Development of a Core Outcome Set for Use in Research Evaluations of Interventions Used for Venous Leg Ulceration

Sarah Kim Hallas

Submitted in accordance with the requirements for the degree of Doctor of Philosophy

University of Leeds

School of Healthcare

Date of submission: June, 2019

Volume 1 of 2

Intellectual Property and Publication Statements

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

The research included in this PhD was supported by the research team and steering group. The research team included Professor Andrea Nelson (EAN), Dr Susan O'Meara (SO'M) and Dr Georgina Gethin (GG). The steering group included Dr Una Adderley, Dr Jan Kottner, Dr Pauline Meskell, Professor Jane Nixon, Dr Aonghus O'Loughlin, Professor Sebastian Probst, Mr Wael Tawfick and Dr Thomas Wild. My contributions and that of the members of the research team are outlined below.

Publication- Hallas, S., Nelson, A., O' Meara, S. and Gethin, G. 2017. Meeting Report: Core outcome set for Venous leg ulceration "CoreVen". *European Wound Management Association* **18**(2), pp.27-31.

Contributions: Sarah Hallas (SH): Presented a PowerPoint presentation at the session held at the EWMA conference. Contributed to the interpretation of the qualitative comments given by the audience. Lead role in drafting and revising the manuscript.

Georgina Gethin (GG): Led the co-ordination of the session and presented a PowerPoint presentation. Contributed to the interpretation of the qualitative comments given by the audience. Contributed to the revison of the manuscript and final approval of the version that was submitted.

Susan O'Meara (SO'M): Facilitated the written recording of qualitative comments provided by the members of the audience. Contributed to the interpretation of the qualitative comments given by the audience. Contributed to the revison of the manuscript and final approval of the version that was submitted.

Andrea Nelson (EAN): Contributed to the revison of the manuscript and final approval of the version that was submitted.

Presentations

National conference (oral)

Hallas, S. Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration. Wounds Research Network (WReN) 2nd Scientific Meeting at the Tissue Viability Society conference, Edgbaston, April 2017.

International conference (oral)

Hallas, S., Gethin, G., and O'Meara, S. Development of a Core Outcome Set for RCTs in Venous Leg Ulcers. EWMA conference, Amsterdam, May 2017.

Local conference (poster)

Hallas, S. Core Outcome Set for Venous Leg Ulceration. PGR conference, University of Leeds, November 2017

International conference (oral)

Hallas, S., and Gethin, G. Core Outcome Set for Reporting of Trials in Venous Leg Ulceration Consensus Meeting. EWMA conference, Krakow, May 2018.

Local conference (oral)

Hallas, S. Development of a core outcome set for use in research evaluations of interventions used for venous leg ulceration. PGR conference, University of Leeds, November 2018.

Acknowledgements

The work of this PhD was made possible by the funding obtained by the University of Leeds.

The research was led by Sarah Hallas and supported by the research team and steering group. The research team included Professor Andrea Nelson (EAN), Dr Susan O'Meara (SO'M) and Dr Georgina Gethin (GG). The steering group included Dr Una Adderley, Dr Jan Kottner, Dr Pauline Meskell, Professor Jane Nixon, Dr Aonghus O'Loughlin, Professor Sebastian Probst, Mr Wael Tawfick and Dr Thomas Wild. The development and writing of the thesis was undertaken solely by myself. Section 4.3 of the thesis contains information that has been published. Details on the publication are located in the intellectual property and publications part of this thesis.

It is with immense gratitude that I acknowledge the support of Andrea Nelson, Susan O'Meara and Georgina Gethin. Their supervision, commitment, and guidance supported me through the ups and downs of undertaking the research and in the writing of this thesis. I am especially grateful for their methodological expertise. Thank you.

I wish to thank the members of the steering group; Una Adderley, Jan Kottner, Pauline Meskell, Jane Nixon, Aonghus O'Loughlin, Sebastian Probst, Wael Tawfick and Thomas Wild for their support, methodological guidance and contributions to the research. The steering group provided crucial support throughout.

I would also like to thank and express my sincere gratitude to the participants that took part in the research and to the gatekeepers of the following organisations who kindly invited their members to take part, and promoted the research; Lindsay Leg Club Foundation, the European Wound Management Association (EWMA), the Wounds Research Network (WReN), the Tissue Viability Society (TVS), Society of Vascular Nurses, Imperial College London

Department of Vascular Surgery, Alliance for Research and Innovation in Wounds, and Wounds UK.

On a personal note, I would like to thank Mat for his continued support through the peaks and valleys, and ability to keep me smiling along the way. Thank you to my Mum and Dad for their unfailing love, support and encouragement over the years. Finally, thank you to my wider family, Himali, Jon, Anne Marie, Michael, Oliver, Eloise, Jay and Amelie. Without you all, this accomplishment would not have been possible.

Abstract

Background

Venous leg ulceration is a recurring condition causing pain, reduced mobility, and depression. Randomised controlled trials evaluating treatments for venous leg ulcers provide evidence to inform clinical decision-making. However, for findings to be useful, outcomes need to be clinically meaningful, consistently reported across trials, and fully reported. Research has identified that the outcomes important to all stakeholders are not always reported. Research has also identified that there are a large number of different outcomes being reported, impacting synthesis of results, and clinical decision-making. A core outcome set is an agreed standardised set of outcomes which should be, as a minimum, measured and reported in all trials which evaluate treatment effectiveness for a given indication.

Aim

To develop a core outcome set for research evaluations of interventions used for venous leg ulceration.

Methods

1) A scoping review identified the outcome domains and outcomes that have been reported in randomised controlled trials and qualitative research.
2) eDelphi consensus study on the outcome domains.
3) eDelphi consensus study on the outcomes.

Results

1) The scoping review identified 807 different outcomes that have been reported in the venous leg ulcer randomised controlled trials included in the review. Fifteen outcomes were identified from qualitative studies.

2) Ten outcome domains were rated as core by participants in the consensus study.
3) The consensus study on the outcomes refined the outcome domains to produce a core outcome domain set comprising of 5 outcome domains. Eleven outcomes were rated as core by participants in the consensus study.

Conclusion

A core outcome domain set and a set of 11 candidate outcomes have been developed. The development of a core outcome set has the potential to reduce research waste, improve the utility of trials, reduce outcome reporting bias, facilitate treatment comparisons across different sources of evidence and expedite the production of systematic reviews, meta-analyses and evidence-based guidelines.

Table of contents

List of Tables

List of Figures

Abbreviations

ABPI Ankle Brachial Pressure Index

AI Asymmetry Index

CDSR Cochrane Database of Systematic Reviews

CFA Correction Factor for Asymmetry

COMET Core Outcome Measures in Effectiveness Trials

CONSORT Consolidated Standards of Reporting Trials

CoreVen Core outcome set for Venous leg ulceration

COS Core outcome set

COSMIN COnsensus-based Standards for the selection of health Measurement INstruments

COS-STAR Core Outcome Set-STAndards for Reporting

CRD Centre for Reviews and Dissemination

EASI Eczema Area and Severity Index

eDelphi Electronic Delphi

EWMA European Wound Management Association

HOME Harmonising Outcome Measures for Eczema

IMMPACT Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

IPRAS Interpercentile Range Adjusted for Symmetry required for disagreement

IPRr Interpencentile Range required for disagreement when perfect symmetry exists

MAD-M Mean Absolute Deviation from the Median

NICE National Institute for Health and Care Excellence

NIH National Institutes of Health

NMC Nursing and Midwifery Council

OMERACT Outcome Measures in Rheumatology

PPM Program Planning Model

RAM RAND/UCLA Appropriateness Method

RAND Research ANd Development

RCN Royal College of Nursing

RCT Randomised Controlled Trial

SHREC School of Healthcare Research Ethics Committee

THIN The Health Improvement Network

VLU Venous Leg Ulcer

WReN Wounds Research Network

Chapter 1 Background

1.1 Introduction

This chapter presents an overview of the PhD and the foundations to the development of a core outcome set. It will begin with an overview of venous leg ulceration, describing the pathophysiology of a venous leg ulcer, its effect on a persons' quality of life and its financial implications for individuals and healthcare organisations. Randomised controlled trials (RCTs) evaluating treatments for venous leg ulceration provide evidence to inform clinical decision making. However, for findings to be useful, outcomes need to be clinically meaningful, consistently reported across trials, and fully reported. Research has identified that the outcomes are not always fully reported and there are a large number of different outcomes reported across RCTs, impacting upon synthesis of results, and clinical decision making. This chapter then gives an explanation to what a core outcome set is, and how it can help. A discussion on core outcome set conceptual frameworks and guidance initiatives then follows. Finally a rationale for the development of a core outcome set for venous leg ulceration is provided.

This PhD is part of a project called the CoreVen (Core outcome set for Venous leg ulceration) project which aims to develop a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration.

1.2 PhD Overview

This PhD examines the need for a core outcome set and critically examines three stages of the research process. The three stages of the research process included:

1. Scoping review of the outcome domains and outcomes reported in venous leg ulcer RCTs and qualitative research.

2. Consensus study on the outcome domains identified during the scoping review.
3. Consensus study on the outcomes identified during the scoping review.

1.3 Venous Leg Ulceration

A venous leg ulcer is a chronic open wound occurring below the knee which lasts longer than six weeks or occurs in a person with a history of venous leg ulceration (Norman et al., 2016). It is a chronic and reoccurring condition (NICE, 2015). People can have an ulcer for 10 years or more with some ulcers never healing (Cullum et al., 2016; Miller et al., 2017). For those that do heal 26-69% experience recurrence within 12 months after healing (Monk and Sarkany, 1982; Moffatt and Dorman, 1995; Vowden et al., 1997).

Venous leg ulceration is caused by venous insufficiency (reduced return of venous blood) which is, in turn, caused by damage to the valves in the lower legs or blockages in the leg veins. The function of the venous system of the legs is to carry deoxygenated blood from the capillaries in the tissue back to the heart before being re-oxygenated in the lungs and filtrated in the kidneys (Moffatt et al., 2007). The combination of the calf muscles and functional valves forms the 'calf-muscle pump', whereby deformation of the calves, through exercise, movement or massage, leads to changes in the pressure in the veins within the calves causing the propulsion of the blood towards the heart from the capillary bed. Damage to the valves of the calves allows the blood to flow in either direction which results in reduced efficiency of the blood returned to the heart (Doughty and Holbrook, 2007). Reduced efficiency of the blood returned to the heart increases the pressure of the blood in the legs; a condition known as chronic venous hypertension, causing swelling of the leg veins, oedema and leakage of circulatory fluid into the surrounding tissue from the capillaries in the lower legs (Smith et al., 1988). The thin walls of the capillaries means when the pressure increases above normal limits (5-15 mmHg) the capillary walls stretch increasing the size of the pores in the walls allowing larger molecules, such as red blood cells and leukocytes, to leak out into the surrounding tissue (Burnand et al., 1981; Moffatt et al., 2007).

When leakage into the surrounding tissue occurs it causes irritation and fragility of the epidermis resulting in ulceration (Doughty and Holbrook, 2007). The full thickness of the skin can be affected from the epidermis to the subcutaneous tissue (Lazarus et al., 2013). The resulting skin lesion is known as a venous leg ulcer.

