing control or placebo based interventions for therapies that involve cognitive and behavioural treatment methods is a significant challenge (Hart et al., 2008) and unlike drug trials when the drug being investigated can be compared against a similar looking placebo pill. Therapy based treatments involve *“cognitive, affective and behavioural change processes such as learning and teaching, practising, developing skills and habits, implementing strategies, and developing mechanisms for coping and adaptation.”* (pg2) (Hart et al., 2008) and therefore it is virtually impossible for therapeutic studies to be compared to a true placebo that can be as inactive as a placebo drug.

There are a number of options though to support control interventions for therapy studies including: no treatment as a control when participants receive no intervention at all; delayed start for intervention when participants are monitored prior to starting intervention; attention control interventions when participants receive no intervention but same attention from therapists or study personnel; sham treatments or placebo/control treatments which are plausible treatments but irrelevant to the target problem; and usual or standard care which is when usual care is compared to the treatment being investigated (Tilling et al., 2005, Whitehead., 2004).

For our study the original study team decided that a control treatment would be best model of intervention to compare our active treatment against for a number of reasons. One of the risks with no intervention, delayed start intervention and attention control interventions are attrition of participants and for our study, which was a relatively small RCT, the risk of attrition had to be minimised. Usual/standard care would have been the control group of choice but currently in the UK standard care for refractory chronic cough patients is not established. As identified in Chapter 1 there are no guidelines written specifically for the management of refractory chronic cough, so treatment options tend to be dependent on the treating Consultant and the availability of access to other services such as Respiratory Physiotherapy or voice specialist Speech and Language Therapists which not all units have. Therefore a control treatment group was the main option available for the research team to use and was also the option chosen by Vertigan et al's (2006) study to investigate the effectiveness of Speech Pathology management.

Therefore our study repeated this control intervention by covering the same topics as Vertigan et al's (2006) study, however the specific information covered could not be replicated as only the topic titles were given in the Vertigan et al's (2006) article. To ensure changes in outcome were not due to changes in attention received by either group, both groups were treated for the same time duration, same number of sessions, same frequency and both saw a trained healthcare professional. The decisions regarding

the non-pharmacological interventions investigated in the RCT were decided based on previous non-pharmacological interventions for refractory chronic cough (Chamberlain et al., 2014a) identified in Chapter 2 and which will be discussed further in Chapter 5.

Lastly blinding of assessors and participants was vital to reduce allocation biases. Blinding of participants was conducted as thoroughly as possible, participants were only informed of their treatment allocation post their 3 month follow up. However as Whitehead (2004) and Hart et al (2008) discuss it is difficult to keep participants in behavioural therapy interventions blinded to their treatment allocation as they can sometimes, without being informed, be aware as to whether they are receiving an active treatment intervention or not. This is a potential limitation of placebo/control interventions. Due to the resources available to the RCT separate assessors were not available for all outcome measure testing. Where a treating assessor did conduct an objective outcome measure for either baseline or end of treatment they did not conduct the testing for the other stage so they were at least blinded to change. Participants completed questionnaires included in the study protocol independently; these were placed in sealed envelopes so assessors were unaware of the participants' responses. The treating therapists could not be blinded to the treatment as they were delivering it and at two of the three research sites, which were delivering intervention, the same therapist delivered both the control and treatment intervention, which standardised the professional delivering the treatment, but is a limitation as the study was not double blinded.

3.4 Summary

This chapter outlined the methodological considerations that informed the choice of methods used to conduct the research studies in this thesis. Subsequent chapters will report the studies introduced in this chapter in detail, those studies are:

- Impact and Management of Chronic cough across Europe
- Physiotherapy, Speech and Language Therapy Intervention (PSALTI) for patients with refractory chronic cough: a multi-centre RCT.

CHAPTER 4

IMPACT AND MANAGEMENT OF CHRONIC COUGH ACROSS EUROPE

4. Impact and management of Chronic Cough across Europe

This chapter has been previously published by Springer in Lung Journal, titled 'The impact of Chronic cough: a cross sectional European Survey', 2015, DOI 10.1007/S00408-015-9701-2, Chamberlain, S.A.F., Garrod, R., Douiri, A., Masefield, S., Powell, P., Bücher, C., Pandyan, A., Morice, A.H., Birring, S.S. Copyright 19 Mar 2015 (Chamberlain et al., 2015a), with permission from Springer Science+Business Media. This version of the manuscript included in this thesis has been updated to include a published erratum for Table 1. Number of figures and tables have been changed for this thesis but no changes to the content have been made.

4.1 Introduction

The prevalence of chronic cough has been estimated as affecting 11-13% of the population (Montnémy et al., 1998, Ford et al., 2006, Cullinan., 1992, Lundbäck et al., 1991). Chronic cough is associated with significant physical and psychological morbidity (Brignall et al., 2008, Birring et al., 2003c). Adverse physical symptoms associated with cough include syncope, incontinence, chest pain, headaches and sore throat. Depression, anxiety and social embarrassment are also common (Brignall et al., 2008, McGarvey et al., 2006, Dicipinigaitis et al., 2006). The impact of chronic cough has largely been investigated in patients attending specialist cough clinics (French et al., 1998, Birring et al., 2003c, Brignall et al., 2008). Few studies have investigated the impact of chronic cough in patients based in the community. The aim of this study, in collaboration with the European Lung Foundation (ELF), was to investigate the impact of chronic cough from the patients' perspective in a wide range of European countries. An internet-based survey

was developed to investigate the impact, medical consultations, diagnoses, treatments and needs of patients with chronic cough.

4.2 Methods

Subjects

Adults with chronic cough (duration >8 weeks) of any cause were recruited using an internet-based survey. Exclusion criteria were acute and sub-acute cough, age <18 years and non-European country of residence. A patient information sheet was provided online on the ELF website. Participants who selected to complete the online survey were considered to have given implied consent. Secondary anonymised data from the survey was analysed.

Survey Development

Phase 1: Item generation

A preliminary survey (21 items) was developed following a review of the chronic cough healthrelated quality-of-life (QoL) literature and published surveys of chronic cough. The survey was also reviewed and discussed within the European Respiratory Society (ERS) Chronic cough Taskforce (15 respiratory physicians from nine countries), a multidisciplinary team (respiratory physician and physiotherapists, Kings College Hospital) and the ELF. The survey contained both open-ended and closed questions with response scales.

Phase 2: Survey refinement

The survey was adapted for use on the internet and reduced to 17 items in response to feedback received during the item generation phase. The items were grouped into five categories: "About your cough," "How are you affected by your cough?" "Diagnosis of your cough," "Treatment of your cough" and "Support for patients with cough" (Appendix 1).

Phase 3: Translation of survey

The survey was translated by Web-Translations (Leeds, UK). Forward-back translation methodology was used by native speakers to ensure accuracy. The back-translated survey was checked by the original author (SSB) for accuracy, and differences were reconciled during a harmonisation process. The survey was translated into 12 languages: English, German, French, Spanish, Greek, Romanian, Lithuanian, Swedish, Italian, Bulgarian, Polish and Russian.

Internet survey

The survey was launched by the ELF on their website www.european-lung-foundation.org (website has now changed to www.europeanlung.org) using a Survey Monkey survey package. Google AdWords was used to advertise the survey on Google searches. This used keywords or search terms entered into a Google search website to return the cough survey in the Google results page and advertisement sidebar. The keywords set for this survey were “chronic cough,” “cough survey,” “a cough that won’t go away” and “can lung disease make you cough”. These key words were identified by the ELF, following review of the literature and online resources for cough. Keywords were translated and applied for each survey language. The survey was promoted by the ELF by developing advertisement posters in all survey languages with dissemination to all ERS members (>10,000) and ELF patient organisation network (>160 organisations). The posters were available on the ELF website to download. The survey was also promoted in the ELF monthly newsletter and via social media (Twitter and Facebook).

4.3 Data Analysis

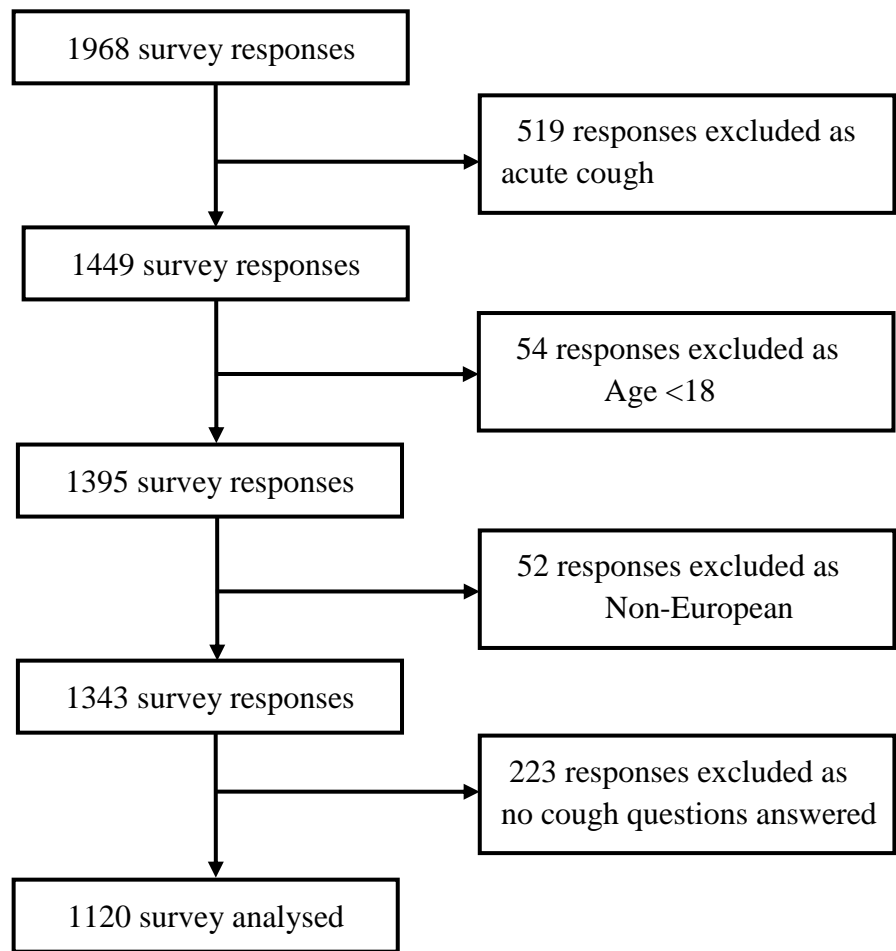
Count data were expressed as frequencies and percentages of the total number of participants responding to each question. The data were analysed as a whole sample and

then as sub-groups according to country of residence (countries with >50 responders) and gender. Categorical data for “the impact of cough” questions (questions 5-8, Appendix 1) were summarised as binary variables to enable calculation of the proportions of participants with the symptom. Open questions (questions 2, 16, 19 and 20; Appendix 1) were analysed by frequency content analysis. Preliminary categories were further refined to generate consolidated themes. The data generated by questions relating to further information and support were merged for analysis (questions 19 and 20).

4.4 Results

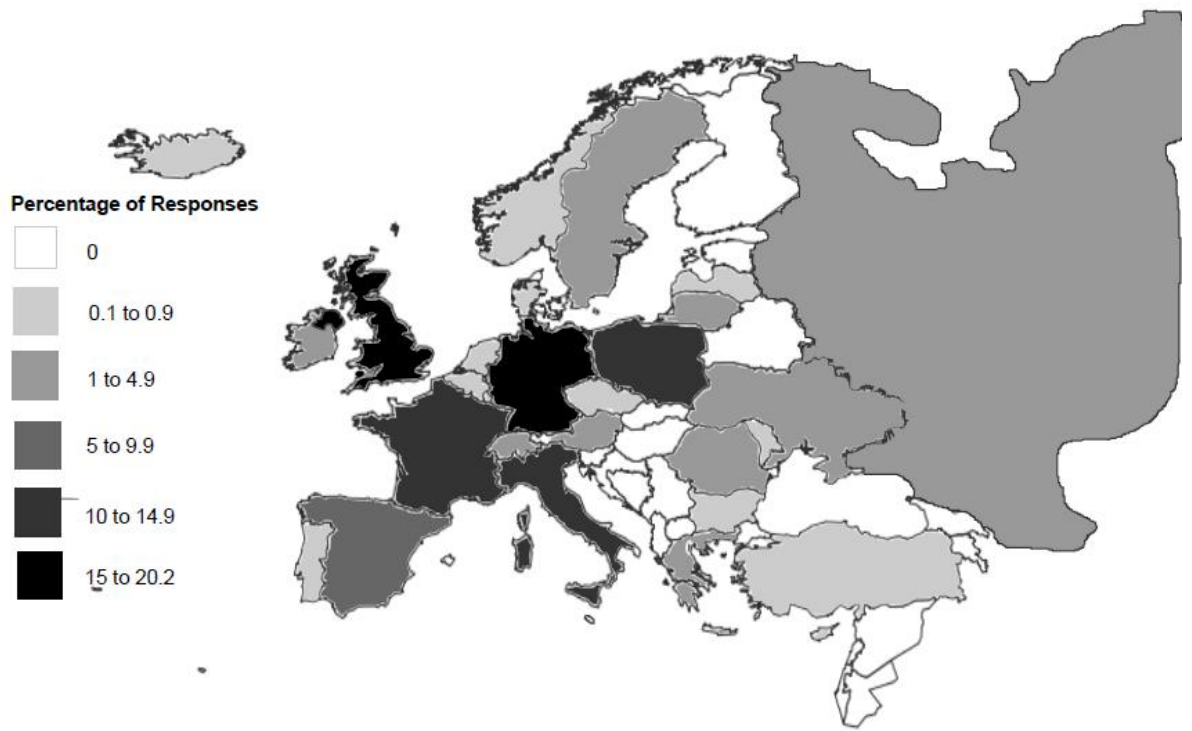
The survey was available between January 2012 and April 2013. 1968 participants responded and completed the survey; 1120 met the inclusion criteria. The reasons for excluding participants are stated in Figure 3. Sixty-seven percent of respondents were female, the mean age of respondents was 51 years (SD 15, range 18-87) and 83% were non-smokers (participant demographics are presented in Table 8). The respondents resided in 29 European countries (Figure 4). The countries with the five highest response rates were United Kingdom (UK) (n=136, 20%), Germany (n=114, 18%), France (n= 76, 11%), Italy (n= 70, 10%) and Poland (n= 67, 10%).

Figure 3: Flowchart of survey responses and exclusions.



Data presented as number of survey responses.

Figure 4: Chloropleth map of survey respondents' country of residence.



Data presented as percentage of survey responses who met inclusion criteria

Table 8: Respondents Demographics

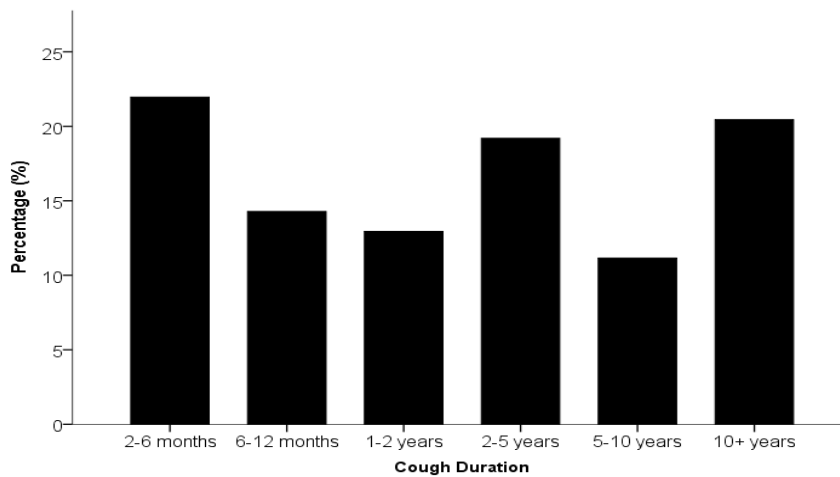
Subjects (n)		1120	
Age (years)	All	51	(15)
	Male	51	(17)
	Female	51	(14)
Female n (%)		489	(67)
Ethnicity n (%)			
	White Caucasian	540	(90)
	Black Caribbean	3	(0.5)
	Black African	3	(0.5)
	East Asian e.g. Japan, China	3	(0.5)
	South Asian e.g. India, Bangladesh	4	(0.7)
	Mixed	5	(0.8)
	Other	42	(7)
Current smokers n (%)		185	(17)
Seen a doctor regarding cough at least once n (%)		1043	(93)
Seen a doctor regarding cough ≥ 3 times n (%)		807	(72)
Attended specialist cough clinic (%)		135	(13)

Data presented as mean (standard deviation) unless otherwise stated

Diagnosis

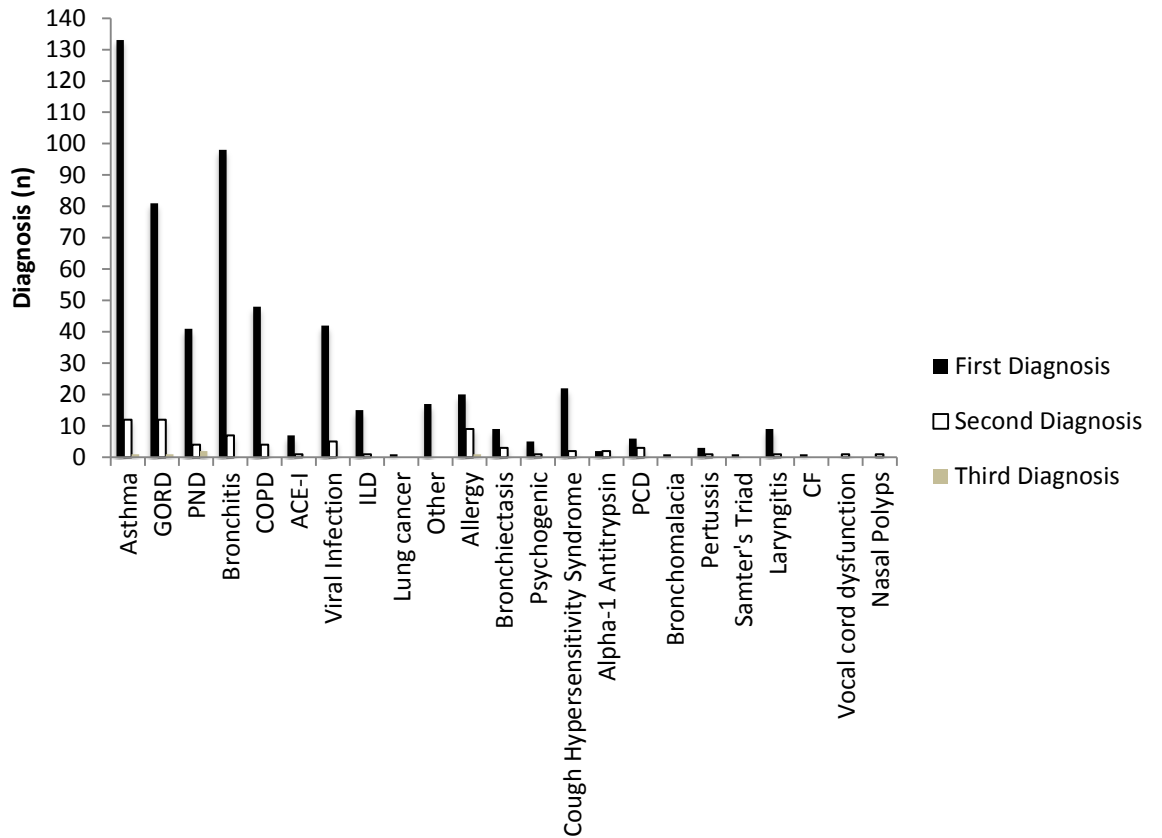
Median duration of cough was between 2 and 5 years. There were two peaks of cough duration; twenty-two percent, reported an early chronic cough (3-6month duration) and a similar number, twenty percent reported a cough duration of 10 or more years (Figure 5). Fifty-three percent (n=562) of respondents reported they had been given a diagnosis for their cough (Figure 6). Seven percent of respondents who had been given a diagnosis had been given two or more diagnoses. Asthma was the most common diagnosis reported (23%; Figure 6).

Figure 5: Cough Duration of Survey Respondents.



Data presented as percentage of survey respondents

Figure 6: Cough Diagnoses of Survey Respondents.



Data presented as number of survey respondents. GORD – Gastro-oesophageal reflux; PND – Post-nasal drip; COPD – Chronic Obstructive Respiratory Disease; ACE-I – Angiotensin-converting-enzyme Inhibitor; ILD – Interstitial Lung Disease; Other – includes non-disclosed diagnoses of cough; PCD – Primary Ciliary dyskinesia. First, second and third diagnoses were defined as the first, second and third diagnoses listed by survey respondents in response to Survey Question 10.

Impact of chronic cough

Ninety-six percent (n=1055) of responders reported that their cough affected their QoL. Eighty-one percent (n=890) reported that their cough affected the activities they liked to do. Ninety-one percent (n=1000) reported feeling fed-up and depressed because of their cough and 94% (n=1030) reported that their cough disturbed or worried their family and friends. The impact of cough was consistent across the top five countries of residence of the respondents (Table 9).

Table 9: Impact of chronic cough (top five response countries).

Country	Negative Impact on activities	Feeling fed up or depressed	Negative Impact on quality of life	Worrying or disturbing family or friends
UK	87 (80-91)	94 (89-97)	96 (91-98)	98 (94-99)
Germany	85 (77-90)	98 (94-100)	98 (94-100)	90 (83-94)
France	75 (64-83)	92 (84-96)	97 (91-99)	95 (87-98)
Italy	74 (63-83)	90 (81-95)	96 (88-99)	94 (86-98)
Poland	90 (80-95)	90 (80-95)	97 (90-99)	99 (92-100)

Data presented as % of responders (95% Confidence Intervals)

There were significant gender differences in the limitation of activities due to cough; a significantly higher proportion of women (87%; Confidence Interval (CI) 84-90%) than men (77%; 95 CI 72-82%) reported limitations (difference in proportion 10%; CI 4-16%). More women (94%; CI 92-96%) than men (90%; CI 85-93%) reported feeling fed up or depressed due to their cough (difference in proportion 5%; 95 CI 0-9%). No significant differences in population proportions were found between gender for impact on QoL or on family and friends.

Management and treatment of chronic cough

The majority of respondents had seen a doctor about their cough (Table 8). Seventy-two percent of respondents had seen a doctor ≥ 3 times in relation to their cough. Thirteen percent reported that they had attended a specialist cough clinic. Only 30% of respondents felt their doctor had dealt with their cough thoroughly. Respondents were asked in an open-ended question why they had first consulted their doctor. This question generated seven themes: the characteristics of the cough (n=422), physical symptoms associated with cough (n=380), possible viral infection symptoms (n=140), psychological symptoms associated with cough (n=88), to consult a doctor about existing respiratory or other health condition (n=80), social symptoms associated with cough (n=76) and for diagnosis/assessment and treatment for the cough (n=31), (Appendix 2). Some examples of quotations from respondents are listed in Appendix 3.

Most respondents reported limited (57%) or no (36%) effectiveness of medications they had tried for cough. Only 7% reported that medications they had tried for their cough were effective. Medications found helpful for their cough were reported by 222 (Question 16 – open ended question; see Table 10). Sixty-nine percent of respondents reported that over-the-counter medications were not effective.

Table 10: Effective medications for cough reported by respondents

Medication	%
Corticosteroids (oral and inhaled)	37
Antibiotics	23
Bronchodilators	21
Over the counter cough medications	17
Gastroesophageal Reflux medications (proton-pump inhibitor (PPI), non-PPI and unspecified reflux medications)	10
Antihistamine/anti-allergy medications	7
Opiates	6
Mucolytics (tablets and nebulised)	6
Unspecified asthma treatment	4
Nasal sprays (decongestant and corticosteroids)	4
Homeopathy/herbal medications	4
Leukotriene antagonists	3
Amitriptyline	0.5
Bronchovaxon (immunostimulant, Bacterial Lysate)	0.5
NSAID	0.5
Gabapentin	0.5
Other	1

Data presented as percentage of the number of respondents who reported 1 or more effective medications. 73% of respondents listed one medication only, 19% listed two medications and 8% listed ≥ 3 medications.

Information and support

Eighty-eight percent of respondents reported that they would like more information on chronic cough to be available and 78% reported that they would like to receive more information about the ERS/ELF Chronic cough Task Force. The open-ended questions concerning further information and support needs of the respondents generated 20 themes (Table 11). The two most common themes were the need for further patient information relating to the treatment and causes of cough. Examples of quotations from respondents requesting further information and support are listed in Appendix 4.

Table 11: Information requested by respondents: a qualitative analysis

Themes	N (Total = 991)
Treatment	308
Causes	127
Self-help and alternative therapies	103
General information in a variety of formats	95
Better understanding, awareness and support from doctors	74
Assessment	68
Information on access to specialist cough clinics	65
Where to get help	33
Information on cough related symptoms	20
Further research and sharing of knowledge between specialists	19
Cough prevention	18
Better public awareness of chronic cough	17
Being able to liaise with other people who suffer with chronic cough	13
Psychological support	11
Information on triggers for cough	6
Why chronic cough reoccurs	4
Information on how to stop smoking	4
Information on prognosis and long term effects of chronic cough	2
Information on types of chronic cough	2
Definition of chronic cough	2

Data presented as number of responses (n) for each theme.

4.5 Discussion

This community-based survey investigated the impact of chronic cough in a large number of participants living in 29 European countries. The demographics of respondents to this survey were consistent with previous studies of chronic cough that report a middle aged, female predominance (Birring et al., 2003b, Morice et al., 2014, Morice et al., 2006, Morice, 2002) There was an adverse impact of cough on health-related QoL in most respondents, which was consistent across the top five response countries. The impact on activities was more significant in females compared to males. Most respondents reported that their doctor had not 'dealt with their cough thoroughly' and that medications were largely ineffective.

This survey has highlighted the significant adverse impact of chronic cough to the individual. The respondents had consulted their physician for a wide range of reasons, such as the severity of cough, adverse physical and psychological symptoms associated with cough and the social impact. The effect on health-related QoL was consistent with previous studies conducted in specialist Cough Clinics by French et al (1998) and Birring et al (2003c). In contrast to French et al (2004), a gender difference was not found in the impact on health-related QoL. This may be because we did not use validated questionnaires such as the cough-specific QoL questionnaire (CQLQ), (French et al., 2002) and the Leicester cough questionnaire (LCQ), (Birring et al., 2003c) to assess health-related QoL. Most respondents also reported feeling 'fed up or depressed' because of their cough. This finding is consistent with those of Dicipingaitis et al (2006) and McGarvey et al (2006), who also reported significant depressive symptomatology in up to 50% of participants. The prevalence of depressive symptoms in our study was greater than this (91%), though again this was not measured by validated questionnaires; hence the severity of these reported symptoms in our respondents is unknown.

Only 53% of the survey respondents had been given a suggested diagnosis for their cough. This was despite the respondents having consulted their doctor on multiple occasions. However, it is possible that some respondents were still undergoing investigations for the cause of their cough and only 13% of our participants had been assessed in specialist cough clinics. These factors may have contributed to the high prevalence of unexplained chronic cough. Only 30% of respondents felt that their doctor had dealt with their cough thoroughly. When a diagnosis was suggested, the most common cause was asthma (23%). Gastro-oesophageal reflux disease and upper airway cough syndrome (post-nasal drip) were also common causes, consistent with previous studies of cough that investigated subjects with the anatomical diagnostic protocol as recommended by chronic cough guidelines (Irwin and Madison., 2000, Morice et al., 2004, Morice et al., 2006, Irwin et al., 2006). As expected, some respondents reported multiple causes of cough.

Our study findings suggest that there is room for improvement in the management of patients with chronic cough. One approach is to increase awareness of this condition, and improve the implementation of chronic cough management guidelines in both primary and secondary care. Another approach could be to improve patient access to specialist cough clinics, by increasing the number of such clinics. A key finding reported by respondents was that their medications, including over-the-counter medications, were ineffective. The reasons why other prescribed and over-the counter medications were ineffective are unclear, and was beyond the scope of this study. Inadequate assessment of patients, dose/duration and non-compliance of medications and misdiagnosis could all be potential explanations (Morice et al., 2004, Irwin and Madison, 2000). The reasons for treatment failure warrant further investigation.

A novel internet-based survey was used in this study to investigate the impact of chronic cough. This method was simple to set up, low-cost and one that provided data output in an electronic format that was ready to analyse. It also facilitated the recruitment of

participants from across Europe. The use of the internet did not inhibit elderly participants; the age range of our study was 18-87 years. Few surveys have specifically assessed the impact of chronic cough in detail. Everett et al (2007) surveyed 373 subjects with chronic cough in the community based in the UK that responded initially to a radio broadcast. Everett et al (2007) also found that chronic cough was associated with a significant adverse impact on physical, psychological and social wellbeing of subjects. The strength of our study in contrast to Everett et al (2007) was a larger sample size of participants with chronic cough, recruitment from 29 European countries and the additional capture of qualitative data (for example, participants' views on information and support for cough). Fujimara et al (2012) surveyed 232 participants with chronic cough registered with a research company via e-mail. The recruitment of volunteers from a research company database is likely to have introduced a selection bias. Seventy-four percent of participants were male, which is in sharp contrast to most studies of chronic cough, which report a female predominance. Forty-four per cent of participants had not consulted their doctor regarding their cough, and 75% were satisfied with over-the-counter cough medications. This reflects the high number of participants with acute and sub-acute cough in their study. Cough, however, was associated with significant psycho-social impact on the subject, and females were more affected than males. Ford et al (2006) identified 481 participants with chronic cough in a survey of a community based in Yorkshire, UK. The cough was considered severe in approximately half of these subjects based on the disruption to activities of daily living. However, this study did not report the psychosocial impact, access to specialist care or treatments used for cough. Adams et al (2009) identified 611 participants with chronic cough in a survey of a community based in Adelaide, Australia. Chronic dry cough was more common in participants who were male, current smokers and elderly. Cough was associated with significant psychological morbidity and impairment in health-related QoL, but this study also did not investigate the access to specialist care, treatments and information/support for participants.

There are a number of limitations with this study. Validated health-related QoL, activity or depression questionnaires were not used. We used a small selection of questions derived from literature review of health-related QoL literature and multi-disciplinary discussion. This was to keep the survey brief, and therefore encourage completion by respondents. A significant number of respondents were excluded as they did not answer any of the cough related questions. This may have been minimised by using a shorter questionnaire. The diagnoses and medications were not verified by checking medical records, as this was not feasible in this study. The use of the internet to recruit participants seeking medical advice may have led to bias, although the wide age range of our participants and a clinical phenotype consistent with previous studies of chronic cough suggests that this bias may not have been as much as expected (Birring et al., 2003b, Morice et al., 2014, Morice et al., 2006, Morice., 2002). Studies of the general population, perhaps by telephone, would minimise selection bias but are likely to be costly and unfeasible. The recruitment of participants is likely to have been greater if we had used a commercial Google search strategy, for example a featured advertisement, rather than the Google AdWords account. The use of other search engines and strategies may have increased recruitment of subjects. Our data does, however, suggest that the internet has the potential to recruit a large number of participants for survey-based research. Our survey focused on exploring the impact of chronic cough however acute cough is also known to cause a significant impact on quality of life (Yousaf et al., 2011). Future studies might explore usefully the impact of acute cough across Europe and serve to allow comparison with the findings of this present study.

In conclusion, chronic cough was associated with a significant impact on their daily activities and health-related QoL in this European study. Cough was undiagnosed in 47% of respondents. The majority of respondents said that they would like further information, support and access to specialist cough clinics. This suggests that much more work needs to be done to promote awareness of this condition, implement clinical guidelines and

improve access to specialist care. This is best achieved in collaboration with patient and healthcare professional societies, such as the ELF and the ERS.

CHAPTER 5

PHYSIOTHERAPY, SPEECH AND LANGUAGE THERAPY INTERVENTION FOR PATIENTS WITH REFRACTORY CHRONIC COUGH: A MULTI-CENTRE RANDOMISED CONTROLLED TRIAL.

5. Physiotherapy, Speech and Language Therapy intervention for patients with refractory chronic cough: a multi-centre randomised controlled trial.

This chapter contains the draft manuscript for this RCT which is being prepared for submission.

5.1 Introduction

Chronic cough, defined as a cough lasting more than 8 weeks, (Morice et al., 2006) is a prevalent disorder in both the community (Ford et al., 2006) and secondary care sectors, accounting for up to 40% of respiratory out-patient clinic referrals (Morice., 2008, Morice et al., 2006). The most common causes of cough in a non-smoking patient with a normal chest radiograph and spirometry are asthma, gastro-oesophageal reflux and rhinitis (upper airway cough syndrome) (Morice et al., 2004, Morice et al., 2006, Irwin et al., 2006). For a significant number of patients, the cough may remain unexplained or refractory to treatment despite extensive investigation and therapeutic trials (Haque et al., 2005). Cough is associated with significant physical, psychological morbidity and impaired QoL (Brignall et al., 2008, Birring et al., 2003c, French et al., 1998). There are few effective antitussive therapies for refractory chronic cough (Chung., 2009, Belvisi and Geppetti., 2004). Recent studies suggest a potential role for Gabapentin and P2X3 receptor inhibitors but both have significant side effects (Ryan et al., 2012, Abdulqawi et al., 2014).

Non-pharmacological therapies for refractory chronic cough have however shown promising results in a few preliminary studies as discussed in chapter 2 (Chamberlain et al., 2014a). Non-pharmacological therapies are generally delivered by Physiotherapists or Speech and Language Therapists (Chamberlain et al., 2014a). Whilst there are no firm guidelines concerning the treatment components of Physiotherapy and Speech and Language Therapy management of chronic cough it generally includes four key components: education, cough suppression techniques including breathing exercises,

vocal hygiene and hydration and psycho-educational counselling (Chamberlain et al., 2014a, Chamberlain et al., 2013b, Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009). Vertigan et al (2006) is the only randomised controlled trial (RCT) of a non-pharmacological intervention for refractory chronic cough and found significantly greater improvements in patient reported symptoms of cough for Speech Pathology management compared to placebo (general healthy lifestyle advice). The benefits of Speech Pathology management on objectively measured cough frequency, cough reflex sensitivity and cough QoL have not been assessed in a controlled clinical trial, limiting the generalisability of the findings. Furthermore, the longer term effect of therapy is not known. A recent study by Patel et al (2011) investigated cough-suppression Physiotherapy for refractory chronic cough in 23 participants and found a significant improvement in cough related QoL, but this study did not include a control group. Ryan et al (2010) evaluated objective measures of cough after an uncontrolled trial of Speech Pathology management using Capsaicin cough challenge and the Leicester Cough Monitor (LCM) as well as evaluating QoL with the LCQ. Whilst their findings were positive, the lack of a control group and the application of the LCM in a non-validated manner similarly limits the interpretation of the findings. RCTs that evaluate the effectiveness of Physiotherapy and Speech Pathology interventions for refractory chronic cough are needed to support/ develop the existing limited evidence base.