There are a number of hypotheses that seek to explain the precise mechanism for ulceration that directs the care of venous leg ulcers and their prevention. Many theories on venous leg ulceration have been suggested however the chronicity of venous leg ulceration remains poorly understood. All hypotheses appear to agree that venous hypertension is a critical condition which leads, if unchecked, to venous leg ulceration (Morison and Moffat, 1997; Ghauri and Nyamekye, 2010).

The 'fibrin cuff' theory was first described by Burnand et al. (1976) who stated that venous hypertension and deficient fibrinolysis was related to pericapillary fibrin (fibrin cuff). The theory recognised that nutritional transfer across the capillary wall is inhibited by fibrin cuffs (Burnand et al., 1976), and forms a barrier to the movement of blood to the epidermal cells (Browse et al., 1977). The theory also suggests that the transfer of oxygen across the capillary wall is impeded (Stacey et al., 2000). Falanga et al. (1987) highlight that whilst in vivo studies have not provided evidence to support the impediment of oxygen; in vitro studies have shown that oxygen cannot transfer across the fibrin layer.

The 'trap' hypothesis suggests that venous leg ulceration is caused by macromolecules leaking into the dermis caused by hypertension which 'traps' growth factors and other factors required for healing such as fibroblasts and keratinocytes, hindering their ability to assist healing and maintain skin integrity (Falanga et al., 1987).

Treatment is directed towards seeking to reduce venous hypertension, through crude mechanical means, for example the application of devices, bandages and pumps, or physiological measures such as the removal of incompetent segments of the vein.

Compression therapy (bandages or hosiery) to treat the underlying venous hypertension is considered as the cornerstone of therapy for patients with venous leg ulceration (Dealey, 2012; O'Meara et al., 2012). Adjunct treatment options include, for example topical agents, debridement, vasoactive drugs,

ultrasound, negative pressure therapy and physical therapies. There are many variants of these treatments and relative effectiveness needs to be established in order to provide optimum information to inform evidence based practice. However the evidence base supporting some of the adjunct treatments is lacking due to the lack of rigorous RCTs. For example Gethin et al. (2015a) concluded in their Cochrane review that there is limited evidence to support that debridement of a venous leg ulcer will lead to a clinically significant impact on healing. Cullum and Liu's (2017) Cochrane systematic review found limited evidence to determine whether ultrasound improves healing. There is also a lack of rigorous RCT evidence to support the use of negative pressure wound therapy (Dumville et al., 2015). The evidence was limited in many Cochrane reviews because the rigour of the RCTs was not adequate; for example Gethin et al. (2015a) found that the included RCTs in their Cochrane review on debridement had a small number of participants, incomplete outcome data and lack of information on the outcomes leading to a high risk of reporting bias. Seven (7/11) RCTs included in Cullum and Liu's (2017) Cochrane review on therapeutic ultrasound had high risk of bias, and three (3/11) had an unclear risk of bias. There was a lack of rigorous RCTs for inclusion in Dumville et al's (2015) Cochrane review on negative pressure therapy.

The diagnosis of a venous leg ulcer is determined by healthcare professionals, such as a nurse or GP, through visual inspection of the leg and the surrounding skin around the ulcer. Diagnosis relies upon a combination of visual inspection, a patient's medical history, clinical tests, signs and symptoms. A patient's history is important in determining a venous leg ulcer; risk factors suggestive of venous disease include increasing age, being female, lipodermatosclerosis, family history, previous ulceration, high BMI, venous thromboembolism, physical inactivity, increasing number of pregnancies and severe trauma to the leg (Lim et al., 2018). Other signs that the ulcer is caused by venous disease includes pain and oedematous skin surrounding the ulcer, dilated veins, venous skin changes and it is warm to touch (Lim et al., 2018). Symptoms such as corona phlebectatica (ankle flare), varicose veins, atrophie blanche, hyperpigmentation and eczematous skin near the ankle and/or lower leg are also indicators of venous disease (Mills and Armstrong, 2018).

A hand-held Doppler ultrasound probe can assist in the assessment of venous reflux (Moffatt and Franks, 2004). A hand-held Doppler ultrasound probe can assist in distinguishing venous leg ulceration from other causes of leg ulcers such as arterial disease. Distinguishing between causes of ulceration is important in determining the safe use of compression therapy. It helps prevent misdiagnosis by assisting the identification of arterial disease for referral to a specialist and assesses the appropriateness of compression bandaging (Liao and Cheater, 2000). However it is one element of assessment and should not be used in isolation (Vowden and Vowden, 2009). Relying on the reading of a hand-held Doppler ultrasound probe alone can be dangerous because it can lead to misdiagnosis, causing incorrect management which affects healing rates and in rare occasions loss of a limb (Moffatt et al., 2007). The hand-held Doppler ultrasound probe is used alongside a sphygmanometer to calculate the ankle brachial pressure index (ABPI). The ABPI is calculated by measuring the brachial and ankle arterial pressures and then dividing the individual ankle pressures by the highest of the brachial pressures to give a ratio (Adderley, 2013).

The ABPI is calculated using the formula:

$$\frac{\text{Ankle systolic pressure}}{\text{Brachial systolic pressure}} = \text{ankle brachial pressure index}$$

An ABPI below 0.5 indicates severe arterial impairment and an ABPI of between 0.5 and 0.8 denotes moderate to severe peripheral arterial disease (Vowden and Vowden, 2001; NICE, 2015). An ABPI of 0.81- 1.0 indicates mild peripheral arterial disease (Staines, 2018). A reading above 1.0 indicates no peripheral arterial disease (Staines, 2018). An ABPI above 1.2 indicates possible calcification and therefore the application of high compression is contraindicated (NICE, 2017).

A hand-held Doppler ultrasound probe test may not be suitable for people with rheumatoid arthritis, diabetes mellitus, atherosclerotic disease and systemic vasculitis because it can give a false high ABPI reading (NICE, 2015).

1.4 Prevalence

Venous leg ulcers are one type of ulcer on the lower leg, other types include arterial leg ulcers and mixed aetiology ulcers. Venous disease and a significant level of arterial disease are present in patients with mixed aetiology ulcers. Venous leg ulcers are the single most common lower limb ulceration type (Harding et al., 2015), accounting for 70% of ulcers of the lower limb (Abbade et al., 2005).

There has been a shortage of good-quality prevalence studies on venous leg ulceration (Graham et al., 2003). Following a systematic review of prevalence studies on lower limb ulceration, Graham et al. (2003) concluded that better-quality prevalence studies are needed. The systematic review included 21 prevalence studies. Graham et al. (2003) found that few of the studies used rigorous methods, did not provide a clear definition of ulceration and did not validate ulceration with diagnostic tests and clinical assessment. Graham et al. (2003) point out that not all prevalence studies may have been included in their review, and studies that were published in another language other than English were not included.

In more recent years leg ulcer prevalence has been investigated along with its impact upon financial burden. It has been estimated that the prevalence of venous leg ulceration affects 1% of the population in the Western World but it could be as high as 3% in people over the age of 65 (Gohel and Poskitt, 2009). The prevalence of current (defined as persisting for four weeks or more) venous leg ulcers has been estimated at 0.29 per 1000 population in the United Kingdom (95% confidence interval 0.25-0.33 per 1000) (Hall et al., 2014). Hall et al's (2014) cross-sectional point prevalence survey was completed by care providers in Leeds, including Leeds NHS community and primary care services (1 community trust, 1 primary care trust, 113 general practices), NHS mental health services (1 trust), NHS acute services (1 trust), independent hospitals (n = 3), prisons (n = 2), nursing homes (n = 46), and hospices (n = 2). Hall et al's (2014) data collection took place over two weeks in 2011.

Guest et al. (2017) analysed data from The Health Improvement Network (THIN) which showed that the annual figures for venous leg ulceration in 2012/2013 in the UK was 277,749 out of a total 731,000 leg ulcers. However of the 731,000 leg ulcers 24,442 were mixed aetiology and 419,956 were not

specified. In Leeds, UK venous leg ulceration is the most common wound type in men with a point prevalence of 0.25 per 1000 (95% CI 0.20 to 0.30 per 1000) (Cullum et al., 2016). Cullum et al's (2016) research included complex wounds described as being wounds that heal by secondary intention and include lower-limb ulcers, pressure ulcers, and surgical wounds that healed by secondary intention.

It has been difficult to estimate the prevalence of venous leg ulcers accurately because studies do not always differentiate between the types of the ulcers, for example whether the ulcer was venous, arterial or mixed aetiology (Vowden and Vowden, 2009; Cullum et al., 2016). Firth et al. (2010) also highlight doubt over the rigour of prevalence studies in terms of diagnostic inclusion criteria, and Firth et al also state that self-report by patients in prevalence studies is open to recall and nonresponse bias.

1.5 Impact of Venous Leg Ulceration

Venous leg ulceration can have a significant impact on a person, causing distress due to pain, malodour, susceptibility to infection and lack of mobility (Nelzen et al., 1994; Briggs and Flemming, 2007; Franks et al., 2016). The moist atmosphere of a venous leg ulcer creates an ideal medium for bacterial growth, and it has been suggested that bacterial burden can prolong healing which impacts quality of life and may have financial implications for patients and healthcare organisations (Miller et al., 2017). Infection is associated with pain, swelling and odour (O'Meara et al., 2014). A person's quality of life is affected through the reduction in social activity, limits on their capacity to work, inability to carry out self-care and maintain personal hygiene (Herber et al., 2007).

A number of studies have sought to explore the experiences of people living with venous leg ulcers, some of which were captured in systematic reviews by Persoon et al. (2004) and Herber et al. (2007). Persoon et al. (2004) and Herber et al. (2007) investigated a total of 49 studies including both quantitative and qualitative methods. The main findings of the studies included pain which restricted physical activity which in turn reduced social interaction. Pain also caused sleep deprivation and an increased need to administer analgesia. Ulceration was also associated with malodour, pruritus, limited capacity to work

and perform leisure activities, and swelling in addition to psychosocial impacts such as depression and helplessness (Herber et al., 2007).

Briggs and Flemming (2007) performed a meta-synthesis on 12 qualitative studies examining patients' experiences associated with venous leg ulceration. One hundred and seventy-two experiences arose which were synthesised into five categories; one: physical effects of ulceration including pain, odour, itch, leakage and infection, two: describing the leg ulcer journey which included experiences such as accepting the chronic nature and cycle of hope and hopelessness, three: patient-professional relationship both positive and negative, four: the cost of a leg ulcer which exemplifies the physical, social and financial limitations including; reduced mobility and social isolation, and five: psychological impact such as feelings of embarrassment.

The consistent reporting of the findings identified by the systematic reviews (Persoon et al., 2004; Herber et al., 2007) and synthesis of qualitative studies (Briggs and Flemming, 2007) means that it can be inferred that venous leg ulceration causes pain, limits mobility, impacts social interaction and causes psychosocial impacts such as depression, helplessness and low self-esteem.

1.6 Financial Burden

Venous leg ulcers are associated with significant direct and indirect costs which are increasing annually, it has been estimated that the cost of open venous leg ulcers to the NHS is at least £168m-£198 million per year (Posnett and Franks, 2007). More recently a retrospective cohort analysis of the records of 2000 patients on The Health Improvement Network (THIN) Database showed that venous leg ulceration cost the NHS an annual sum of approximately £941.13 million (including ambulance and A and E attendances) between 2012 and 2013 (Guest et al., 2017). Of which, community nurse visits cost £131.27 million, practice nurse visits cost £60.31 million, GP visits cost £44.82 million, specialist nurse visits cost £0.27 million, Allied health care cost £2.86 million, hospital outpatient appointments cost £56.92 million, hospital admissions and day cases cost £102.33 million, diagnostic tests cost £28.90 million, wound care products cost £168.08 million, non-wound devices cost £23.94 million and drug prescriptions cost £319.48 million (Guest et al., 2017 p. 327).

There is a considerable financial impact to patients and carers with prescription costs (dressings, bandages and medication), increased laundry expense due to leakage from the ulcer and loss of work days (Charles, 1995; Rabe and Pannier, 2010).

1.7 Evidence-based Practice

As discussed in the previous sections, venous leg ulceration is a problem for individuals and for society therefore effective management is required. Good quality evidence is needed on the effectiveness of interventions for the treatment of venous leg ulceration to guide practice. Evidence-based practice, also termed evidence-based medicine, evidence based-nursing or evidence-based decision making has been explained by Sackett et al. (1996) as being "about integrating individual clinical expertise and the best external evidence" (p. 71). It is also about integrating patient's preferences and predicaments (Sackett et al., 1996). It is concerned with the use of the best source of evidence to answer a research question with clinical expertise to assist decision making.

Healthcare professionals have a responsibility to ensure that patients receive high quality care through evidence-based practice. This in turn can improve an individual's quality of life and it means NHS resources are used more efficiently and effectively. Healthcare professionals often have to make decisions (with the patient wherever possible) about a patient's care. Sub-optimal care will have a negative effect on a patient's quality of life as well as increasing the cost of managing venous leg ulcers for the NHS (NHS RightCare, 2017).

The Nursing and Midwifery Council code (NMC, 2018) contains professional standards of practice that must be upheld by registered nurses and midwives. Under the standard 'Practise effectively' the code states that practice should be in line with the best available evidence by using evidence-based information. It also states under the standard 'Preserve safety' that the current evidence, knowledge and developments should be taken into account so that mistakes and their effects are reduced.

The NHS's Five Year Forward View includes its' 'Triple Aim' which is: 'better experiences for people, better outcomes and better use of resources' (NHS, 2016). There are 10 aspirational commitments to help achieve the 'Triple Aim',

one being; “We will lead and drive research to evidence the impact of what we do” which encompasses a key message that research should be used to improve care (NHS, 2016, p.126). However this can only happen if the available evidence is of high quality, coherent, relevant, clinically meaningful and consistently reported.

The generation of high quality evidence is reflected in the development of trial networks such as Trial Forge (2018) which aims to improve trial efficiency in systematic reviews using an evidence based approach to designing, running, analysing and reporting trials. In addition, organisations have also sought to improve the reporting of trials through initiatives such as the Equator Network (2018) and CONSORT (Consolidated Standards of Reporting Trials, 2018). Further, the decisions that trialist’s make on what to report is also being improved through the development of core outcome sets which standardise the outcomes reported in RCTs.

1.8 The Current Problem

It is vital that the outcomes reported in trials are important to decision makers including patients, their nurses, doctors and family. However, the outcomes reported in RCTs are not always what are regarded as important to patients (Chalmers and Glasziou, 2009). Patients hold unique knowledge about venous leg ulceration through living with and experiencing the effects it can have therefore it is essential that the outcomes reported in trials are outcomes that are important to patients as well as other stakeholders. Research that reports on the outcomes that are of the greatest importance to patients will assist patients and their clinicians to communicate more effectively and efficiently enabling better informed choices about their care (Franks et al., 2016).
A qualitative study by Cullum et al. (2016) which identified the most important outcomes for complex wounds, including venous leg ulcers, from the perspectives of patients, carers, and healthcare professionals, found that healing of the wound was the primary treatment goal yet patients were also greatly troubled by the social consequences of having a complex wound. It is essential that the outcomes measured and reported in trials are outcomes that are needed by all decision makers. Research cannot help patients and healthcare professionals if it is not usable, meaningful or comparable. A lack of

consideration over the choice of outcomes has led to waste in the production and reporting in trials which could be avoidable with the use of a core outcome set (Chalmers and Glasziou, 2009; Williamson et al., 2017; van 't Hooft et al., 2018). An intervention may be tested for its impact on healing whilst other outcomes important to patients and carers such as pain, harms and costs are not reported on. It is a waste of research to not report on outcomes that are core to important stakeholders, such as patients, rather than just the trialist.

There are many types of study designs such as cohort, cross-sectional, case-control, RCT, case study, and observational studies. The selection of the most suitable study design depends upon the research question. For example qualitative research has been praised for its ability to reveal additional insights when a person is given the freedom to talk (Mason, 2002; Briggs and Flemming, 2007). However, non-experimental approaches to testing whether something works have been criticised for giving false positive conclusions on efficacy (Sackett et al., 1996). Venous leg ulcer RCTs provide evidence to inform decision making in healthcare. RCTs are a rigorous way of establishing the clinical effectiveness, and the efficacy and safety of an intervention (Pocock, 1983; Jadad and Enkin, 2007). RCT's randomly allocate all participants to two or more treatment options, often participants are randomly allocated to either a control group and to an experimental group. The effects of the intervention are observed by assessing the outcomes of both the experimental group(s) and the control group(s) (Torgerson and Torgerson, 2008).

The large number of outcomes that are reported in venous leg ulcer RCTs pose challenges in comparing the outcomes and limits the ability for meta-analysis and impedes systematic reviews (Gethin et al., 2015b). High quality systematic reviews and meta-analyses are vital tools in summarising the evidence. They help keep clinicians up to date with the evidence, aid decision making, provide evidence for policy makers, assist clinical guideline developers and summarise the evidence for patients and carers (Liberati et al., 2009). Systematic reviews collate and synthesise studies using tools to minimise bias (Higgins and Green, 2011). Systematic reviews are further explained in chapter 3.

Systematic reviews can sometimes include a meta-analysis. A meta-analysis combines the results of two or more studies to produce a statistical estimate (Deeks et al., 2011). The results of the studies are pooled together to produce a single overall effect size (Petticrew and Roberts, 2006). Effect size is the magnitude of difference between the intervention groups (Sullivan and Feinn, 2012). A meta-analysis has the potential to increase power and precision, and may help resolve controversies that arise from conflicting claims (Deeks et al., 2011). When trial outcomes are not similar or at least comparable it means a meta-analysis cannot be performed (Eysenck, 1994). The use of a core outcome set can improve the reliability of systematic reviews and meta-analyses because it increases the amount of usable information (Kirkham et al., 2013).

The reported outcomes need to be easily interpreted, evaluated and compared. However literature reviews suggest that the outcomes measured in venous leg ulcer trials vary considerably (Dwan et al., 2008; Gottrup et al., 2010; Gethin et al., 2015b; Liu et al., 2017). A vast and varied number of outcomes create challenges in comparing and contrasting the outcomes. It potentially means that a partial view of important findings is presented, affecting synthesis of the results and clinical decision making. Liu et al. (2017) analysed outcomes pre-specified in Cochrane Wounds systematic reviews and found a large number (n=126) of different outcome domains (such as wound healing) were specified. Liu et al (2017) state that the large number reflects the variation of reported outcomes in trials.

In addition to the variation in outcomes, there are also issues with the definition of the outcomes. Gottrup et al. (2010) produced a recommendation document to improve the quality of evidence in wound management. The recommendations are based on position documents, systematic reviews and an analysis of comparative studies. As part of the recommendation document Gottrup et al (2010) performed a literature review on studies published between 2003-2009 whose objectives included the examination of chronic wounds and ulcer endpoints, and endpoint definitions. Gottrup et al (2010) define an endpoint as being “the objective of an evaluation or study” (p. 249). They found that 45% of 176 articles did not predefine their endpoints or their definition was not sufficient; for example of the 53 articles whose endpoint included wound

closure, 36% did not define what was meant by wound closure. In a systematic review by Gethin et al. (2015b) a lack of wound healing definitions was also found with 61% (62/102) of RCTs on venous leg ulceration not providing a definition. The systematic review assessed the heterogeneity of wound outcome measures in RCTs of treatment for venous leg ulceration published between 1998 and 2013.

There are also issues with the reporting of measurement instruments used to measure the outcomes. Seventy percent (123/176) of studies defined the measurement instrument that was used but 76% (134/176) of the instruments did not meet the reproducibility criteria and 30% (53/176) were not robust. Gottrup et al. (2010) defined robustness as the adequacy of information on the measurement method used in order for another to replicate the data collection and defined reproducibility as (p.262):

> the inclusion of a verifiable source of data, e.g. photos, to secure the possibility of validation from an external source by reproducing the study, or the involvement of an external validation source as part of the study design

Similarly, Gethin et al. (2015b) found problems with the reporting of measurement methods. Gethin et al. (2015b) found that only 5% (5/102) of the studies made a reference to the reliability or validity of the measurement methods.

Different types of bias can arise when trials do not adequately report outcomes. Outcome reporting bias is the selective reporting of data for an outcome, the selective reporting of subsets of the data and the selective reporting of the analyses using the same data, for example when a researcher changes from an intended comparison of the final values to the difference between baseline to the final value (Higgins et al., 2011). Outcome reporting bias can result in the reader having an overly optimistic estimate of an interventions effect which wrongly influences decision making (Clarke, 2007). Post-hoc decisions to report on other outcomes not specified in the protocol due to the results of the trial results in a biased data environment.

Reporting bias is the reporting of statistically significant findings of a trial opposed to reporting both significant and non-significant findings (Higgins et al.,

2011). Publication bias is the reporting or non-reporting of the results of a trial dependent upon its results (Song et al., 2010).
Data dredging is a slang term for when analysis is done post hoc which is not relevant to a pre-stated hypothesis (Porta, 2016). It has also been called "cherry picking" whereby a biased selection of favourable results are reported or a subset of data is analysed (Porta, 2016). Multiple analyses whereby comparisons of groups for more than one outcome can lead to a false positive (Lord et al., 2004). The standardisation of outcomes reported in venous leg ulceration research will potentially reduce data dredging.

Gethin et al's (2015b) systematic review showed that 39% (40/102) of RCTs did not report any endpoints in the methods section. Forty percent (41/102) of RCTs did not state whether the outcome was primary or secondary. Hodgson et al. (2014) performed a methodological overview of chronic wound trials published between 2004 and 2011 which investigated the influence of industry funding on methodological quality. Hodgson et al. (2014) found that only 59% (98/167) of trials defined their primary outcome. Failure of RCTs to report outcomes in full is likely to result in only a subset of data being available for synthesis. A methodological study (Outcome Reporting Bias In Trials - ORBIT) found that only 55% (157/283) of the eligible trials in a cohort of Cochrane reviews, published in three issues of the Cochrane library between 2006 and 2007, included full data for primary outcomes (Kirkham et al., 2010). The CONSORT guidelines state that the primary and secondary outcomes should be pre-specified (Moher et al., 2010). The pre-specified primary outcome is thought of as being the most important to stakeholders and it is normally used to base the sample size calculation upon (Moher et al., 2010). In a systematic review by Dwan et al. (2008) it was found that 40-62% of wound care studies had a primary outcome that was either changed, omitted or introduced in the studies publication compared to the protocol.