This study aimed to assess the effect of an intervention utilising both Physiotherapy and Speech and Language therapy techniques (Physiotherapy, Speech and Language Therapy Intervention, PSALTI) on cough related QoL, severity, objective cough frequency and cough reflex sensitivity using a RCT design.

5.2 Methods

A multi-centre, single blinded RCT was conducted initially across two Foundation Trust hospitals (Research site - King's College Hospital NHS Foundation Trust, Recruitment site – Guy's and St Thomas' NHS Foundation Trust) in December 2011. By August 2012 the trial was extended across five Foundation Trust hospitals within the UK (King's College Hospital NHS Foundation Trust, Lancashire Teaching Hospitals NHS Foundation Trust and Northumbria Healthcare NHS Foundation Trust; Recruitment sites – Royal Brompton & Harefield NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust). The study began in December 2011 and was completed in April 2014.

Eligible patients were identified as adults with chronic cough (defined as >2 months duration), with normal chest x-ray, minimal sputum production (<10ml sputum a day) and who had had negative investigations and/or failed treatment trials for asthma, gastroesophageal reflux and rhinitis (Morice et al., 2006).

Patients were excluded if they: were suffering with active aspiration, had had an upper respiratory tract infection in past 4 weeks, were taking ACE inhibitor medication, were current smokers or had known respiratory disease (lung cancer, pneumonia, pulmonary fibrosis, sarcoidosis, pleural effusion, bronchiectasis). Patients were also excluded if they had vocal cord pathology and/or suspicious malignancy. All participants were assessed for presence of abnormal vocal cord pathology, suspicious malignancy and active aspiration by undergoing a Modified Fiberoptic Endoscopic Evaluation of Swallowing (FEES) by a trained Speech and Language therapist or an Ear-Nose and Throat assessment by an ENT specialist (see Appendix 5).

Once participants had given written consent (Appendix 6) and completed baseline assessments (Appendix 7 – 15), their data were added to the online randomisation service provided by the King's CTU supplied by King's College London (<http://www.ctu.co.uk/>). This strategy prevented foreknowledge of treatment assignment for researchers. Treatment assignment was concealed from participants, they were not aware of which treatment group was expected to be more beneficial for chronic cough. Patients were blocked randomised, stratified by age (<50 and >50 years old) and gender. In this trial random block sizes of two and four were used.

Participants were allocated to one of two interventions; Control and PSALTI. For each intervention participants attended four weekly one to one sessions. The initial session was an hour long and the subsequent sessions were 45 minutes long. The timings of the sessions were determined from a Patient Public involvement event that was held with chronic cough patients who were familiar with PSALTI and the outcome measures included in the trial. Initially it was intended that the treatment sessions would be 30 minutes long but the patients felt this was too short to cover the issues adequately and therefore timings of an hour for initial sessions and 45 minutes for subsequent sessions were agreed by the researchers and patients involved in the event.

Control arm

Participants attended four weekly one to one standardised healthy lifestyle advice sessions with a health care professional (nurse (Northumbria Healthcare NHS Foundation Trust), physiotherapist (King's College Hospital NHS Foundation Trust) or speech and language therapist (Lancashire Teaching Hospitals NHS Foundation Trust)). As identified in chapter 3 the control intervention was based on Vertigan et al's (2006) previous RCT placebo intervention which included healthy lifestyle advice and education on diet, exercise, stress management and relaxation.

The participant's initial session covered general advice on exercise and physical activity covering what it is, what happens when you exercise, the benefits of exercise, what the Department of Health's (2011) recommended guidelines are for physical activity and exercise and how the participants could meet these recommended guidelines (see Appendix 16). The second session covered dietary and nutritional advice, for this session participants were asked to record their diet for the past week and bring this diet diary to this session (Appendix 17 shows a participant's example diary). This diet diary was then reviewed and advice was made on healthy eating, including 5 portions of fruit and vegetables a day, portion sizes of different food groups, reducing salt, sugar and saturated fat intake as well as recommended guidelines for fluid intake, this was all based on advice from the National Health Service (NHS), (see Appendix 18). The third session was on stress management, for which a stress management booklet (Appendix 19) that had previously been used for COPD patients in pulmonary rehabilitation at King's College Hospital was used. It covered what is stress, how patients can notice they are stressed, what causes stress, how stress can make you feel breathless and tired, as well as giving patients strategies to help deal with their stress. During this session participants were involved in an active activity of writing down what their stresses were in order to illustrate to themselves their stress levels and tolerances for stress by using the analogy of a stress jug. The participants' final session was a progressive relaxation session which was based on a NHS progressive relaxation technique (Appendix 20).

The material covered in each session was based on healthy lifestyle advice by the Department of Health and NHS. Sessions were standardised for all sites as the same written prompts or information for the education was given by all sites (Appendix 16 to 20) and face to face training was provided for all therapists who delivered the healthy lifestyle intervention by the main study researcher (thesis author).

PSALTI arm

Participants received this treatment by either a Physiotherapist (King's College Hospital) or Speech and Language Therapist (Northumbria Healthcare NHS Foundation Trust, Lancashire Teaching Hospitals NHS Foundation Trust). The intervention was based on previous Speech Pathology management and cough-suppression Physiotherapy studies for refractory chronic cough (Vertigan et al., 2006) as well as Vertigan et al (2007a) tutorial guide for Speech-Language Pathologists on chronic cough (Vertigan et al., 2007a). The first session focused on educating the participants about chronic cough, what it is, what causes it and how this treatment aimed to improve their symptoms. Participants were introduced to laryngeal hygiene and hydration techniques of promoting nose breathing rather than mouth breathing, increasing their non-caffeinated and reducing their caffeinated fluid intake. Cough suppression/distraction techniques were also introduced including taking sips of water and sucking a non-medicinal sweet to help suppress cough. Participants were advised to eliminate triggers for cough that they could and realistic goals were set and discussed with the patients (Appendix 21). All participants were issued with an information booklet on the treatment (Appendix 22) at their initial treatment session.

The second and third treatment sessions (Appendices 23 and 25) covered cough control techniques in more detail including teaching relaxed breathing control to promote relaxed diaphragmatic breathing technique. Laryngeal hygiene and hydration were re-emphasised during these sessions, if participants were struggling with breathing via their nose, nasal douching or steam inhalations were discussed. In the third session psycho-educational counselling techniques were also covered. All participants were issued with a stress and anxiety handbook related to chronic cough, which was developed by the thesis author and a clinical psychologist at the primary research site prior to the start of the study (Appendix 26). If participants were progressing well the reintroduction of triggers for their cough that they were avoiding was discussed.

The fourth treatment session consisted of reinforcing all aspects of PSALTI and exploring the participants' coping strategies for their cough (Appendix 27). All components of PSALTI were delivered, however the focus and emphasis on individual techniques varied for each participant, determined by the treating therapist. Airway clearance techniques were included in the PSALTI treatment if the participant's sputum production was close to the upper limit of sputum exclusion criteria (Appendix 24). The standardisation of treatment between different hospitals was increased by the use of written treatment plans (written by thesis author) and standardised educational material (Appendix 21 to 27). All therapists delivering the treatment were trained prior to commencing the study by the main study researcher (thesis author).

Efficacy Endpoints

Primary Efficacy Endpoint

Cough related QoL was assessed using the Leicester Cough Questionnaire (LCQ) at week 4 (after 4th treatment session) as the primary endpoint (Birring et al., 2003c). The LCQ is a validated 19-item cough-specific health-related QoL questionnaire. Overall scores range from 3 to 21 with a higher score indicating a better cough related QoL (Appendix 10). The minimal important difference for this outcome is 1.3 (Raj et al., 2009). Participants independently completed LCQ at baseline, 4 weeks (after the 4th treatment session) and at 3 month follow up. Questionnaires were then placed in sealed envelopes to avoid influencing the treating therapist.

Secondary Efficacy Endpoints

Objective cough frequency was assessed with the Leicester Cough Monitor (LCM) (Birring et al., 2008) a validated, objective, ambulatory cough monitoring device. The LCM

consists of a MP3 recording device (Phillips 662 MP3 recorder, UK), external microphone and cough detection software. The LCM has been used in previous clinical trials of Gabapentin and Erythromycin (Ryan et al., 2012, Yousaf et al., 2010). Participants wore the device for 24 hours at baseline, 4 weeks (after the 4th treatment session) and 3 month follow up and were instructed to resume their normal daily activities during this time period. The number of coughs per hour (CF_{perhour}) were recorded (Appendix 9).

Capsaicin cough challenge was assessed in a subset of the trial participants (Kings College Hospital Foundation Trust and Northumbria Healthcare NHS Foundation Trust) to measure participants' cough reflex sensitivity at baseline and 4 weeks (after the 4th treatment session). Capsaicin solutions were prepared as per the standard operating procedure written for the study based on the ERS Chronic cough assessment guidelines (Morice et al., 2007a) (Appendix 28). Capsaicin cough challenge was administered via a dosimeter (Koko-Digidoser, nSpire health Inc, Hertford, UK) connected to a 30 p.s.i air cylinder as per manufacturer's instructions. A modified characterised nebuliser (model 646, DeVilbiss Health Care Inc, Somerset, PA, USA) and mouthpiece were then attached to the dosimeter (Koko-Digidoser, nSpire health Inc, Hertford, UK). Two different characterised nebulisers were used (1.232ml per minute and 1.205 per ml per minute). Both of these nebulisers were modified to have an inspiratory flow regulator valve (nSpire health Inc, Hertford UK) to limit the inspiratory flow to 0.5L.S-1. This was done to standardise inspiratory flow rate during each inhalation of aerosol.

To standardise nebuliser output and ensure the same amount of aerosol was delivered per inhalation, nebuliser output was set at 10 μ l which has been previously used in capsaicin cough testing (Prudon et al., 2005). To do this the nebuliser output duration was altered according to the nebuliser aerosol delivery rate. This was done separately for both nebulisers used:

Since $10\mu\text{l} = 0.01\text{ml}$, 0.01ml was the target volume of aerosol to be delivered with each breath.

Since $\text{volume (ml)} = \text{rate (ml per second)} \times \text{duration (seconds)}$

Nebuliser 1 (1.232ml per minute)

$$0.01 = (1.232/60) \times \text{duration}$$

$$\text{Duration} = (0.01 \times 60) / 1.232$$

$$\text{Duration} = 0.49 \text{ s}$$

Nebuliser 2 (1.205ml per minute)

$$0.01 = (1.205/60) \times \text{duration}$$

$$\text{Duration} = (0.01 \times 60) / 1.205$$

$$\text{Duration} = 0.5 \text{ s}$$

Capsaicin cough challenge testing was completed as per the standard operating procedure written for the study (Appendix 29) which was based on the ERS cough assessment guidelines (Morice et al., 2007a). A dose-response capsaicin cough testing method was used (Morice et al., 2007a). Doubling concentrations of capsaicin solution ranging from, $0\mu\text{m}$ (saline), $0.49\mu\text{m}$ to $1000\mu\text{m}$ were administered. The test was discontinued when five or more coughs were induced (C5). In addition, the dose that induced two or more coughs (C2) was recorded (Appendix 7). After each inhalation participants were asked whether they felt an urge to cough (Young et al., 2009). The concentration at which they reported their first urge to cough was recorded (Cu), (Appendix 8).

Cough severity in the past 2 weeks was assessed by a visual analogue scale, (VAS), (0-100mm), (Appendix 13), (Morice et al., 2007a) at baseline, 4 weeks (after the 4th treatment session) and 3 month follow up. A modified 1 week VAS scale for cough severity was used at the beginning of participants' second treatment session as they had

only received 1 week of treatment at this point (Appendix 12). The Vocal Performance Questionnaire (VPQ), (Carding and Horsley., 1992) a 12 item tool was used to assess patients' perceived impact on their voice (Appendix 15). A score >12 indicates dysphonia (Chamberlain et al., 2013a). General health and mood was assessed by Short-Form 36 (SF-36) (Brazier et al., 1992) and Hospital anxiety and depression scale (HADS) (Zigmond and Snaith, 1983). HADS is 14-item questionnaire, a higher score indicates greater anxiety or depression. A score for either subscale ≥ 8 indicates mild symptoms, ≥ 11 moderate and ≥ 15 severe (Appendix 14). SF-36 generates two summary scores, physical component summary score (PCS) and mental component summary score (MCS); both range from 0 to 100 and a higher score indicates better self-reported health (Lacson et al., 2010), (Appendix 11). VPQ, HADS and SF-36 were independently completed by participants at baseline, 4 weeks (after the 4th treatment session) and at 3 month follow up. All questionnaires were then placed in sealed envelopes to avoid influencing the treating therapist as per the completion of the LCQ described above.

Objective respiratory assessment of participants' breathing pattern was assessed for participants this included assessing and documenting the participants' respiratory rate, route of breathing (nose or mouth breathing) and primary region of movement (upper thoracic expansion or abdominal expansion), (Bruton et al., 2011). This was assessed in all participants at baseline and a subgroup of participants at 4 weeks (after the 4th treatment session).

Ethics and trial registration

All protocols were approved by the London-Chelsea National Research Ethics Service (NRES) Committee (Appendix 30). During the study period two substantial amendments were made by the thesis author post the initial London-Chelsea NRES Committee approval. The first substantial amendment was approved on 23rd November 2011 to

include the Vocal Performance Questionnaire in the study (Appendix 31), the second substantial amendment was approved 17th May 2012 (Appendix 32) to include the HADS questionnaire in the study.

All participants provided written informed consent (Appendix 6), and the study was registered with the UK Clinical Research Network (UKCRN ID 10678) and ISRCTN (ISRCTN 73039760).

5.3 Data Analysis

Sample size calculation was completed by the study Statistician (Appendix 33). For each of the variables analysed, univariate descriptive statistics were summarised by randomised group to provide an overview of the data. Summary measures for the baseline characteristics of each group were presented as mean and standard deviation for continuous normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Normality testing was completed using Shapiro-Wilk tests (Appendix 34), for baseline variables for which one treatment group was non-normally distributed both groups' baseline data was presented as non-normality distributed data to allow comparisons. Univariate analyses were performed to compare study groups at baseline using appropriate statistical tests according to the type and the distribution of the data: independent t-test for normally distributed variables, Mann-Whitney for non-normally distributed variables and Chi Square for categorical variables. Cough frequency data was log transformed prior to any analysis. Capsaicin cough challenge data was analysed without log transformation for univariate analyses and summary measures at baseline.

For both primary efficacy endpoint analysis and secondary efficacy endpoint analysis, analysis of covariance (ANCOVA) adjusted for the baseline variables were completed for all variables. Analysis of both the primary and secondary efficacy endpoint analyses were completed as a per-protocol analysis, only observed data was included without imputation for missing data. A p-value of less than 0.05 was considered statistically significant.

Within group changes from baseline to 4 weeks and 4 weeks to 3 month follow up were analysed using paired T-tests. For the secondary efficacy endpoint analysis for capsaicin cough challenge (C2 and C5) data was log transformed.

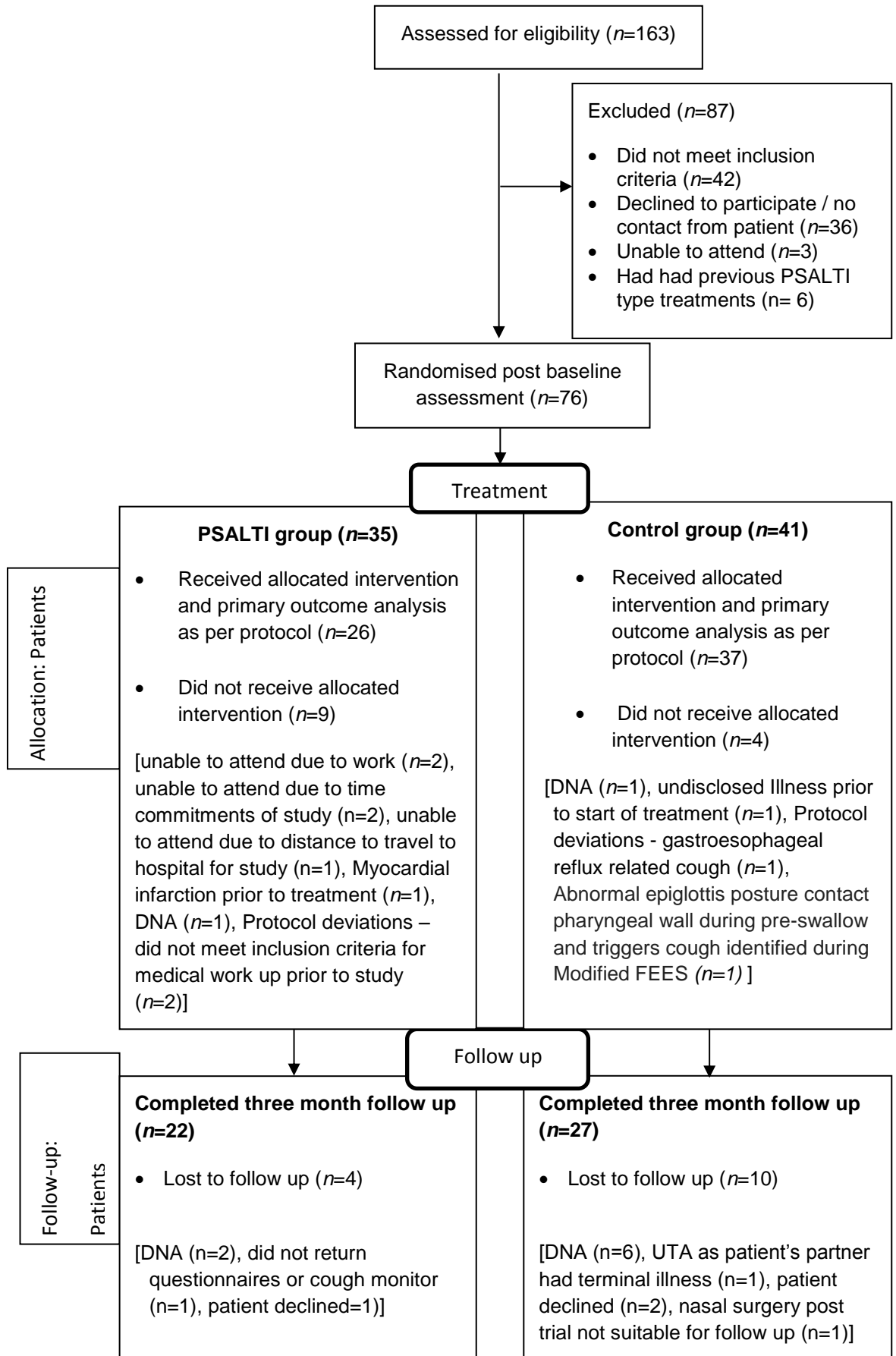
All analyses were made using SPSS 21 software (IBM, UK) and were verified by the study statistician using STATA version 12 software (StataCorp LP, College Station, TX).

5.4 Results

Participants

Seventy-six participants were randomised post baseline assessment. Four patients in control group and nine patients in the PSALTI group did not receive or complete treatment for reasons stated in Figure 7. Primary outcome (LCQ) analysis was therefore completed on 63 participants post treatment. 49 participants completed 3 month follow up. The consort study flow diagram is described in Figure 7.

Figure 7: Trial CONSORT study flow diagram



The baseline characteristics of the randomised participants are described in Table 12. The two groups were balanced with no statistically significant differences at baseline with the exception of SF-36 Physical Component Summary Scores (higher-positive in the control group).

Table 12: Baseline demographic and clinical characteristics of study participants recruited.

Characteristic	Control (n=41)		PSALTI (n=35)		p value
	n		N		
Age (years)	41	56 (48 to 67)	35	61 (53 to 67)	0.239
Female, n (%)	41	26 (63)	35	25 (71)	0.459
Cough duration (months)	39	48 (24 to 126)	31	60 (30 to 126)	0.279
FEV1 (L, observed), mean(SD)	36	2.7 (0.9)	30	2.6 (0.7)	0.517
FEV1/FVC (%), mean(SD)	36	76 (8.2)	30	76 (5.0)	0.686
LCQ, mean(SD)	41	11.9 (3.5)	34	10.4 (3.6)	0.073
Cough Severity VAS	37	65 (40 to 83)	32	63 (49 to 75)	0.652
SF-36 PCS,	41	47.1 (41.7 to 53.6)	31	41.1 (35.6 to 49.1)	0.033*
SF-36 MCS	41	47.7 (38.3 to 54.9)	31	49.9 (40.5 to 57.0)	0.763
HADS –Anxiety	33	7 (3 to 10)	26	7 (4 to 10)	0.785
HADS – Depression	33	4 (1 to 8)	26	5 (2 to 6)	0.620
VPQ	40	17 (11 to 22)	28	21 (13 to 27)	0.158
CF _{perhour} , Geometric mean (log SD)	39	17 (0.36)	30	17 (0.38)	0.983
C2 (µm)	35	3.90 (1.95 to 7.80)	25	3.9 (1.47 to 15.60)	0.749
C5 (µm)	35	7.80 (3.90 to 15.60)	25	7.80 (3.90 to 31.25)	0.994
Cu (µm)	33	0.00 (0.00 to 2.93)	22	0.00 (0.00 to 0.98)	0.810

Data presented as median (IQR) unless otherwise stated.

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LCQ, Leicester cough questionnaire; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; MCS, Mental component score; HADS, hospital anxiety and depression scale; VPQ, vocal performance questionnaire; CF_{perhour}, average cough frequency per hour over a 24 hour period; C2, capsaicin cough challenge – concentration that resulted in two or more coughs; C5, capsaicin cough challenge – concentration that resulted in five or more coughs; Cu, capsaicin cough challenge – first capsaicin concentration that caused participants to report a perceived urge to cough

Cough related QoL - Primary Efficacy Endpoint

Total LCQ score at 4 weeks improved by a mean 1.53 (95% CI [0.21 to 2.85]) units more in the PSALTI group than in control ($p=0.024$) (see table 13). The LCQ improvement was sustained at 3 month follow up for both groups (see table 13). Table 14 shows the within group differences for LCQ.

Table 13: Primary and Secondary efficacy endpoint analysis: Change between PSALTI and control groups at baseline to four weeks and four weeks to three month follow up

	Between group difference Baseline to four weeks		Between group difference Four weeks to three month follow up	
	Mean Difference (95% CI)	p value	Mean Difference (95% CI)	p value
LCQ Total	1.53 (0.21 to 2.85)	0.024*	0.01 (-1.62 to 1.64)	0.994
CF_{perhour}(Geometric Mean (log 95% CI)[†]	0.30 (-1.01 to -0.06)	0.030	1.02 (-0.59 to 0.62)	0.966
VAS severity	-9.72 (-20.80 to 1.36)	0.084	1.6 (-15.48 to 18.74)	0.848
SF36 PCS	0.56 (-2.52 to 3.64)	0.717	0.48 (-3.27 to 3.37)	0.977
SF36 MCS	0.81 (-3.10 to 4.72)	0.680	0.72 (-3.06 to 4.51)	0.703
VPQ	3.90 (-0.33 to 8.12)	0.070	-0.20 (-3.43 to 3.03)	0.901
HADS – Anxiety	-0.42 (-1.96 to 1.13)	0.590	0.88 (-0.57 to 2.34)	0.225
HADS – Depression	-0.44 (-1.69 to 0.81)	0.486	-0.18 (-1.36 to 0.99)	0.753
Cu	3.12 (0.61 to 5.64)	0.016*	NA	NA
C5 Geometric Mean (log 95%CI)	1.28 (-0.22 to 0.43)	0.512	NA	NA

Between group differences were calculated using ANCOVA adjusted for baseline values.

*p<0.05

Positive change in LCQ, SF36 PCS, SF36 MCS, Cu and C5 indicates improvement in symptoms.

Negative change in VAS, HADS and VPQ indicates improvement in symptom.

† Interpret CF_{perhour} as a ratio.

LCQ, Leicester cough questionnaire; logCF_{perhour}, average log cough frequency per hour over a 24 hour period; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; MCS, Mental component score; VPQ, vocal performance questionnaire; HADS, hospital anxiety and depression scale; Cu, concentration of capsaicin which participants' first rated a perceived urge to cough; C5, concentration of capsaicin that caused ≥5 coughs.

Table 14: Primary and Second Efficacy Endpoints: within group change

	Change from baseline to four weeks				Change from four weeks to three month follow up			
	PSALTI Mean Difference (95% CI)	P	Control Mean Difference (95% CI)	P	PSALTI Mean Difference (95% CI)	P	Control Mean Difference (95% CI)	P
LCQ Total mean(SD)	3.40 (2.26 to 4.55)	0.000*	1.66 (0.78 to 2.54)	0.000*	-0.17 (-1.49 to 1.15)	0.794	0.27 (-0.82 to 1.35)	0.616
CF_{perhour}[†] (Geometric Mean (log 95% CI)	0.20 (-1.12 to -0.29)	0.002	0.63 (-0.51 to 0.11)	0.2053	1.70 (-0.18 to 0.64)	0.236	0.81 (-0.52 to 0.33)	0.655
VAS severity	-21.18 (-29.83 to -12.53)	0.000*	-11.84 (-20.11 to -3.57)	0.007*	9.74 (-3.60 to 23.08)	0.143	0.79 (-10.73 to 12.31)	0.888
SF36 PCS	1.62 (-0.96 to 4.21)	0.208	0.50 (-1.30 to 2.31)	0.574	0.54 (-1.82 to 2.89)	0.639	0.76 (-1.66 to 3.18)	0.522
SF36 MCS	0.53 (-2.69 to 3.75)	0.736	-0.26 (-2.92 to 2.40)	0.843	1.09 (-1.91 to 4.09)	0.456	0.49 (-2.35 to 3.32)	0.727
VPQ	4.04 (0.12 to 7.97)	0.044*	0.73 (-1.94 to 3.39)	0.582	-1.63 (-4.17 to 0.91)	0.193	-0.57 (-3.29 to 2.15)	0.666
HADS – Anxiety	-1.27 (-2.51 to -0.032)	0.045*	-0.90 (-1.96 to 0.17)	0.095	-0.11 (-1.16 to 0.94)	0.826	0.95 (-0.22 to 2.11)	0.104
HADS – Depression	-0.68 (-1.57 to 0.21)	0.126	-0.21 (-1.11 to 0.69)	0.641	0.06 (-1.42 to 1.53)	0.937	0.05 (-0.66 to 0.76)	0.878

*p<0.05

Positive change in LCQ, SF36 PCS, SF36 MCS indicates improvement in symptoms.

Negative change in VAS, HADS and VPQ indicates improvement in symptoms.

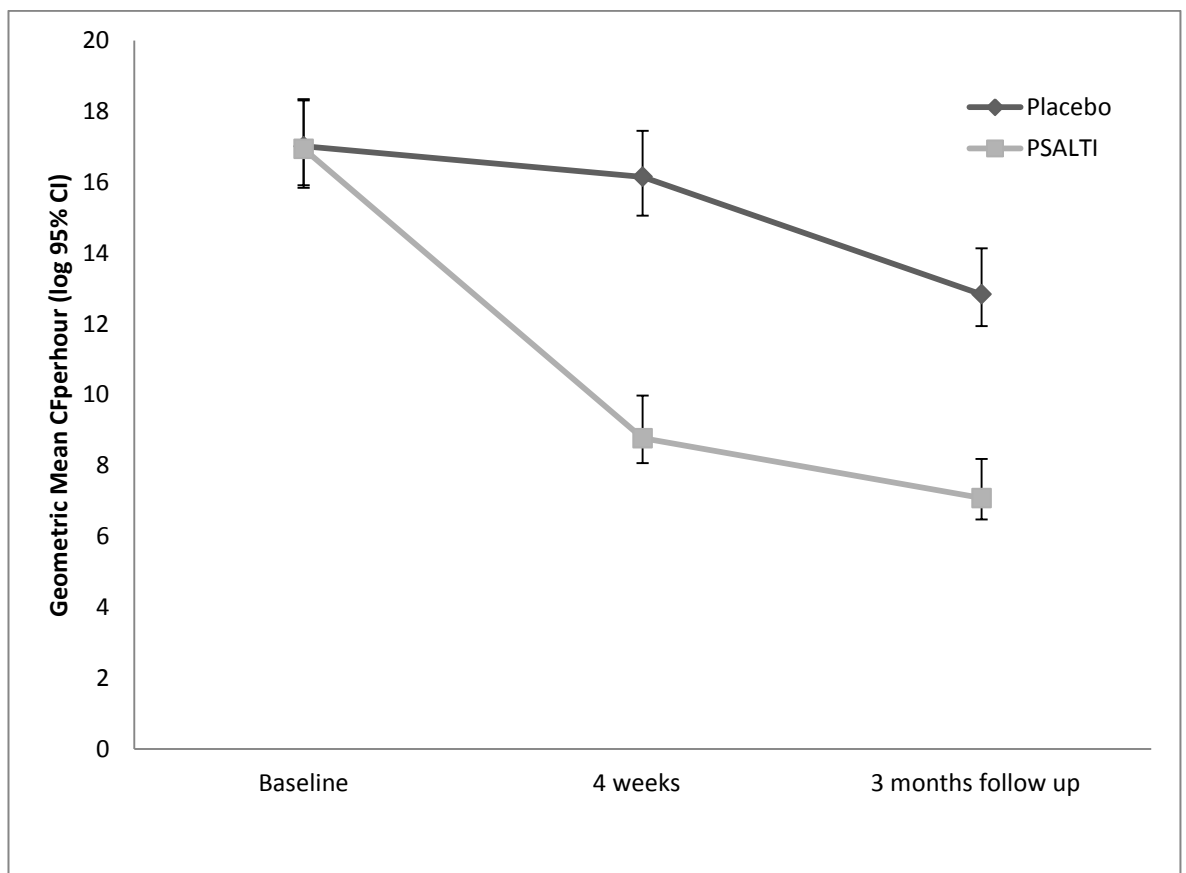
[†] Interpret CF_{perhour} as a ratio.

LCQ, Leicester cough questionnaire; CF_{perhour}, average log cough frequency per hour over a 24 hour period; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; SF-36 MCS, Mental component score; VPQ, vocal performance questionnaire HADS, hospital anxiety and depression scale.

Objective Cough Frequency

There was a significant reduction in cough frequency after four weeks of treatment in the PSALTI group; geometric mean 17.0 (2.4) to 9.0 (3.3) coughs per hour ($p=0.002$) versus 17.0 (2.3) to 16.0 (2.2) coughs per hour after control ($p=0.205$), (Figure 8). The control-adjusted reduction in cough frequency per hour in PSALTI was 41% (95% CI [36.4-94.7%], $p=0.030$) at 4 weeks. This improvement was also sustained up to three months (Figure 8).

Figure 8: Geometric mean (95%CI) change in cough per hour frequency in PSALTI and control groups, baseline data includes all data, 4 weeks and 3 month follow up includes per-protocol data.



Urge to cough during capsaicin challenge

No significant between group differences were observed for C2 ($p=0.575$) or C5 ($p=0.512$), however a significant difference between groups was observed for participants' reported urge to cough during the capsaicin cough challenge. Cu improved in the PSALTI group by mean 3.1 (95% CI [0.6 to 5.6]) $\mu\text{mol/L}$ compared to control ($p=0.016$) at four weeks, indicating that participants in the PSALTI group were able to tolerate a higher capsaicin dose before reporting an urge to cough (Table 13).

Other questionnaire data

There were no significant between group differences for change (4 weeks - baseline) in depression, anxiety or SF-36 (Table 13). However there was a trend towards improvement in VAS severity in PSALTI group compared to control ($p=0.084$). There were significant within group differences for change (4 weeks – baseline) in both groups for VAS severity (control $p=0.007$; PSALTI $p=0.000$), (Table 14). Although for VPQ and HADS-anxiety significant within group changes (4 weeks – baseline) only occurred in the PSALTI group ($p=0.044$ and $p=0.045$ respectively), (Table 14).

Sub-analyses

Breathing pattern

At baseline there were no significant differences between PSALTI and control groups for any breathing pattern characteristics (Table 15). In both groups participant's respiratory rate was within normal limits and predominantly most participants' main route for breathing was via their nose. However around half of the participants in both groups had an altered breathing pattern in regards to the primary region of movement; as for these

participants the primary region of movement observed was upper thoracic expansion rather than abdominal excursion.

There were no significant differences in age, gender, cough duration or any of the other baseline characteristics between those participants who at baseline were observed to have a primarily upper thoracic expansion breathing pattern or an abdominal expansion breathing pattern.

Table 15: Baseline breathing pattern characteristics of participants

Characteristic	Control (n=41)		PSALTI (n=35)		p value
	N		n		
Respiratory Rate	27	15 (4)	25	16 (5)	0.376
Primary region of movement (% abdominal expansion)	28	50%	25	48%	0.884
Route of breathing (% nose)	28	89%	25	92%	0.736

At the end of treatment (4 weeks) there was a significant difference between PSALTI and control groups for primary region of movement ($p=0.013$). Seven of the eleven PSALTI participants whose breathing pattern was reassessed after the 4 weeks had changed their breathing pattern to primary abdominal expansion; therefore by week 4 all 11 PSALTI participants who were reassessed, were found to have a primary abdominal excursion breathing pattern. In contrast, in the control group only 4 of the 9 participants reassessed had altered their breathing pattern to primary abdominal excursion. Therefore by week four in the control group, 5 of the 9 participants had a primary abdominal excursion breathing pattern.

Despite the changes in breathing pattern there were no significant within group changes in respiratory rate for PSALTI (Mean 1.7 (95% CI -1.6 to 5.1, $n=11$)) or control group (Mean 0.5 (95%CI -1.9 to 2.9, $n=11$)) or between group changes (4 weeks - baseline) in

respiratory rate (Mean -1.08 (95%CI -5.02 to 2.86, n=21). For route of breathing by the end of the 4th session (end of treatment) 100% of the participants were breathing via their nose.