1.9 Core Outcome Sets

A core outcome set is an agreed standardised set of outcomes which should be, as a minimum, measured and reported in all RCTs or other forms of research which evaluate treatment effectiveness for a given indication (COMET, 2019). It includes *what* to measure and *how* to measure. An

outcome is a precisely defined method of assessing the effectiveness (benefit) or adverse effects (risk) of a healthcare intervention (Williamson et al., 2017). The core outcome set is a minimum list therefore trialists can add additional outcomes relevant to their trial if they wish. An agreed standardised set of outcomes is a set of outcomes that have been agreed by stakeholders to be core and should be reported in all RCTs or other forms of research which evaluate treatment effectiveness.

A core outcome set for use in research evaluations of interventions used for venous leg ulceration has the potential to:

- include the outcomes that really matter to all stakeholders
- reduce research waste
- increase the utility of RCTs which in turn assists decision making
- reduce publication and outcome reporting bias
- facilitate treatment comparisons across different sources of evidence
- expedite the production of systematic reviews, meta-analyses and evidence-based clinical guidelines

Many areas of healthcare across varying populations and condition types have developed core outcome sets. Examples of other core outcome set developers include HOME (Harmonizing Outcome Measures for Eczema) (Schmitt et al., 2011), OMERACT (Outcome Measures in Rheumatology) (Boers et al., 2014), BARIACT (Coulman et al., 2016) which is a project developing a core outcome set for bariatric and metabolic surgery, and Millar et al. (2017) who developed a core outcome set for optimising prescribing in older adults in care homes. The reasons for core outcome set development in these areas are similar to the problems faced in venous leg ulceration research. For example HOME (Schmitt et al., 2011) aimed to achieve a better standardisation of outcomes in eczema rather than the wide variation that existed before the core outcome set and Millar et al (2017) found that heterogeneity of outcomes hindered comparisons of interventions aimed to optimise prescribing. OMERACT (Boers et al., 2014) found that rheumatologists used trial outcomes very differently resulting in varied conclusions about treatment efficiency. Similarly, BARIACT (Coulman et al., 2016) also found heterogeneity of reported outcomes causing challenges to cross-study comparisons and meta-analysis.

There is currently no core outcome set for use in research that evaluates interventions used for venous leg ulceration therefore this PhD set out to develop a core outcome set for use in research evaluations of interventions used for venous leg ulceration.

1.10 Guideline Initiatives and Conceptual Frameworks

COMET (Core Outcome Measures in Effectiveness Trials, 2019) is an initiative which brings together researchers interested in the development and standardisation of core outcomes. The initiative's website contains many protocols and published papers on core outcome sets.

The COMET initiative provides guidance and resources on the development of a core outcome set. The COMET database is home to completed and ongoing projects. Further details on the CoreVen project can be found on the COMET database: http://www.comet-initiative.org/studies/details/680.

Methodological frameworks have been developed by experienced core outcome set developers to help guide the process of core outcome set development, such as the frameworks by OMERACT (Boers et al., 2014) and HOME (Schmitt et al., 2015).

OMERACT established over 20 years ago, is an initiative of international health professionals developing outcome measures in rheumatology. Boers et al. (2014) developed the OMERACT filter 2.0, shown in Figures 1 and 2, which is a conceptual framework that guides the development of core outcome measurement sets for rheumatology but it can also be used for other areas of healthcare.

The first OMERACT filter was designed in 1998 (Boers et al., 1998) and it was then updated to the OMERACT filter 2.0 in 2014. The first filter was developed through a consensus process, involving various health research experts and patients. It was grounded in a framework by Fries et al. (1982), and later adapted by Kirwan (1992). Then in 2014 Idzerda et al, who are part of the OMERACT team, performed a scoping review to establish if there were any other available conceptual frameworks or models. Idzerda et al. (2014) concluded that there was a lack of frameworks on measurement in trials of efficacy and effectiveness, and those that were identified lacked sufficient

documentation to their development process thus prompting the development of the OMERACT filter 2.0 in 2014.

The OMERACT filter 2.0 was used to help guide the development of the core outcome set for venous leg ulceration and to ensure comprehensiveness of the core outcome set.

The first part of the filter shown in Figure 1 aims to ensure comprehensiveness of the core outcome set by specifying key areas. It specifies the core concepts of the health condition, these being; “Impact of Health Conditions” and “Pathophysiological Manifestations”. ‘Impact of health conditions’ includes aspects that directly ‘impact’ service users and other stakeholders. It contains three ‘core areas’; Death, Life Impact and Resource Use. The core concept and core area ‘Pathophysiological manifestations’ contains important markers of the disease, for example organ function (e.g. lung function).

The second part of the filter (Figure 2) shows the process for the core outcome set development (the process for deciding *what* to measure). OMERACT provide a stepwise process to aid the development of a core outcome domain set. The first step involves investigation into which (if any) contextual factors need to be measured and whether there are specific adverse events that need to be included. The ‘what’ to measure should be determined by performing a literature review on the domains and instruments. Simultaneously, stakeholders are consulted on what they think should be measured.

The list of ‘what’ to measure, which has been matched to their specific domains, is then put through a consensus process involving stakeholders resulting in a core domain set (Boers et al., 2014).

The framework highlights that the choice of the ‘domains’ is influenced by context, therefore meaning the domains are dependent upon the health condition.

Figure 1 OMERACT filter 2.0 core concepts of the health condition

(Boers et al., 2014, p. 748)

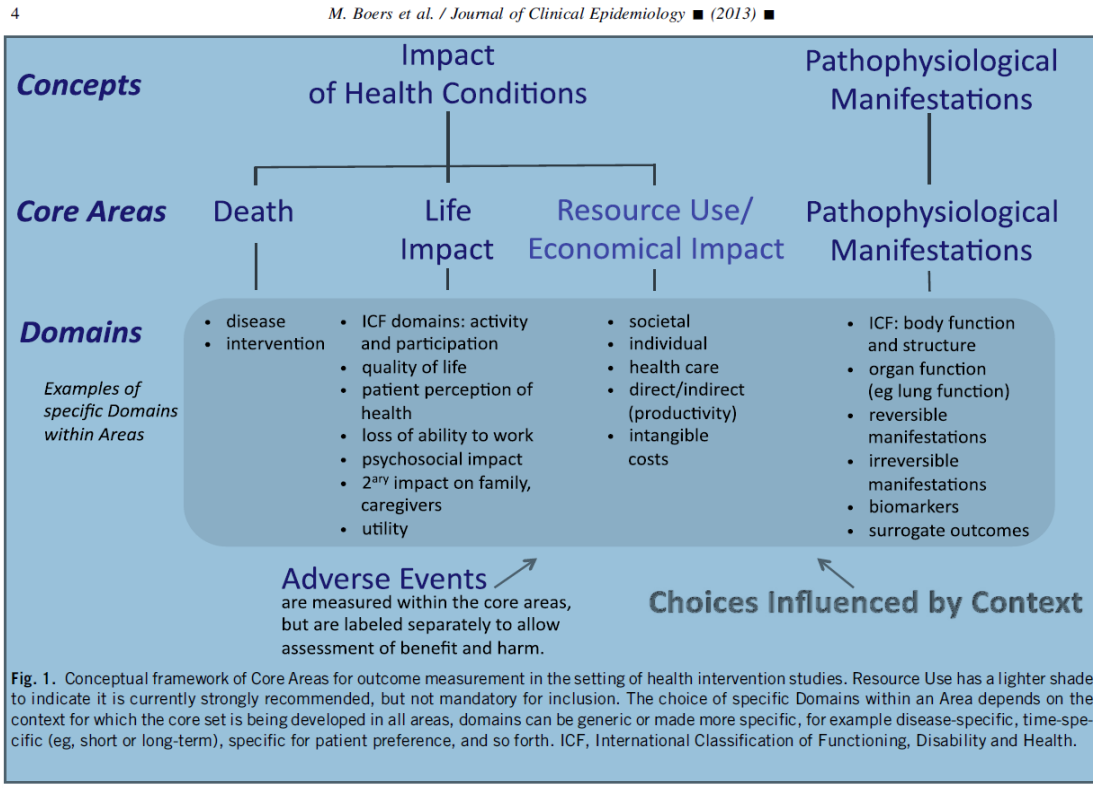
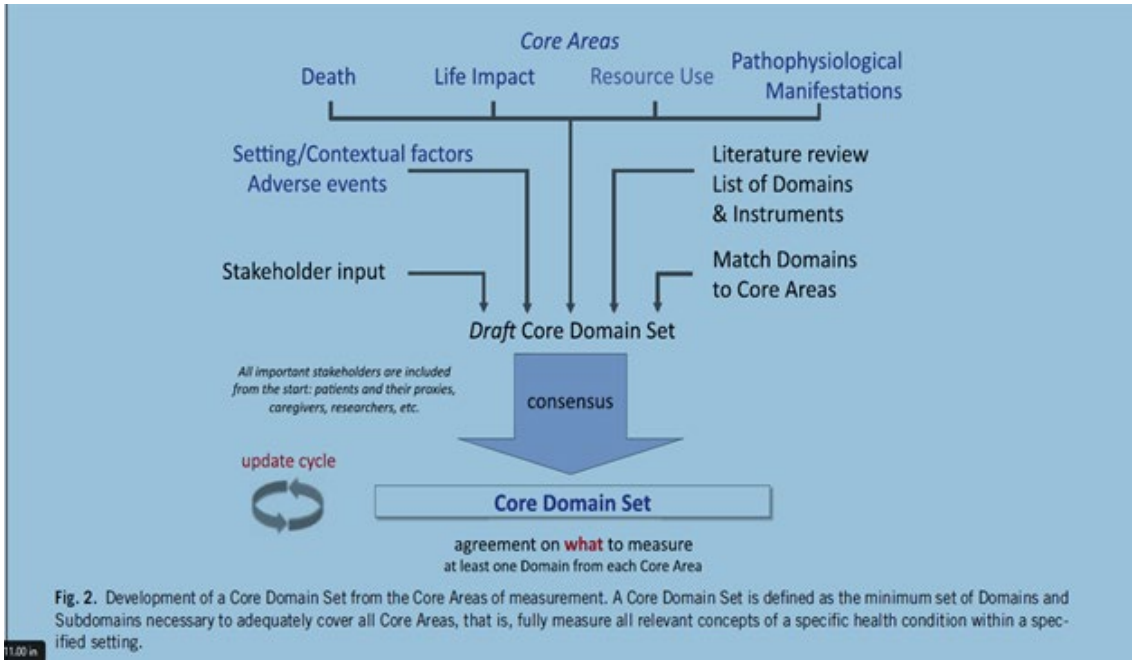


Figure 2 OMERACT filter 2.0 stepwise process to the development of a core domain set

(Boers et al., 2014, p. 750)



HOME have published a ‘roadmap’ which guides the development of core sets of outcome measurements (Schmitt et al., 2015). The first part of the ‘roadmap’ gives guidance on the development of a core outcome set and the second part guides the development of outcome measurements. HOME shares their experience of developing a core outcome set and the methods they used which is useful for other core outcome set developers whilst increasing the transparency of their methods. The experiences that HOME encountered were drawn upon during the development of the core outcome set for venous leg ulceration. The roadmap provided a robust approach to agreeing what is ‘core’.

The first part of the roadmap contains two steps; the first step outlines the scope and applicability of a core outcome set, including:

- Population (i.e. healthcare area, venous leg ulcers)
- Setting (e.g. clinical trial)
- Geographical scope
- Stakeholders (e.g. patients, researchers, healthcare professionals)

Step two recommends that the development of the core outcome set is done using a consensus study, ideally the Delphi technique or the Nominal Group Technique (NGT). Consensus methods are discussed in chapter 2.

OMERACT and HOME also provide guidance on the development of a core set of measurement instruments which is discussed in chapter 6, section 6.9.3.

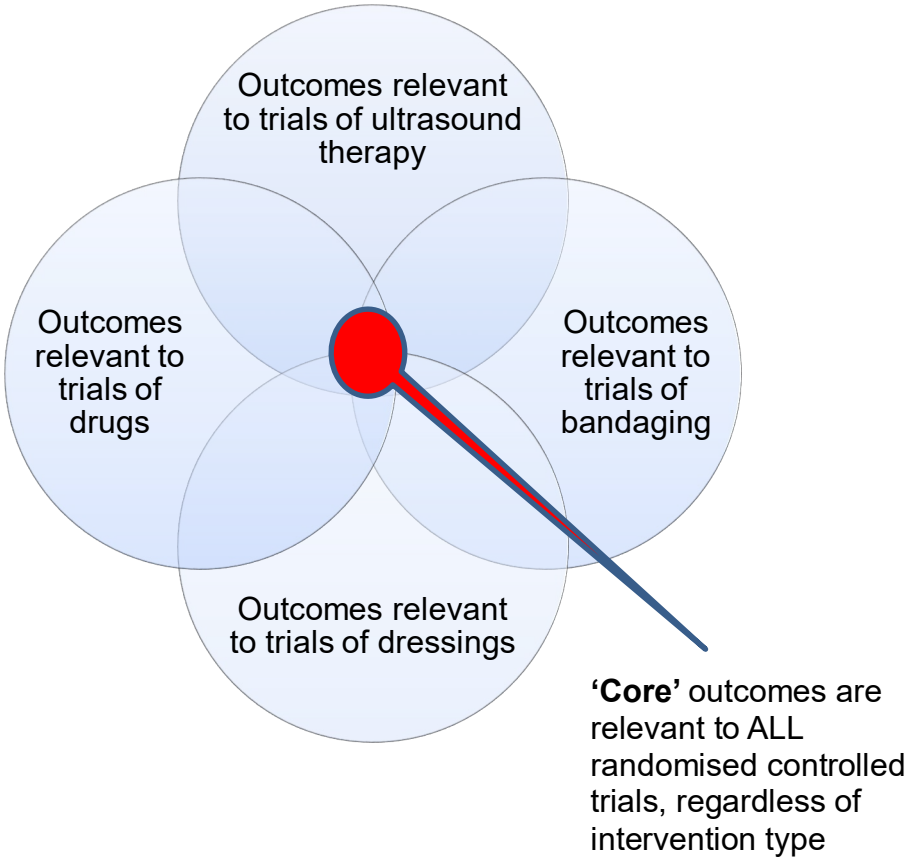
The COMET initiative, the OMERACT filter 2.0, and the HOME ‘roadmap’ were chosen to help guide the development of a core outcome set. They are workable models, produced by established core outcome set developers.

1.11 Core Outcome Set for Venous Leg Ulceration

The outcomes in the core outcome set need to be applicable, and therefore core, to every venous leg ulcer trial. Figure 3 displays a pictorial representation of what is meant by ‘core’. An example of an important but not core outcome might be sub-bandage pressure, it is an important outcome for a trial that is focusing on compression but it is not applicable in trial evaluating other types of

interventions such as dressings. The trials on the interventions displayed in Figure 3 are examples and there are many more interventions that trials investigate.

Figure 3 What is meant by 'core'?



1.12 Scope of the Core Outcome Set

Kirkham et al. (2017) recommend defining the scope of the core outcome set which includes outlining the research setting to which the core outcome set is to be applied, the health condition, the population and the intervention(s) covered by the core outcome set.

The core outcome set will be aimed for use in research evaluations of venous leg ulceration interventions, for example randomised controlled trials, audits, clinical guidelines, systematic reviews and meta-analyses.

The core outcome set will pertain to all patients regardless of sex, age, duration of disease and the severity of the ulceration.

Although venous leg ulceration can be treated by various interventions (discussed in section 1.3), the intention of the core outcome set is to relate to all research evaluations of venous leg ulcer interventions, regardless of the type of intervention.

1.13 Definitions

This section provides the definitions used in this PhD. The definitions are summarised in Table 1. Chapter 4, section 4.2, discusses the rationale behind the definitions.

Table 1 Definition of the terms used

Outcome domain	This relates to *what* is being measured. Outcome domains are broad, descriptive categories under which several, more specific, outcomes might be grouped. An example of an outcome domain is 'healing'. Outcome domains have also been referred to as 'domains' by some core outcome set developers (Boers et al., 2014).
Outcome	This also relates to *what* is being measured. An outcome should be a precisely defined method of assessing the effectiveness (benefit) or adverse effects (risk) of a healthcare intervention (Williamson et al., 2017). Where the outcome domain is defined as 'healing' (as in the example above), examples of related outcomes could include: time to healing; the number of ulcers completely healed at 3 months, or; the change in ulcer surface area relative to baseline at 3 months.
Candidate outcome domain	The candidate outcome domains were the outcome domains that were subjected to the consensus process.
Candidate outcome	A candidate outcome is an outcome which could potentially be included in the core outcome set.

Core outcome set	An agreed standardised set of outcomes which should be, as a minimum, measured and reported in all RCTs or other forms of research which evaluate treatment effectiveness for a given indication (COMET, 2019). It includes *what* outcome domains and outcomes should be measured and *how* the outcome domains and outcomes should be measured.
Outcome measurement instrument	An agreed set of measurement instruments to measure the core outcome domains and outcomes. For example the 36-Item Short Form Health Survey (SF-36).

1.14 Summary

Venous leg ulceration continues to be a significant problem, impacting upon people worldwide, affecting their quality of life and causing financial burden to patients and healthcare organisations. One of the key clinical challenges is therefore to identify effective methods for treating venous leg ulcers, reducing their impact on people, providing effective care, and make the best use of resources. RCTs, systematic reviews and meta-analyses are fundamental in establishing the clinical effectiveness, and the efficacy and safety of interventions to treat venous leg ulceration. However RCTs do not always report outcomes that matter to patients, nurses and doctors. The heterogeneity of reported outcomes across RCTs causes problems in the comparing and contrasting of the outcomes, impeding different sources of evidence synthesis thus obstructing decision making.

The development of a core outcome set has the potential to help overcome the problems identified in the reporting of outcomes in venous leg ulceration research, therefore prompting the development of a core outcome.

Consensus methods are a useful way of gaining agreement from stakeholders on what the most important outcomes are and should be reported in research evaluations of interventions used for venous leg ulceration.

The next chapter will explain what is meant by consensus, it will discuss the different methods for arriving at consensus, and it will evaluate four main consensus methods.

Chapter 2 Consensus Methods

2.1 Introduction

This chapter begins by explaining what consensus is, it will then discuss the different methods for arriving at consensus (individual, group, informal and formal). It will explore the four main consensus methods being the Delphi method, Nominal Group Technique, consensus development conference and the RAND/UCLA Appropriateness method before comparing the methods and examining their methodological issues. Finally it will discuss the rationale behind selecting the Delphi method as the main consensus method used in this PhD.

Consensus is concerned with the level of agreement that respondents have with an issue, cue, item or statement under investigation, which is commonly rated on a numerical or categorical scale (Jones and Hunter, 1995). Consensus methods are used to define levels of agreement amongst individuals on a controversial issue (Fink et al., 1984). The objective of consensus is to reach a final statement or set of statements. The level of consensus is contingent upon the sample size, the aim of the research and resources available (Hasson et al., 2000). The methods used, including how consensus was defined and its rationale, need to be clearly reported for a study to demonstrate rigour. The optimum level of consensus would be 100% however many researchers have not been able to achieve unanimity. A universally agreed level (other than 100%) of consensus does not exist (Hasson et al., 2000). A variety of ways to define consensus have been suggested but the majority do not justify their reasons (Williamson et al., 2017).

Judgements made by one person (the 'best person' model) have a number of issues: how is the 'best person' identified?, it is not possible for one person to have access to all the relevant evidence, and they may have limited credibility restricting the credibility of the results (Murphy et al., 1998), therefore a group

decision by means of consensus is advantageous. The 'group' decision enables a wider range of experience and expertise to be voiced, whilst encouraging group members to consider a range of options they might not have considered if making a decision individually (Murphy et al., 1998). A group view may also carry more weight than an individuals' view and idiosyncrasies are filtered out, however sometimes wrongly (Murphy et al., 1998).

Informal methods of consensus, such as face-to-face discussions are often used but they are at risk of dominance by individuals with powerful and intimidating personalities (Jaeschke et al., 2008). The presence of individuals with authority, for example a manager, may threaten the integrity of elicited views. Face-to-face discussions can lead to a person defending their stand point without consideration to other options and opinions, or a person can be persuasively influenced by the opinions of more dominant individuals in the group (Dalkey and Helmer, 1963; Sinha et al., 2011). Thus demonstrating that the way in which consensus methods are conducted is important.

Formal consensus methods can provide structure to the consensus process, allowing for the synthesising of judgements when there is uncertainty (Black et al., 1999). They are a way of establishing shared agreement on a topic where there is a lack of agreement (Moules et al., 2017). Formal methods can define the levels of agreement on contentious topics (Fink et al., 1984).

Formal consensus methods have been used by many researchers to develop core outcome sets (Taylor et al., 2008 (OMERACT team) ; Schmitt et al., 2011 (HOME team) ; Sinha et al., 2012; Gargon et al., 2014; Coulman et al., 2016; Gorst et al., 2016a; Gorst et al., 2016b; MacLennan et al., 2017; Millar et al., 2017; Orbai et al., 2017; Davis et al., 2018).

There are four main formal consensus method approaches that have been used in healthcare over the last 69 years. The Delphi method was introduced in the 1950s, then the nominal group technique in the 1970s, then the consensus development conference in 1977, followed by the RAND/UCLA Appropriateness Method (RAM) in the 1980s.

The four main formal consensus methods will now be presented and each method will be critically considered whilst comparing and contrasting their methodological features. Comparisons of the four formal consensus methods

including the Delphi method, Nominal Group Technique, consensus development conference and RAND/UCLA Appropriateness Method are presented in Table 3, section 2.6.

2.2 Delphi Method

In an exploratory study on 'How good are expert predictions in areas germane to policy' by Kaplan et al (1950) it was found that the statistical combination of individual responses is stronger than face-to-face group responses which may be affected by specific effects of collective effort. Statistical combination is for example the combination of ratings in a survey to produce an overall result i.e. the overall rating score for an item on a survey. A measure of central tendency is needed to analyse the levels of agreement. Following Kaplan et al's (1950) findings, the Delphi method was developed, also termed the Delphi technique or Delphi study, which was originally named Project Delphi during 1950-1960's. The then named 'Project Delphi' was first used at the RAND (Research ANd Development) corporation as part of a military defence project. The RAND corporation is a non-profit research organisation that develops solutions to challenges that arise in public policy with an aim to make communities safer and more secure (RAND Corporation, 2018).

Due to security reasons the first publication on RAND Corporation's Delphi method was first published thirteen years later by Dalkey and Helmer (1963). The aim of 'Project Delphi' was to estimate the number of A-bombs to reduce munitions output by a prescribed amount (Dalkey and Helmer, 1963). The object of the Delphi method was "to obtain the most reliable consensus of opinion of a group of experts…by a series of intensive questionnaires interspersed with controlled opinion feedback" (Dalkey and Helmer, 1963 p. 458).