Table 16 shows the within group changes in the study outcome measures for those participants in the PSALTI treatment arm who by 4 weeks had changed their breathing pattern to primary abdominal excursion compared to participants whose breathing pattern at start of the trial was already primary abdominal excursion. For those with no change in breathing pattern there was no significant changes in any of the study outcome measures (4 weeks – baseline). However for participants who had altered their breathing pattern in the PSALTI arm their LCQ total score significantly improved (Mean (95%CI) 3.94 (1.69 to 6.19), p=0.005), their cough VAS severity significantly decreased (Mean(95%CI -25.67 [-51.03 to -0.30], p=0.048) and their cough frequency per hour decreased (Mean (95%CI -0.34 [-0.68 to 0.00], p=0.051) which was borderline significant.

When between group differences for change was assessed only cough VAS severity was significantly different between those participant in the PSALTI group who had altered their breathing pattern and those who had not (Table 17). Cough VAS severity score at 4 weeks had decreased by Mean -30.19 (95%CI [-56.87 to -3.50]) points more in those participants who had altered their breathing pattern compared to those who did not.

Caution does have to be taken with the data analyses in Table 16 and 17 as the above analysis is based only on 7 participants who changed their breathing pattern and 4 who did not.

Table 16: Within-group change in primary and secondary endpoints for those participants in the PSALTI arm who changed their primary region of movement of their breathing pattern and those who did not.

	Change from baseline to four weeks in PSALTI arm			
	Change in breathing pattern Mean Difference (95% CI)	P	No change in breathing pattern Mean Difference (95% CI)	P
LCQ Total	3.94 (1.69 to 6.19)	0.005*	1.82 (-4.01 to 7.64)	0.394
CF_{perhour}[†] (Geometric Mean (log 95% CI))	0.46 (-0.68 to 0.00)	0.051	0.27 (-1.66 to 0.51)	0.190
VAS severity	-25.67 (-51.03 to -0.30)	0.048*	-1.50 (-30.83 to 27.83)	0.881
SF36 PCS	1.43 (-6.01 to 8.87)	0.655	3.34 (-12.62 to 19.29)	0.554
SF36 MCS	-1.28 (-8.04 to 5.49)	0.661	2.76 (-17.07 to 22.59)	0.688
VPQ	5.86 (-2.32 to 14.03)	0.130	12.33 (-17.61 to 42.28)	0.218
HADS – Anxiety	-1.50 (-6.23 to 3.23)	0.452	-1.50 (-7.85 to 4.85)	0.205
HADS – Depression	-1.33 (-3.88 to 1.21)	0.235	1.00 (-11.71 to 13.71)	0.500

Positive change in LCQ, SF36 PCS and SF36 MCS; Negative change VAS, HADS and VPQ indicates improvement in symptoms.

[†] Interpret CF_{perhour} as a ratio.

LCQ, Leicester cough questionnaire; CF_{perhour}, average log cough frequency per hour over a 24 hour period, VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; MCS, Mental component score; VPQ, vocal performance questionnaire HADS, hospital anxiety and depression scale.

Table 17: Between-group change in primary and secondary endpoints for those participants in the PSALTI arm who changed their primary region of movement of their breathing pattern those who did not.

	Between group difference	
	Baseline to four weeks	
	Mean Difference (95% CI)	p value
LCQ Total	2.10 (-2.89 to 7.09)	0.361
CF_{perhour}[†] (Geometric Mean (log 95% CI))	1.74 (-0.59 to 1.08)	0.510
VAS severity	-30.19 (-56.87 to -3.50)	0.032*
SF36 PCS	-1.90 (-15.33 to 11.52)	0.862
SF36 MCS	-2.87 (-17.55 to 11.82)	0.345
VPQ	-7.97 (-22.06 to 6.13)	0.223
HADS – Anxiety	0.30 (-8.21 to 8.81)	0.931
HADS – Depression	-2.03 (-7.21 to 3.16)	0.362
Cu	-3.78 (-8.63 to 1.08)	0.102
C5 (Geometric Mean (log 95% CI))	1.74 (-0.41 to 0.89)	0.401

*p<0.05

Positive change in LCQ, SF36 PCS and SF36 MCS; Negative change in VAS, HADS and VPQ indicates improvement in symptoms.

[†] Interpret CF_{perhour} as a ratio.

LCQ, Leicester cough questionnaire; CF_{perhour}, average log cough frequency per hour over a 24 hour period; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; MCS, Mental component score; VPQ, vocal performance questionnaire HADS, hospital anxiety and depression scale.

Participants whose LCQ total score improved by week four vs those who did not

Of the 26 participants who completed the 4 weeks of PSALTI, 23 participants improved their LCQ scores from baseline to 4 weeks (improvements ranged from 0.1 to 8.9 points, twenty participants' improvements were >1.3 points which is the LCQ MID). Due to the small number of participants who did not improve their LCQ score, analysis of this data is limited.

When participants in the PSALTI group are split as to who improved greater than the LCQ MID of 1.3 (n=20) and those who did not (n=6) no significant differences were found in baseline variables (Table 18 and 19).

Table 18: Difference in baseline values for participants in PSALTI group who improved greater than LCQ MID (1.3) and those who did not continue

	Gender	Age	Cough duration	FEV1	FEV1/FVC	LCQ Total
<1.3 change of LCQ (n=6)	83% female	59 (42 to 74)	90 (24 to 139.5)	2.48 (1.93 to 3.07)	78 (76.75 to 82.00)	13.34 (9.67 to 18.06)
>1.3 change of LCQ (n=20)	75% female	62 (58 to 69)	54 (28 to 144)	2.40 (1.76 to 2.83)	75.85 (72.00 to 78.75)	9.93 (7.67 to 11.86)
p value	0.67	0.84	0.98	0.82	0.09	0.083

Table 19: Difference in baseline values for participants in PSALTI group who improved greater than LCQ MID (1.3) and those who did not continue

	VAS severity	SF36 PCS	SF36 MCS	C2	C5	Urge to cough	VPQ	HADS-A	HADS-D	CF _{perhour} (Geometric mean (log 95%CI))
<1.3 change of LCQ (n=6)	69 (22.50 to 82.75)	48.72 (24.81 to 58.17)	51.12 (38.15 to 57.10)	3.9 (1.95 to -)	3.9 (3.9 to -)	0 (0 to 0)	20 (10.5 to 25.00)	5 (2.5 to 16)	2 (0.5 to 12.00)	10.72 (0.94 to 1.37)
>1.3 change of LCQ (n=20)	60.00 (49.25 to 72.75)	40.17 (35.03 to 47.36)	44.59 (39.04 to 56.53)	3.9 (0.98 to 7.8)	7.8 (3.9 to 15.60)	0.49 (0 to 1.71)	19 (13.5 to 26.00)	6.5 (3.75 to 9.25)	5 (2 to 6.25)	23.44 (1.20 to 1.50)
p value	0.70	0.46	0.53	0.65	0.50	0.16	0.71	0.80	0.33	0.10

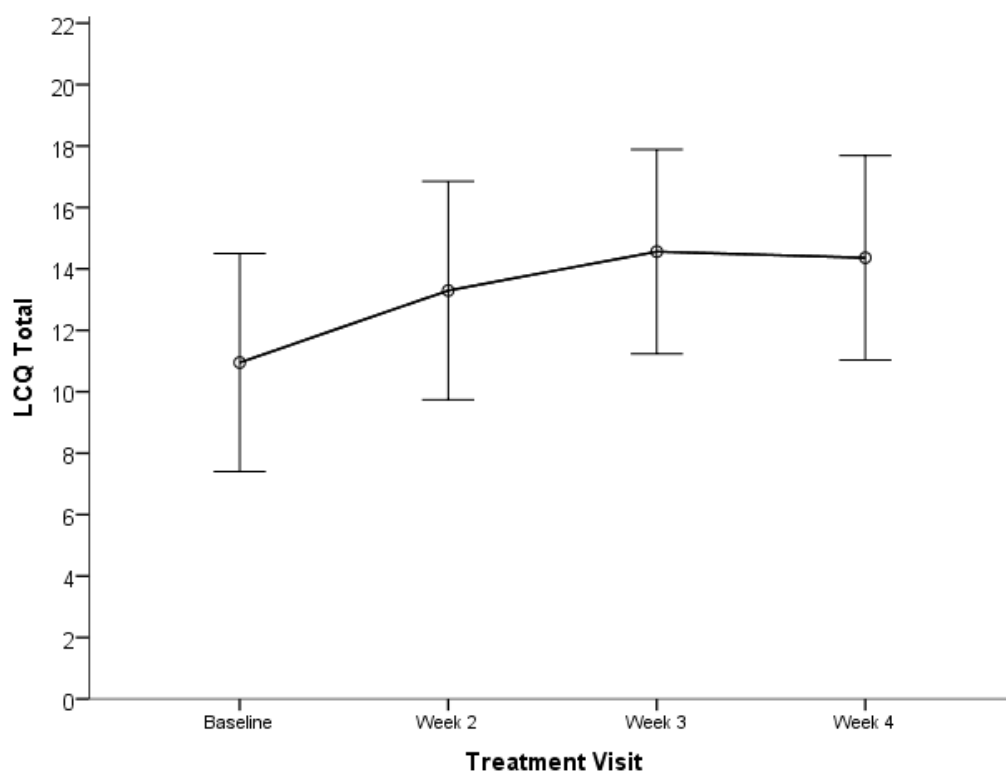
† Interpret CF_{perhour} as a ratio.

In the control group by 4 weeks, 18 of the 37 participants who completed the study improved their LCQ total score by equal to or greater than 1.3 points. When these participants were compared to those participants who did not improve or their improvements were less than 1.3 points no statistically significant differences were found for any of the baseline variables.

Week by week comparison of change in participants in PSALTI group

Week by week LCQ scores were recorded for the majority of PSALTI participants (n=26 baseline, n=20 week 2, n=21 week 3, n=26 week 4). For LCQ the greatest mean change in score was between baseline assessment and beginning of week two (at the beginning of 2nd treatment session), (Figure 9).

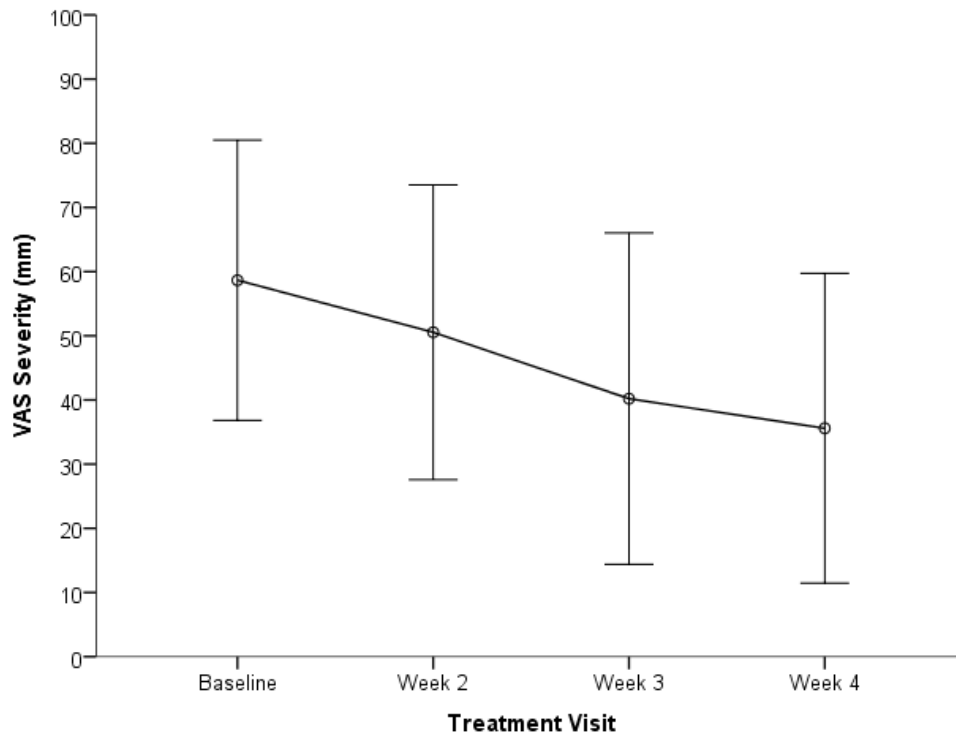
Figure 9: LCQ at each treatment visit for PSALTI treatment arm



Data displayed as Mean(SD)

For week by week changes in VAS severity peak decrease was reached by week 3 (beginning of 3rd treatment session) with the biggest decrease between week 2 and week3. VAS continued to decline between week 3 and week 4 however this change was less than between any other visit (Figure 10).

Figure 10: VAS Severity score at each treatment visit for PSALTI treatment arm



Data displayed as Mean(SD)

Attrition and Retention

When the 8 dropouts across both treatment arms (excluding the protocol violations and 1 participant who had no baseline data) are compared to the participants who did not drop out (see Table 20 and 21). Only FEV1 was significantly different ($p=0.011$). Those participants who dropped out had a significantly higher FEV1 (Median (IQR) 3.10 (2.89 to 4.20) than those who completed (Median (IQR) 2.50(1.85 to 3.02).

Table 20: Difference in baseline values for participants who dropped out of study and those who completed treatment

	Gender	Age	Cough duration	FEV1	FEV1/FVC	LCQ Total
Drop-outs (n=8)	50% female	49 (36 to 61)	78.00 (60.50 to 102.00)	3.10 (2.89 to 4.20)	78.00 (69.00 to 79.00)	9.35 (7.21 to 10.83)
Completers (n=63)	71% female	58 (50 to 67)	48.00 (24.00 to 127.50)	2.50 (1.85 to 3.02)	76.00 (72.00 to 79.25)	11.16 (8.68 to 14.08)
p value	0.217	0.061	0.186	0.011*	0.857	0.079

Table 21: Difference in baseline values for participants who dropped out of study and those who completed treatment continued

	VAS severity	SF36 PCS	SF36 MCS	C2	C5	Urge to cough	VPQ	HADS-A	HADS-D	CF _{perhour} (Geometric mean (log 95%CI))
Drop-outs (n=8)	58.50 (50.00 to 76.25)	47.27 (44.29 to 54.32)	51.80 (37.71 to 59.20)	19.53 (3.05 to 39.06)	31.25 (5.97 to 85.94)	0.00 (0.00 to 17.09)	21 (13 to 28)	8 (6 to 12)	3 (1 to 7)	19.50 (0.56 to 1.62)
Completers (n=63)	65.50 (45.25 to 77.75)	46.22 (38.07 to 52.63)	47.73 (38.40 to 55.22)	3.90 (1.95 to 7.80)	7.80 (3.90 to 15.60)	0.00 (0.00 to 0.98)	18 (12 to 24)	7 (4 to 10)	5 (2 to 7)	19.05 (0.99 to 1.49)
p value	0.870	0.447	0.553	0.145	0.069	0.904	0.634	0.401	0.341	0.866

† Interpret CF_{perhour} as a ratio

5.5 Discussion

This study is the first multi-centred RCT to evaluate the effects of a non-pharmacological intervention, in the form of Physiotherapy and Speech and Language Therapy intervention (PSALTI) using validated outcome measures. In this RCT, the PSALTI group showed a statistically significant improvement in cough related QoL compared to equal attention control group, the difference between groups was greater than MID (1.3) of LCQ. Cough frequency was reduced by more than half in the PSALTI group compared to control. This finding is likely to be clinically as well as statistically relevant since the minimum clinical important difference in cough frequency in acute cough is estimated at 54% (Lee et al., 2013). Urge to cough during capsaicin cough challenge was also significantly improved in the PSALTI group compared with control.

PSALTI was compared to an 'equal attention' control group to account for treatment time with a therapist. Clinically there are limited Physiotherapy and Speech and Language therapy services available for refractory chronic cough patients and in many areas usual care consists of no active treatment. As expected the control group showed significant benefits demonstrating a hawthorn effect occurrence, it could be hypothesised that if compared with usual care (often no active treatment) the differences between groups would have been bigger.

Despite PSALTI showing a clear benefit in cough related QoL there were no significant differences between groups in anxiety, depression, patient perceived physical or mental health scores. This may reflect the lack of disease specific tools available for these outcomes. As disease specific tools are likely to show greater responsiveness to such interventions than generic tools, as shown by Wiebe et al (2003) who found in a large systematic review of generic and specific quality-of-life instruments across Neurological,

Musculoskeletal, Cardiovascular and Pulmonary disorders that specific quality-of-life instruments were more responsive to change than generic quality-of-life instruments (Wiebe et al., 2003). There was however a statistically significant within group change in anxiety for the PSALTI group. This is in contrast to the findings of Ryan et al (2010) who reported no significant change in anxiety and depression scores post Speech Pathology management. This difference between the studies is likely to be due to subtle differences in the treatments delivered. Although both our study and Ryan et al (2010) delivered similar treatments small differences are to be expected. For example both studies included counselling but participants in PSALTI were guided from a booklet specifically designed by a Clinical Psychologist to address stress and anxiety associated with chronic cough.

Participants' reported urge to cough in response to capsaicin was significantly different between groups in favour of greater tolerance in PSALTI group. Urge to cough sensation has been shown to precede the motor response of cough and increases with increasing dosages of Capsaicin (Davenport, 2008). However, no differences were observed in cough motor response to capsaicin in our study. PSALTI appears to have positively affected the perceived urge to cough sensation but failed to influence the cough motor response. This is in contrast to Ryan et al's (2010) study who investigated the effect of Speech Pathology management for refractory chronic cough and found a significant reduction in cough sensitivity (C5) after three to four 30 minute sessions over eleven to sixteen weeks. In addition they showed a significant improvement in participants' perceived urge to cough in response to capsaicin and significant improvements in patients' cough reflex sensitivity (C5) after each individual treatment session. Differences in the results of the studies may reflect subtle differences in treatments included within the two studies. Although PSALTI was based on previous studies of Speech Pathology management the interpretation and delivery of the key components is likely to be different

between the two studies. Caution should also be taken when interpreting Ryan et al (2010) results as this was an uncontrolled trial with a small sample size (n=17).

The sub-analyses of the RCT data provide some interesting further perspectives on the PSALTI treatment. This is the first study to explore the breathing pattern technique of patients with chronic cough and 50% of those included in the study were found to have breathing pattern dysfunction with an increased apical breathing pattern. Breathing pattern re-education exercises were included in the PSALTI treatment arm and breathing pattern was found to be significantly improved in the PSALTI arm at end of treatment. Interestingly it was only those who improved their breathing pattern technique in the PSALTI arm who had significant improvements in LCQ, cough severity and borderline significant improvements in cough frequency. Those in the PSALTI arm whose breathing pattern remained unchanged (and showed no evidence of dysfunction) at the end of the study showed no significant improvements in any of the outcome measures. This finding may be a relevant indicator in identifying those participants for whom PSALTI treatment is most effective. A limitation of our study though is that breathing pattern was only assessed on a limited number of participants and was assessed by observation by the leading Physiotherapist in the trial, who was unblinded to treatment allocation of the participants. Future studies are needed that investigate breathing pattern in people with refractory chronic cough using an objective outcome measure, this will be discussed further in Chapter 6.

Week by week changes in LCQ and cough severity VAS were taken in this study and identify that the greatest change in LCQ was between baseline and the beginning of the treatment session in week 2 for the PSALTI group, which would have been after only the first treatment session. For cough severity the greatest change was between the treatments in week two and the treatment in week 3, therefore after 2 treatment sessions. Our data showed a plateau in LCQ score after week 3 (beginning of third treatment

session). So it may be suggested that possibly only three treatments of PSALTI may be required to improve cough related QoL. Potentially the treatments delivered in session 1 and 2; education on chronic cough, cough suppression techniques and breathing exercises have a greater impact on cough related QoL than the subsequent treatments in session 3 and 4; which were delivering the stress and anxiety booklet for chronic cough and reinforcement of taught techniques.

However caution needs to be taken with these sub-analyses as the mechanisms of action of the treatment were not explored in this study and the sub-analyses sample sizes are small. Therefore these sub-analyses should be considered hypothesis generating only.

We were unable to establish from these limited sub-analyses why some participants showed improvements greater than the MID of LCQ and others did not. No significant differences were found in baseline characteristics between these participants. Again this is likely to be due to the fact that this study did not aim to explore the mechanistic effects of PSALTI and therefore was not sufficiently powered for the sub-analyses. This is an important aspect for consideration in future studies.

One of the strengths of this study was the involvement of different centres and the use of standardised treatment protocols for the different sites. This improves the generalizability of the findings and facilitates implementation into clinical practice. The fact that our therapists were a multi- professional group (nurses, physiotherapists and speech and language therapists) reinforces the notion that content rather than profession specific delivery is of primary importance. Improvements for future multi-centre studies of PSALTI would be to, as well as providing crib sheets and initial training as we did in our study, monitor the professionals delivering the treatment in the study to ensure they keep to the crib sheets and standardised material. This could be done through regular follow up training and video analysis.

Limitations of the study include the fact that mechanical failure led to five cough recordings that were less than 24 hours in total duration and were therefore excluded from analysis, recordings of 4 hours or more were included in the analysis (Lee et al., 2012). Participant adherence with therapy was not measured and we are therefore unable to determine whether lack of compliance was a confounding variable for this study. However one could argue that not monitoring adherence reflects real life clinical practice and therefore the analysis is more likely to reflect changes that would be observed if the treatment was part of clinical practice. Therapist focussed elements of the PSALTI treatment were applied differently according to clinical presentation, which may be considered both a limitation and a strength of the work, in that repeatability may be reduced however real clinical practice is better reflected. The main limitation of our study was that by week 4 our sample size did not meet the trial sample size calculation based on effect size. This may have affected the power of our analyses and undermined the robustness of the results. Despite this however the sample size in our study is still larger than the pharmacological trials that have been conducted for people with refractory chronic cough (Jeyakumar et al., 2006, Morice et al., 2007b, Abdulqawi et al., 2014, Ryan et al., 2012, Dicipinigaitis and Rauf, 1998b, Mintz and Lee, 2006).

Future research and support for non-pharmacological therapies for chronic cough are needed to identify the most appropriate patients likely to gain the greatest benefit from the treatment. The optimum frequency and intensity of treatment is presently unknown as is the most cost-effective delivery. In addition the optimal combination of components of non-pharmacological interventions should be established as well as the mechanistic effects of the different components. Currently patients are only referred to non-pharmacological interventions for chronic cough when they are diagnosed as refractory. However the potential of incorporating non-pharmacological interventions for chronic cough at an earlier stage and/or in combination with pharmacological treatments could be explored.

In conclusion this study provides a compelling argument for the benefit of Physiotherapy, Speech and Language Therapy interventions in the management of refractory chronic cough. Both subjective measures of QoL and objective measures of cough frequency and urge to cough improved compared to a control. Improving access to these therapies should become local and national priorities.

CHAPTER 6
THESIS DISCUSSION
AND CONCLUSIONS

6. Thesis Discussion

The studies in this thesis have demonstrated that:

- There is a significant European burden and impairment of QoL associated with chronic cough
- PSALTI, a non-pharmacological intervention for refractory chronic cough, has been shown to significantly greater improve cough related QoL, cough frequency and urge to cough compared to control intervention.

This chapter will discuss the key findings of the studies included in this thesis as well as explore what needs to be done in future studies to build upon and further develop research into non-pharmacological interventions for refractory chronic cough.

As identified in Chapter 1 there is a need to further explore non-pharmacological interventions for refractory chronic cough due to the current failings of pharmacological treatments. The first study of this thesis was a systematic review to explore the effectiveness of previous studies of non-pharmacological interventions for refractory chronic cough. This study identified that most non-pharmacological studies have been conducted by Speech and Language therapists and Physiotherapists and therefore have mostly been named after the professions delivering the treatment; 'Speech Pathology management' (Vertigan et al., 2006, Ryan et al., 2010, Ryan et al., 2009) and 'cough-suppression Physiotherapy' (Patel et al., 2011). Though differences were found in the different non-pharmacological treatments that have been investigated there was a composite package of care that had generally been delivered consisting of education regarding cough and/or identification of cough triggers; instruction in cough suppression techniques, breathing exercises, and sometimes vocal hygiene and hydration techniques, interventions also include some form of counselling (Vertigan et al., 2006, Patel et al., 2011, Ryan et al., 2010, Ryan et al., 2009). The main

difference between the studies tended to be the terminology used for breathing exercises. However despite the different terminology, both relaxed throat breathing control techniques and breathing control/diaphragmatic breathing were used in order to relax the throat, neck and shoulder muscles whilst increasing abdominal excursion and reducing upper chest movement (Mathers-Schmidt., 2001, Bruton et al., 2011). Studies generally delivered 2 to 4 treatment sessions but the frequency of sessions varied from weekly to within 11 to 16 weeks (Chamberlain et al., 2014a).

Our review found that non-pharmacological interventions have been shown to improve cough related QoL and reduce cough reflex sensitivity. Some of the studies also showed a reduction in cough frequency and cough severity but these were not measured using validated objective outcome measures. There is a need therefore, for further studies investigating non-pharmacological interventions for refractory chronic cough. Studies require adequate sample sizes and appropriate control/placebo arm as well as the use of validated objective outcome measures (Chamberlain et al., 2014a).

Therefore our study included in this thesis of a non-pharmacological intervention for refractory chronic cough was designed to be a RCT with the inclusion of validated objective outcome measures to assess cough related QoL, cough frequency, severity, cough reflex sensitivity, patient perception of voice and mood. The non-pharmacological intervention in our study included all the treatment components described above as part of the general composite package of care of non-pharmacological treatments. However it is important to mention there will probably have been subtle differences to previous studies as there will have been differences in interpretation and delivery of the treatment components. For example education on chronic cough has been listed as a treatment component but how one study teaches this to their participants is likely to be different to another; equally the largest area for different interpretation is the counselling aspect. The number and frequency of treatment sessions included in our study was based on the previous non-pharmacological

studies; four sessions once a week. In contrast to previous studies of non-pharmacological interventions, the researchers involved in our study wanted to reflect the fact that this treatment can be delivered by both Physiotherapists and Speech and Language Therapists. Therefore the treatment was titled 'Physiotherapy, Speech and Language Therapy Intervention (PSALTI)' and involved both professions.

Our study of the efficacy of Physiotherapy, Speech and Language Therapy intervention (PSALTI) for patients with refractory chronic cough is the first multi-centred RCT of any non-pharmacological intervention for refractory chronic cough. It also is the first study to include both Physiotherapists and Speech and Language Therapists as the treating clinicians, as participants in the study who were randomised to the PSALTI arm received the same treatment, but this was either delivered by a Physiotherapist or Speech and Language Therapist depending on which site they were treated at. This reflected the clinical set up and access to allied health care professionals within respiratory outpatients for chronic cough patients at each site involved.

Our study found that PSALTI caused a significantly greater increase in cough related QoL, significantly greater decrease in cough frequency and a significantly improved urge to cough compared to control (general healthy lifestyle advice) intervention. This study has clearly shown that PSALTI is an effective treatment option for refractory chronic cough and when compared to the current pharmacological interventions one could argue it is a safer and more effective treatment option.

As discussed and described in Chapter 1 table 5 (pg 57) five main medications have been investigated for their effects on refractory chronic cough, those being; slow release Morphine, Amitriptyline, Gabapentin, Baclofen and P2X3 receptor antagonist (AF-219). In comparison to our study of PSALTI for refractory chronic cough, the quality of some of these

pharmacological studies has been poor and many of the medications have caused adverse side effects.

For the majority of the medication studies sample sizes have been small; slow release morphine (Morice et al., 2007b), Amitriptyline (Bastian et al., 2006, Jeyakumar et al., 2006), Baclofen (Dicpinigaitis and Rauf, 1998b) and P2X3 receptor antagonist (AF-219) (Abdulqawi et al., 2014) have all been investigated in studies with less than thirty participants. Baclofen has only been explored in 2 refractory chronic cough participants in Dicpinigaitis and Rauf (1998) study. Although PSALTI did not meet the sample size calculation based on effect size, the number of participants who completed treatment at four weeks (n=63) is greater than all the pharmacological studies' sample sizes. In addition to many of the pharmacological studies having small sample sizes some have included limited objective cough outcome measures. Bastian et al (2006) study of Amitriptyline and Mintz and Lee (2006) study of Gabapentin for refractory chronic included no objective cough outcome measures. Cough reflex sensitivity has only been explored in the studies of Baclofen, Morphine and Gabapentin (Dicpinigaitis and Rauf, 1998b, Morice et al., 2007b, Ryan et al., 2012). Cough frequency and cough severity have only been objectively measured in Abdulqawi et al (2014) P2X3 receptor antagonist (AF-219) trial and Ryan et al (2012) Gabapentin trial. However in the Ryan et al (2012) Gabapentin trial the cough monitor was used in a non-validated way. In comparison to our study of PSALTI we included objective cough outcome measures for cough related QoL, cough frequency, cough reflex sensitivity, cough severity and mood.

Another limitation of the pharmacological treatments for refractory chronic cough is that the majority of the medications that have shown significant beneficial results for refractory chronic cough; morphine, amitriptyline, gabapentin and P2X3 receptor antagonist (AF-219) have been found to also have significant adverse side effects. Morphine was found to cause constipation and drowsiness (Morice et al., 2007b). Gabapentin caused blurred vision,

disorientation, confusion, dizziness, dry mouth, fatigue, headaches, memory loss, nausea and stomach pains (Ryan et al., 2012). P2X3 receptor antagonist (AF-219) caused 88% of participants to have Dysgeusia, other side effects included hypogeusia, nausea, oropharyngeal pain, headaches, salivary hypersecretion, cough, anosmia, constipation, GORD, glossodynia, depressed mood and blurred vision (Abdulqawi et al., 2014). A number of participants in each of the above trials subsequently withdrew from the studies due to these side effects.

This thesis has established there is a clear role for non-pharmacological interventions for refractory chronic cough and there are potentially benefits of these treatments over the conventional pharmacological therapy. However our study of PSALTI in this thesis is only one of the beginning steps into exploring the role of non-pharmacological interventions for refractory chronic cough. More research is required to determine the optimum treatment components, treatment frequency and duration, as well as the mechanisms behind the beneficial effects of the treatment.

With regards to exploring the mechanisms of action this was not an aim of our PSALTI study however the sub-analysis of the trial data highlighted some interesting findings regarding breathing pattern dysfunction, which is an aspect that may shed some light on a mechanism of action of the PSALTI treatment. Our PSALTI study is the first study to explore breathing pattern dysfunction in people with refractory chronic cough. Prior to treatment 50% of participants in the study whose breathing pattern was assessed were found to have breathing pattern dysfunction with an increased apical breathing pattern. Interestingly it was only those who improved their breathing pattern technique in the PSALTI arm who had significant improvements in cough related QoL, cough severity and borderline significant improvements in cough frequency. Those in the PSALTI arm whose breathing pattern remained unchanged (and showed no evidence of dysfunction) at the end of the study showed no significant improvements in any of the outcome measures.

As discussed in Chapter 5, in our study breathing pattern was only assessed on a limited number of participants and was assessed by observation by the leading Physiotherapist in the trial. Future studies are required that investigate breathing pattern in people with refractory chronic cough using an objective outcome measure. If an abnormal breathing pattern is still observed when compared to healthy adults using an objective measurement tool, then future studies investigating non-pharmacological treatments for refractory chronic cough should include objective measurement of breathing pattern.

As to which objective measure should be used Respiratory Inductive Plethysmography has been used in other respiratory diseases to measure breathing pattern including COPD and Asthma (Cancelliero-Gaiad et al., 2014, Tobin et al., 1983). Respiratory Inductive Plethysmography devices consist of two elastic straps which contain a coil of wire (transducer) embedded in each; one strap is placed around the ribcage and the other around the abdomen, both are connected to an oscillator and computer. The self-inductance of the coils and the frequency of their oscillations are altered by changes in the cross-sectional area of the ribcage and the abdomen which reflects changes in volume of the ribcage and abdomen (Cancelliero-Gaiad et al., 2014). A number of different measurements can be taken from Respiratory Inductive Plethysmography including tidal volume, respiratory rate, inspiratory and expiratory time, minute ventilation, percent rib cage inspiratory contribution to tidal volume ratio and laboured breathing index (which is the ratio of the sum of the ribcage and abdomen inspiratory volumes divided by the corresponding tidal volume), (Warren et al., 1997, Cancelliero-Gaiad et al., 2014).

Another type of plethysmography, structured light plethysmography (SLP) which is a non-contact method of monitoring lung function and chest wall movement, is a new device still undergoing early studies and development but may be an alternative to the Respiratory Inductive Plethysmography device described above (Alimohamed et al., 2011). This device projects a light grid onto a patient's thoraco-abdominal surface, which is imaged by two

cameras. This therefore gives a 3D reconstruction of the patient's thoraco-abdominal surface whilst the patient breathes (Alimohamed et al., 2011).

For assessment of breathing pattern in refractory chronic cough these plethysmography devices need to be investigated in this patient group, to determine which is the most appropriate device for assessment of breathing pattern. The most appropriate device then needs to be used to objectively measure breathing pattern in people with refractory chronic cough and compare this to healthy adults. If a difference is established this measurement should then be incorporated into future studies of non-pharmacological interventions for refractory chronic cough to see if changes in breathing pattern is a mechanism of action of the treatment.

As well as breathing exercises, PSALTI and other non-pharmacological interventions have included as part of the treatment; vocal hygiene and hydration, education regarding chronic cough, cough suppression techniques as well as counselling or anxiety management regarding the cough. Therefore these other components of treatment need to be investigated in future studies to see if they are part of the mechanism of action of the treatment.

With regards to vocal cord hydration, phonation threshold pressure (PTP) is a measurement which measures the minimum amount of pressure required for the vocal folds to vibrate (Vertigan et al., 2006). It measures the ease of phonation, as the ease of phonation is affected by the biomechanics of the vocal cords (the tissue thickness, elasticity and viscosity) PTP has been used to give an indication of the hydration status of the vocal cords (Sivasankar and Leydon, 2010). Greater hydration of the vocal cords lowers the vocal cords viscosity and therefore reduces PTP. The opposite has also been shown, that dehydration causes an increase in PTP (Sivasankar and Leydon, 2010). Although studies by Vertigan et al (Vertigan et al., 2007b, Vertigan et al., 2006) have mentioned PTP as being an indication of vocal cord hydration, this outcome measure has not be used or studied in people with

refractory chronic cough; neither prior to treatment or after non-pharmacological treatment. As discussed above for using Plethysmography to measure breathing pattern, initially for measuring PTP the most effective method needs to be investigated to be used to measure PTP in people with refractory chronic cough. Comparisons could then be made with healthy aged matched participants. PTP may also prove to be of value in other non-pharmacological intervention studies for refractory chronic cough examining the effect of the treatment on vocal cord hydration.