The method was made up of five questionnaires which were completed in private and submitted at weekly intervals. The first and third questionnaires were followed by interviews.

The rationale behind the series of questionnaires lies in Dalkey and Helmer's (1963) belief that the repeated individual questioning and the design of the questions elicits reasoning behind respondents' answers to the primary

question. Respondents also consider the factors involved when they think about the question/topic (Dalkey and Helmer, 1963).
The interviews that followed the first questionnaire asked participants to estimate the number of bombs required to reduce munitions output with 10% and 90% confidence of success, and they were asked what type of data is most useful in helping him or her to work out the estimate. The interview that followed the third questionnaire clarified any uncertainties. No further details were given on the interviews, such as how the interviews were performed and structured, therefore it is difficult to fully assess the rigour of the study.

The method was found to elicit responses that are more conducive to independent opinion compared to face-to-face discussions and helped guide participants to the consider another's opinion (Dalkey and Helmer, 1963). In the context of developing of a core outcome set, a participant may alter his or her opinion once he or she has seen the opinions of other stakeholder groups (e.g. patients) without the risk of dominance by individuals with powerful personalities or with positional power. Dalkey and Helmer (1963) stated that direct confrontation provokes a response of defending ones stance, a predisposition to be influenced by dominant others and a tendency to close one's mind to novel ideas.

Dalkey and Helmer (1963) pointed out a number of limitations to their 'experimental procedure' and state that further experimentation is required because the design was in the preliminary stages. The limitations included the potential for respondents to have discussed their responses with each other (some respondents worked alongside each other), and Dalkey and Helmer (1963) state that the information supplied by the "experts" may have caused some "leading" by the researchers however they do not explain this further.

Following the development of the Delphi method by Dalkey and Helmer (1963), Dalkey (1967) summarised the Delphi method into three characteristics: anonymity, controlled feedback and statistical group response whereby the respondents ratings are aggregated to produce an overall result (e.g. overall rating score). Dalkey (1967) stated that anonymity reduces the effect of a dominant individual by provoking individual responses in private without the risk of another person influencing them. Conversely, anonymity may lead to a lack of accountability (Lelkes et al., 2012), thus suggesting responses in an

anonymous survey may not elicit ‘true’ responses because participants are not accountable for their answers.

Controlled feedback, whereby the results of each questionnaire is fed back to the respondents, reduces “noise” allowing respondents to focus on the issue at hand (Strauss and Zeigler, 1975). Dalkey (1967) highlighted that the method was still in the experimental stages. Since then there has been a broadening of the Delphi method which has been used across a variety of disciplines including nursing, health services and medical research (Chin et al., 1990; Beers et al., 1991; Mobily et al., 1993; Smith and Murphy, 1994; Palmer and Batchelor, 2006).

An overview of the method is displayed below (Jones and Hunter, 1995):

> Round one: Relevant (based on knowledge or experience) individuals are invited to provide their opinions, and the research team express their opinions. The opinions are collated in preparation for a survey. Appropriate ‘experts’ to take part in subsequent survey rounds are selected.
>
> Round two: Participants rate their agreement with the survey statements.
>
> Round three: Summarised ratings of participant’s agreement with the survey statements are shown to participants. Participants are asked to re-rate their agreement with the same statements with an opportunity to change their score in light of the group’s responses. If an acceptable level of consensus is achieved the survey round process may cease, if not, the third round is repeated.

In more recent years, the Delphi process has been modified (thus called the ‘modified Delphi’) by researchers dependent upon their research question, for example the use of the Delphi method in the development of a core outcome set may start by asking participants open questions to generate a list of outcomes instead of the list being produced by the research team (Sinha et al., 2012). Alternatively researchers have performed a literature/systematic review to identify outcomes for the list of outcomes to be presented to participants in round one of the Delphi study (Al Wattar et al., 2017). Others have opted for a combination of a literature/systematic review and interviews with participants to

generate a list of outcomes for the consensus process (Millar et al., 2017). The number of rounds have also been modified. The number of rounds is an important factor to consider because reliability increases as the number of rounds increase, however too many rounds can result in participant fatigue (Hasson et al., 2000). Reliability is the extent to which similar ratings are produced under constant conditions on every occasion (Hasson et al., 2000). Traditionally the Delphi method used five rounds (Dalkey and Helmer, 1963), but two to three rounds with an optional face-to-face meeting or consensus meeting have been used in the modified Delphi (COMET, 2019).

The different types of Delphi methods that have evolved since Dalkey and Helmer's (1963) 'classical Delphi' are summarised in Table 2 (Dalkey and Helmer, 1963; Beretta, 1995; Keeney et al., 2011; Donohoe et al., 2012; Al Wattar et al., 2017).

Table 2 Type of Delphi methods and their characteristics

Classical Delphi	Open first round which generates ideas, and elicits opinions Five postal rounds Optional interviews
Modified Delphi	First postal round is replaced with face-to-face interviews or focus groups And/or a literature/systematic review is conducted May use fewer than three rounds The surveys are sent out via post or email Optional face to face meeting or consensus meeting
e-Delphi (electronic Delphi)	Similar to the modified Delphi but the survey uses an online platform to collect data, and communicate
Real Time Delphi	Similar to the classical Delphi but consensus is gained anonymously by an electronic app in real time instead of by post Also referred to as a consensus conference

The Delphi method, namely the modified Delphi, is a multistage method used to gain consensus among experts. The benefits of the Delphi method include; an opportunity to include a diverse population in terms of experience and/or expertise, a greater number of people can participate compared to methods that only use face-to-face meetings, costs are low and logistics are more feasible (Linstone and Turoff, 1975). An electronic Delphi (eDelphi) also enables the views of many and geographically dispersed to be included at a relatively cheap cost because it can be accessed remotely (Jones and Hunter, 1995). This is an important factor because reliability increases as the number of respondents increase (Keeney et al., 2011). Respondent 'side tracking' is avoided due to the controlled feedback between rounds (McKenna, 1994). It allows for a convergence of opinion and it allows for views of all participants to be equally heard (Murphy et al., 1998). It is believed that it encourages honest opinions free from dominance of peers (Williams and Webb, 1994). Hirsch et al. (2016) suggest that an online Delphi allows participants to score each item without the influence of dominant individuals so reducing the possibility that participants provide sociably desirable scores or scores that are agreeable with senior members. There is a greater likelihood that anonymity will be maintained compared to methods that only use face-to-face discussions (McKenna, 1994).

One of the main characteristics of the Delphi method is anonymity, however Sackman (1975) criticised the method stating that anonymity can lead to a lack of accountability and produce quick responses without thought.
The lack of face-to-face interaction has been criticised for the lack of positive effects that visual interactions can have, such as the interactions between participants and body language which can identify reasons for any disagreements that may arise (Sackman, 1975; Murphy et al., 1998). The modified Delphi does however offer an optional face-to-face meeting for participants to discuss the results, or an optional consensus meeting to finalise the results (Schneider et al., 2016; Tomkins-Lane et al., 2016).
Sackman (1975) also criticised the validity and reliability of the Delphi method stating that the questionnaire items are ambiguous and not clearly defined. However Sackman (1975) critiqued the studies rather than the Delphi method. Sackman (1975) focused on the studies poor survey design, the methods used

to select ‘experts’, their analysis methods and how authors tested reliability and validity thus suggesting the flaws in the Delphi were to do with poor study design as opposed to the use of the Delphi method. For example Sackman (1975) criticised a study by Gordon and Helmer (1964) for not including more than medians, quartiles and descriptive scatter-plots in their analysis, and a study by Nanus et al. (1973) for only providing frequency distributions and some percentages for quantitative results.

The reliability and validity of the Delphi method was tested by Tomasik (2010) who analysed the responses of 55 physicians who took part in a two-round Delphi study to develop guidelines for the management of hypertension. Tomasik (2010) found the Delphi method to have good reliability and satisfactory validity. Internal correlation coefficient, or Cronbach’s alpha, was the method used to assess reliability. Cronbach’s alpha assesses internal consistency (Bland and Altman, 1997). Internal consistency is the extent to which items on a scale measure the same thing (Vogt, 1999). The results for reliability of the first round in Tomasik’s (2010) study was high with a Cronbach’s alpha of 0.944, and round two was 0.850. Tomasik (2010) provides a detailed description of the methods used to assess three types of validity including; construct, content and criterion validity. Tomasik found construct validity was good, content validity was satisfactory but criterion validity was only fulfilled in part. Construct validity is the extent to which the scores of a measurement instrument are consistent with hypotheses (if the content validity is adequate) (COSMIN, 2018). Content validity is concerned with the extent to which the content of a measurement instrument is an adequate reflection of the construct it is measuring (COSMIN, 2018). Criterion validity is the degree to which the scores of a measurement instrument reflect the ‘gold standard’ (COSMIN, 2018). It is the correlation of a measure with another which is accepted as a valid criterion measure (referred to as the ‘gold standard’) (Bowling, 2009). When no ‘gold standard’ exists concurrent and predictive validity are used. Concurrent validity is the independent corroboration that the measurement instrument measures what it intends to measure and predictive validity is the ability of the instrument to predict changes of variables in the future (Bowling, 2009). However, because a variety of participants from a range of backgrounds and countries can take part in an

eDelphi confounding variables can rarely be controlled. Confounding variables can rarely be controlled therefore opinion is not static which limits the assessment of methodological rigour (Hasson and Keeney, 2011). Various writers have declared that the method provides evidence of content and face validity (Goodman, 1987; Morgan et al., 2007; Huang et al., 2008). Face validity is a subjective assessment on whether the instrument appears to measure what it intends to measure (Bowling, 2005).

The Delphi method has been used by many core outcome set developers (Taylor et al., 2008 (OMERACT team) ; Schmitt et al., 2011 (HOME team) ; Sinha et al., 2012; Gargon et al., 2014; Coulman et al., 2016; Gorst et al., 2016a; Gorst et al., 2016b; MacLennan et al., 2017; Millar et al., 2017; Davis et al., 2018).

2.3 Nominal Group Technique

The Nominal Group Technique, originally called the Program Planning Model (PPM) was developed by Delbacq and Van de Ven (1971). Unlike the Delphi method, the Nominal Group Technique's main method involves a structured face-to-face meeting which attempts to gain qualitative information in an orderly manner (Van de Ven and Delbecq, 1972). Delbacq and Van de Ven (1971) developed the structured group process to structure committee decision making such as the development of a service program for elderly people in a small community where there is no existing service. The development of the service program required assistance from a number of social agencies and health service institutions. They aimed to design a method which had an explicit process, and structured participation within each phase to cater for the internal exchange across internal and external organisational units. Delbacq and Van de Ven (1971) proposed the group process model for identifying strategic problems and for developing programs to solve the problems. The technique was developed using social-psychological studies of decision-conferences and from studies on program planning in a Community Action Agency.

Since Delbacq and Van de Ven (1971) the model, now termed Nominal Group Technique, has been modified but the main aims of the method continue. The

main aim of the technique is to structure interactions of participants within groups. Participants record their ideas privately to begin with then the ideas are listed in turn by a group facilitator. Each item is discussed by the group. Delbacq and Van de Ven (1971) state that the specific voting procedure used depends upon the specificity of the information that is required from the group, therefore if only general, preliminary information is required then listing of priorities is adequate. Whereas, if the researcher wants to know the magnitude of the difference between priorities then the ratings of the priorities is required. Participants are then asked to vote (by number) on the items in private. Further rounds of discussion and voting may follow. The votes are aggregated statistically to produce a group judgement (Murphy et al., 1998). Classically, the Nominal Group Technique involves groups of five to eight participants (Van de Ven and Delbecq, 1972).

The classical nominal group technique is summarised below (Van de Ven and Delbecq, 1972):

1. Introduction to the meeting including an explanation to the purpose of the research
2. Silent generation of ideas on critical barriers in writing by individual participants
3. Round-robin listing of each participant's ideas on a flip chart until all the participants have exhausted their individual lists
4. Discussion of ideas on the flip-chart to clarify, elaborate, defend or dispute the ideas
5. Break
6. Ranking priorities and problem elements: private ranking of the ideas to produce a top 10, tallied, list for each participant
7. Voting of the top 10
8. Discussion on the vote
9. Re-ranking and rating priorities in private
10. Conclusion of the meeting

Delbacq and Van de Ven (1971) state that the use of nominal groups and the specific group processes increased creativity amongst participants. Delbacq and Van de Ven's reasoning behind participants' initial generation of ideas

individually lay in their belief that when groups are allowed to interact they “fall into a rut” because they concentrate on a single dimension.

The advantages of the Nominal Group Technique include structured interaction of a group which enables all group members to voice their opinions. The structured interaction makes it more difficult for individual’s with more dominant personalities to inhibit others from speaking (Murphy et al., 1998). The technique brings a small group of people together to make a relatively quick decision on a subject.

The disadvantages of the Nominal Group Technique include the dominance of group members when the items are discussed prior to the vote which could drive the results, and time limits meaning the amount of time to discuss each item may be limited (Nair et al., 2011). Additionally, bringing people together for a face-to-face meeting can be costly (Nair et al., 2011). It makes the involvement of internationally dispersed individuals challenging and potentially costly. Concerns over small group sizes facilitated by the technique raises questions over whether there are enough “experts” involved to be representative of the subject area which in turn raises questions over its reliability (Raine et al., 2005; Black, 2006).

A series of four systematic reviews were performed by Gargon et al. (2014), Gorst et al. (2016a), Gorst et al. (2016b) and Davis et al. (2018) whose objectives were to report on the methodological techniques used to develop a core outcome set and examine the quality of core outcome sets. The systematic reviews suggest that the Nominal Group Technique has not been used often by core outcome set developers. Davis et al. (2018) collated all three systematic reviews (Gargon et al., 2014; Gorst et al., 2016a; Gorst et al., 2016b) and included 18 studies carried out since Gorst et al’s systematic review in 2016. Davis et al. (2018) found that the Nominal Group Technique has been used by less than 1% (n=1/259) of core outcome set developers and the technique was used as part of a mixed method design by only four studies (4/259). Further details on the systematic reviews can be found in section 2.6.1. If the Nominal Group Technique has not been used and tested in core outcome set development it is difficult to establish the validity and reliability of the technique for use in core outcome set development.

The technique has been used in different fields including health and education, for example Bajracharya (2006) used the technique to clarify the perceived barriers to accessing screening for colorectal cancer, and Chasens and Olshansky (2008) developed a list of issues that people with type 2 diabetes have with sleeplessness.

2.4 Consensus Development Conference

The National Institutes of Health (NIH) in the United States introduced the consensus development conference in 1977. A selected group are invited to an open meeting where evidence on the topic is presented by “experts” who are not part of the decision-making group. The participants are then left in private to discuss, in an informal format, the topic in light of the “experts” presentation. The chairperson of the group then encourages the participants to reach consensus. If no consensus is met then minority or alternative views are considered (Murphy et al., 1998). The consensus development conference has been used by the National Heart, Lung, and Blood Institute, NIH Center for Drugs and Biologics of the Food and Drug Administration and the NIH Office of Medical Applications of Research who convened a consensus development conference on Platelet Transfusion Therapy in 1986 to resolve issues associated with the increase in platelet transfusion such as the transmission of diseases. The panel at the consensus development conference aimed to agree on the following questions:

1. What are the appropriate indications for platelet transfusion?
2. What products are available, and what are their relative merits?
3. What are the risks associated with platelet transfusion?
4. What are the most important directions for future research?

The consensus development conference brings a group of people together to make a relatively quick decision on a subject. A disadvantage of the method is that it facilitates an interaction that is not structured and there is a lack of a formal feedback system (Nair et al., 2011). Similarly to informal methods the interactions at a consensus development conference are at risk of dominance by individuals with powerful and/or intimidating personalities and the presence of individuals with authority threatening the integrity of elicited views.

The consensus development conference has been used by 5% (13/259) of core outcome set developers whose studies were included in Davis et al's (2018) systematic review.

2.5 RAND/UCLA Appropriateness Method

The RAND Corporation collaborated with clinicians at the University of California, Los Angeles (UCLA) in the 1980s to develop the RAND/UCLA Appropriateness Method. The method was developed in response to a lack of evidence at a sufficient level, or the 'gold standard' (Fitch et al., 2001). The aim of the method was to combine scientific evidence and the assessment of indicators by panellists on the appropriateness of carrying out surgical procedures with consideration to a patient's symptoms, medical history and diagnostic test results (Fitch et al., 2001).

The RAND/UCLA Appropriateness Method was developed to determine the appropriateness (the relative weight) of the benefits and harms of surgical or medical procedures. The method is used to collate the opinions of experts and it has been applied to different health conditions and procedures (Fitch et al., 2001). An overview of the method is given below:

1. A detailed literature review is performed to collate the scientific evidence on a topic. A list of indications and definitions are produced concurrently.
2. A panel of experts are then sent the literature review along with the list of indications and definitions. The panel are asked to rate the benefit-to-harm ratio of the procedure on a scale of 1 to 9 (1 being expected harms greatly outweigh the expected benefits and 9 being the expected benefits greatly outweigh the expected harms). A "modified Delphi" process takes place over two rounds. In round one the panellists rate the procedures individually at home then in round two the panellist meet for 1 to 2 days with a moderator present. The distribution of all the panellists' first round ratings are given to each panellist along with their own ratings. The results are discussed in the meeting, especially the areas of disagreement. Round two of voting takes place. The aim of two rounds is to decipher whether discrepant ratings are due to real clinical disagreement, due to fatigue or due to misunderstanding.

3. A face-to-face meeting is facilitated over 1-2 days to allow the expert panel to discuss the results of the above. Any areas of disagreement are discussed, if necessary, resulting in an adjustment to the indications and definitions. Each indication is then rated by the panel in private.
4. Each indication is then classified as “appropriate”, “uncertain” or “inappropriate” depending on the panellists’ median score and the level of disagreement among the panel members. Procedures with median scores of between 1 and 3 are classified as inappropriate, scores between 4 and 6 are classified as uncertain, and scores between 7 and 9 are classified as appropriate. However, all procedures rated “with disagreement” (irrespective of the median) are classified as uncertain. “Disagreement” means there is either a lack of consensus, judgements are spread over the 1 to 9 scale or there is polarisation of the group. The levels of agreement (i.e. with agreement or indeterminate agreement) are sometimes reported alongside the results.

Although the method was originally designed for use in determining the appropriateness of procedures in healthcare such as surgical or medical procedures, it has been used widely in different areas of healthcare (Buetow and Coster, 2000; To et al., 2010; Saust et al., 2017). Buetow and Coster (2000) used the method to produce angina and heart failure criteria for quality assessment in general practice, To et al. (2010) produced performance indicators of primary care for asthma, and Saust et al. (2017) produced quality indicators for the diagnosis and antibiotic treatment of acute respiratory tract infections in general practice.

Shekelle et al. (1998) support the method and present evidence for the predictive validity of the method for performing carotid endarterectomy. The method uses elements of the Delphi method and Nominal Group Technique such as private rating of items and face-to-face meeting of participants which allows areas of disagreement to be refined, increasing the likelihood that agreement is achieved. Tan et al. (2007) criticised the method for being too complex and time consuming.

Panellists are asked to rate predetermined statements. Although panellists are encouraged to suggest, and in turn rate amendments, they are not asked to provide ideas (Campbell and Cantrill, 2001).

The method has had limited use in the development of a core outcome set (Howell et al., 2013). Some researchers have opted to use a different method for the consensus process and the RAND/UCLA disagreement index to determine agreement (Prowse et al., 2013).

2.6 Comparison of the Consensus Methods

Table 3 displays the characteristic comparisons between the four different consensus methods (Black et al., 1999; Schneider et al., 2016; COMET, 2017). Aggregation of the methods in the table refers to the methods used to combine participants' views. It is a measure of central tendency which is needed to analyse the levels of agreement. Implicit means consensus is implied and not expressed directly, whereas explicit means consensus is clear and detailed, leaving nothing implied.

The modified Delphi and the RAND/UCLA Appropriateness Method seem essentially the same except that the face to face contact is optional in the modified Delphi method. The RAND/UCLA Appropriateness Method uses an initial literature/systematic review whereas the classic Delphi does not, however it is optional for the modified Delphi.

Table 3 Characteristic comparisons of consensus methods

Consensus method characteristic	Delphi	Nominal Group Technique	Consensus development conference	Rand/UCLA Appropriateness Method
Literature/ systematic review evidence	No Modified versions incorporate evidence	No Modified versions incorporate evidence	Yes	Yes
Mailed surveys	Yes Modified versions include option of online surveys	No	No	Yes
Private decisions elicited	Yes	Yes	No	Yes
Feedback of group scores	Yes	Yes	No	Yes
Face-to-face contact	Optional	Yes	Yes	Yes
Structured interaction	Yes	Yes	No	Yes
Aggregation method	Explicit	Explicit	Implicit	Explicit

2.6.1 Use of Consensus Methods in Core Outcome Set Development

A series of four systematic reviews were performed by Gargon et al. (2014), Gorst et al. (2016a), Gorst et al. (2016b) and Davis et al. (2018) whose objectives were to report on the methodological techniques used to develop a core outcome set and examine the quality of core outcome sets. The reviews

searched a variety of databases including MEDLINE via OVID, EMASE, SCOPUS, and the Cochrane Methodology Register without language restrictions. The COMET database was also searched in reviews by Gorst et al. (2016a), Gorst et al. (2016b) and Davis et al. (2018). All four reviews used the PRISMA checklist which is guides the reporting of systematic reviews (PRISMA, 2015). A multifaceted search strategy was applied and a comprehensive selection process was performed. Davis et al's. (2018) systematic review incudes all the studies from the three preceding reviews by Gargon et al. (2014) Gorst et al. (2016a) and Gorst et al. (2016b). Table 4 displays the combined studies reviewed by the four systematic reviews (Davis et al., 2018, p.8). The studies included in the systematic reviews were published between 1981 and December 2016. The table displays the number and percentage of each method used by core outcome set developers assessed by the systematic reviews.