Treatment for anxiety and stress related to the chronic cough was included in the PSALTI study. In our study we used HADS as our outcome measure for refractory chronic cough. This outcome measure did not detect significant levels of anxiety and depression in our refractory chronic cough population. However this does not reflect opinions shared by the participants in the study with the treating clinicians. This raises the debate as to whether this is the most appropriate and specific measure for measuring anxiety and depression in people with refractory chronic cough. As discussed in chapter 5 disease specific tools have been found to have greater responsiveness than generic tools (Wiebe et al., 2003). Therefore maybe a more specific tool for refractory chronic cough needs to be developed to measure anxiety and depression.

Education and counselling was included in PSALTI and has been in other non-pharmacological studies of refractory chronic cough. How we measure the effectiveness of this is tricky however the aim of this aspect of the treatment is to increase a person's understanding of their chronic cough, understand the non-pharmacological treatment they are undertaking and increase their ability to self-manage their chronic cough symptoms. Illness perception has been measured in other conditions such as diabetes and asthma using illness perception questionnaires (IPQ). IPQs measure an individual's response to a perceived health threat, how a person perceives a health threat involves the individual's perception of their illness, the behaviours they adopt to cope with the illness and their

perceived efficacy of their behaviours to cope with their illness (Broadbent et al., 2006). IPQs cover the five dimensions of cognitive representation of illness: identity, consequences, cause, timeline and cure or control. Identity being the terms a person uses to describe the condition or symptoms; consequences being the expected effects of the condition; cause is the person's perceived cause of the condition; timeline is how long the person expects to have the condition and cure or control is the person's expectation of the likelihood of recovering from the condition (Broadbent et al., 2006). Changing a person's perception of their illness has been shown to improve recovery in conditions such as myocardial infarction, asthma, diabetes and AIDS (Petrie et al., 2003).

Illness perception has not been explored in refractory chronic cough, there may be some value in considering this outcome in this population and exploring illness perception pre and post treatment. There are a number of IPQs that could be used: IPQ was the first questionnaire designed, this is 38 item questionnaire (Weinman et al., 1996); IPQ-revised was a revision of the original IPQ and is a 80 item questionnaire (Moss-Morris et al., 2002) and the Brief IPQ is a nine item questionnaire (Broadbent et al., 2006). Again as with Plethysmography and PTP the most appropriate measure for illness perception would need to be explored for people with refractory chronic cough. A benefit of all these IPQs is that the wording of the questions can be made specific to chronic cough as it has been done for other conditions.

Lastly another measurement that is important to include in future studies of non-pharmacological interventions of refractory chronic cough is urge to cough assessment. PSALTI as well as other non-pharmacological interventions aim to reduce the hypersensitivity of the cough reflex and teach participants cough suppression techniques to suppress their cough. Therefore assessment of urge to cough can provide a measure of whether participants' perception of the urge to cough has changed. Unlike the above measures discussed this assessment was included in the PSALTI study and was included in

Ryan et al (2001) study of speech pathology management for refractory chronic cough. Both studies showed a significant improvement in urge to cough following treatment.

Once initial studies have been completed that explore the best outcome measures to investigate breathing pattern, PTP, anxiety and depression as well as illness perception in people with refractory chronic cough and these have been explored in people with refractory chronic cough compared to healthy adults. There should be a clearer understanding of which components of PSALTI and other non-pharmacological interventions are essential and may be involved in the mechanism of action. This could then allow the current treatments to be revised, removing elements that may not have beneficial results and re-emphasising those that do. Finally a large scale multi-centred trial could then be performed of this revised treatment using the outcome measures identified to explore the mechanism of action, whilst also exploring the optimum frequency and duration of treatment. This could be completed by designing the study to have different groups receiving treatment over different durations and with different frequencies of the treatment sessions. The study would have to be sufficiently powered though to allow this subgroup analysis and therefore only a few variations in frequency and duration of treatments would be able to be studied. Cost effectiveness analysis is another aspect that would need to be included as this needs to be explored prior to recommending non-pharmacological interventions becoming part of routine clinical practice.

Additionally to exploring the mechanisms of action of PSALTI and other non-pharmacological treatments for refractory chronic cough, the timing of when patients should be referred to these treatments also needs to be reviewed. People with refractory chronic cough tend to only be referred to non-pharmacological interventions once they have completed extensive medical investigations and treatment trials for the main causes of chronic cough, and then after trialling medications to treat refractory chronic cough. In our study of PSALTI participants prior to the study had, had their cough for up to 45 years, with a third of our

participants having had their cough for over 8 years. Why should refractory chronic cough patients wait this length of time to trial non-pharmacological interventions? Why are these treatments not implemented earlier either as a sole treatment option or alongside medical treatment for refractory chronic cough. An argument could also be made that non-pharmacological treatments could be delivered even before a person is diagnosed as refractory chronic cough and may even have benefits for a broader range of chronic cough patients. This is an area that needs further exploration and development.

The need to further develop treatment options in chronic cough and refractory chronic cough specifically is not just a highlighted priority by researchers and clinicians but was also highlighted by respondents in our European chronic cough survey (Chamberlain et al., 2015a). Respondents' opinions on the effectiveness of their current treatment options and management was poor and the main aspect they wanted more information on was treatment options.

6.1 Conclusions

This thesis has provided a greater insight into the impact chronic cough has across Europe and gathered opinions of those with chronic cough on the current treatment and management of the condition. It has highlighted that people with refractory chronic cough want more information to be made available on chronic cough with the priorities being information on treatment and causes. This survey also highlighted that advances need to be made in the treatment and management of chronic cough due to current perceived poor efficacy of these by those with chronic cough.

The main findings of this thesis are related to the non-pharmacological management of refractory chronic cough. This thesis has shown that Physiotherapy, Speech and Language Therapy Intervention (PSALTI) is an effective treatment option for people with refractory chronic cough. PSALTI was shown to significantly improve cough related QoL, reduce cough

frequency and improve participants' perceived urge to cough greater than control in a multi-centred RCT.

**ABSTRACTS OF PRESENTATIONS PRESENTED
AT CONFERENCES FROM WORK FROM THESIS**

7. Conference Abstracts and Presentations arising from Thesis studies

7.1 Evaluation of Vocal Performance questionnaire in people with chronic refractory cough abstract presented at European Respiratory Society Conference September 2013 (Chamberlain et al., 2013a)

Background: Perceptual voice analysis has shown a high prevalence of abnormal voice quality in people with chronic refractory cough (CRC). However little is known regarding patients' perception of voice in this population.

Aims: This study aims to explore vocal problems using the Vocal Performance Questionnaire (VPQ) and to evaluate its possible relationships with cough outcome measures.

Methods: 27(10 male) people with CRC, defined as cough>8weeks and refractory to medical management, completed Leicester Cough Questionnaire (LCQ), capsaicin cough challenge (log C5), cough frequency (24 hour Leicester Cough Monitor); and severity (VAS) outcome measures. The VPQ; a 12 item tool assesses impact of voice disorders with a score >12 indicating dysphonia. It has not previously been used in CRC. Mann-U Whitney and Spearman's statistical tests were performed.

Results: Of 27 CRC participants, mean age 58 (SD:13); 17 reported a change in voice since onset of cough, 22 reported talking as a trigger for cough and 19 laughing. When VPQ scores for those participants who reported voice changes were compared to those who did not, there was a significant difference; median (IQR), 22(13) for those who reported voice changes, and 12(6) ($p=0.02$) for those who did not. A significant correlation was found between VPQ and cough frequency per hour ($r=0.42$, $p=0.039$), but not between VPQ and LCQ ($r_s=-0.16$, $p=0.444$); capsaicin cough challenge ($r_s=-0.30$, $p=0.146$); and VAS ($r_s=0.06$, $p=0.786$).

Conclusions: This study shows that VPQ may be a useful tool to assess voice impairment in CRC and that an increased cough frequency was associated with a higher VPQ score; therefore an increased patient perceived dysphonia.

7.2 The Impact of chronic cough: A European perspective abstract presented as a poster at European Respiratory Society Conference September 2013 (Chamberlain et al., 2013c)

Background and Aims: In collaboration, the European Lung Foundation (ELF) and European Respiratory Society Chronic cough Taskforce launched a European-wide patient survey to explore the management and impact of chronic cough in Europe.

Methods: An Internet based survey was launched in January 2012 on the ELF website and was available in 12 languages by October 2012. The survey was promoted via Google through a Google Ad account, and was promoted by the ELF. Survey responses were collected between 05/01/2012 and 06/01/2013 and are reported as an interim analysis, with Chi-Square analysis to explore relationships between variables.

Results: 1868 subjects responded; 1234 responses were excluded due to incomplete demographic data, non-European responses, age <18 years, or cough duration <2 months.

634 (66% females) responses from 28 European countries were analysed. Mean age was 50 (SD:15) years, median cough duration ≥ 10 years, and 84% were non-smokers. Only 56% reported they had been given a diagnosis, despite 93% having seen a doctor regarding their cough. Asthma was the most common diagnosis at 13%. 97% reported their quality of life was impaired and 95% reported a limitation in the activities they liked to do due to their cough; females compared to males reported a significantly greater limitation ($p=0.004$). 95% reported their cough worried or disturbed their family or friends and 93% felt fed-up or depressed at least sometimes, the latter was significantly greater in women ($p=0.004$).

Conclusions: This European survey highlights many patients with chronic cough are undiagnosed, or unaware of their diagnosis, and the impact of chronic cough on daily life and mood is considerable.

7.3 Breathing pattern characteristics in refractory chronic cough patients abstract as a Platform presentation at Physiotherapy UK Conference October 2013

Introduction: Cough suppression treatment (CST) programmes have been shown to be effective in reducing cough symptoms for chronic cough (CC) sufferers refractory to medical management. Breathing pattern retraining exercises are included as a component in CST. However little is known regarding the baseline breathing pattern characteristics of CC sufferers.

Relevance: Initially CST programmes were developed by speech and language therapists and therefore the effects of breathing exercises have focused on the larynx. However clinically both physiotherapists and Speech and Language therapists are now involved in treating CC sufferers. A greater understanding of CC sufferers' breathing patterns would help to increase understanding of the possible effects and mechanisms of breathing patterns on cough.

Participants: n=30 (11males) refractory CC sufferers were recruited. Median cough duration 42 months (IQR 117), mean age 58(SD:12).

Methods: Breathing pattern was assessed in sitting, over 1 minute by one trained respiratory physiotherapist. Normal RR was defined as 12-16. Route and region of most movement during breathing was also recorded and documented as mostly upper chest movement (UCM) or abdominal movement (ABM).

Analysis: Mann-U Whitney and Spearman's test were used.

Results: We found that 50% of the participants had increased UCM on examination, 33% had an increased RR, and 13% had a reduced RR. RR significantly correlated with breathing pattern ($r_s=0.44$, $p=0.02$) and when UCM breathers were compared to ABM breathers a significant difference in respiratory rate was found ($p=0.02$).90% of the participants were nose breathers.

Conclusion: These preliminary data show that a high proportion of CC sufferers had increased UCM, and a third had an increased RR.

Implications: These data provide some evidence to support the role of breathing pattern retraining techniques in people with CC. However more research is needed in this area to investigate further the effects of different breathing patterns on cough and whether CST is effective in changing breathing patterns.

7.4 Efficacy of a Physiotherapy, Speech and Language Therapy Intervention (PSALTI) on cough health related quality of life (HRQoL) for patients with refractory chronic cough (RCT) abstract presented as a Poster Discussion at the BTS Conference December 2014 (Chamberlain et al., 2014b)

Introduction: Refractory chronic cough has a significant negative impact on HRQoL. There are currently limited effective antitussive therapies. Few studies have explored the effectiveness of nonpharmacological interventions for refractory chronic cough. This study investigated the efficacy of PSALTI on HRQoL for people with refractory chronic cough in a multi-centred RCT.

Methods: Participants were recruited across five NHS hospitals trusts. 76 participants were randomised to PSALTI or placebo (equal attention) intervention. PSALTI consisted of education, laryngeal hygiene and hydration advice, cough control techniques and psycho-educational counselling. Placebo consisted of general education on exercise, diet, stress and relaxation. Both groups attended 4 weekly sessions of 1:1 therapy. HRQoL was measured at baseline, four weeks (end of treatment) and 3 month follow up by Leicester cough questionnaire (LCQ). Cough reflex sensitivity was assessed at baseline and four weeks by capsaicin cough challenge (C2, C5, concentration that caused first urge to cough (Cu)) and was analysed by geometric means (GM). Outcomes between groups were analysed using ANCOVA.

Results: The PSALTI (n=35) and Placebo groups (n=41) were well matched ($p>0.05$) for age [mean (SD)] 58(15) vs. 56(11) years; gender 71% vs 63% females; cough duration [median (IQR)] 60(30 to 126) vs 48(24 to 126) months and baseline LCQ [mean (SD)] 10.4(3.6) vs 11.9(3.5). At four weeks HRQoL improved in both groups, mean LCQ increase in PSALTI was 3.4 (95%CI 2.26 to 4.55) vs placebo 1.7 (95%CI 0.78 to 2.54); difference in LCQ change between groups was 1.5 (95%CI 0.27 to 7.31, $p=0.02$) points more on average in the PSALTI group. This effect is greater than the MCID for LCQ and was sustained at 3 months (mean difference change between groups after 4 weeks to 3 months was -0.28 (95%CI -1.83 to 1.38). There was a significant increase in Cu in the PSALTI group compared to placebo (GM(SD) change $2\mu\text{m}(5.07)$ vs $0.612\mu\text{m}(3.26)$, $p=0.02$). There was no significant difference in cough reflex sensitivity between the groups (C2, $p=0.46$; C5, $p=0.74$).

Conclusions: PSALTI significantly improved HRQoL compared with equal attention placebo intervention and this improvement was sustained at three months. PSALTI also significantly increased Cu compared to placebo.

7.5 World Congress Physical Therapy Conference Abstract presented as a platform presentation in May 2015 (Chamberlain et al., 2015b)

Background: Chronic cough (cough present for >8 weeks) has an estimated prevalence of approximately 12% in the general population and causes significant physical and psychosocial morbidity. In up to 42% of cases, despite extensive investigations and treatments trials, the cause of cough remains unexplained, often called refractory chronic cough. Physiotherapy and speech and language therapy are emerging nonpharmacological treatments for refractory chronic cough. The efficacy of these treatments have not been evaluated with objective cough outcome measures in a randomised control trial (RCT).

Purpose: This study aimed to assess the effect of Physiotherapy, speech and language therapy intervention (PSALTI) on quality of life (QoL), severity, frequency and reflex sensitivity of cough for patients suffering with refractory chronic cough.

Methods: A multi-centre, single blinded RCT was conducted across five hospitals. Eligible patients were adults diagnosed with refractory chronic cough. Participants were randomised to PSALTI or placebo intervention. PSALTI consisted of education, laryngeal hygiene and hydration advice, cough control techniques and psycho-educational counselling. Placebo consisted of general education on exercise, diet, stress and relaxation. Both groups attended 4 weekly sessions of 1:1 therapy. Outcome measures included were: Leicester cough questionnaire (LCQ- cough related QoL questionnaire, primary outcome); Capsaicin cough challenge to assess cough reflex sensitivity (concentration that caused 5 or more coughs (C5), concentration that caused first urge to cough (Cu)); Leicester cough monitor (LCM) to assess cough frequency (ambulatory cough-monitoring device worn for 24 hours); Visual analogue scale (VAS) to assess cough severity (0-100mm); Short-form 36 (SF-36) to assess general QoL and hospital anxiety and depression scale (HADS) to assess mood and anxiety. With the exception of Capsaicin cough challenge all measures were completed at baseline, 4 weeks (end of treatment) and 3 months. Differences in baseline characteristics were analysed using Mann-Whitney or independent t-test. Between group analysis was assessed using analysis of covariance (ANCOVA).

Results: 76 participants were randomised post baseline assessment for the trial. Both PSALTI (n=35) and placebo (n=41) arms were well matched for baseline characteristics. At 4 weeks mean LCQ scores had improved in both arms but the PSALTI arm improved more than placebo (Mean difference (MD) 1.53, 95% CI 0.21 to 2.85, p=0.02). The difference between arms appeared to be sustained up to 3 months. The PSALTI arm had a greater decrease in cough frequency than placebo (MD 41%, 95% CI 5% to 64%, p=0.03) and greater increase in their tolerance to capsaicin before reporting an urge to cough (MD 3.1, 95% CI 0.6 to 5.6, p=0.02). No significant differences between groups were found for SF-36, HADS, VAS or C5.

Conclusions: PSALTI significantly improved cough related QoL, decreased cough frequency and improved patients' tolerance to capsaicin before reporting an urge to cough compared with placebo intervention.

Implications: This study is the first to provide evidence for the efficacy of this new Physiotherapy treatment for RCC within a multi-centred RCT with validated outcomes. It will hopefully promote the need for Physiotherapy in this new and exciting area.

References

- Abdulqawi, R., Dockry, R., Holt, K., Layton, G., McCarthy, B. G., Ford, A. P. and Smith, J. A. (2014) 'P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study', *Lancet*, 385(9974), pp.1198-1205.
- Adams, R. J., Appleton, S. L., Wilson, D. H., Taylor, A. W. and Ruffin, R. E. (2009) 'Associations of physical and mental health problems with chronic cough in a representative population cohort', *Cough*, 5, pp. 10-18.
- Alimohamed, S., Prosser, K., Weerasuriya, C., Iles, R., Cameron, J., Lasenby, J. and Fogarty, C. (2011) 'P134 Validating structured light plethysmography (SLP) as a non-invasive method of measuring lung function when compared to Spirometry', *Thorax*, 66(Suppl 4), pp. A121-A121.
- Barbee, R. A., Halonen, M., Kaltenborn, W. T. and Burrows, B. (1991) 'A longitudinal study of respiratory symptoms in a community population sample. Correlations with smoking, allergen skin-test reactivity, and serum IgE', *Chest*, 99(1), pp. 20-6.
- Barry, S. J., Dane, A. D., Morice, A. H. and Walmsley, A. D. (2006) 'The automatic recognition and counting of cough', *Cough*, 2, pp. 8.
- Bastian, R. W., Vaidya, A. M. and Delsupehe, K. G. (2006) 'Sensory neuropathic cough: a common and treatable cause of chronic cough', *Otolaryngol Head Neck Surg*, 135(1), pp. 17-21.
- Belvisi, M. G. and Geppetti, P. (2004) 'Cough • 7: Current and future drugs for the treatment of chronic cough', *Thorax*, 59(5), pp. 438-440.
- Bickerman, H. A. and Barach, A. L. (1954) 'The experimental production of cough in human subjects induced by citric acid aerosols; preliminary studies on the evaluation of antitussive agents', *Am J Med Sci*, 228(2), pp. 156-63.
- Bier, S. and Watson, C. (2012) 'Electroglottographic Analysis of Young and Old Speakers of New Zealand English', *14th Australasian International Conference on Speech Science and Technology*, Sydney, Australia: The Australasian Speech Science & Technology Association Incorporated, pp.65-69.
- Birring, S. S. (2011) 'Controversies in the evaluation and management of chronic cough', *Am J Respir Crit Care Med*, 183(6), pp. 708-15.
- Birring, S. S., Brightling, C. E., Symon, F. A., Barlow, S. G., Wardlaw, A. J. and Pavord, I. D. (2003a) 'Idiopathic chronic cough: association with organ specific autoimmune disease and bronchoalveolar lymphocytosis', *Thorax*, 58(12), pp. 1066-70.
- Birring, S. S., Fleming, T., Matos, S., Raj, A. A., Evans, D. H. and Pavord, I. D. (2008) 'The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough', *Eur Respir J*, 31(5), pp. 1013-8.
- Birring, S. S., Morgan, A. J., Prudon, B., McKeever, T. M., Lewis, S. A., Falconer Smith, J. F., Robinson, R. J., Britton, J. R. and Pavord, I. D. (2003b) 'Respiratory symptoms in patients with treated hypothyroidism and inflammatory bowel disease', *Thorax*, 58(6), pp. 533-6.

- Birring, S. S., Murphy, A. C., Scullion, J. E., Brightling, C. E., Browning, M. and Pavord, I. D. (2004a) 'Idiopathic chronic cough and organ-specific autoimmune diseases: a case-control study', *Respir Med*, 98(3), pp. 242-6.
- Birring, S. S., Parker, D., Brightling, C. E., Bradding, P., Wardlaw, A. J. and Pavord, I. D. (2004b) 'Induced sputum inflammatory mediator concentrations in chronic cough', *Am J Respir Crit Care Med*, 169(1), pp. 15-9.
- Birring, S. S. and Pavord, I. D. (2009) 'Assessment of gender differences in health status with the Leicester Cough Questionnaire (LCQ)', *Thorax*, 64(11), pp. 1008-9.
- Birring, S. S., Prudon, B., Carr, A. J., Singh, S. J., Morgan, M. D. and Pavord, I. D. (2003c) 'Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ)', *Thorax*, 58(4), pp. 339-43.
- Blager, F. B., Gay, M. L. and Wood, R. P. (1988) 'Voice therapy techniques adapted to treatment of habit cough: a pilot study', *J Commun Disord*, 21(5), pp. 393-400.
- Bolser, D. C., DeGennaro, F. C., O'Reilly, S., Chapman, R. W., Kreutner, W., Egan, R. W. and Hey, J. A. (1994) 'Peripheral and central sites of action of GABA-B agonists to inhibit the cough reflex in the cat and guinea pig', *Br J Pharmacol*, 113(4), pp. 1344-8.
- Brazier, J. E., Harper, R., Jones, N. M., O'Cathain, A., Thomas, K. J., Usherwood, T. and Westlake, L. (1992) 'Validating the SF-36 health survey questionnaire: new outcome measure for primary care', *BMJ*, 305(6846), pp. 160-4.
- Brignall, K., Jayaraman, B. and Birring, S. S. (2008) 'Quality of life and psychosocial aspects of cough', *Lung*, 186 Suppl 1, pp. S55-8.
- Broadbent, E., Petrie, K. J., Main, J. and Weinman, J. (2006) 'The brief illness perception questionnaire', *J Psychosom Res*, 60(6), pp. 631-7.
- Bruton, A., Garrod, R. and Thomas, M. (2011) 'Respiratory physiotherapy: towards a clearer definition of terminology', *Physiotherapy*, 97(4), pp. 345-9.
- Cancelliero-Gaiad, K. M., Ike, D., Pantoni, C. B., Borghi-Silva, A. and Costa, D. (2014) 'Respiratory pattern of diaphragmatic breathing and pilates breathing in COPD subjects', *Braz J Phys Ther*, 18(4), pp. 291-9.
- Canning, B. (2009) 'Central regulation of the cough reflex: therapeutic implications', *Pulmonary Pharmacology & Therapeutics*, 22, pp. 75-81.
- Canning, B. J., Chang, A. B., Bolser, D. C., Smith, J. A., Mazzone, S. B. and McGarvey, L. (2014) 'Anatomy and Neurophysiology of Coughing: CHEST Guideline and Expert Panel Report', *Chest*. 146(6), pp. 1633-48.
- Canning, B. J., Mori, N. and Mazzone, S. B. (2006) 'Vagal afferent nerves regulating the cough reflex', *Respiratory Physiology & Neurobiology*, 152(3), pp. 223-242.
- Carding, P. N. and Horsley, I. A. (1992) 'An evaluation study of voice therapy in non-organic dysphonia', *Eur J Disord Commun*, 27(2), pp. 137-58.

- Carding, P. N., Wilson, J. A., MacKenzie, K. and Deary, I. J. (2009) 'Measuring voice outcomes: state of the science review', *J Laryngol Otol*, 123(8), pp. 823-9.
- Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D. and Julius, D. (1997) 'The capsaicin receptor: a heat-activated ion channel in the pain pathway', *Nature*, 389(6653), pp. 816-24.
- Cerveri, I., Accordini, S., Corsico, A., Zoia, M. C., Carrozzi, L., Cazzoletti, L., Beccaria, M., Marinoni, A., Viegi, G., de Marco, R. and Group, I. S. (2003) 'Chronic cough and phlegm in young adults', *Eur Respir J*, 22(3), pp. 413-7.
- Chamberlain, S., Birring, S., Clark, L., Douiri, A. and Garrod, R. (2013a) 'Evaluation of vocal performance questionnaire in people with chronic refractory cough.', *European Respiratory Journal*, 42(Suppl 57), pp. P1338.
- Chamberlain, S., Birring, S. S. and Garrod, R. (2014a) 'Nonpharmacological interventions for refractory chronic cough patients: systematic review', *Lung*, 192(1), pp. 75-85.
- Chamberlain, S., Garrod, R. and Birring, S. S. (2013b) 'Cough suppression therapy: does it work?', *Pulm Pharmacol Ther*, 26(5), pp. 524-7.
- Chamberlain, S., Masefield, S., Powell, P., Douiri, A., Garrod, R., Morice, A. and Birring, S. (2013c) 'The impact of chronic cough: A European perspective', *European Respiratory Journal*, 42(Suppl 57).
- Chamberlain, S. A., Garrod, R., Douiri, A., Masefield, S., Powell, P., Bücher, C., Pandyan, A., Morice, A. H. and Birring, S. S. (2015a) 'The Impact of Chronic Cough: A Cross-Sectional European Survey', *Lung*, 193, pp. 401-408.
- Chamberlain, S. A. F., Birring, S. S., Clarke, L., Douiri, A., Pandyan, A. and Garrod, R. (2015b) 'Efficacy of a physiotherapy, speech and language therapy intervention (PSALTI) for patients with refractory chronic cough: a multi-centred RCT', *Physiotherapy*, 101, Supplement 1, pp. e206-e207.
- Chamberlain, S. A. F., Birring, S. S., Clarke, L., Douiri, A., Parker, S. M., Fowler, S. J., Hull, J., Chung, K. F., Pandyan, A. and Garrod, R. (2014b) 'P3 Efficacy Of A Physiotherapy, Speech And Language Therapy Intervention (psalti) On Health Related Quality Of Life (hrqol) For Patients With Refractory Chronic Cough: A Randomised Control Trial', *Thorax*, 69(Suppl 2), pp. A78-A78.
- Check, J. and Schutt, R. K. (2012). *Research Methods in Education*. USA: SAGE Publications Inc.
- Cho, Y. S., Park, S. Y., Lee, C. K., Yoo, B. and Moon, H. B. (2003) 'Elevated substance P levels in nasal lavage fluids from patients with chronic nonproductive cough and increased cough sensitivity to inhaled capsaicin', *J Allergy Clin Immunol*, 112(4), pp. 695-701.
- Choudry, N. B., Fuller, R. W., Anderson, N. and Karlsson, J. A. (1990) 'Separation of cough and reflex bronchoconstriction by inhaled local anaesthetics', *Eur Respir J*, 3(5), pp. 579-83.
- Choudry, N. B., Fuller, R. W. and Pride, N. B. (1989) 'Sensitivity of the human cough reflex: effect of inflammatory mediators prostaglandin E2, bradykinin, and histamine', *Am Rev Respir Dis*, 140(1), pp. 137-41.

- Chung, K. F. (2007) 'Chronic cough: future directions in chronic cough: mechanisms and antitussives', *Chron Respir Dis*, 4(3), pp. 159-65.
- Chung, K. F. (2009) 'Clinical cough VI: the need for new therapies for cough: disease-specific and symptom-related antitussives', *Handb Exp Pharmacol*, (187), pp. 343-68.
- Chung, K. F. (2014) 'Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome', *J Thorac Dis*, 6(Suppl 7), pp. S699-707.
- Chung, K. F., McGarvey, L. and Mazzone, S. B. (2013) 'Chronic cough as a neuropathic disorder', *The Lancet*, 1(5), pp.414-422.
- Chung, K. F. and Pavord, I. D. (2008) 'Prevalence, pathogenesis, and causes of chronic cough', *The Lancet*, 371(9621), pp. 1364-1374.
- Cohen, S. M. and Misono, S. (2013) 'Use of Specific Neuromodulators in the Treatment of Chronic, Idiopathic Cough: A Systematic Review', *Otolaryngology -- Head and Neck Surgery*, 148(3), pp. 374-382.
- Collier, J. G. and Fuller, R. W. (1984) 'Capsaicin inhalation in man and the effects of sodium cromoglycate', *Br J Pharmacol*, 81(1), pp. 113-7.
- Cope, W. (2011) 'The Cougher', *Family Values*. London: Faber and Faber.
- Coultas, D. B., Mapel, D., Gagnon, R. and Lydick, E. (2001) 'The health impact of undiagnosed airflow obstruction in a national sample of United States adults', *Am J Respir Crit Care Med*, 164(3), pp. 372-7.
- Coyle, M. A., Keenan, D. B., Henderson, L. S., Watkins, M. L., Haumann, B. K., Mayleben, D. W. and Wilson, M. G. (2005) 'Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease', *Cough*, 1, pp. 3.
- Crown, S. and Crisp, A. H. (1966) 'A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.)', *Br J Psychiatry*, 112(490), pp. 917-23.
- Cullinan, P. (1992) 'Persistent cough and sputum: prevalence and clinical characteristics in south east England', *Respir Med*, 86(2), pp. 143-9.
- D'Agostino, R. B. (2009) 'The delayed-start study design', *N Engl J Med*, 361(13), pp. 1304-6.
- Davenport, P. W. (2008) 'Urge-to-cough: what can it teach us about cough?', *Lung*, 186 Suppl 1, pp. S107-11.
- Davenport, P. W., Bolser, D. C., Vickroy, T., Berry, R. B., Martin, A. D., Hey, J. A. and Danzig, M. (2007) 'The effect of codeine on the Urge-to-Cough response to inhaled capsaicin', *Pulm Pharmacol Ther*, 20(4), pp. 338-46.
- Dejonckere, P. H., Bradley, P., Clemente, P., Cornut, G., Crevier-Buchman, L., Friedrich, G., Van De Heyning, P., Remacle, M. and Woisard, V. (2001) 'A basic protocol for functional assessment of voice pathology, especially for investigating the efficacy of (phonosurgical) treatments and evaluating new assessment techniques. Guideline elaborated by the

Committee on Phoniatrics of the European Laryngological Society (ELS)', *Eur Arch Otorhinolaryngol*, 258(2), pp. 77-82.

- Dickinson, R. S., Morjaria, J. B., Wright, C. E. and Morice, A. H. (2014) 'Is opiate action in cough due to sedation?', *Ther Adv Chronic Dis*, 5(5), pp. 200-5.
- Dicpinigaitis, P. V. (2003) 'Short- and long-term reproducibility of capsaicin cough challenge testing', *Pulm Pharmacol Ther*, 16(1), pp. 61-5.
- Dicpinigaitis, P. V. (2004) 'Cough. 4: Cough in asthma and eosinophilic bronchitis', *Thorax*, 59(1), pp. 71-2.
- Dicpinigaitis, P. V., Allusson, V. R., Baldanti, A. and Nalamati, J. R. (2001) 'Ethnic and gender differences in cough reflex sensitivity', *Respiration*, 68(5), pp. 480-2.
- Dicpinigaitis, P. V. and Rauf, K. (1998a) 'The influence of gender on cough reflex sensitivity', *Chest*, 113(5), pp. 1319-21.
- Dicpinigaitis, P. V. and Rauf, K. (1998b) 'Treatment of chronic, refractory cough with baclofen', *Respiration*, 65(1), pp. 86-8.
- Dicpinigaitis, P. V., Rhoton, W. A., Bhat, R. and Negassa, A. (2012) 'Investigation of the urge-to-cough sensation in healthy volunteers', *Respirology*, 17(2), pp. 337-41.
- Dicpinigaitis, P. V., Tso, R. and Banauch, G. (2006) 'Prevalence of depressive symptoms among patients with chronic cough*', *CHEST Journal*, 130(6), pp. 1839-1843.
- Dreary, I. J., Wilson, J. A., Garding, P. N. and Mackenzie, K. (2003) 'Voiss: A patient derived voice symptom scale', *Journal of Psychosomatic Research*, 54(5), pp. 483-489.
- Everett, C. F., Kastelik, J. A., Thompson, R. H. and Morice, A. H. (2007) 'Chronic persistent cough in the community: a questionnaire survey', *Cough*, 3, pp. 5-11.
- Falconer, A., Oldman, C. and Helms, P. (1993) 'Poor agreement between reported and recorded nocturnal cough in asthma', *Pediatr Pulmonol*, 15(4), pp. 209-11.
- Farrell, M. J., Cole, L. J., Chiapoco, D., Egan, G. F. and Mazzone, S. B. (2012) 'Neural correlates coding stimulus level and perception of capsaicin-evoked urge-to-cough in humans', *Neuroimage*, 61(4), pp. 1324-35.
- Felisbino, M. B., Steidle, L. J., Gonçalves-Tavares, M., Pizzichini, M. M. and Pizzichini, E. (2014) 'Leicester Cough Questionnaire: translation to Portuguese and cross-cultural adaptation for use in Brazil', *J Bras Pneumol*, 40(3), pp. 213-21.
- Fletcher, K. E., French, C. T., Irwin, R. S., Corapi, K. M. and Norman, G. R. (2010) 'A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure', *J Clin Epidemiol*, 63(10), pp. 1123-31.
- Ford, A. C., Forman, D., Moayyedi, P. and Morice, A. H. (2006) 'Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms', *Thorax*, 61(11), pp. 975-9.

- Fox, A. J., Laloo, U. G., Belvisi, M. G., Bernareggi, M., Chung, K. F. and Barnes, P. J. (1996) 'Bradykinin-evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough', *Nat Med*, 2(7), pp. 814-7.
- French, C. L., Irwin, R. S., Curley, F. J. and Krikorian, C. J. (1998) 'Impact of chronic cough on quality of life', *Arch Intern Med*, 158(15), pp. 1657-61.
- French, C. T., Fletcher, K. E. and Irwin, R. S. (2004) 'Gender differences in health-related quality of life in patients complaining of chronic cough', *Chest*, 125(2), pp. 482-8.
- French, C. T., Fletcher, K. E. and Irwin, R. S. (2005) 'A comparison of gender differences in health-related quality of life in acute and chronic coughers', *Chest*, 127(6), pp. 1991-8.
- French, C. T., Irwin, R. S., Fletcher, K. E. and Adams, T. M. (2002) 'Evaluation of a cough-specific quality-of-life questionnaire', *Chest*, 121(4), pp. 1123-31.
- Fujimura, M. (2012) 'Frequency of persistent cough and trends in seeking medical care and treatment-results of an internet survey', *Allergol Int*, 61(4), pp. 573-81.
- Groves, R. M. (1989) *Survey Errors and Survey Costs*. New Jersey: John Wiley & Sons Inc.
- Halum, S. L., Sycamore, D. L. and McRae, B. R. (2009) 'A new treatment option for laryngeal sensory neuropathy', *Laryngoscope*, 119(9), pp. 1844-7.
- Han, J. M., Jung, I. C., Kang, W., Kim, S. S., Yeo, Y. and Park, Y. C. (2014) 'Reliability and validity of Leicester Cough Questionnaire Korean version', *Chron Respir Dis*, 11(3), pp. 147-152.
- Haque, R. A., Usmani, O. S. and Barnes, P. J. (2005) 'Chronic idiopathic cough: a discrete clinical entity?', *Chest*, 127(5), pp. 1710-3.
- Harding, S. (2006) 'Gastroesophageal reflux and chronic cough.', *GI Motility Online*.
- Harkness, J. (2011) 'Cross-Cultural Survey Guidelines: VIII. Translation'.
- Harsoliya, M., VM., P., Pathan, J., Singh, S. and Rahman, A. (2011) 'A Review - Mechanism of Cough', *International Journal of Pharmaceutical & Biological Archives*, 2(3), pp. 840-846.
- Hart, T., Fann, J. R. and Novack, T. A. (2008) 'The dilemma of the control condition in experience-based cognitive and behavioural treatment research', *Neuropsychol Rehabil*, 18(1), pp. 1-21.
- Higgins, J. and Green, S. (eds.) (2011) *Cochrane Handbook for Systematic Reviews of Interventions*. version 5.1.0 edn: The Cochrane Collaboration.
- Hillis, B. R. (1952) 'The assessment of cough suppressing drugs', *Lancet*, 1(6721), pp. 1230-5.
- Ho, C., Gu, Q., Hong, J. and Lee, L. (2000) 'Prostaglandin E(2) enhances chemical and mechanical sensitivities of pulmonary C fibers in the rat', *Am J Respir Crit Care Med*, 162, pp. 528 - 533.
- Hope-Gill, B. D., Hilldrup, S., Davies, C., Newton, R. P. and Harrison, N. K. (2003) 'A study of the cough reflex in idiopathic pulmonary fibrosis', *Am J Respir Crit Care Med*, 168(8), pp. 995-1002.

- Hsu, J. Y., Stone, R. A., Logan-Sinclair, R. B., Worsdell, M., Busst, C. M. and Chung, K. F. (1994) 'Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder', *Eur Respir J*, 7(7), pp. 1246-53.
- Huisman, A. N., Wu, M. Z., Uil, S. M. and van den Berg, J. W. (2007) 'Reliability and validity of a Dutch version of the Leicester Cough Questionnaire', *Cough*, 3, pp. 3.
- Höglund, N.-J. and Michaëlsson, M. (1950) 'A Method for Determining the Cough Threshold with Some Preliminary Experiments on the Effect of Codeine', *Acta Physiologica Scandinavica*, 21(2-3), pp. 168-173.
- Ing, A., Ngu, M. C. and Breslin, A. B. X. (1992) 'Chronic persistent cough and clearance of esophageal acid', *Chest*, 102, pp. 1668-1671.
- Irwin, R., Baumann, M., Bolser, D., Boulet, L., Braman, S., Brightling, C., Brown, K., Canning, B., Chang, A., Dicipinigitis, P., Eccles, R., Glomb, W., Goldstein, L., Graham, L., Hargreave, F., Kvale, P., Lewis, S., McCool, F., McCrory, D., Prakash, U., Pratter, M., Rosen, M., Schulman, E., Shannon, J., Smith Hammond, C., Tarlo, S., Tarlo, S. and Physicians, A. C. o. C. (2006) 'Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines', *Chest*, 129(1 Suppl), pp. 1S - 23S.
- Irwin, R. S., Corrao, W. M. and Pratter, M. R. (1981) 'Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy', *Am Rev Respir Dis*, 123, pp. 413-417.
- Irwin, R. S. and Madison, J. M. (2000) 'Anatomical diagnostic protocol in evaluating chronic cough with specific reference to gastroesophageal reflux disease', *Am J Med*, 108 Suppl 4a, pp. 126S-130S.
- Irwin, R.S., Madison, J. M. and Fraire, A. E. (2000) 'The cough reflex and its relation to gastroesophageal reflux'. *Am J Med*. 108 Suppl 4a: p. 73s-78s.
- Jacobson, B. H., Johnson, A., Grywalski, C., Silbergleit, A., Jacobson, G., Benninger, M. S. and Newman, C. W. (1997) 'The Voice Handicap Index (VHI): Development and Validation', *American Journal of Speech-Language Pathology*, 6, pp. 66-70.
- Janson, C., Chinn, S., Jarvis, D. and Burney, P. (2001) 'Determinants of cough in young adults participating in the European Community Respiratory Health Survey', *Eur Respir J*, 18(4), pp. 647-54.
- Jeyakumar, A., Brickman, T. M. and Haben, M. (2006) 'Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy', *Laryngoscope*, 116(12), pp. 2108-12.
- Johansson, E. L., Ternesten-Hasséus, E. and Millqvist, E. (2009) 'Down-regulation of cough sensitivity after eucapnic dry air provocation in chronic idiopathic cough', *Pulm Pharmacol Ther*, 22(6), pp. 543-7.
- Jones, B. and Kenward, M. G. (2015) *Design and Analysis of Cross-over Trials*. 3rd Edition edn. USA: CRC Press.

- Julian, L. J. (2011) 'Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A)', *Arthritis Care Res (Hoboken)*, 63 Suppl 11, pp. S467-72.
- Kalpakioglu, A.F., Kara, T., Kurtipek, E., Kocyigit, P., Ekici, A. and Ekici, M. (2005) 'Evaluation and impact of chronic cough: a comparison of specific vs generic quality-of-life questionnaire', *Annals of Allergy, Asthma & Immunology*, 94(5), pp. 581-585.
- Kastelik, J. A. (2003) 'Abnormal oesophageal motility in patients with chronic cough', *Thorax*, 58, pp. 699-702.
- Kauffmann, F. and Varraso, R. (2011) 'The epidemiology of cough', *Pulmonary Pharmacology & Therapeutics*, 24(3), pp. 289-294.
- Kendall, J. M. (2003) 'Designing a research project: randomised controlled trials and their principles', *Emerg Med J*, 20(2), pp. 164-8.
- Lacson, E., Xu, J., Lin, S. F., Dean, S. G., Lazarus, J. M. and Hakim, R. M. (2010) 'A comparison of SF-36 and SF-12 composite scores and subsequent hospitalization and mortality risks in long-term dialysis patients', *Clin J Am Soc Nephrol*, 5(2), pp. 252-60.
- Leconte, S., Liistro, G., Lebecque, P. and Degryse, J. M. (2011) 'The objective assessment of cough frequency: accuracy of the LR102 device', *Cough*, 7(1), pp. 11.
- Lee, K. K. and Birring, S. S. (2012) 'Cough', *Medicine*, 40(4), pp. 173-177.
- Lee, K. K., Matos, S., Evans, D. H., White, P., Pavord, I. D. and Birring, S. S. (2013) 'A Longitudinal Assessment of Acute Cough', *American Journal of Respiratory and Critical Care Medicine*, 187(9), pp. 991-997.
- Lee, K. K., Savani, A., Matos, S., Evans, D. H., Pavord, I. D. and Birring, S. S. (2012) 'Four-hour cough frequency monitoring in chronic cough', *Chest*, 142(5), pp. 1237-43.
- Lundbäck, B., Nyström, L., Rosenhall, L. and Stjernberg, N. (1991) 'Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey', *Eur Respir J*, 4(3), pp. 257-66.
- Lúdvíksdóttir, D., Björnsson, E., Janson, C. and Boman, G. (1996) 'Habitual coughing and its associations with asthma, anxiety, and gastroesophageal reflux', *Chest*, 109(5), pp. 1262-8.
- Mathers-Schmidt, B. (2001) 'Paradoxical Vocal Fold Motion: A Tutorial on a Complex Disorder and the Speech-Language Pathologist's Role', *American Journal of Speech-Language Pathology*, 10, pp. 111-125.
- Matos, S., Birring, S. S., Pavord, I. D. and Evans, D. H. (2007) 'An automated system for 24-h monitoring of cough frequency: the leicester cough monitor', *IEEE Trans Biomed Eng*, 54(8), pp. 1472-9.
- Mazzone, S. (2005) 'An overview of the sensory receptors regulating cough', *Cough*, 1(1), pp. 2-10.
- Mazzone, S. B., McLennan, L., McGovern, A. E., Egan, G. F. and Farrell, M. J. (2007) 'Representation of Capsaicin-evoked Urge-to-Cough in the Human Brain Using Functional

- Magnetic Resonance Imaging', *American Journal of Respiratory and Critical Care Medicine*, 176(4), pp. 327-332.
- McEwan, J. R., Choudry, N., Street, R. and Fuller, R. W. (1989) 'Change in cough reflex after treatment with enalapril and ramipril', *BMJ*, 299(6690), pp. 13-6.
- McGarvey, L., Carton, C., Gamble, L., Heaney, L., Shepherd, R., Ennis, M. and MacMahon, J. (2006) 'Prevalence of psych morbidity among patients with chronic cough', *Cough*, 2(1), pp. 4.
- McGarvey, L. P., Forsythe, P., Heaney, L. G., MacMahon, J. and Ennis, M. (1999) 'Bronchoalveolar lavage findings in patients with chronic nonproductive cough', *Eur Respir J*, 13(1), pp. 59-65.
- McGuinness, K., Holt, K., Dockry, R. and Smith, J. (2012) 'P159 Validation of the VitaloJAK™ 24 Hour Ambulatory Cough Monitor', *Thorax*, 67(Suppl 2), pp. A131-A131.
- Medical Research Council (1965) 'Committee report on definition and classification of chronic bronchitis.', *The Lancet*, i, pp. 775-779.
- Mintz, S. and Lee, J. K. (2006) 'Gabapentin in the treatment of intractable idiopathic chronic cough: case reports', *Am J Med*, 119(5), pp. e13-5.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. and Group, P. (2009) 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', *J Clin Epidemiol*, 62(10), pp. 1006-12.
- Montnémy, P., Adelroth, E., Heuman, K., Johannisson, A., Johansson, S. A., Lindholm, L. H., Lundbäck, B. and Löfdahl, C. G. (1998) 'Prevalence of obstructive lung diseases and respiratory symptoms in southern Sweden', *Respir Med*, 92(12), pp. 1337-45.
- Morice, A. (2008) 'Chronic cough: epidemiology', *Chron Respir Dis*, 5(1), pp. 43-7.
- Morice, A., Jakes, A., Faruqi, S., Birring, S., McGarvey, L., Canning, B., Smith, J., Parker, S., Chung, K., Pavord, I., van den Berg, J., Song, W., Milqvist, E., Farrell, M., Mazzone, S. and Dicipinigitis, P. (2014) 'A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response', *European Respiratory Journal*, 44(5), pp. 1149-55.
- Morice, A. H. (2002) 'Epidemiology of cough', *Pulm Pharmacol Ther*, 15(3), pp. 253-9.
- Morice, A. H., Fontana, G. A., Belvisi, M. G., Birring, S. S., Chung, K. F., Dicipinigitis, P. V., Kastelik, J. A., McGarvey, L. P., Smith, J. A., Tatar, M., Widdicombe, J. and European Respiratory, S. (2007a) 'ERS guidelines on the assessment of cough', *Eur Respir J*, 29(6), pp. 1256-76.
- Morice, A. H., Fontana, G. A., Sovijarvi, A. R., Pistolesi, M., Chung, K. F., Widdicombe, J., O'Connell, F., Geppetti, P., Gronke, L., De Jongste, J., Belvisi, M., Dicipinigitis, P., Fischer, A., McGarvey, L., Fokkens, W. J., Kastelik, J. and Force, E. T. (2004) 'The diagnosis and management of chronic cough', *Eur Respir J*, 24(3), pp. 481-92.
- Morice, A. H., Marshall, A. E., Higgins, K. S. and Grattan, T. J. (1994) 'Effect of inhaled menthol on citric acid induced cough in normal subjects', *Thorax*, 49(10), pp. 1024-6.
- Morice, A. H., McGarvey, L., Pavord, I. and Group, B. T. S. C. G. (2006) 'Recommendations for the management of cough in adults', *Thorax*, 61 Suppl 1, pp. i1-24.

- Morice, A. H., Menon, M. S., Mulrennan, S. A., Everett, C. F., Wright, C., Jackson, J. and Thompson, R. (2007b) 'Opiate therapy in chronic cough', *Am J Respir Crit Care Med*, 175(4), pp. 312-5.
- Morice, A. H., Millqvist, E., Belvisi, M. G., Bieksiene, K., Birring, S. S., Chung, K. F., Dal Negro, R. W., Dicipinigaitis, P., Kantar, A., McGarvey, L. P., Pacheco, A., Sakalauskas, R. and Smith, J. A. (2014) 'Expert opinion on the cough hypersensitivity syndrome in respiratory medicine', *European Respiratory Journal*. 44(5), pp 1132-48.
- Moss-Morris, R., Weinman, J., Petrie, K., Horne, R., Cameron, L. and Buick, D. (2002) 'The revised illness perception questionnaire (IPQ-R)', *Psychology and Health*, 17(1), pp. 1-16.
- Mund, E., Christensson, B., Gronneberg, R. and Larsson, K. (2005) 'Noneosinophilic CD4 lymphocytic airway inflammation in menopausal women with chronic dry cough', *Chest*, 127(5), pp. 1714-21.
- Mund, E., Christensson, B., Larsson, K. and Gronneberg, R. (2001) 'Sex dependent differences in physiological ageing in the immune system of lower airways in healthy non-smoking volunteers: study of lymphocyte subsets in bronchoalveolar lavage fluid and blood', *Thorax*, 56(6), pp. 450-5.
- Murry, T., Branski, R. C., Yu, K., Cukier-Blaj, S., Duflo, S. and Aviv, J. E. (2010) 'Laryngeal sensory deficits in patients with chronic cough and paradoxical vocal fold movement disorder', *Laryngoscope*, 120(8), pp. 1576-81.
- NICE (2009) *Methods for the development of NICE public health guidance*. London: National Institute for Health and Clinical Excellence.
- O'Bryne, P. M. (2005) 'Cough and airway hyperresponsiveness', in Chung, F., Widdicombe, J. & Boushey, H. (eds.) *Cough: Causes, Mechanisms and Therapy*. 2nd Edition ed. Oxford, UK: Blackwell Publishing Limited.
- O'Connell, F., Thomas, V. E., Studham, J. M., Pride, N. B. and Fuller, R. W. (1996) 'Capsaicin cough sensitivity increases during upper respiratory infection', *Respir Med*, 90(5), pp. 279-86.
- Palombini, B. C. and Araujo, E. (2005) 'Cough in postnasal drip, rhinitis and rhinosinusitis', in Chung, F., Widdicombe, J. & Boushey, H. (eds.) *Cough: Causes, Mechanisms and Therapy*. Oxford, UK: Blackwell Publishing Limited, pp. 107-115.
- Patel, A. S., Watkin, G., Willig, B., Motalithas, K., Bellas, H., Garrod, R., Pavord, I. D. and Birring, S. S. (2011) 'Improvement in health status following cough-suppression physiotherapy for patients with chronic cough', *Chron Respir Dis*, 8(4), pp. 253-8.
- Petrie, K., Broadbent, E. and Meechan, G. (2003) 'Self-regulatory interventions for improving the management of chronic illness.', in Cameron, L. & Leventhal, H. (eds.) *The self-regulation of health and illness behaviour*. New York: Routledge, pp. 257-277.
- Polverino, M., Polverino, F., Fasolino, M., Andò, F., Alfieri, A. and De Blasio, F. (2012) 'Anatomy and neuro-pathophysiology of the cough reflex arc', *Multidiscip Respir Med*, 7(1), pp. 5.
- Prudon, B., Birring, S. S., Vara, D. D., Hall, A. P., Thompson, J. P. and Pavord, I. D. (2005) 'Cough and glottic-stop reflex sensitivity in health and disease', *Chest*, 127(2), pp. 550-7.

- Raj, A. A. and Birring, S. S. (2007) 'Clinical assessment of chronic cough severity', *Pulm Pharmacol Ther*, 20(4), pp. 334-7.
- Raj, A. A., Pavord, D. I. and Birring, S. S. (2009) 'Clinical cough IV: what is the minimal important difference for the Leicester Cough Questionnaire?', *Handb Exp Pharmacol*, (187), pp. 311-20.
- Riegel, B., Warmoth, J. E., Middaugh, S. J., Kee, W. G., Nicholson, L. C., Melton, D. M., Parikh, D. K. and Rosenberg, J. C. (1995) 'Psychogenic cough treated with biofeedback and psychotherapy. A review and case report', *Am J Phys Med Rehabil*, 74(2), pp. 155-8.
- Ryan, N. M., Birring, S. S. and Gibson, P. G. (2012) 'Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial', *Lancet*, 380(9853), pp. 1583-9.
- Ryan, N. M., Vertigan, A. E., Bone, S. and Gibson, P. G. (2010) 'Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough', *Cough*, 6, pp. 5.
- Ryan, N. M., Vertigan, A. E. and Gibson, P. G. (2009) 'Chronic cough and laryngeal dysfunction improve with specific treatment of cough and paradoxical vocal fold movement', *Cough*, 5, pp. 4.
- Schulz, K. F. and Grimes, D. A. (2002) 'Generation of allocation sequences in randomised trials: chance, not choice', *Lancet*, 359(9305), pp. 515-9.
- Shannon, R., Baekey, D., Morris, K. and Lindsey, B. (1998) 'Ventrolateral medullary respiratory network and a model of cough motor pattern generation', *J Appl Physiol*, 84, pp. 2020 - 2035.
- Sibbald, B. and Roland, M. (1998) 'Understanding controlled trials. Why are randomised controlled trials important?', *BMJ*, 316(7126), pp. 201.
- SIGN (2011) *SIGN 50 A guideline developer's handbook*. Edinburgh, Scotland.
- Sivasankar, M. and Leydon, C. (2010) 'The role of hydration in vocal fold physiology', *Curr Opin Otolaryngol Head Neck Surg*, 18(3), pp. 171-5.
- Smith, J. and Woodcock, A. (2008) 'New developments in the objective assessment of cough', *Lung*, 186 Suppl 1, pp. S48-54.
- Smith, J. A. (2008) *Cough: Assessment and Equipment*. The Buyer's Guide to Respiratory Care products.
- Spielberger, C., Gorsuch, R., R, L. and Jacobs, G. (1984) *Manual for the state-Trait Anxiety Inventory (form Y)*. 1st Edition edn. California: Consulting Psychologists Press.
- Spinou, A. and Birring, S. S. (2014) 'An update on measurement and monitoring of cough: what are the important study endpoints?', *J Thorac Dis*, 6(Suppl 7), pp. S728-34.
- Tilling, K., Sterne, J., Brookes, S. and Peters, T. (2005) 'Handbook of Health Research methods', in Bowling, A. & Ebrahim, S. (eds.) *Handbook of Health research methods: Investigation, measurement and analysis*. Maidenhead; England: Open University Press.

- Tobin, M. J., Jenouri, G., Lind, B., Watson, H., Schneider, A. and Sackner, M. A. (1983) 'Validation of respiratory inductive plethysmography in patients with pulmonary disease', *Chest*, 83(4), pp. 615-20.
- Torgerson, D. J. and Roberts, C. (1999) 'Understanding controlled trials. Randomisation methods: concealment', *BMJ*, 319(7206), pp. 375-6.
- Vertigan, A., Theodoros, D., Winkworth, A. and Gibson, P. (2007a) 'Chronic cough a tutorial for speech-pathologists. Journal of medical speech-language pathology', *Journal of Medical Speech-Language Pathology*, 15(3), pp. 189-206.
- Vertigan, A. E. and Gibson, P. G. (2011) 'Chronic refractory cough as a sensory neuropathy: evidence from a reinterpretation of cough triggers', *J Voice*, 25(5), pp. 596-601.
- Vertigan, A. E., Theodoros, D. G., Gibson, P. G. and Winkworth, A. L. (2006) 'Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy', *Thorax*, 61(12), pp. 1065-9.
- Vertigan, A. E., Theodoros, D. G., Gibson, P. G. and Winkworth, A. L. (2007b) 'Review series: chronic cough: behaviour modification therapies for chronic cough', *Chron Respir Dis*, 4(2), pp. 89-97.
- Vertigan, A. E., Theodoros, D. G., Gibson, P. G. and Winkworth, A. L. (2007c) 'Voice and upper airway symptoms in people with chronic cough and paradoxical vocal fold movement', *J Voice*, 21(3), pp. 361-83.
- Vertigan, A. E., Theodoros, D. G., Winkworth, A. L. and Gibson, P. G. (2007d) 'Perceptual voice characteristics in chronic cough and paradoxical vocal fold movement', *Folia Phoniatr Logop*, 59(5), pp. 256-67.
- Vertigan, A. E., Theodoros, D. G., Winkworth, A. L. and Gibson, P. G. (2008a) 'A comparison of two approaches to the treatment of chronic cough: perceptual, acoustic, and electroglottographic outcomes', *J Voice*, 22(5), pp. 581-9.
- Vertigan, A. E., Theodoros, D. G., Winkworth, A. L. and Gibson, P. G. (2008b) 'Acoustic and electroglottographic voice characteristics in chronic cough and paradoxical vocal fold movement', *Folia Phoniatr Logop*, 60(4), pp. 210-6.
- Ware, J. E., Kosinski, M. and Gandek, B. (2000) SF-36 Health Survey: Manual Interpretation Guide. Lincoln: QualityMetric Incorporated.
- Warren, R. H., Horan, S. M. and Robertson, P. K. (1997) 'Chest wall motion in preterm infants using respiratory inductive plethysmography', *Eur Respir J*, 10(10), pp. 2295-300.
- Webb, A. L., Carding, P. N., Deary, I. J., MacKenzie, K., Steen, I. N. and Wilson, J. A. (2007) 'Optimising outcome assessment of voice interventions, I: Reliability and validity of three self-reported scales', *J Laryngol Otol*, 121(8), pp. 763-7.
- Weinman, J., Petrie, K., Moss-Morris, R. and Horne, R. (1996) 'The illness perception questionnaire: A new method for assessing the cognitive representation of illness', *Psychology & Health*, 11(3), pp. 431-446.

- Whitehead, W. E. (2004) 'Control groups appropriate for behavioral interventions', *Gastroenterology*, 126(1 Suppl 1), pp. S159-63.
- Widdicombe, J. G. (2005) 'A brief overview of the mechanisms of cough', in Chung, F., Widdicombe, J. & Boushey, H. (eds.) *Cough: Causes, Mechanisms and Therapy*. 2nd Edition ed. Oxford, UK: Blackwell Publishing Limited, pp. 83-147.
- Wiebe, S., Guyatt, G., Weaver, B., Matijevic, S. and Sidwell, C. (2003) 'Comparative responsiveness of generic and specific quality-of-life instruments', *J Clin Epidemiol*, 56(1), pp. 52-60.
- Wilson, R. (2005) 'Cough in suppurative airway diseases', in Chung, F., Widdicombe, J. & Boushey, H. (eds.) *Cough: Causes, Mechanisms and Therapy*. Oxford, UK: Blackwell Publishing Limited, pp. 137-147.
- Young, E. C., Brammer, C., Owen, E., Brown, N., Lowe, J., Johnson, C., Calam, R., Jones, S., Woodcock, A. and Smith, J. A. (2009) 'The effect of mindfulness meditation on cough reflex sensitivity', *Thorax*, 64(11), pp. 993-8.
- Yousaf, N., Lee, K.K., Jayaraman, B., Pavord, I.D., Birring, S.S. (2011) 'The assessment of quality of life in acute cough with the Leicester Cough Questionnaire (LCQ-acute)', *Cough*, 7, pp. 4.
- Yousaf, N., Monteiro, W., Matos, S., Birring, S. S. and Pavord, I. D. (2013) 'Cough frequency in health and disease', *European Respiratory Journal*, 41(1), pp. 241-243.
- Yousaf, N., Monteiro, W., Parker, D., Matos, S., Birring, S. and Pavord, I. D. (2010) 'Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial', *Thorax*, 65(12), pp. 1107-10.
- Zigmond, A. S. and Snaith, R. P. (1983) 'The hospital anxiety and depression scale', *Acta Psychiatr Scand*, 67(6), pp. 361-70.

APPENDICES

Appendices

Appendix 1: Chronic Cough Survey

1. How long have you had your cough?

(<3 weeks, 3-8 weeks, 2-6 months, 6-12 months, 1-2 years, 2-5 years, 5-10 years, 10+ years)

2. What was the reason(s) for first visiting your doctor for your cough?*

3. How many times have you seen your doctor regarding your cough?

(0, 1, 2, 3, 4, 5+ times)

4. When did you last see you doctor regarding your cough?

(1 week ago, 1 month, 1-2 months, 2-6 months, 6-12 months, 1-2 years, 2-5 years, 5+ years)

5. Does your cough stop you from doing the things you would like to do?

(Frequently, sometimes, never)

6. Do you feel fed-up or depressed because of your cough?

(Yes, sometimes, never)

7. Does your cough disturb or worry your partner, family or friends?

(Yes, sometimes, never)

8. Does your cough affect your quality of life?

(Severely, moderately, a little, not at all)

Question 9. Has a diagnosis for your cough been given?

(Yes/No)

10. If you received a diagnosis for your cough, what was it?

11. Do you feel your doctor/specialist has dealt with your cough thoroughly?

(Yes/no)

12. Have you ever attended a specialist Cough Clinic?

(Yes/no)

13. Would you consider attending a specialist Cough Clinic if available to you?

(Yes/no)

14. Do you currently smoke?

(Yes/no)

15. Have the treatment(s) for your cough worked?

(Yes, a little, no)

16. Please tell us what, if anything, has worked?*

17. Have you found over the counter pharmacy (non-prescription) cough suppressant medications effective?

(Yes, a little, no)

18. Would you like more information on chronic cough to be available?

(Yes/no)

19. If yes, what further information would you like?*

20. What other support do you think would be beneficial?*

21. Would you like to receive further information about the ELF/ERS chronic cough taskforce and patient involvement?

(Yes, no)

Demographics

Age

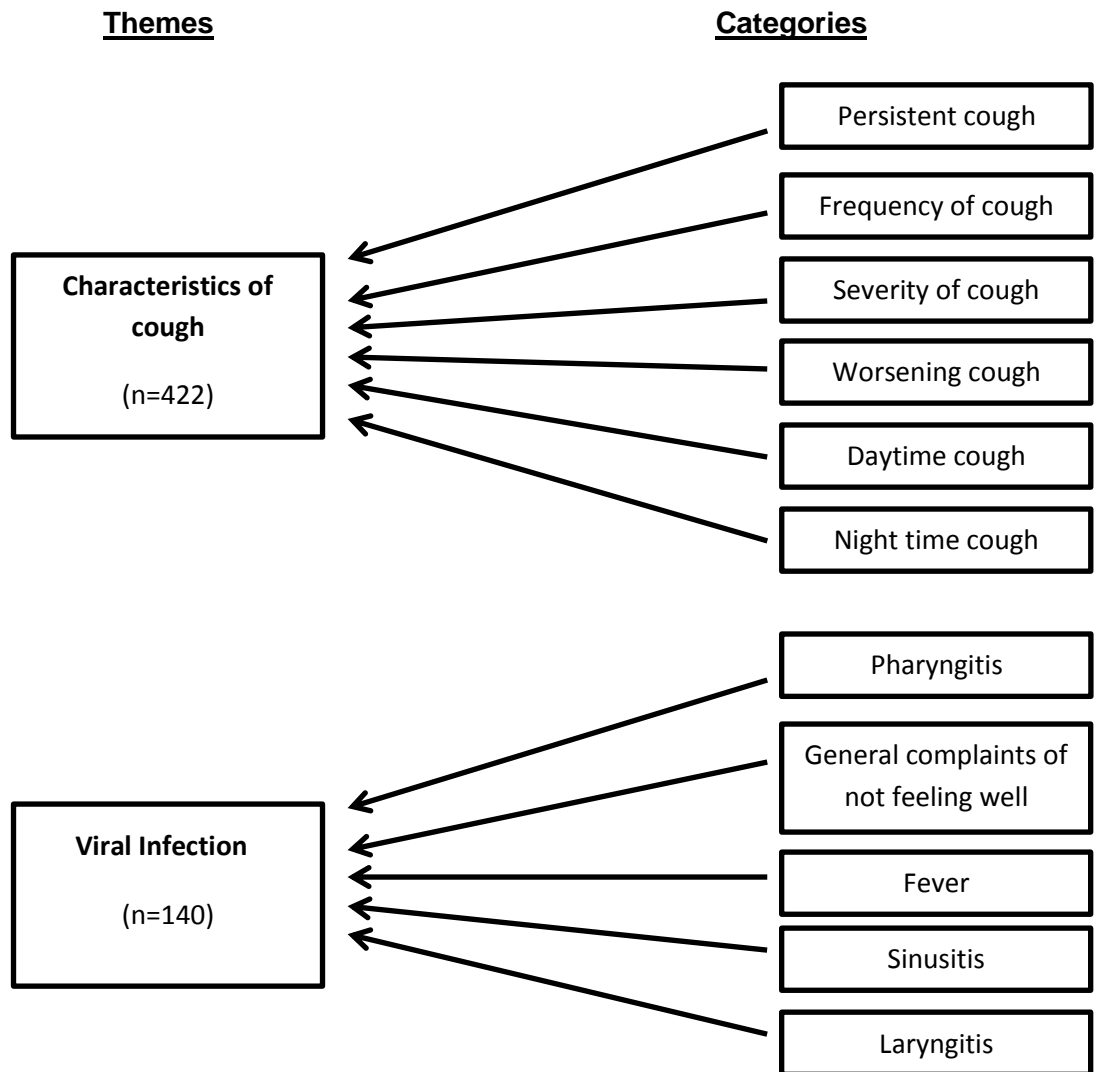
Country of Residence

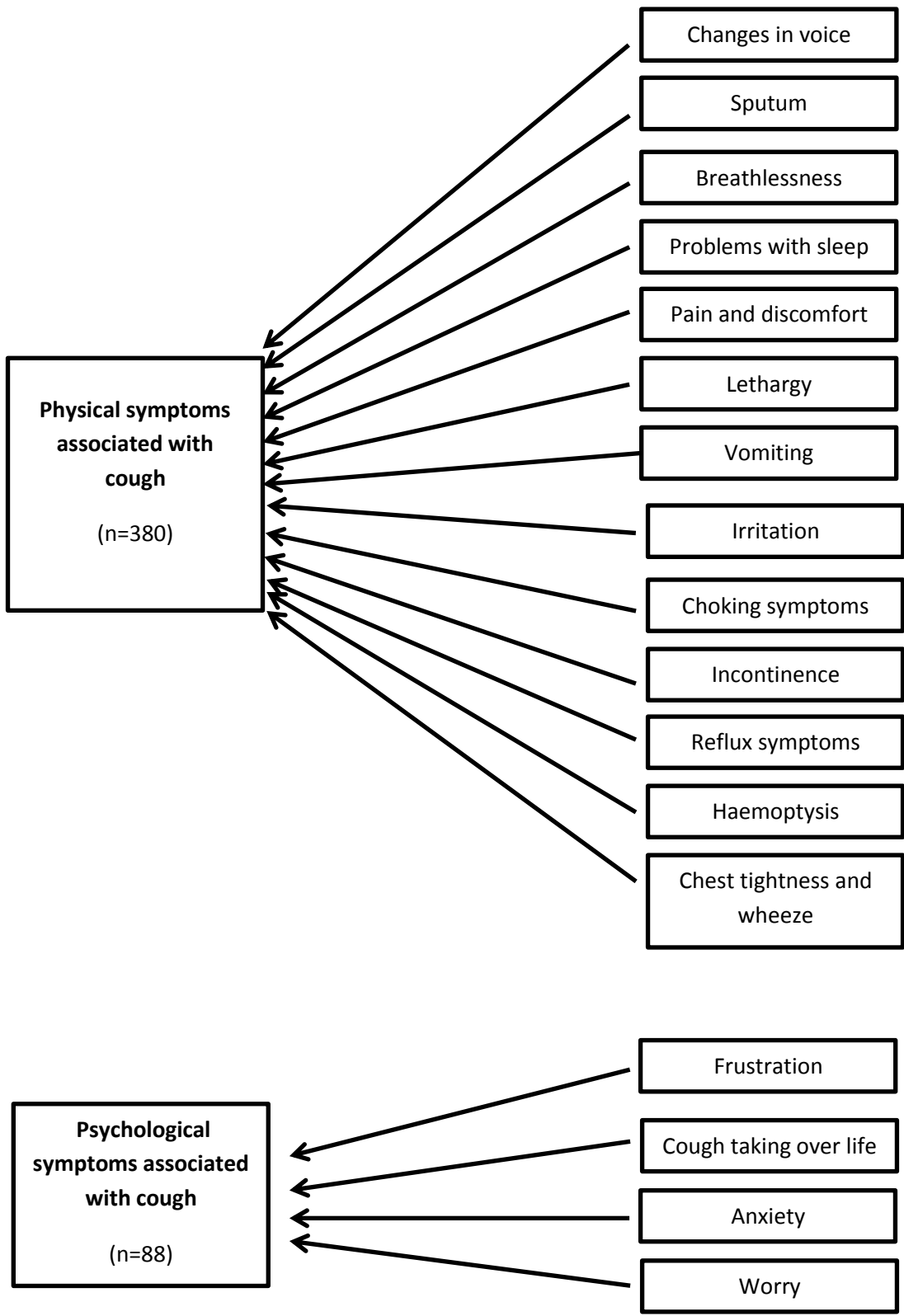
Gender

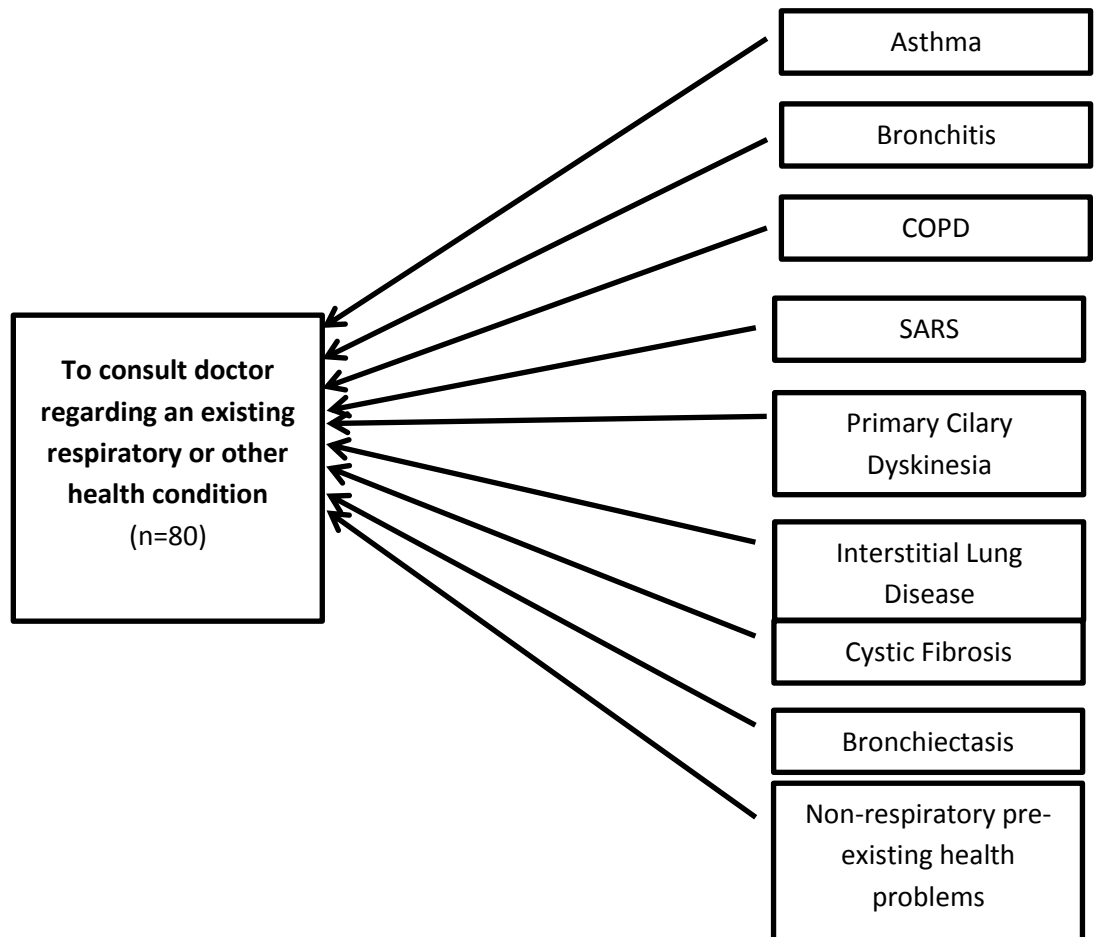
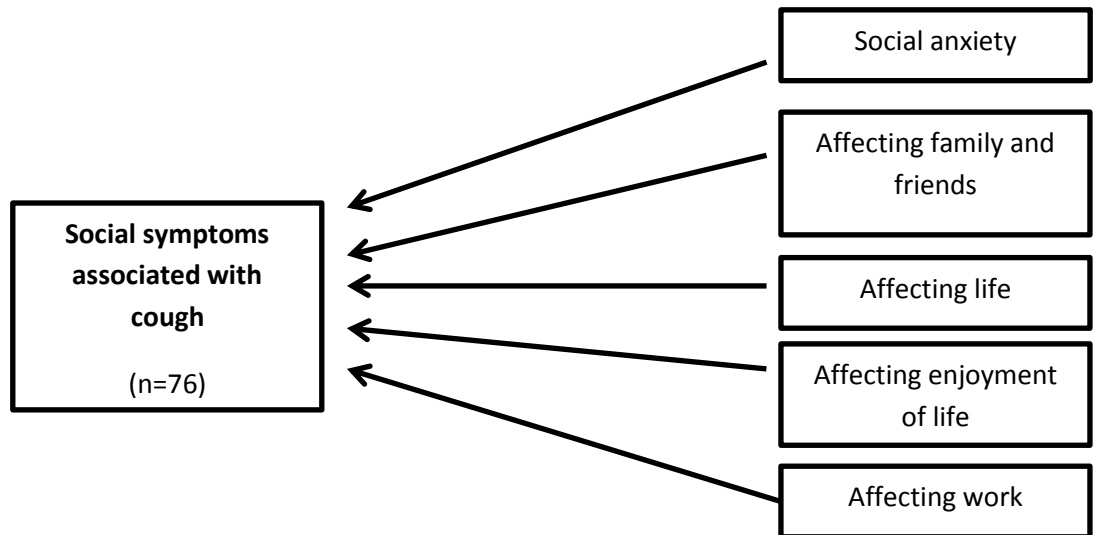
Ethnicity

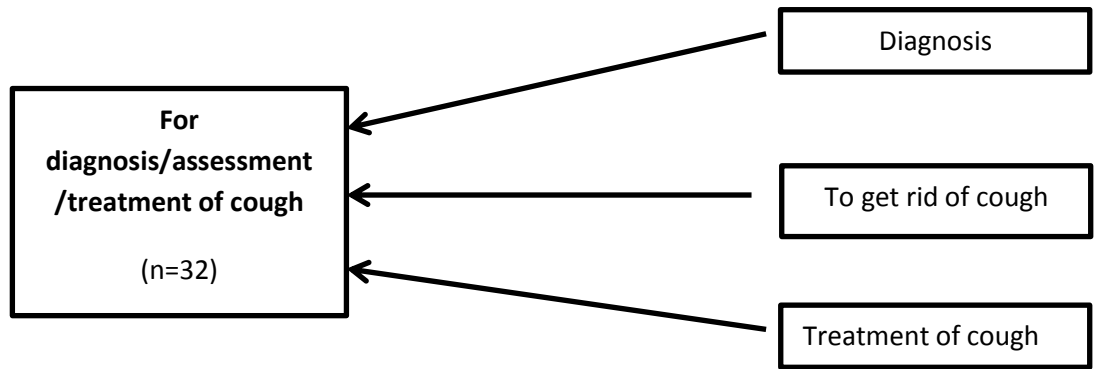
(White Caucasian, Black Caribbean, Black African, East Asian, South Asian, Mixed, Other)

Appendix 2: Reasons for why respondents initially consulted their doctor about their cough









Appendix 3: Quotations from participants: why they first consulted their doctor

Characteristics of the cough

“Because it was continuous” (Italian responder)

“An increase in the number of coughing fits each day: between 10 and 15” (day and night)

(French responder)

Physical symptoms associated with cough

“I was coughing so much my chest hurt” (Spanish survey responder)

“Breathlessness and wheezing” (Polish survey responder)

“I couldn’t hold conversation without coughing” (English survey responder)

Viral infection symptoms

“Chest infection” (English survey participant)

Psychological symptoms associated with cough

“Because my cough was beginning to take over my life” (French survey responder)

“Because of the distress it was causing myself and other close persons” (English survey responder)

To consult a doctor about existing respiratory or other health condition

“Pulmonary fibrosis, COPD” (Polish survey responder)

“Have cystic fibrosis” (English survey responder)

Social symptoms associated with the cough

“The coughing interfered with my interactions with other people” (Lithuanian survey responder)

“My cough was degrading my quality of life” (Bulgarian Survey responder)

For diagnosis/assessment and treatment of the cough

“Clarify causes” (German responder)

“To try to get a cure” (German responder)

Appendix 4: Information and support requested by participants (Themes and quotations)

Treatment

“How to treat it” (English responder)

“An effective cure” (Italian responder)

Causes

“Explanation of the cause” (German responder)

“Explain the causes of the cough because I am lost” (Polish responder)

Self-help and alternative therapies

“I don’t know, something we could do about it on our own” (Spanish responder)

“How to manage the coughing, things to avoid etc” (English responder)

“Herbal alternatives when medication simply does not work” (English responder)

General information in a variety of formats

“Provide information on-line, with daily updates if possible” (Spanish responder)

“All info that might help me get rid of this inconvenience” (Swedish responder)

“Links to internet sites so that I can obtain information on my problem” (Greek responder)

“Brochure for patients” (Russian Responder)

Better understanding, awareness and support from doctors

“To be taken seriously by the doctors” (German responder)

“Information for Doctors on how to treat as they don’t seem to be very aware” (English responder)

Assessment

“What specific test to get done” (Italian responder)

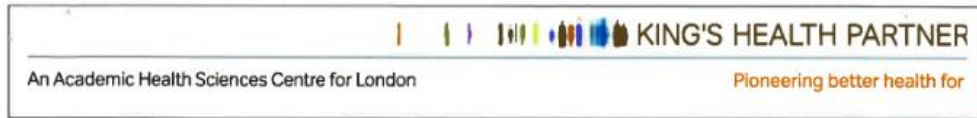
“Differential diagnosis” (English responder)

Information on access to specialist cough clinics

“Details of specialist cough clinics” (Italian responder)

“Referrals to specialist to be made when symptoms have persisted for an extended period” (English responder)

Appendix 5: Modified FEES protocol



King's College Hospital 
NHS Foundation Trust

PSALTI MODIFIED FEES PROTOCOL KING'S COLLEGE HOSPITAL

Aims: To screen for factors associated with chronic cough which would;

- Contraindicate inclusion into study (aspiration / dysphagia which causes chronic coughing (where the cough is related to clearance of aspirated material / secretions or where cough suppression would be contraindicated as an appropriate course of action)
- Require treatment prior to inclusion into the study, or would require increased awareness of during the study (presence of untreated reflux, post nasal drip / rhinitis, vocal fold pathology / masses / abnormal function contraindicates PSALTI inclusion prior to management)
- To screen for any voice / laryngeal pathology which may require treatment after the study

Process: Modified FEES to be carried out by SLT with ENT visualisation of images post procedure

Patient Name Hospital Number DOB Date of Modified FEES	
Explanation by endoscopist re: aim of session and scoping procedure (To check there is nothing we can see which might be the cause of the cough). Show camera, explain route and reassure, requesting verbal feedback re: tolerance during the procedure). Check aware will ask to carry out some speech / voice tasks, drink some milk / coloured water, eat a biscuit / yoghurt (local anaesthetic not routinely used). Record procedure.	
1. Check consent for procedure (already consented to PSALTI study)	
2. Brief history of cough from patient, including any relevant medical history (nasal ops?, nose bleeds?, cardiac history?), note refs to swallowing difficulties, voice quality)	History:..... Swallow Reports (circle) : Normal / Abnormal dietary modifications, weight-loss, chest hx associated with asp..... Voice (circle): normal, dysphonic (Mild, mod, severe, variable), other: state

3. Reflux Symptom Index – carry out and rate

Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess throat mucous or post nasal drip	0	1	2	3	4	5
Difficulty swallowing foods, liquids or pills	0	1	2	3	4	5
Coughing after you ate or lie down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensations of something sticking in your throat, or a lump in your throat	0	1	2	3	4	5
Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
	TOTAL					

11 or above Y / N Composite score over 11 is an indicator for reflux, and may require treatment / investigation (Silent Gastroesophageal Reflux Disease / GERD) – Inform Dr Birring & PSALTI THERAPISTS

Perform Modified FEES

Pass scope and record as pass through nasal passages, ensuring visibility of middle turbinate pre-passage

Note:

Prev surgery	Y / N / ?
Polyps	Y / N / ?
Dryness	Y / N / ?
Blood / sores / crusting	Y / N / ?

<p>At nasopharynx, screen and record superiorly as well as laterally and posteriorly to check for signs of rhinitis / post nasal drip /infection</p>	<p>Abnormal areas Y / N / ?</p> <p>Rhinitis / nasal secretions Y / N / ?</p> <p>Abnormal pathology / infect Y / N / ?</p>
<p>Palatal structure & pharyngeal structure and function on rest and speech task</p> <p>Larynx structure and function on rest and speech task & challenge</p> <p>(rest breathing, deep breaths in and out, sustained vowel phonation – normal and high pitch (plus slide), normal speech, sniff, cough, throat clear, laugh, counting to 20 quickly, whistle / straw, panting)</p>	<p>Normal</p> <p>Abnormal (pathology, structure, movement, symmetry, strength, tension /tone, hypersensitivity, tonsillar hyperplasia / enlarged lymph glands, candida,).....</p> <p>Normal</p> <p>Abnormal (pathology, movement, symmetry, strength, tension / tone)</p> <p>-VF palsy (Uni / Bilat)</p> <p>-VF / laryngeal lesion</p> <p>-Signs of reflux</p> <p>-Vocal cord dysfunction (Ins, Ex, Fixed), under 50% or over 50% adduction of the vocal folds?</p> <p>-Constriction (circumferential / lateral, AP, false cord)</p> <p>-Signs of spasmodic dysphonia</p> <p>Other.....</p> <p>When - Rest, Challenge, Both</p>

Score)	<p>Erythema/hyperaemia 2(arytenoids) 4 (diffuse)</p> <p>Vocal fold oedema 1 (mild), 2 (mod), 3 (severe)</p> <p>Diffuse laryngeal oedema 1 (mild), 2 (mod), 3 (severe), 4 (obstructing)</p> <p>Posterior commissure hypertrophy 1 (mild), 2 (mod), 3 (severe), 4 (obstructing)</p> <p>Granulation tissue / granuloma 0 (absent), 2 (present)</p> <p>Thick endolaryngeal mucous, 0 (absent), 2 (present)</p>
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Appendix 6: PSALTI RCT Consent Form

Centre Number: 01

Study Number: 11/LO/O504 KCH 11-103

Patient Identification Number for this trial: 0103

CONSENT FORM

Title of Project: Physio and Speech Therapy Management of Chronic Cough

Name of Researcher: Rachel Garrod / Sarah Chamberlain / Rachel Harding

Please Initial Box

1. I confirm that I have read and understand the Patient Information Sheet dated 17.05.12 version 3 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 any reason, without my medical care or legal rights being affected
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, 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 _____ Date _____

Signature
taking consent _____

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Appendix 7: Capsaicin Cough Challenge Assessment Forms

Capsaicin challenge Test

Spirometry			
	Predicted	Observed	%predicted
FVC			
FEV1			
FEV1/FVC			

Capsaicin Challenge Test Results			
Capsaicin concentration (μM)	Urge VAS	Cough VAS	Number of coughs
Saline			
0.49			
0.98			
1.95			
3.9			
7.8			
15.6			
31.25			
62.5			
125			
250			
500			
1000			
		Capsaicin concentration	
Extrapolated C2			
Extrapolated C5			

Appendix 8: Urge to cough Assessment Form

Cough Hypersensitivity Testing

Please mark on the scales below after each test:

Visual analogue score (1)

WORST COUGH EVER



NO COUGH

Visual analogue score (2)

***WORST URGE TO COUGH
EVER***



NO URGE TO COUGH

Appendix 9: Leicester Cough Monitor Assessment Form

Participant Number:

DATE:

1

24 Hour Cough Monitoring

You have agreed to have a cough monitoring investigation to be recorded for 24 hours. This will be analysed automatically by a computer program and only cough sounds are listened to. All recorded information will be **strictly confidential**.

Please complete this questionnaire for the duration of the recording, and return both the monitor and questionnaire to the Chest Unit, 2nd Floor Cheyne Wing, King's College Hospital.

Additional advice

If you want to take a shower, take off the microphone and leave it in your room with the monitor bag. Put the microphone back on when you finish.

When you go to bed, place the monitor bag on a bedside table. If you feel uncomfortable sleeping with the microphone around your neck, take it off and place it on your bedside table together with the monitor bag. Put the microphone back on when you get up in the morning.

- Please tell us the times that you ate your main meals.

Main Meals	Start	Finish
e.g. Breakfast	07:30	07:40

- Please tell us the times that you went to bed, and got up in the morning

Went to bed at : Woke up at :

- Please write down the time of day you felt your cough was worst
- Also record any pain or other sensation that you have experienced

Symptom	Time
Worst cough	

If there are any problems, please telephone Sarah Chamberlain at King's College Hospital on 0203 299 9000 ext 2080

Appendix 10: Leicester Cough Questionnaire Assessment Form

Date:

Questionnaire completed at: Baseline / week 1 / week 2 / week 3 / week 4

LEICESTER COUGH QUESTIONNAIRE

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the number of the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1. Every time
2. Most times
3. Several times
4. Some times
5. Occasionally
6. Rarely
7. Never

3. In the last 2 weeks, have you been tired because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

6. In the last 2 weeks, my cough has made me feel anxious

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough:

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

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10. In the last 2 weeks, has your cough disturbed your sleep?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

11. In the last 2 weeks how many times a day have you had coughing bouts?

1. All the time (continuously)
2. Most times of during the day
3. Several times during the day
4. Some times during the day
5. Occasionally through the day
6. Rarely
7. None

12. In the last 2 weeks, my cough has made me feel frustrated

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last 2 weeks, my cough has made me feel fed up

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

15. In the last 2 weeks, have you had a lot of energy?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1. Every time
2. Most times
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1. Every time I cough
2. Most times when I cough
3. Several times when I cough
4. Some times when I cough
5. Occasionally when I cough
6. Rarely
7. Never

Thank you for completing this questionnaire.© 2001. University of Leicester NHS Trust, Glenfield Hospital, UK.

LCQ CC V3 30.11.09

Appendix 11: Short Form 36 Assessment Form

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
	▼	▼	▼
a. <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Lifting or carrying groceries.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Climbing <u>several</u> flights of stairs.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Climbing <u>one</u> flight of stairs.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Bending, kneeling, or stooping.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Walking <u>more than a mile</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Walking <u>several hundred yards</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Walking <u>one hundred yards</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j. Bathing or dressing yourself.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
1. Cut down on the <u>amount of time</u> you spent on work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. Were limited in the <u>kind of</u> work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
1. Cut down on the <u>amount of time</u> you spent on work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. Did work or other activities <u>less carefully than usual</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Did you feel full of life? 1 2 3 4 5
 b. Have you been very nervous? 1 2 3 4 5
 c. Have you felt so down in the dumps that nothing could cheer you up? 1 2 3 4 5
 d. Have you felt calm and peaceful? 1 2 3 4 5
 e. Did you have a lot of energy? 1 2 3 4 5
 f. Have you felt downhearted and low? 1 2 3 4 5
 g. Did you feel worn out? 1 2 3 4 5
 h. Have you been happy? 1 2 3 4 5
 i. Did you feel tired? 1 2 3 4 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
a. I seem to get ill more easily than other people.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. I am as healthy as anybody I know.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. I expect my health to get worse.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. My health is excellent.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

Appendix 12: Visual Analogue Scale (VAS) Severity – Week 1

Please mark on the scales below how SEVERE you cough has been and how severe the URGE to cough has been in the past two weeks:

Cough Severity Scale

WORST COUGH EVER



NO COUGH

Urge to Cough Scale

***WORST URGE TO COUGH
EVER***



NO URGE TO COUGH

Appendix 13: Visual Analogue Scale (VAS) Severity – Week 2 onwards

Please mark on the scales below how SEVERE you cough has been and how severe the URGE to cough has been since your last treatment session:

Cough Severity Scale

WORST COUGH EVER



NO COUGH

Urge to Cough Scale

***WORST URGE TO COUGH
EVER***



NO URGE TO COUGH

Appendix 14: Hospital Anxiety and Depression Scale (HADS) Assessment form

HAD scale

Name: Date:
 Hospital number: Pre / post rehab

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he/she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a tick in the box opposite to the reply, which comes closest to how you have been feeling over the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

Tick on one box in each section

I feel tense or wound up

- Most of the time
- A lot of the time
- From time to time, occasionally
- Not at all

I still enjoy things I used to enjoy

- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a frightened feeling as if something awful is about to happen

- Very definitely & quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I can laugh & 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

Worrying thoughts go through my mind

- A great deal of the time
- A lot of the time
- From time to time but not that often
- Only occasionally

I feel cheerful

- Not at all
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed

- Definitely
- Usually
- Not often
- Not at all

I feel as if I am slowed down

- Nearly all the time
- Very often
- Sometimes
- Not at all

I get a frightened feeling like 'butterflies in the stomach'

- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance

- Definitely
- I don't take as much care as I should
- I may not take as much care
- I take just as much care as ever

I feel restless as if I have to be on the move

- Very much indeed
- Quite a lot
- Not very much
- Not at all

I look forward with enjoyment to things

- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic

- Very often indeed
- Quite often
- Not very often
- Hardly at all

I can enjoy a good book or radio or TV programme

- Often
- Sometimes
- Not often
- Very seldom



Appendix 15: Vocal Performance Questionnaire (VPQ) Assessment form

THE VOCAL PERFORMANCE QUESTIONNAIRE

By Paul Carding
Freeman Hospital, Newcastle upon Tyne, UK

Name.....Date:

Tick or Circle an answer for each question

1. How do you think your voice sounds now (as compared to before your voice problems started)?

- (a) No different from usual voice
- (b) Only slightly different from usual voice
- (c) Quite different from usual voice
- (d) Very different from usual voice
- (e) Totally different from usual voice

2. Does your voice give you any physical discomfort when you talk?

- (a) No discomfort
- (b) Slight discomfort
- (c) Moderate discomfort
- (d) A lot of discomfort
- (e) Severe discomfort

3. Does your voice get worse as you talk?

- (a) Not at all – it stays the same
- (b) Occasionally when I talk
- (c) Often gets worse when I talk
- (d) Often gets a lot worse when I talk
- (e) Always gets a lot worse when I talk

4. Do you find it an effort to talk?

- (a) No effort at all
- (b) Slight effort sometimes (i.e. at the end of the day or when talking loudly etc.)
- (c) Quite an effort sometimes
- (d) An effort most of the time
- (e) A constant effort to talk

5. How much are you using your voice at present?

- (a) As much as I usually would
- (b) A little less than I usually would
- (c) Somewhat less than usual
- (d) A lot less than usual
- (e) Hardly at all

6. Does your voice problem stop you from doing anything that you would otherwise normally do?

- (a) Doesn't stop me doing anything that involves me using my voice
- (b) Stops me doing a few things that involve using my voice
- (c) Stops me doing a lot of things that involve using my voice
- (d) Stops me doing most things that involve using my voice
- (e) I can hardly do anything that involves me using my voice

7. In your opinion do you think that your voice is ever difficult to hear or understand?

- (a) Not at all
- (b) A little difficult
- (c) Quite difficult
- (d) Very difficult
- (e) Extremely difficult

8. Do OTHER people (eg. close family) ever comment that your voice is difficult to hear or understand?

- (a) No comments
- (b) Occasional comments
- (c) Quite often there are comments
- (d) Frequent comments
- (e) Very frequent comments

9. Since your voice problem started has your voice. . . ?

- (a) Improved a lot
- (b) Improved a little
- (c) Not improved at all
- (d) Deteriorated a little
- (e) Deteriorated a lot

10. Since your voice problem started have OTHER people (eg close family) commented that your voice has improved?

- (a) Other people say that my voice has improved a lot
- (b) Other people say that my voice has improved a little
- (c) Other people say that my voice has not improved at all
- (d) Other people say that my voice has got a little worse
- (e) Other people say that my voice has got a lot worse

11. Would you say that the sound of your voice was. . .

- (a) Normal
- (b) Not quite normal
- (c) Mildly abnormal
- (d) Quite abnormal
- (e) Very abnormal

12. How much do you worry about your voice problem now?

- (a) Not at all
- (b) Hardly at all
- (c) Quite a lot
- (d) A good deal
- (e) Almost all of the time

Assign a value of 1 to each (a) answer, a 2 to each (b) answer, and so on.
Total range of scores is therefore 12 (normal) to 60 (very severe dysfunction).

Total Score

Appendix 16: Control Intervention – Exercise Session Information

Exercise Session

What is Exercise/ Physical Activity

- ✚ Includes all forms of activity such as everyday walking or cycling, work related activity active recreation (such as working out in a gym), dancing, gardening or playing active games, as well as organised and competitive sport.

What happens when you exercise?

- ✚ When you exercise, your muscles demand more oxygen to create the energy they need to perform the activity you are doing.
- ✚ To increase the oxygen supplied to your muscles, your heart rate and the strength of each heartbeat increases to increase the amount of blood that is pumped with each heartbeat.
- ✚ Your breathing rate increases to increase the amount of oxygen breathed in and thus supplied to your muscles.
- ✚ This all causes your body temperature to increase making you feel hot, your blood vessels expand to help release this heat which causes you to sweat and appear red as the blood vessels appear closer to the skin surface.
- ✚ Overtime with increased exercise your muscles become more efficient, this then reduces the muscles' demand for oxygen and energy, therefore reducing your breathlessness when exercising.

Benefits of Physical activity

- ✚ There are many benefits of physical activity.
- ✚ For adults, doing 30 minutes of at least moderate intensity physical activity on at least 5 days a week helps to prevent and manage over 20 chronic conditions, including coronary heart disease, stroke, type 2 diabetes, cancer, obesity, mental health problems and musculoskeletal conditions.
- ✚ For adults based on physical activity of 30 minutes of at least moderate physical activity on at least 5 days a week are:
 - 20 to 35% lower risk of cardiovascular disease, coronary heart disease and stroke.
 - 30 to 40% lower risk of metabolic syndrome and type 2 diabetes
 - Reduced risk of hip fracture by 36% to 68%.
 - 30% lower risk of colon cancer and approximately 20% lower risk of breast cancer.
 - 20 to 30% reduction in risks for dementia and depression.
 - Exercise can also improve self-perception, self-esteem, mood and sleep quality, and reduce levels of anxiety and fatigue.
 - Can help to reduce weight.

Recommended Guidelines for Exercise

1. Adults should aim to be active daily. Over a week, activity should add up to at least 150 minutes (2½ hours) of moderate intensity activity in bouts of 10 minutes or more – one way to approach this is to do 30 minutes on at least 5 days a week.

- *Moderate Intensity Exercise* - Is at a level when your breathing rate and heart becomes faster and you start to feel a bit warmer and sweaty.
- Overall volume of physical activity is more important than the specific type of activity intensity or frequency of sessions.
- Should aim to be active everyday and therefore spread the 150 hours over the week.
- Accumulated short sessions of physical activity (≥10 minutes in duration) can provide similar health benefits to the same volume of exercise performed in longer continuous sessions.
- Higher volumes of activity (i.e. greater than 150 minutes per week) are associated with additional health benefits. There is insufficient evidence to determine whether there are health benefits from undertaking volumes of activity greater than 300 minutes per week

2. Alternatively, comparable benefits can be achieved through 75 minutes of vigorous intensity activity spread across the week or a combination of moderate and vigorous intensity activity.

- *Vigorous Intensity Exercise* - Is at a level that you breathing becomes very hard, so you are short of breath, have a rapid heart rate and will not be able to have a full conversation comfortably.

3. Adults should also undertake physical activity to improve muscle strength on at least two days a week.





- The optimum dose of muscle strengthening activity is to perform 8-12 repetitions of muscle strengthening activities involving all major muscle groups on two or more days per week.

4. All adults should minimise the amount of time spent being sedentary (sitting) for extended periods.

Source: Department of Health (2011) Start Active, Stay Active. UK, Department of Health.

Safety when exercising

If you feel any of the symptoms below then stop exercising:

-  Chest pain
-  Unexplained breathlessness
-  Dizziness or lightheadness
-  Feeling sick

Exercise Level of Different Activities

Table 4. Intensities and energy expenditure for common types of physical activity

Activity	Intensity
Ironing	Light
Cleaning and dusting	Light
Walking – strolling, 2mph	Light
Painting/decorating	Moderate
Walking – 3mph	Moderate
Hoovering	Moderate
Golf – walking, pulling clubs	Moderate
Badminton – social	Moderate
Tennis – doubles	Moderate
Walking – brisk, 4mph	Moderate
Mowing lawn – walking, using power-mower	Moderate
Cycling – 10–12mph	Moderate
Aerobic dancing	Vigorous
Cycling – 12–14mph	Vigorous
Swimming – slow crawl, 50 yards per minute	Vigorous
Tennis – singles	Vigorous
Running – 6mph (10 minutes/mile)	Vigorous
Running – 7mph (8.5 minutes/mile)	Vigorous
Running – 8mph (7.5 minutes/mile)	Vigorous

MET = Metabolic equivalent

1 MET = A person's metabolic rate (rate of energy expenditure) when at rest

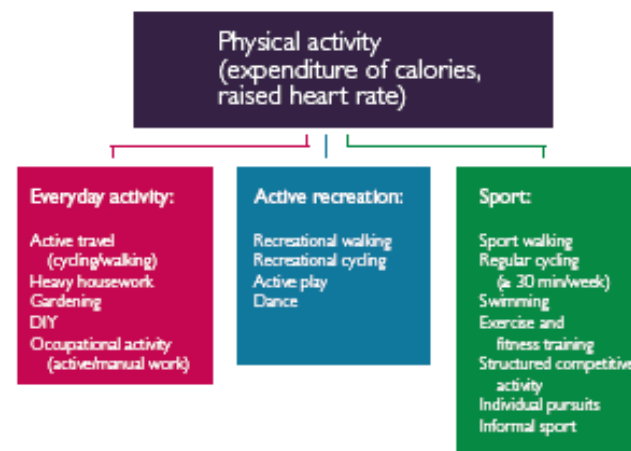
2 METS = A doubling of the resting metabolic rate

For a full definition of METS, see Annex B.

Source: Department of Health (2004) *At least five a week: Evidence on the impact of physical activity and its relationship to health.*

A report from the Chief Medical Officer

Different Types of Physical Activity/Exercise



Types of activity

Type of activity	Examples
Moderate intensity	Brisk walking, bike riding, dancing, swimming, active travel
Vigorous intensity	Running, playing sport, taking part in aerobic exercise classes, using cardiovascular gym equipment
Muscle strengthening	Weight training, working with resistance bands, carrying heavy loads, heavy gardening, push ups, sit ups

Source: Department of Health (2011) *Start Active, Stay Active.* UK, Department of Health.

FACTSHEET 4

Physical activity guidelines for

ADULTS (19–64 YEARS)



1. Adults should aim to be active daily. Over a week, activity should add up to at least 150 minutes (2½ hours) of moderate intensity activity in bouts of 10 minutes or more – one way to approach this is to do 30 minutes on at least 5 days a week.
2. Alternatively, comparable benefits can be achieved through 75 minutes of vigorous intensity activity spread across the week or combinations of moderate and vigorous intensity activity.
3. Adults should also undertake physical activity to improve muscle strength on at least two days a week.
4. All adults should minimise the amount of time spent being sedentary (sitting) for extended periods.

Individual physical and mental capabilities should be considered when interpreting the guidelines.

Examples of physical activity that meet the guidelines

Moderate intensity physical activities will cause adults to get warmer and breathe harder and their hearts to beat faster, but they should still be able to carry on a conversation. Examples include:

- Brisk walking
- Cycling

Vigorous intensity physical activities will cause adults to get warmer and breathe much harder and their hearts to beat rapidly, making it more difficult to carry on a conversation. Examples include:

- Running
- Sports such as swimming or football

Physical activities that strengthen muscles involve using body weight or working against a resistance. This should involve using all the major muscle groups. Examples include:

- Exercising with weights
- Carrying or moving heavy loads such as groceries

Minimising sedentary behaviour may include:

- Reducing time spent watching TV, using the computer or playing video games
- Taking regular breaks at work
- Breaking up sedentary time such as swapping a long bus or car journey for walking part of the way

What are the benefits of being active daily?

- Reduces risk of a range of diseases, e.g. coronary heart disease, stroke, type 2 diabetes
- Helps maintain a healthy weight
- Helps maintain ability to perform everyday tasks with ease
- Improves self-esteem
- Reduces symptoms of depression and anxiety

For further information: *Start Active, Stay Active: A report on physical activity for health from the four home countries' Chief Medical Officers* (2011)



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Physical activity guidelines for OLDER ADULTS (65+ YEARS)



- Older adults who participate in any amount of physical activity gain some health benefits, including maintenance of good physical and cognitive function. Some physical activity is better than none, and more physical activity provides greater health benefits.
- Older adults should aim to be active daily. Over a week, activity should add up to at least 150 minutes (2½ hours) of moderate intensity activity in bouts of 10 minutes or more – one way to approach this is to do 30 minutes on at least 5 days a week.
- For those who are already regularly active at moderate intensity, comparable benefits can be achieved through 75 minutes of vigorous intensity activity spread across the week or a combination of moderate and vigorous activity.
- Older adults should also undertake physical activity to improve muscle strength on at least two days a week.
- Older adults at risk of falls should incorporate physical activity to improve balance and co-ordination on at least two days a week.
- All older adults should minimise the amount of time spent being sedentary (sitting) for extended periods.

Individual physical and mental capabilities should be considered when interpreting the guidelines.

Examples of physical activity that meet the guidelines

Moderate intensity physical activities will cause older adults to get warmer and breathe harder and their hearts to beat faster, but they should still be able to carry on a conversation. Examples include:

- Brisk walking
- Ballroom dancing

Vigorous intensity physical activities will cause older adults to get warmer and breathe much harder and their hearts to beat rapidly, making it more difficult to carry on a conversation. Examples include:

- Climbing stairs
- Running

Physical activities that strengthen muscles involve using body weight or working against a resistance. This should involve using all the major muscle groups. Examples include:

- Carrying or moving heavy loads such as groceries
- Activities that involve stepping and jumping such as dancing
- Chair aerobics

Activities to improve balance and co-ordination may include:

- Tai chi
- Yoga

Minimising sedentary behaviour may include:

- Reducing time spent watching TV
- Taking regular walk breaks around the garden or street
- Breaking up sedentary time such as swapping a long bus or car journey for walking part of the way

What are the benefits of being active daily?

- Helps maintain cognitive function
- Reduces cardiovascular risk
- Helps maintain ability to carry out daily living activities
- Improves mood and can improve self-esteem
- Reduces the risk of falls

For further information: *Start Active, Stay Active: A report on physical activity for health from the four home countries' Chief Medical Officers* (2011)

Appendix 17: Control Intervention – Diet Diary example from participant in Control group

Lis from 6/2 - 10/2/12

	Breakfast	Lunch	Supper	Activities
14/2/12 Wednesday 8/2/12 v. little cough	museli & poached pinnis n orange juice 1x coffee 9:30 1x bic.	First Frawn 4x salad on brown 1x apple cake Water + +	Sausages Spiced red cabbage, Potatoes Water +	Kings, shopped in Bromley home with prepared m. lade
Thursday 9/2/12	museli etc 2x coffee 2x water	Smoked mackerel n roll + 1 pear Water 1x tea	Chicken & veg stew with tomatoes 1/2 mango Water x2	made marmalade cleaned up odds & ends v. little cough
Friday 10/2/12 v. little cough	museli + pinnis n apple juice 2x coffee 2x water	Sardines & cucumber on brown soup, water 1x tea 1x apple	Baked Trout & sweet potato mash + porc chor water	Sorted out larder, cleaned kitchen + marmalade put away laundry etc
Saturday 11/2/12 v. little cough	museli & fruit n apple juice 1x coffee, 2x water	hot choc, * full English choc cake water	Small Carbonara & roasted tomatoes water	* out with family!
Sunday 12/2/12 coughed ? Cashmere jumper?	Museli, fruit, apple juice, coffee & water x1.	ham & salad roll + 1x apple water 1x tea	Roast beef & veg choc pudding cream 1x water 1x wine	Church + duties read papers tidied odds ends
Monday 13/2/12 coughed more	museli etc 2x coffee 1x water	ham salad roll, 1x banana water 2x 2x tea	goulash & noodles 2 wine 2 water	Housework incl. hoovering & moving stuff around
Tuesday 14/2/12 coughed	The usual 2x coffee 1x water	chorizo stew & mash 1x wine	homemade curries	lunch out * after guys Guys Museum delivered Church

Appendix 18: Control Intervention – Diet Session Information

The below information is from NHS choices website available at <http://www.nhs.uk/Livewell/Goodfood/Pages/eight-tips-healthy-eating.aspx>



Eight tips for healthy eating



Eating a healthy, balanced diet is an important part of maintaining good health, and can help you feel your best. It can be simple, too. Just follow these eight tips to get started.

The two keys to a healthy diet are:

- Eat the right number of calories for how active you are, so that you balance the energy you consume with the energy you use. If you eat or drink too much, you'll put on weight. If you eat too little you'll lose weight. The average man needs around 2,500 calories a day. The average woman needs 2,000 calories. Most adults are eating more calories than they need, and should eat fewer calories.
- Eat a wide range of foods to ensure that you're getting a balanced diet and that your body is receiving all the nutrients it needs.

Get started

The eatwell plate

- To help you get the right balance of the five main food groups, take a look at the eatwell plate.
- To maintain a healthy diet, the eatwell plate shows you how much of what you eat should come from each food group

These practical tips cover the basics of healthy eating, and can help you make healthier choices:

1. **Base your meals on starchy foods**

Starchy foods include potatoes, cereals, pasta, rice and bread. Choose wholegrain varieties when you can: they contain more fibre, and can make you feel full for

longer. Starchy foods should make up around one third of the foods you eat. Most of us should eat more starchy foods: try to include at least one starchy food with each main meal. Some people think starchy foods are fattening, but gram for gram they contain fewer than half the calories of fat. Learn more in [Starchy foods](#).

2. Eat lots of fruit and veg

It's recommended that we eat at least five portions of different types of fruit and veg a day. It's easier than it sounds. A glass of 100% unsweetened fruit juice can count as one portion, and vegetables cooked into dishes also count. Why not chop a banana over your breakfast cereal, or swap your usual mid-morning snack for some dried fruit? Learn more in [5 A DAY](#).

3. Eat more fish

Fish is a good source of protein and contains many vitamins and minerals. Aim for at least two portions a week, including at least one portion of oily fish. Oily fish is high in omega-3 fats, which may help to prevent heart disease. You can choose from fresh, frozen and canned; but remember that canned and smoked fish can be high in salt. Oily fish include salmon, mackerel, trout, herring, fresh tuna, sardines and pilchards. Non-oily fish include haddock, plaice, coley, cod, tinned tuna, skate and hake. Anyone who regularly eats a lot of fish should try to choose as wide a variety as possible.

4. Cut down on saturated fat and sugar

We all need some fat in our diet. But it's important to pay attention to the amount and type of fat we're eating. There are two main types of fat: saturated and unsaturated. Too much saturated fat can increase the amount of cholesterol in the blood, which increases your risk of developing heart disease. Saturated fat is found in many foods, such as hard cheese, cakes, biscuits, sausages, cream, butter, lard and pies. Try to cut down, and choose foods that contain unsaturated rather than saturated fats, such as vegetable oils, oily fish and avocados. For a healthier choice, use a just a small amount of vegetable oil or reduced fat spread instead of butter, lard or ghee. When you're having meat, choose lean cuts and cut off any visible fat. Learn more, and get tips on cutting down, in [Eat less saturated fat](#).

Most people in the UK eat and drink too much sugar. Sugary foods and drinks, including alcoholic drinks, are often high in calories, and could contribute to weight gain. They can also cause tooth decay, especially if eaten between meals. Cut down on sugary fizzy drinks, alcoholic drinks, cakes, biscuits and pastries, which contain added sugars: this is the kind of sugar we should be cutting down on rather than sugars that are found naturally in foods such as fruit and milk. Food labels can help: use them to check how much sugar foods contain. More than 15g of sugar per 100g means that the food is high in sugar.

5. Eat less salt

Even if you don't add salt to your food, you may still be eating too much. About three-quarters of the salt we eat is already in the food we buy, such as breakfast cereals, soups, breads and sauces. Eating too much salt can raise your blood pressure. People with high blood pressure are more likely to develop heart disease or have a stroke. Use food labels to help you cut down. More than 1.5g of salt per 100g means the food is high in salt. Adults and children over 11 should eat no more than 6g of salt a day. Younger children should have even less.

6. Get active and be a healthy weight

Eating a healthy, balanced diet plays an important part in maintaining a healthy weight, which is an important part of overall good health. Being overweight or obese can lead to health conditions such as type 2 diabetes, certain cancers, heart disease and stroke. Being underweight could also affect your health. Check whether you're a healthy weight by using our [Healthy weight calculator](#). Most adults need to lose weight, and need to eat fewer calories in order to do this. If you're trying to lose weight, aim to eat less and be more active. Eating a healthy, balanced diet will help: aim to cut down on foods that are high in fat and sugar, and eat plenty of fruit and vegetables. Don't forget that alcohol is also high in calories, so cutting down can help you to control your weight. You can find information and advice to help in [Lose weight](#). If you're underweight, see [Underweight adults](#). If you're worried about your weight, ask your GP or a dietitian for advice.

Physical activity can help you to maintain weight loss or be a healthy weight. Being active doesn't have to mean hours at the gym: you can find ways to fit more activity into your daily life. For example, try getting off the bus one stop early on the way home from work, and walking. Being physically active may help reduce the risk of heart disease, stroke and type 2 diabetes. For more ideas, see [Get active your way](#). After getting active, remember not to reward yourself with a treat that is high in calories. If you feel hungry after activity choose foods or drinks that are lower in calories but still filling.

7. Don't get thirsty

We need to drink about 1.2 litres of fluid every day to stop us getting dehydrated. This is in addition to the fluid we get from the food we eat. All non-alcoholic drinks count, but water, milk and fruit juices are the most healthy. Try to avoid sugary soft and fizzy drinks that are high in added sugars and can be high in calories and bad for teeth. When the weather is warm, or when we get active, we may need more. Learn more in [Drinks](#).

8. Don't skip breakfast

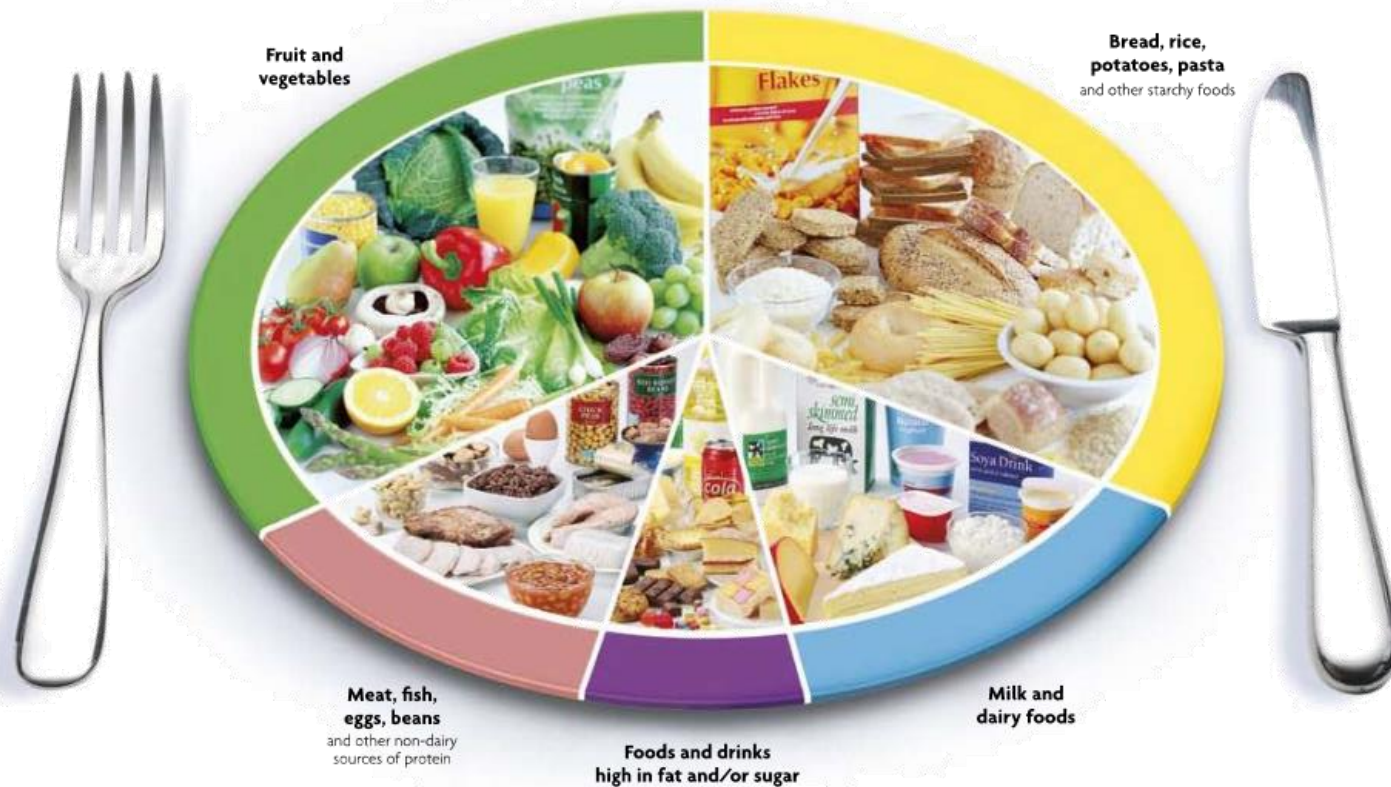
Some people skip breakfast because they think it will help them lose weight. In fact, research shows that eating breakfast can help people control their weight. A healthy breakfast is an important part of a balanced diet, and provides some of the

vitamins and minerals we need for good health. Wholemeal cereal, with fruit sliced over the top is a tasty and nutritious breakfast.

From: <http://www.nhs.uk/Livewell/Goodfood/Pages/eight-tips-healthy-eating.aspx>

The eatwell plate

Use the eatwell plate to help you get the balance right. It shows how much of what you eat should come from each food group.



Department of Health in association with the Welsh Government, the Scottish Government and the Food Standards Agency in Northern Ireland

Available at: <http://www.nhs.uk/Livewell/Goodfood/Pages/eatwell-plate.aspx>

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Eat 5 A DAY – what counts as 1 portion?



1 medium apple



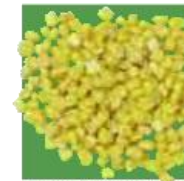
3 celery sticks



1/2 a large courgette



8 cauliflower florets



3 heaped tbsp of
canned sweetcorn



8 Brussels sprouts



12 chunks of pineapple



1 slice (2-inch slice)
of melon



2 kiwi fruit



1/2 an avocado



7 cherry tomatoes



1 medium pear



3 heaped tbsp of
cooked kidney beans



1 medium onion



1 handful of chopped
carrot sticks



2 broccoli florets



1 handful of
vegetable sticks



3 whole dried apricots



2 small satsumas



16 medium okra



2 medium plums



1 leek



1 medium banana



3 heaped tbsp of
fresh or frozen peas

nhs.uk/5aday

Available at:

http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/publichealth/healthimprovement/fiveaday/dh_4069867



Just Eat More

Add flavour to a sandwich – throw in some lettuce and sliced tomato.

What counts?

- Fresh, frozen, chilled, canned, 100% juice, and dried fruit and vegetables all count.
- A portion of your 5 A DAY weighs approximately 80 grams, which is roughly a handful.
- Potatoes and other related vegetables such as yams and cassava do not count, because they are classified as starchy foods.
- The fruit and vegetables contained in convenience foods – such as ready meals, pasta sauces, soups and puddings – can contribute to 5 A DAY.
- Convenience foods can also be high in added salt, sugar or fat – which should only be eaten in moderation – so it's important to always check the nutrition information on food labels.

For more 5 A DAY information and tips, visit: nhs.uk/5aday

Just Eat More

For a healthier dessert try tinned peaches in their own juice.



Remember, frozen, canned, 100% juice, plus dried fruit and veg all count as well as fresh produce.

nhs.uk/5aday



180207 1M AUG 08

5 A DAY: what's it all about?

- Eating a variety of fruit and vegetables, whether fresh, frozen, canned or dried, can all count towards your 5 A DAY. And, eating 5 A DAY may help to reduce the risk of heart disease, stroke and some cancers.
- Eating a variety of fruit and vegetables will give you plenty of vitamins and minerals. They are also a good source of fibre and other essential nutrients, all of which are important for your health.

Just Eat More

For a healthier snack try dipping veg sticks into a dip.



Just Eat More

Have a glass (150ml) of 100% fresh juice with your lunch.



Are you getting your 5 A DAY?

1. How many portions of fruit* do you eat on a typical day? Portions of fruit
 2. How many portions of vegetables* do you eat on a typical day? Portions of vegetables
- (One portion = approximately 80 grams)
* See overleaf for examples of fruit and veg portion sizes.

Add up the numbers from your answers to questions 1 and 2:

If the total is 5 portions or more, that's great. Remember, you need to eat a variety of fruit and vegetables.

If your total is less than 5 portions, then have a look at the 5 A DAY website for more hints and tips on how you can reach your 5 A DAY: nhs.uk/5aday

Just Eat More

Frozen fruit and veg count towards your 5 A DAY.



Just Eat More (fruit & veg)

nhs.uk/5aday

Look out for the 5 A DAY portion indicator on food packets

Where you see the portion indicator, it will feature how many portions of fruit or veg are in each serving.



1 portion



2 portions



Just Eat More

Feel like a snack? Reach for an apple instead of chocolate.

Eat a variety of fruit and vegetables, and aim for at least 5 A DAY.



Available at:

http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/publichealth/healthimprovement/fiveaday/dh_4069867

A quick guide to labels

	A lot	A little
Sugar	15g or more per 100g	5g or less per 100g
Salt	1.5g or more per 100g	0.3g or less per 100g
Sodium	0.6g sodium or more per 100g	0.1g sodium or less per 100g
Fat	20g or more per 100g	3g or less per 100g
Saturated fat	5g or more per 100g	1.5g or less per 100g

Stress and Relaxation

Managing your stress levels and knowing how to relax is important for your health, particularly as stress can make your breathing feel worse.

1. What is stress?

Stress is a normal response to the demands put on us in life.

We all need a little bit of stress to keep us going but the problem comes when the stresses become overwhelming.

2. How do you know when you are stressed? What changes about you when you are stressed?

Physical Response

Increase heart rate
Blood pressure rises
Breathing gets faster
decisions

Muscles become tense and sore

Sweating

Nausea/diarrhoea

Clenching of jaw/fists

Palpitations

Headaches

Blurred vision

Frequent urination

Change in appetite

Dry mouth

Pins and needles

Physical symptoms due to 'fight or flight' response
(Describe)

Emotional Response

(how you think or feel)

Racing thoughts

Difficulty concentrating

Harder to make

Loss of confidence

Increased cravings for
alcohol/cigs/food

Fear and panic

Feeling low

Difficulty sleeping

Negative thoughts

The chemical adrenalin is released and this causes our \uparrow HR, \uparrow BP and \uparrow RR. We don't really run away or begin to fight and the chemical builds up in our bodies and gives us our symptoms as listed above.

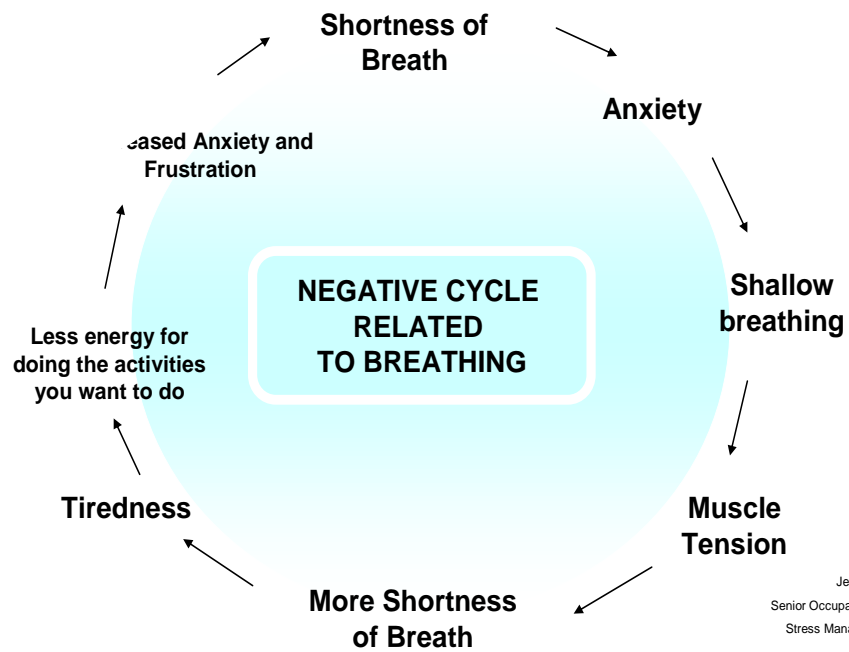
Your behaviour may change as well - e.g you may avoid situations, start snapping at people etc

3. What causes your stress?

(Patients ideas)

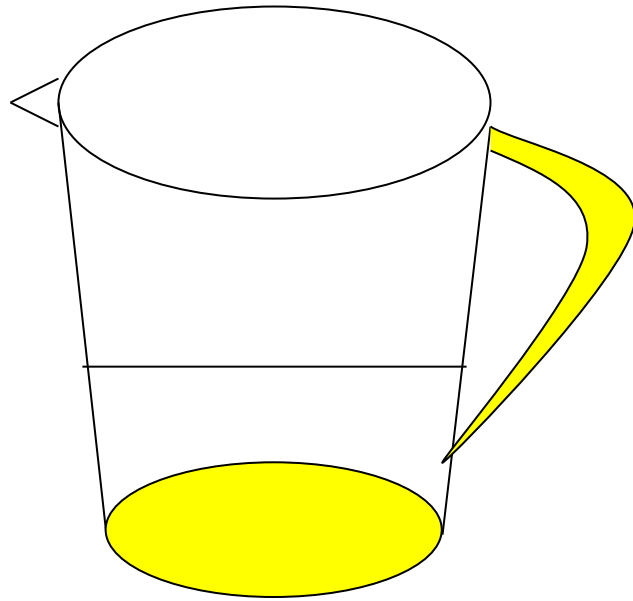
e.g's public transport, hospital visit, your breathing problems, family, financial, traffic jams

4. Your breathing is closely related to how you are feeling. If you feel stressed or anxious, you may then feel more breathless, but being breathless can also make you feel anxious. Go through the negative cycle of anxiety and breathlessness



5. We all have different abilities to deal with stress: The stress jug

This is all about how we contain our stress.
Ideally draw jug on flipchart



Everyone's jug is a different size - some of us have a larger capacity for stress than others

This is due to our genetic makeup - just the way we are - plus how much support we have, your upbringing and life experience

Put into the jug all the things that cause us stress with the everyday things that aren't going to go away at the bottom (e.g breathing problems)

Eventually this jug gets fuller and fuller and you get to the point when a very small thing can cause the jug to overflow and you see a behavioural change.

e.g you burst into tears because you can't find a parking space, or because someone snaps at you

It is important that we try to empty the jug of stress regularly to stop it overflowing. Sustained high stress levels can be detrimental to our health. It is important

that we recognise when we are stressed and find ways to reduce our stress levels

6. Ways to deal with stress

What do you do to 'empty the jug'??

(get examples from group.. listen to music, go for a walk, talk to someone, watch tv, hot bath, glass of wine etc.)

- **Lifestyle**

You need to schedule in time for 'me', for things you enjoy and even time to relax. Also helpful to be aware of your diet, exercise and even sleep as they are significant little things that can affect your ability to cope.

- **Hobbies or interests**

Do things you enjoy

- **Distraction**

Things that distract you from worrying thoughts or from the physical symptoms of stress. Happy memories, counting or reciting, focussing on an object, reading or listening to the radio, word or number games, getting out and talking to somebody.

- **Using a Diary**

Writing down how you're feeling can help you to feel you have off loaded some of your stress. Can also increase your self-awareness.

- **Positive thinking**

Calming words or positive self talk. Be kind to yourself.

- **Be realistic**

Don't have too high expectations of yourself.

- **Acceptance**

Look at the situation - think about it - change what you can - accept what can't be changed

- **Relaxation**

To release your tense muscles and slow down your heart.

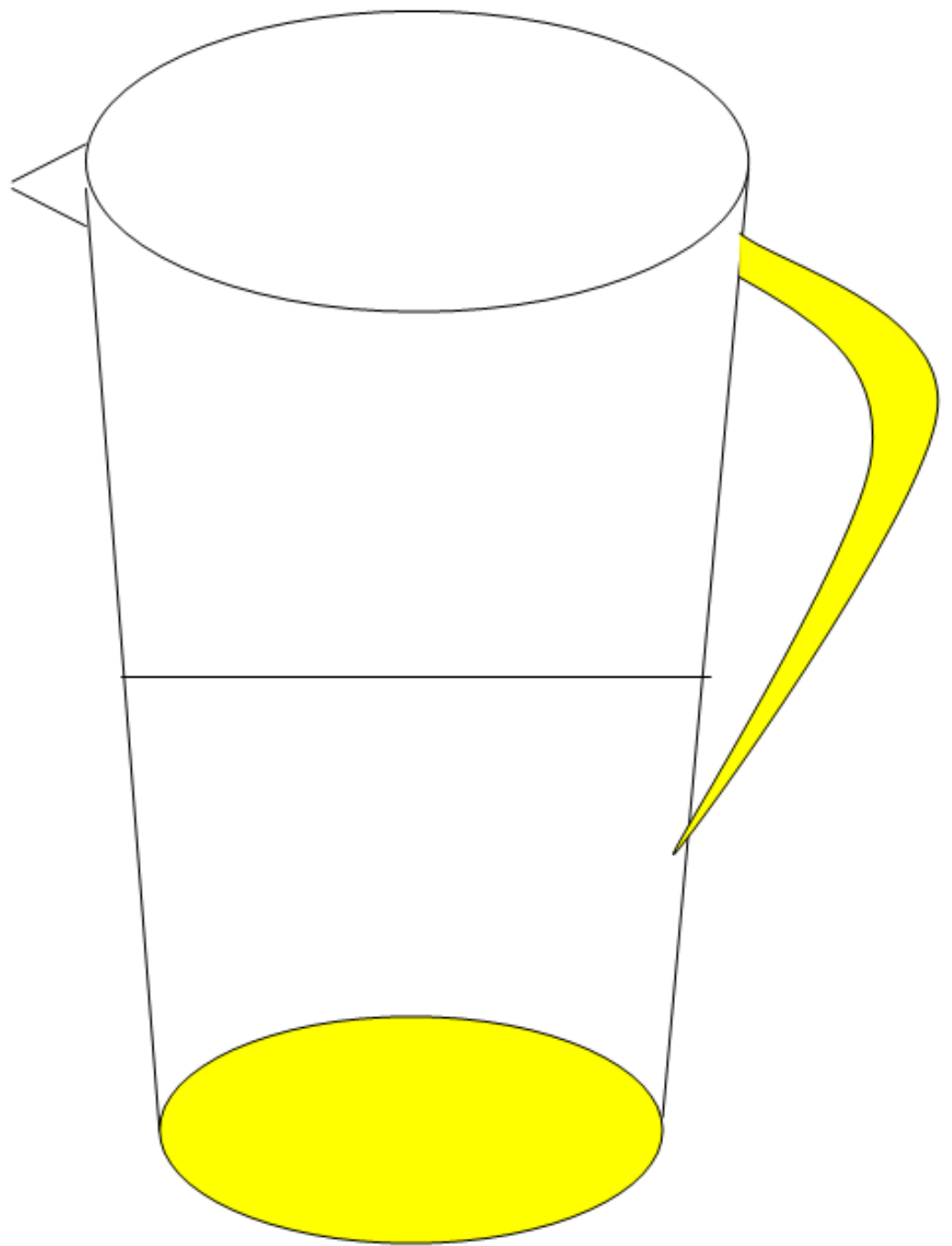
Relaxation

Prevent the build up of stress through the use of short, frequent periods of physical and mental relaxation

As physical tension is eased, your mind starts to empty and feel relaxed too. Learning to relax can be difficult. Just as you have to practise a new skill, you must also practise relaxation.

Relaxation will help to:

- Calm you
- Regulate your breathing
- Lower your blood pressure/heart rate
- Help you sleep
- Help you feel able to cope with life a bit better



Relaxation tips for stress



Relaxation can help to relieve the symptoms of stress. It can help you calm down and take a step back from a stressful situation.

Although the cause of the anxiety won't disappear, you will probably feel more able to deal with it once you've released the tension in your body and cleared your thoughts.

All relaxation techniques combine breathing more deeply with relaxing the muscles.

Don't worry if you find it difficult to relax at first. It's a skill that needs to be learned and it will come with practice.

Relaxed breathing

Practise deep breathing at a regular time and in a quiet place where you won't be disturbed. Loosen or remove any tight clothes, such as shoes or jackets. Be completely comfortable.

Sit in a comfy chair which supports your head or lie on the floor or bed. Place your arms on the chair arms, or flat on the floor or bed, a little bit away from the side of your body with the palms up. If you're lying down, stretch out your legs, keeping them hip-width apart or slightly wider. If you're sitting in a chair, don't cross your legs.

Good relaxation always starts with focusing on your breathing. The way to do it is to breathe in and out slowly and in a regular rhythm as this will help you to calm down.

- Fill up the whole of your lungs with air, without forcing. Imagine you're filling up a bottle, so that your lungs fill from the bottom.
- Breathe in through your nose and out through your mouth.
- Breathe in slowly and regularly counting from one to five (don't worry if you can't reach five at first).
- Then let the breath escape slowly, counting from one to five.

- Keep doing this until you feel calm. Breathe without pausing or holding your breath.

Practise this relaxed breathing for three to five minutes, two to three times a day (or whenever you feel stressed).

Deep muscle relaxation

This technique takes around 20 minutes. It stretches different muscles in turn and then relaxes them, to release tension from the body and relax your mind.

Find a warm, quiet place with no distractions. Get completely comfortable, either sitting or lying down. Close your eyes and begin by focusing on your breathing; breathing slowly and deeply, as described above.

If you have pain in certain muscles, or if there are muscles that you find it difficult to focus on, spend more time on relaxing other parts.

You may want to play some soothing music to help relaxation. As with all relaxation techniques, deep muscle relaxation will require a bit of practice before you start feeling its benefits.

For each exercise, hold the stretch for a few seconds, then relax. Repeat it a couple of times. It's useful to keep to the same order as you work through the muscle groups:

- **Face:** push the eyebrows together, as though frowning, then release.
- **Neck:** gently tilt the head forwards, pushing chin down towards chest, then slowly lift again.
- **Shoulders:** pull them up towards the ears (shrug), then relax them down towards the feet.
- **Chest:** breathe slowly and deeply into the diaphragm (below your bottom rib) so that you're using the whole of the lungs. Then breath slowly out, allowing the belly to deflate as all the air is exhaled.
- **Arms:** stretch the arms away from the body, reach, then relax.
- **Legs:** push the toes away from the body, then pull them towards body, then relax.
- **Wrists and hands:** stretch the wrist by pulling the hand up towards you, and stretch out the fingers and thumbs, then relax.

Spend some time lying quietly after your relaxation with your eyes closed. When you feel ready, stretch and get up slowly.

From : <http://www.nhs.uk/Livewell/Stressmanagement/Pages/Relaxation.aspx>

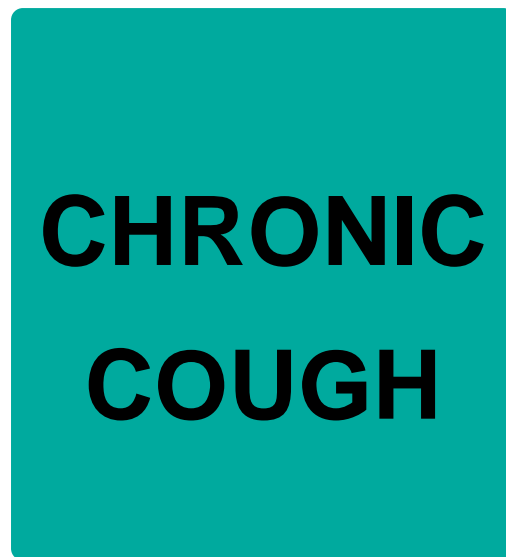
Appendix 21: PSALTI Participant Treatment session Therapist Instructors for Session 1

Session 1 (1 hour)

- **Remember administer outcome measures first.**
- **Complete assessment**
- **Issue with cough handout**
- Start **education +++++** about negative effects of coughing.
 - Cough reflex is voluntary and involuntary. Explain cough receptors.
 - There are negative effects from repeated coughing - exacerbation of irritation and perpetuation of coughing. **Talk about eczema example, scratching the throat causing irritation.**
 - Encourage participants to internalise control over their cough, to view cough as a response to irritating stimuli rather than a phenomenon outside their control. Talk about the need for them to suppress their cough even when there is a sensation to cough to reduce repeated irritation.
- Discuss **eliminating triggers.**
- Set realistic **goals** and emphasise to participants that treatment is demanding, there is no easy cure and that results may not be observed immediately.
- Start the **minimisation techniques**: water, sweets, increasing hydration, gum, nasal pattern etc.....
 - They keep water bottle with them and when they feel the tickle they sip water.
 - When talking having sweets etc ready so they know they producing saliva and swallow.
 - Possibly talking about food re: what eating etc.. if related to cough/ night time coughing with GOR.
- **Slightly productive patients discuss trying to suppress non-productive coughs – so if patient is normally only slightly productive first thing in the morning, get them to try to suppress their coughs in the afternoon.**

Appendix 22: PSALTI Participant Handout

King's College Hospital 
NHS Foundation Trust



This booklet is aimed at giving you easy-to-read information about chronic cough. It aims to tell you what the condition is, some of the symptoms you may experience and what treatment with physiotherapy comprises.

Produced by: Respiratory Physiotherapy Department.

What is Cough?

A cough is one of our strongest reflexes and is a defence mechanism that aims to clear the lungs of secretions or any foreign bodies that enter it.

Who develops a Cough?

Chronic cough is a cough that lasts longer than eight weeks. It is present in 3% of the general population and if a cause for this is not found it is called Refractory cough.

The cause of most cases of chronic cough in patients with normal spirometry (breathing tests) who are non-smokers and have a normal chest x-ray is asthma, gastro-oesophageal reflux (acid coming back up your throat from your stomach) and rhinitis (inflammation of the nasal passages) or a combination of these.

Chronic cough can be associated with distressing symptoms such as joint and muscle pain, chest pains, fainting, incontinence, disturbed sleep, and social embarrassment.

What causes Chronic Cough?

There are cough receptors in the upper airways that when stimulated cause the cough reflex. Most cases of chronic cough are associated with increased sensitivity of these receptors, especially if the cough is dry.

Some people however have no underlying diagnosis or cause. Coughing can be caused by dry irritable airways, increasing the sensitivity of the cough receptors. The habit of coughing and throat clearing continues to worsen the cycle.

How is it diagnosed?

A variety of tests can be performed to rule out the different causes of cough and to assess the irritability of your airways:

- Lung Function Tests
- Chest X-ray
- Metacholine challenge/Capsaicin challenge
 - Inhale an irritant and then perform breathing tests to check for hyperactivity of airways or hypersensitivity of the cough reflex
- Cough recording
 - Wear a monitor that records the number of times you cough over a 24hour period
- Trial of corticosteroid medications
 - Preventer inhalers and/or tablets used in asthma
- Gastrointestinal (stomach and bowel) investigations
 - Trial of anti-reflux medications
 - 24hour pH monitor
- Ear Nose and Throat (ENT) examination
- CT scan
- Bronchoscopy
 - Tube with a camera is passed into your lungs to have a close-up look.

How is it treated?

If a diagnosis or cause for the cough is found, appropriate medication will be given to help decrease the irritating cause and improve your cough. Some people remain symptomatic despite optimal medical therapy.

PSALTI will aim to show you how to:

- Reduce your sensitivity of your cough reflex
- Increase your control of your cough
- Retrain your breathing pattern
- Clear secretions if you have any

Methods for Reducing Cough

1. Nose breath as much as you can, try to build it up slowly so you are eventually using your nose all the time (except when talking!)
2. Retraining breathing pattern with the help of your physiotherapist.
3. Ensuring your airways are clear of secretions if you have any.
4. Take frequent sips of water to ensure that your throat is moist and less irritable. Have a bottle of water with you at all times to keep you upper airways moist and clear.
5. Sucking a sweet, this also helps ensure that your throat is kept moist. This is particularly helpful prior to talking on the phone or talking for long periods.
6. If you feel a cough coming on swallow hard, relax your shoulders and concentrate on breathing slowly and gently out.

What are my triggers?

It is important to know what your triggers are so that you can pre-empt a cough. This will help you to regain control over your cough.

Some Common triggers:

- Changes in temperature
- Sprays
- Stress or Anxiety
- Smoky atmosphere
- Exertion
- Changing position
- Talking

Your triggers:

-
-
-
-
-
-
-

Normal breathing

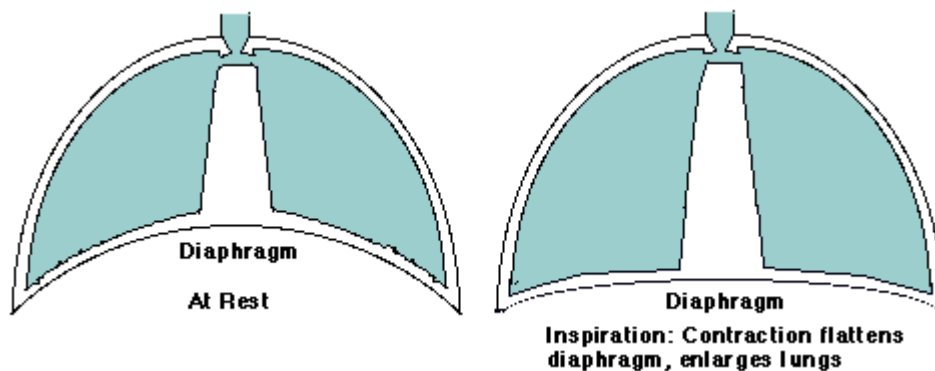
'Normal breathing' means moving air in and out of the chest with minimum effort and using the airways and chest muscles to their best advantage. This should be a relaxed, silent process including nose breathing.

Your nose is designed to warm, moisten and filter the air around us so that it is the right temperature, humidity and volume when it reaches your lungs.

If you breathe in and out through your mouth there is little opportunity for any of the above to occur making the air move faster, be drier and colder and be more irritable to your airways and cough reflex.

Diaphragm:

The main breathing muscle is the diaphragm. It is a strong flat muscle that is attached to the lower edges of the ribs. It separates the chest from the gut. It is shaped like the dome of an umbrella when it is relaxed.



As you breathe in, your diaphragm flattens and moves down to give your more space for your lungs to expand and this causes your stomach to push outwards. When you breathe out your stomach relaxes back to where it started and the diaphragm moves back up.

In normal breathing:

The diaphragm does 70-80% of the work,

20-30% by the lower chest muscles (intercostals),

All breaths should go in and out of the nose quietly,

A healthy breathing rate is 10-12 breaths/minute.

Breathing Retraining

First, let's check your breathing:



- Rest one hand on your upper chest and one on your abdomen (just below your ribs)
- Breathe in and out through your **nose**
- Your breathing should be completely **quiet**. If you can hear yourself breathing you are 'over breathing'
- Be aware of the movement under your hands as you breathe – notice which hand is moving most.

As you breathe **in** you should feel the hand on your abdomen rise up to the ceiling as air enters your lungs.

- As you breathe **out** you should feel this hand fall as air exits your lungs

It can be tempting to take big breaths when you are doing this but try not to.

Appendix 23: PSALTI Participant Treatment session Therapist Instructors for Session 2

Session 2: (45 min)

- **Remember administer outcome measures first.**
-
- Questions from them and answers.

- Check if they have noticed anything else with coughing? Any other triggers that they have now realised.

- Reiterate cough control, strategies – drinking water, chewing gum, sucking sweets.

- Reiterate avoidance of triggers, reduce caffeine intake and increase hydration, decrease intake of acidity foods.

- Teach them the **swallow technique**.

- Teach them **breathing control**. You need to **educate** the diaphragm, how it works. What is normal breathing. Continue re-inforcing nose breathing etc.....


- **Nose** breathing ++++ talk about how important the nose is for the body etc....

- Discussing how these techniques can be used as **distraction techniques**. They need to stop coughing fits (the coughs that turns into an attack. So they will be good at stopping the little ones but they need to nip the big ones, if appropriate)

- **Positive re-inforcement**. Talk about how long it has been, talking about bad behaviours and how they have control over this.

- Airway clearance if needed (ACBT – sheet)

Appendix 24: PSALTI Airway clearance technique

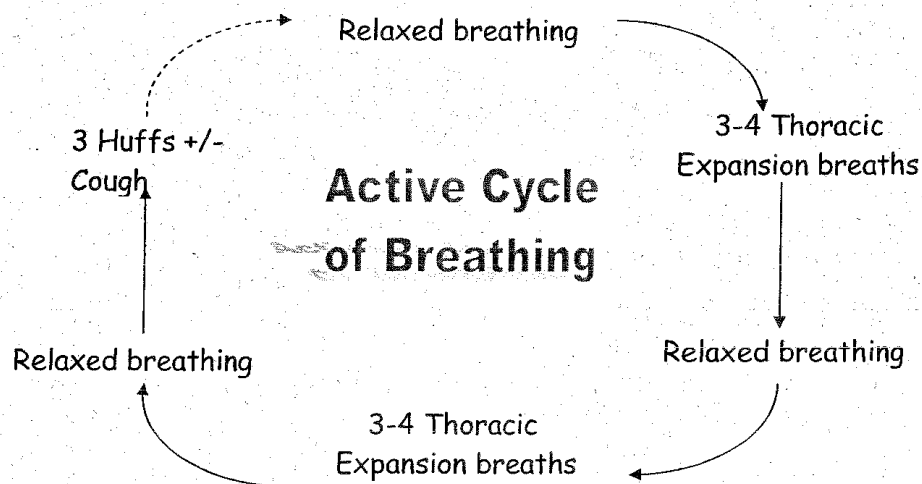
King's College Hospital 

NHS Foundation Trust

THE ACTIVE CYCLE OF BREATHING TECHNIQUE

The active cycle of breathing is designed to clear secretions with minimal effort. It comprises 3 parts:

- 1) Relaxed breathing
Slow rhythmical breathing (10-12 breaths/minute). Your stomach should rise as you breathe IN and relax/flatten as you breathe OUT. Your shoulders and neck should be relaxed and your upper chest should not move. Place your hand on your stomach to feel it rise and fall.
- 2) Thoracic expansion exercises
3 or 4 deep breaths (feeling the air reach the bottom of your lungs), holding the breath in for 3 - 5 sec, whilst keeping your shoulders relaxed. Expiration should be gentle and relaxed. This gets air down to the bottom of your lungs and helps to move the phlegm.
- 3) Huff or forced expiration
3 huffs: first take a small breath in followed by a forceful breath out, using your tummy muscles (It is like steaming up a mirror with your mouth open), then taken a medium breath in and forceful huff out, then a deep breath in and forceful huff. If you feel phlegm at the back of the throat you can cough, if not, repeat the whole cycle.



By doing this breathing technique you should not have to cough as much to clear your lungs. You should not feel so exhausted, and your chest should not get so sore, which often happens when you cough a lot.

Drink plenty of fluids as this will help keep your sputum less sticky. Try to exercise regularly as this helps to clear phlegm and is good for your general well being!

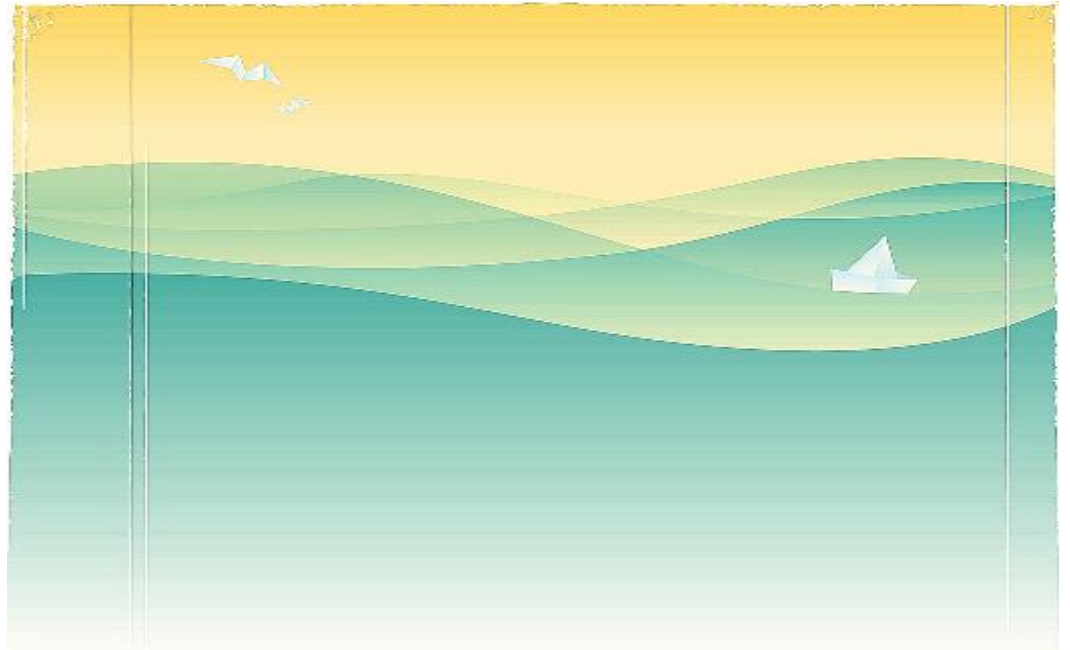
Appendix 25: PSALTI Participant Treatment session Therapist Instructors for Session 3

Session 3: (45 min)

- **Remember administer outcome measures first.**
- Review from last week.
- Possibly **more breathing control techniques** (may be that you need to include exercise and breathing control as they cough when they get to the top of the stairs, or progress to more functional movements if they were only able to do in lying when first taught technique).
- May need to start **introducing lifestyle** techniques? Looking at stress and anxiety and how this can feed into cough and maybe they can start thinking about regular exercise etc... This is the ones when you know that it could be work related etc....**use stress and anxiety with cough handbook**
- Or you may need to briefly go through **relax techniques** etc..... as this may be **integral to breathing control**.
- Maybe thinking about **re-introducing triggers**, smells etc..... they need to see how they handle these situations.
- If really **struggling with nose breathing** may need to look into nasal sprays, steam inhalations or trying nasal douching...
- This session of session 2: May be that they feel it is not working it may be that you go through all the triggers and minimisation stuff again. Reinforce need for them to control their cough.

Appendix 26: Stress and Anxiety Booklet for PSALTI Participants

Stress and Anxiety



Stress and anxiety can make the urge to cough more troublesome.
This booklet will help you learn ways of overcoming them.



Anxiety is very common, particularly at stressful times in our lives. For some people, stress and anxiety can be intense and seem overwhelming, but they can be overcome. This booklet will go through some of the ways this can be done.

You might find it useful to look at this booklet with a health care professional and discuss which of the suggestions might work best for you.

Our minds and bodies affect each other in many ways

- For example, when we are ill, we often feel low in mood.
- You might have noticed “butterflies” in your stomach when you are nervous or excited.
- You may also have seen a child no longer troubled by the pain from a grazed knee once they have been given an ice cream or a hug.

Understanding anxiety

The first step to overcoming anxiety is to understand it. Everyone experiences anxiety at some time or other. It is a normal reaction to feelings of danger and stress. When you are feeling anxious, you might think that it will get worse and worse, but anxiety does go away on its own, unless it is kept going by anxious thinking.

Anxiety can affect the body in many ways. The physical sensations you experience are not harmful, but they can be unpleasant and frightening, particularly if you do not know what is causing them. It is useful to be able to recognise these sensations so you can learn to work through them. You might want to tick the ones on this list which apply to you.

Common physical sensations of anxiety

- Pain or tightness in your chest

- Fast, shallow breathing
- Fast or pounding heart beat
- Feeling dizzy or faint
- Tense or aching muscles
- Headaches
- Sweating
- Stomach churning
- Needing to go to the toilet
- Trembling
- Pins and needles or numbness

It is worth remembering that these sensations can be caused by anxiety and that, even when they are caused by medical problems, they can be made worse by anxiety. You will probably feel more anxious at times when you are feeling unwell or run down.

Stress hormones, such as adrenalin, can often be the cause of these feelings of anxiety. These hormones are vital as they allow us to react quickly in emergencies, for example, if we need to move quickly to avoid an accident but they are troublesome when you don't need them.

The good news is that you can learn ways of counteracting these changes.

How can anxiety make coughing worse?

- When we are anxious, we think less clearly. This makes it harder to spot the triggers which make us cough, and to do something about these triggers.
- Thinking less clearly also makes it harder to remember to use the cough suppression techniques.
- The more anxious we are, the more we tend to focus on wanting to cough. This, in turn, can make us cough more.
- Anxiety makes us breathe faster and less deeply. This may make us more likely to want to cough.

What can help?

Using your techniques for cough suppression

- These techniques tend to work best if they are used in a calm, relaxed way.

Noticing your thoughts

- How you think about a situation can affect how you feel and what action you take.
- Some thoughts are unhelpful. For example, if you think “I can’t cope with having a coughing fit in public”, you may stay indoors more often. You might miss out on socialising with friends and family, doing things you enjoy or taking part in exercise. This would leave you less confident, and less fit and active.
- It would be more helpful to think “I feel a bit self-conscious when I cough a lot while I’m out and about, but I can keep calm and cope with it, using the techniques that work for me, that I have been taught and practiced”.
- Another unhelpful thought might be “I need to cough to ease this lump or tickle in my throat” or “I need to cough to clear my throat”. In fact, coughing might just make you focus more on your throat and so feel more uncomfortable and increase the urge to cough.



- Trying **not** to think something tends not to work very well. As an example of this, try not to think of a polar bear right now. Many people find that the polar bear tends to come back into our minds if we try not to think about it.
- It’s better to notice the thought, and to remind yourself that it is just a thought, and not necessarily true.

Distraction and dealing with worry

- Distraction can help. Depending on the circumstances, you might distract yourself by getting up and doing something else or talking to someone about a different subject.
- It can also help to occupy your mind, for example, by thinking of a girls’ name or a country beginning with every letter of the alphabet, or making a list of your top-ten films of all time.
- If you worry a lot, it can help to sit down with a pen and paper for about twenty minutes a day to focus on your worries and try to resolve them. For the rest of the day, gently put them aside until that time. At the end of the twenty minutes, put your pen and

paper away. If any worries seem unresolved, you can come back to them afresh the following day.

- The more you practice this, the easier it will get to put them aside until the allotted time.
- When a particular worry is playing on your mind, it can be helpful to ask yourself "Can I do anything about this situation?" and "Can I do anything about it right now?". If the answer to either question is **no**, it would be more useful to distract yourself, rather than carrying on worrying.

Balanced awareness

- Being aware of your body can help you to make wise choices...but over-awareness can make it hard to focus on other things.
- This can mean you miss out on fully enjoying the good things in life.
- Over-awareness can also mean unnecessary worry and distress, which can make you focus more on your cough.
- It can help to put your feet flat on the ground and just notice how the ground feels underneath your feet.
- You could also try focusing on what you can see and hear in the world around you.

Learning to relax

Learning how to relax your mind and body can reduce the adrenalin response we talked about above. This is a breathing exercise to help you relax.

- Breathe out first, then just let your body breathe in.
- Breathe as deeply down into your belly as you can, and do this as gently as you can.
- Breathe out first, then just let your body breathe in gently through your nose, counting "One... two... three". Breathe as deeply down into your belly as you can, and do this as gently as you can. Pause a second, then breathe out through your mouth, counting "One... two... three... four". The counting protects you from fast, panicky breathing. Make sure you breathe out for one beat longer than you breathe in. This will help you empty your lungs between breaths.
- As you do this, you can keep track of your anxiety. Before you start, rate how anxious you are feeling on a scale of one to ten, where ten is the worse you've ever felt. Then, after a couple of minutes, rate it again. You will probably notice that it has come down to a more manageable level.

Being physically active also helps to relax your mind and body.

Reducing your stress levels

- Take time to do the things which you enjoy doing, and help you to relax your mind and body.
- Think about how you can make looking after yourself a priority.
- Eat a well-balanced diet, allow yourself enough time for sleep, exercise
- Learn not to take too much on, and to say 'no' to the things you don't have time for.



Your family and friends

- Your family and friends may be unsure what to do for the best when you are coughing.
- It's good to plan ahead for this, and to explain what the person can do to help.

Getting the information you need



- If there is anything you are at all unsure about, do ask your doctor (or other health professional).

- Doctors are busy, but your appointment is your time to get the information you need.
- Before the appointment, it can help to write down questions you would like to ask.
- In the appointment, it can be useful to make notes of the important things the doctor says, or to take someone with you to help you remember what was said.
- You might be worried that the doctor will give you bad news, but the more information you have, the better you can take care of yourself.

**Written by Dr Jane Hutton, Consultant
Clinical Psychologist, King's College
Hospital, February 2012**

What makes you feel stressed or anxious?



Make a list here of all the things you can think of which cause you stress...

...then pick out **one** you can do something about and **circle** it

Now make another list here, of everything you could possibly do about it...

...and pick out the **one** you would like to try first and **circle** it

Write down here how you will put this option into practice, and how you will be able to tell if it's working...

Appendix 27: PSALTI Participant Treatment session Therapist Instructors for Session 4

Session 4: (45 min)

- Review of last week.
- Discuss how it went with triggers? What went well or wrong.
- This is looking at their **coping strategies**. You need to give them an example:

You are sitting on a crowded bus/ in the theatre and you start to feel the tickle (whatever their feeling is). And you are starting to feel warm and your heart starts racing. You are really trying to keep this cough at bay and you are getting anxious about it.

Discussing how they would handle this situation: not getting anxious staying calm, sipping water or getting out that sweet. Using the swallow technique or breathing control techniques etc..... From this Gauge their coping strategies.

- **All outcome measures at the end of the session!!!**

Appendix 28: Standard Operating Procedure for Capsaicin Solution preparation

Preparation of Capsaicin Solutions for Capsaicin Cough Challenge in PSALTI Study

Standard Operating Procedure #1

December 2011

Reviewed in March 2012

By

Sarah Chamberlain

A. SCOPE AND APPLICATION

The purpose of this standard operating procedure (SOP) is to establish a standardised methodology for the preparation of capsaicin solutions for Capsaicin Cough challenge testing in the PSALTI study.

B. SUMMARY OF METHOD

A stock solution of capsaicin is prepared and then serially diluted with saline to obtain doubling concentrations of Capsaicin solution ranging from 0.49µm-1000µm.

C. SAFETY

1. Capsaicin in its raw powder form is toxic if swallowed, causes irritation if inhaled or comes into contact with skin or eyes. Therefore each Institution's health and safety risk assessment form for Capsaicin preparation and Cough Challenge must be followed. Personal protective clothing, gloves and goggles, must be worn when preparing the capsaicin solutions and the preparation of the solutions must be prepared in a fume cupboard.

2. Capsaicin in its raw powder form needs to be kept in the dark in a fridge set at 2-8°C, as per manufacturer's instructions (Sigma-Aldrich, Sigma Aldrich Company Ltd, Dorset, UK)

3. Stock solutions of Capsaicin area to only be kept for one month and stored at 4 °C.

4. Fresh dilutions of Capsaicin from the stock solutions are prepared on the day of testing and are only kept for 24hours then disposed of (ERS Guidelines 2007).

5. Tween 80 is to be stored at room temperature as per manufacturer's instructions (Sigma-Aldrich, Sigma Aldrich Company Ltd, Missouri, US).

D. APPARATUS AND MATERIALS

1. Fume cupboard
2. Digital scales
3. 15 test tubes/jars with screw tops
4. Test tube rack
5. 3ml or 5ml Pipettes
6. Spatula

E. REAGENTS AND CHEMICALS

1. Capsaicin (Sigma -Aldrich, Sigma Aldrich Company Ltd, Dorset, UK)

2. 100% alcohol
3. Tween 80(Sigma-Aldrich, Sigma Aldrich Company Ltd, Missouri, US)
4. Saline (at least 75mls)

F. PREPARATION PROCEDURE

1. Preparation of the stock solution

- 1.1 Place one test tube/ jar on the digital scales and using the spatula weigh out 30.5mg of capsaicin into the test tube/jar.
- 1.2 Place the test tube of measured capsaicin in the fume cupboard and using a pipette add 1ml 100% alcohol to the capsaicin.
- 1.3 Using a fresh pipette add 1ml Tween 80 to the above solution.
- 1.4 Using another fresh pipette add 8ml of saline to the above solution.
- 1.5 Screw test tube/jar lid on and gently turn jar from side to side to mix, do not shake as the Tween 80 causes the solution to bubble, which will make the solution harder to pipette if you are going to continue straight away to make the capsaicin solutions that are used in the Capsaicin Cough Challenge.
- 1.6 If the diluted capsaicin solutions are not going to be made straight away label the test tube/jar as Stock and date the jar.
- 1.7 Place the stock solution in the fridge away from sunlight at 4 °C.

2. Preparation of Capsaicin Cough Challenge Solutions (to make enough solutions for one capsaicin Cough Challenge)

- 2.1 In the fume cupboard pipette 1ml of the stock solution into a new test tube.
- 2.2 Then add 9ml of saline using a new pipette to the 1ml of stock solution.
- 2.3 Screw the cap onto the test tube and gently tilt side to side to mix. This creates the 1000µm solution.
- 2.4 Return the stock solution to the fridge at 4 °C until you are next making up another set of solutions.
- 2.4 Then pipette 5ml of the 1000µm Capsaicin solution into a new test tube and add 5ml of saline solution. This creates the 500 µm solution. (Ensure that a new pipette is used when pipetting each capsaicin solution).

2.5 Screw cap on, gently mix. Then repeat as before pipetting 5ml of 500µm capsaicin solution into a test tube with 5ml saline creating 250 µm.

2.6 Repeat the above process with 5ml of the capsaicin solution and 5ml of saline until you dilute down to 0.49 µm strength of capsaicin solution. (see table 1.1 below).

Table 1.1 Serial dilutions of Capsaicin stock solutions

<u>Original Solution</u>	<u>Saline</u>		<u>Original Solution</u>	<u>New Solution</u>
1ml stock	9ml saline	=	10,000µm	→ 1000 µm
5ml 1000 µm	5ml saline	=	1000 µm	→ 500 µm
5ml 500 µm	5ml saline	=	500 µm	→ 250 µm
5ml 250 µm	5ml saline	=	250 µm	→ 125 µm
5ml 125 µm	5ml saline	=	125 µm	→ 62.5 µm
5ml 62.5 µm	5ml saline	=	62.5 µm	→ 31.25 µm
5ml 31.25 µm	5ml saline	=	31.25 µm	→ 15.6 µm
5ml 15.6 µm	5ml saline	=	15.6 µm	→ 7.8 µm
5ml 7.8 µm	5ml saline	=	7.8 µm	→ 3.9 µm
5ml 3.9 µm	5ml saline	=	3.9 µm	→ 1.95 µm
5ml 1.95 µm	5ml saline	=	1.95 µm	→ 0.98 µm
5ml 0.98 µm	5ml saline	=	0.98 µm	→ 0.49 µm

2.7 If more than one Capsaicin Cough Challenge worth of Capsaicin solutions are needed, then doubling the above solution quantities creates three Capsaicin cough challenge worth of solutions, as 3ml of each solution is needed for one Capsaicin Cough Challenge. So if you were to double the above amounts you would pipette 2ml of stock to 18ml of saline, then the subsequent dilutions would be 10ml solution to 10ml saline.

2.8 Refrigerate the solutions at 4 °C until they are needed for testing, if any of the solutions are left post Capsaicin Cough challenge they need to be disposed of on the day of testing.

G. Cleaning of equipment

1. Test tubes should be sterilised after use, in accordance to institute's guidelines. At Kings College Hospital the equipment should be sterilised in Tristel (Tristel plc, Suffolk, UK) for 15 minutes. Then washed in hot water and air dried.

Reference

Morice, A.H., Fontana, G.A., Belvisi, M.G., Biring, S.S., Chung, K.F., Dicipinigatis, P.V., Kastelik, J.A., McGarvey, L.P., Smith, J.A., Tatar, M., Widdicombe, J (2007) ERS guidelines on the assessment of cough. *European Respiratory Journal*, 29:1256-1276.

Appendix 29: Standard Operating Procedure for Capsaicin Cough challenge testing

Capsaicin Cough Challenge

Standard Operating Procedure #2

May 2002 by S. Birring

Reviewed in April 2012 by S. Chamberlain

CAPSAICIN COUGH SENSITIVITY TEST PROTOCOL

EQUIPMENT

- Digidoser filters
- 3 litre calibration syringe
- Koko digidoser with connector valve for tubing from air cylinder
- Digidoser connection tube to nebuliser pot.
- Digidoser laptop connector cable
- Laptop with Koko Digidoser programme on.
- Nebulisers pots x2
- Mouthpiece for nebuliser pots
- Nose-clips
- Thermometer Hyborometer
- Air Cylinder with head valve
- Air Cylinder key
- Capsaicin solutions prepared as per Capsaicin Preparation Standard Operating Procedure
- 3ml/5ml pipettes
- Cough Monitor
- Gloves
- Weighing scales
- Stadiometer

DIGIDOSER POWER SUPPLY

Connect digidoser to laptop via USB lead, ensure laptop is plugged into to power supply so battery does not run out during testing.

AIR TUBING

One end into base of digidoser via connector valve (twist+click)

Other end to air cylinder regulator

AIR VALVE

1. Open main air valve with key, turn anticlockwise until loose, and dial moves up.

CALIBRATION

1. Open Koko software on laptop

2. Select calibrate icon – 9th icon from the left in the tool bar
3. Enter the room details – temperature, humidity, barometric pressure (in mmHg, if thermometer hyborometer used measures in inHg need to multiple measurement by 25.4).
5. Attach new filter to digidoser
6. Make sure calibration syringe is set to 3L (dial on base where syringe is)
7. Attach calibration syringe to other end of filter
8. Single L click green circle
9. Pull syringe out and Click OK
10. Follow instructions on screen (computer will ask you to pull syringe in/out 3 times- smooth action)
11. Click OK when done
12. Close calibration screen
13. Detach syringe

ENTER DETAILS OF NEW PATIENT

1. Prior to starting measure patients height and weight
2. Click 5th icon from left (perform challenge test)
3. Click 1st icon from left OR if it asks do you want to continue his test series / do you want to select new patient – click on latter option – new patient
4. Click entering new patient then next.
5. Enter patient's first name initial as first name, first initial of surname as surname, participant's number in study as study I.D, date of birth, sex, height and weight.
6. Click OK when done
7. Click OK again, maximise screen

SPIROMETRY

Must do this to proceed to capsaicin cough challenge!

1. Select Setup in the toolbar, then challenge protocol, then edit challenge protocol. You need to select which nebuliser you are going to use after the spirometry by selecting either: Capsaicin 1.232ml/min or capsaicin 1.205ml/min. This is etched into the bottom and top of the nebulisers. You need to ensure that both the top and bottom parts of the nebuliser match. **DO NOT CONNECT NEBULISER YET.**
2. Place new filter on end of digidoser.
3. Give patient noseclip to place on their nose.
4. Give instructions to the participant first:
 - You will asked to put the mouth piece into your mouth, and take four normal breaths first
 - Then I will ask you to take a deep breath IN and then a deep/fast breath OUT, blowing out all the air you can
 - Then I will ask you to take the mouth piece out of your mouth
5. Press SPACEBAR when you are ready to start
6. Follow instructions that will display at the bottom of the screen. Initially it will ask you to maintain zero flow. Then the bottom display with the instructions will turn black, at that point give the digidoser to the participant and tell them to place the filter in their mouth, ask them to take four normal breaths. Then the display will say perform maximal inspiration at any time, instruct the participant to do so. Then it will ask for a maximal exhalation and again instruct participant to do so.
7. Take digidoser back when patient has had a breath in & out
8. Click YES
9. Write down actual and predicted spirometry reading on results sheet

ASSEMBLE NEBULISER

1. Connect short plastic tubing from base of nebuliser to digidoser
2. Add 3ml normal saline (or capsaicin solution later) to base using a pipette
3. Screw on top of the nebuliser (ensuring it matches the same flow volume as the bottom nebuliser, check ml/min value on it)
4. Attach nebuliser to filter, and a mouthpiece to the nebuliser.
5. Make sure nebuliser well is level and fluid doesn't tip back into digidoser!

START COUGH TESTING!

1. Verbally instruct patient
 - When I ask you to, put the mouthpiece into your mouth
 - When I ask you to, take a sustained 2-3 second breath in
 - Do not try to stop or suppress your cough, allow yourself to cough if you need to.
2. Click 2nd icon from left, to go to next stage, then click OK
3. To start click on 3rd button from left
4. When bottom half of screen is BLACK tell patient to put mouth piece in mouth (never when screen is red) and carry out above instructions (PRESS space bar during initial breath out). At the point of administering the dose press record on the cough monitor at the same time.
5. Count coughs for 15 seconds after administering, if needed listen back to cough monitor to check number of coughs and write it down on results sheet

6. *NEXT DOSE* – take off nebuliser well from filter, unscrew base, dispose of solution in nebuliser pot, put 3ml of next dose in
7. Start again with clicking 2nd icon from left, go to next stage, then 3rd icon from left administer dosage, always press OK.
8. Finish cough testing when they cough 5 or more times

9. *TO START ON PREVIOUSLY TESTED PATIENT* – select options, type patient's ID number, click show all matches, single click on the name, click test series: new (bottom of screen), click OK, click yes to save (previous data), now do spirometry stage above

SHUTTING DOWN - DISCONNECT AIR

1. Close valve on air cylinder (clockwise)
2. Disconnect Digidoser

Appendix 30: Ethical Approval Letter



National Research Ethics Service

NRES Committee London - Chelsea
Room 4W/12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Telephone: 020 331 17251
Facsimile: 020 331 17280

08 June 2011

Dr Rachel Garrod
Consultant Physiotherapist
Kings College NHS Foundation Trust
Dulwich Hospital
East Dulwich Grove
East Dulwich
SE228PT

Dear Dr Garrod

Study title: Efficacy of a Physiotherapy, Speech and Language
Therapy Intervention (PSALTI) for patients with chronic
cough: a randomised controlled trial.
REC reference: 11/LO/0504
Protocol number: 1

Thank you for your letter of 31 May 2011, 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.

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.

Ethical review of research sites

NHS sites

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

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

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.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

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

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

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
① GP/Consultant Information Sheets Investigator CV	1	17 March 2011
② Letter of invitation to participant Other: Letter from funder	1 David Atkinson	17 March 2011 13 December 2010
3 Participant Consent Form	1	17 March 2011
④ Participant Information Sheet	✓ 1	17 March 2011
⑤ Protocol	✓ 1	17 March 2011
6 Questionnaire: SF-36 Health Survey	2	05 November 2009
7 Questionnaire: Leicester Cough Questionnaire		
REC application	74457/204671/1/39	09 May 2011
Referees or other scientific critique report		
Response to Request for Further Information		31 May 2011

Statement of compliance

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

After ethical review

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

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

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

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

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

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

11/LO/0504

Please quote this number on all correspondence

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

Yours sincerely



**pp. Dr Shelley Dolan
Chair**

Email: Rosalind.cooke@imperial.nhs.uk

Enclosures: "After ethical review – guidance for researchers" [SL-AR2]

Copy to: Dr Zoe Harris, R&D Department, King's College Hospital

Appendix 31: Substantial Amendment Approval Letter – November 2011



NRES Committee London - Chelsea

Room 4W/12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Tel: 020 331 17251

19 December 2011

Dr Rachel Garrod
Consultant Physiotherapist
Kings College NHS Foundation Trust
Dulwich Hospital
East Dulwich Grove
East Dulwich
SE228PT

Dear Dr Garrod

Study title: Efficacy of a Physiotherapy, Speech and Language Therapy Intervention (PSALTI) for patients with chronic cough: a randomised controlled trial
REC reference: 11/LO/0504
Protocol number: 1
Amendment number: AM1
Amendment date: 23 November 2011

The above amendment was reviewed at the meeting of the Sub-Committee held on 12 December 2011

Ethical opinion

The members of the Committee taking part in the review gave a **favourable ethical opinion of the amendment** on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	2	23 November 2011
Notice of Substantial Amendment (non-CTIMPs)	AM1	23 November 2011
Covering Letter	from Sarah Chamberlain, Research Physiotherapist	24 November 2011
GP/Consultant Information Sheets	2	22 November 2011
Letter of invitation to participant	Patient Invitation Sheet Version 2	23 November 2011
Participant Consent Form	2	23 November 2011
Participant Information Sheet	2	21 November 2011
Questionnaire: Vocal Performance	N/A	
Questionnaire: Cough Hypersensitivity	5	23 November 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

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.

11/LO/0504: Please quote this number on all correspondence

Yours sincerely


PP Dr Shelley Dolan
Chair

E-mail: Rosalind.cooke@imperial.nhs.uk

Copy to: Dr Zoe Harris, R&D Department, King's College Hospital

**NRES Committee London - Chelsea
Attendance at Sub-Committee of the REC meeting on 12 December 2011**

Name	Profession	Capacity
Dr Shelley Dolan	Chief Nurse	Expert
Mrs Laura Royde	School Governor	Lay Plus

Appendix 32: Substantial Amendment Approval Letter – May 2012

NRES Committee London - Chelsea

Room 4W/12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Tel: 020 331 17251

08 June 2012

Dr Rachel Garrod
Consultant Physiotherapist; Kings College NHS Foundation Trust
Dulwich Hospital
East Dulwich Grove
East Dulwich SE228PT

Dear Dr Garrod

Study title: Efficacy of a Physiotherapy, Speech and Language Therapy Intervention (PSALTI) for patients with chronic cough: a randomised controlled trial

REC reference: 11/LO/0504

Amendment number: 2

Amendment date: 17 May 2012

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

No ethical issues were raised. The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
GP/Consultant Information Sheets	3- tracked version	17 May 2012
Participant Information Sheet	3 - tracked version	17 May 2012
Protocol	3 - tracked version	17 May 2012
Notice of Substantial Amendment (non-CTIMPs)		17 May 2012
Covering Letter		18 May 2012
Questionnaire: Hospital Anxiety and Depression Scale		
Questionnaire: Your Experience of Cough Trial Questionnaire	1	17 May 2012
Letter of invitation to participant	3 - tracked version	17 May 2012
Participant Consent Form	3 - tracked version	17 May 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

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

11/LO/0504:

Please quote this number on all correspondence

Yours sincerely,



Dr Shelley Dolan
Chair

E-mail: lara.callaghan@imperial.nhs.uk

Appendix 33: Sample Size calculation for PSALTI RCT

Power calculations for the primary outcome (LCQ score) were performed based on estimates from a previous study (Birring and Pavord, 2009), reporting a mean LCQ score in patients with chronic cough of 14.03 (SD: 3.87) (Birring and Pavord, 2009). Group sample sizes of 33 in each group achieve 80% power with a significance level of 5% to detect a clinically relevant LCQ change of 2.7 (seen in the pilot study completed prior to this thesis). Allowing for a 25% drop out we aimed to recruit 88 patients in total.

Appendix 34: Shapiro-Wilk Normality Testing p values for Baseline variables (PSALTI RCT)

Characteristic	Control (p value)	PSALTI (p value)
Age	0.284	0.006
Cough Duration	0.000	0.000
FEV1	0.121	0.641
FEV1/FVC	0.534	0.983
LCQ	0.504	0.387
Cough Severity VAS	0.041	0.179
SF-36 PCS	0.052	0.796
SF-36 MCS*	0.048	0.047
HADS – anxiety	0.257	0.098
HADS – depression	0.024	0.001
VPQ	0.012	0.154
CF _{per hour}	0.633	0.703
C2	0.000	0.001
C5	0.000	0.000
Cu	0.000	0.000

For variables which were non-normally distributed for one treatment arm; both variables were reported as non-parametric data.

* Though SF-36 MCS was normally distributed for both treatment arms, as SF-36 PCS was non-normally distributed it was decided to report both as non-parametric data, as this is two halves of the same questionnaire.