Table 4 Methods used to develop core outcome sets

Main methods	**N (%)**
Mixed methods	**116 (45)**
Delphi + another method(s)	48 (19)
Semi-structured group discussion + another method(s)	42 (16)
Literature/systematic review + another method(s)	14 (5)
Consensus development conference + another method(s)	7 (3)
Nominal group technique + another method(s)	4 (2)
Semi-structured group discussion only	**59 (23)**
Unstructured group discussion only	**18 (7)**
Literature/systematic review only	**19 (7)**
Consensus development conference only	**13 (5)**
Delphi only	**10 (4)**
Survey only	**3 (1)**
Nominal Group Technique	**1 (<1)**
No methods described	**20 (8)**
Total	**259 (100%)**

The most used single method for developing a core outcome set appears to be the semi-structured group discussion approach, such as workshops, meetings, and round the table discussions (Gargon et al., 2014).
The second most used method to develop a core outcome set is the Delphi method as part of a mixed method approach. A higher proportion of core outcome set developers have used mixed methods (45%, n= 116/259) of which the Delphi was the most used technique combined with another method (48%, n=19/45).

2.7 Methodological Issues

2.7.1 Validity

There has been debate over the validity of consensus methods because it is difficult to assess (Jones and Hunter, 1995; Murphy et al., 1998; Tan et al., 2007; Hasson and Keeney, 2011). Validity is the term used to describe whether a research method measures what it intends to measure (Vogt, 1999). Validity assessment includes different types of validity such as content validity, face validity and criterion validity. Content validity is concerned with the degree of agreement between the instrument and its relevance (Polit and Beck, 2006). Face validity is a subjective assessment on whether the instrument appears to measure what it intends to measure (Bowling, 2005). Criterion validity refers to how reliably a variable can be measured (Bowling, 2005) and how able the instrument is to make accurate predictions (Vogt, 1999).
In the context of consensus it is difficult to determine whether a 'good' judgement is made at the time it is made, however the use of a rigorous method can increase the likelihood that a 'good' judgement is derived (Murphy et al., 1998).
Comparison with the 'gold standard', concurrent validity and internal logic are ways of assessing validity (Murphy et al., 1998). Comparison with the 'gold standard' involves testing the method against questions that have a correct answer, however because there is no conclusive evidence (no 'correct' answer) when it comes to judgements on peoples' opinions the answers cannot be compared against 'correct' answers. Consensus on a topic does not mean the

"correct" answer has been derived. There is a risk that collective ignorance is established through consensus rather than wisdom (Jones and Hunter, 1995). Concurrent validity is the extent of how well the method correlates with another method which is believed to be valid (Vogt, 1999). Internal logic is a concurrent approach which looks at the internal logical order of a group's results which determines the consistency of decisions made by respondents (Murphy et al., 1998).

Consensus methods are liable to paradoxes that can potentially undermine validity, for example the notion of alliance formation whereby a respondent will vote for another respondents 'favourite' if they return the favour (Murphy et al., 1998). Alliance formation might take shape in the context of the consensus process when a participant rates an item favourably because a co-participant will return the favour later on, possibly on another survey which has meaning for them. However, the risk of alliance formation is reduced in such methods as the Delphi method and the RAND/UCLA Appropriateness Method which maintain privacy between participants thus reducing interaction with each other which may have influenced responses.

2.7.2 Reliability

Consensus methods have been criticised for their lack of reliability (Jones and Hunter, 1995; Murphy et al., 1998; Hasson and Keeney, 2011). Reliability is concerned with the ability and stability of the method to produce the same results with different groups (Hasson et al., 2000; Raine et al., 2005; Keeney et al., 2011). Reliability is the consistency that the instrument repeatedly measures the same thing with identical or nearly identical results every time (Vogt, 1999). Sensitivity is the instruments ability to respond to change over time (Bowling, 2005).

Inter-rater reliability is the degree to which results obtained by two or more raters agree for the same population (Bowling, 2009). Intra-rater reliability is concerned with variation within a rater, often as a result of multiple exposures or ratings (Streiner and Norman, 2008).

Uhl (1975) tested the reliability of the Delphi method using the test-retest method. Uhl (1975) gave 26 faculty members a Delphi questionnaire to

complete. The questionnaire sought their perceptions on the degree of importance given by an institution to different goals and their opinion on what they think the degree of importance should be placed on the goals. An identical questionnaire was completed by the same faculty members' a year on. It was found that the faculty members' ratings in the final round (a year on) were similar to the first round suggesting that the Delphi method was reliable in Uhl's (1975) study. Duffield (1993) found that 93% (156/168) of competencies were agreed upon by two panels using the Delphi methods, thus indicating a high level of similarity when the Delphi method was used. Duffield (1993) compared two panels' agreement on competencies expected on first-line nurse managers. However Duffield (1993) points out that further research is needed to determine whether the results were due to a lack of disagreement on the subject or if they did in fact reflect the reliability of the Delphi method.

Reliability of group judgement can be increased with more group members (Richardson, 1972; Black et al., 1999), however this can lead to costly logistics especially when participants are being invited to take part in a series of face-to-face discussions.

The reliability of results can be affected by the judgments made by "experts". A number of influences can play a role in the extent to a person's expertise in an area, such as level of experience, exposure to the area of interest and qualifications (Hasson and Keeney, 2011). International differences may also affect the agreements between participants. A systematic review by Hutchings and Raine (2006) assessed factors affecting judgements produced by formal consensus development methods. Hutchings and Raine (2006) found that there were international differences in the overall and chance-corrected agreement on healthcare interventions between different countries (Switzerland, US, UK, Israel, Netherlands). Hutchings and Raine (2006) suggested that the difference may have been due to differences in healthcare resources between the countries, for example the UK's health resources are funded by the National Health Service whereas healthcare resources in Switzerland are regulated by the Swiss Federal Law on Health Insurance, each healthcare resource may have different policies and procedures. Raine et al. (2005) point out that because it is challenging to determine the validity and

reliability of judgements at the time they are made then it is essential that the methods are rigorous.

2.7.3 Experts

The definition and use of ‘experts’ has been debated over the years. Sackman (1975) questioned the use of ‘experts’ stating it is a manipulated group suggestion instead of real consensus, and stated that non-experts (a person without professional or lived experience of the subject in question) and experts have been found to give undistinguishable responses. Many argue that the participants should be experts because they have a deep understanding of the issue (Lomas, 1991; Jones and Hunter, 1995; Williamson et al., 2017). However, Skvoretz (1988) suggested that people with a higher status (supposedly more expertise) attempt to dominate the group thus influencing another’s judgement on a topic. It is suggested that it is better to have a heterogeneous group on a consensus panel rather than a homogenous group (Jackson, 1992). A multidisciplinary panel reflects the different specialities involved in the field of interest (Fitch et al., 2001). However diverse opinions can lead to disagreement which can inhibit consensus (Nair et al., 2011). Nursing literature which has applied the Delphi method was examined by Beech (2001) who performed a literature review to understand the diversity of a Delphi panel. Beech (2001) concluded that the definition of an ‘expert’ and sample selection varied across the 146 included studies dated between 1995 and 2001.

McKenna (1994) stated that the panel should be composed of ‘informed individuals’ and Fink et al. (1984) suggest that a panel should be representative of their profession, they should have the ability to implement the findings, or the panel should be chosen because they will not be challenged as experts in their subject area. Whereas, Williams and Webb (1994) provide explicit criteria of whom would constitute as an expert for inclusion on a Delphi panel including; a proven track record of practice, experience of greater than two years, able to demonstrate continuing professional education and makes an active contribution to current educational needs of others. Weinstein (1993) argued that there are two types of expert; one that has gained expertise through the

function of what they *know* and one that has gained expertise through what they *do.* The COMET initiative (COMET, 2017) states that 'experts' are those with personal experience such as patients and carers, and healthcare professionals that have expertise in the area and experience of treating and caring for people with the health condition.

The selection of participants is important because the results can be affected by the variation of stakeholders on a panel (Jones and Hunter, 1995). Given that the aim of a consensus method is to make judgements that will be implemented into research it is important that the participants are representative of the target audience affected by the implementation of the core outcome set.

The composition of the group is essential to ensure that the consensus reached is representative of all relevant stakeholders. The credibility of a consensus study can be enhanced when the full range of respondents reflect the vital stakeholders affected by the topic that the consensus is concerning and the methods to select and recruit the respondents should be explicit (Black et al., 1999). Researchers need to demonstrate that bias was assessed in the selection and recruitment of respondents by providing clear methods (Black et al., 1999).

There can be a risk of selection bias when the participants that are willing to take part are not be representative of their targeted stakeholder group (Bowling, 2009). Also, researchers that select participants based on their expected judgements will affect the overall results which are not likely to represent a variety of stakeholders.

2.7.4 Patient and Carer Involvement

Although it has been advocated in consensus studies that patients should be part of the stakeholder group (Fink et al., 1984; Jones and Hunter, 1995; Black et al., 1999), there is little evidence that patients have been involved in consensus studies. In a systematic review by Gargon et al. (2014) it was found that only 16% of 198 (n= 31) studies included patients, carers, patient support group representatives or service users in the development of core outcome sets. Gargon et al's (2014) review included studies that developed a core

outcome set between 1981 and 2013, since then the involvement of patients and carers appears to be gradually improving. In a systematic review by Davis et al. (2018) it was found that 80% of 15 (n=12) studies involved patients, carers and service users in core outcome set development. However the attrition rates for patient representatives in some studies has been high (Al Wattar et al., 2017). In a study by Al Wattar et al. (2017) which developed a core outcome set for epilepsy in pregnancy, 24 patient representatives completed round one but none completed rounds two and three, two patient representatives did however attend a final consultation meeting. The reasons for the high attrition are not discussed in the paper. The most popular method which involved patients and carers has been the Delphi method mixed with another method (n=48/259, 45%), for example a systematic review and a modified Delphi which includes a consultation meeting (Davis et al., 2018).

It has been found that patients identify outcomes that have not been suggested by others (Arnold et al., 2008; Sanderson et al., 2010; Cullum et al., 2016). A qualitative study performed by Arnold et al. (2008) explored how fibromyalgia affects the lives of 48 women living with fibromyalgia. Arnold et al. (2008) highlight that the domains identified by the women are not always assessed in RCTs on fibromyalgia. Sanderson et al. (2010) developed a core set for pharmacologic treatments and found that the outcomes identified by patients are not included in the commonly used professional core sets for pharmacologic treatments. It is therefore recommended that patients, carers and healthcare professionals participate in core outcome set development (Williamson et al., 2017).

The James Lind Alliance have brought patients, carers and clinicians together to identify and prioritise uncertainties which affect clinical practice and treatment effects on urinary incontinence (Buckley et al., 2010; Snape et al., 2014; Madden and Morley, 2016). The James Lind Alliance identified that there was a disparity between the priorities of clinicians and researchers, and those of patients and carers. Priority Setting Partnerships were established by the James Lind Alliance which includes at least one patient organisation and one clinical organisation. Priority Setting Partnerships are made up clinicians, patients and carers working together to identify and prioritise evidence uncertainties which can be resolved by conducting research (James Lind

Alliance, 2019). Each partnership identified their own method for eliciting questions and uncertainties relating to the management and treatment of incontinence (Buckley et al., 2007; Buckley et al., 2010). The James Lind Alliance acknowledges that the task of involving patients and clinicians together as a partnership is ambitious and challenging (Madden and Morley, 2016). The unstructured approach of the partnerships determining their own methods of initial information gathering, prioritisation, and selection of participants meant that the partnerships found it difficult to structure meaningful discussions with patients, carers and healthcare professionals (Madden and Morley, 2016). Similarly Rolls and Elliott (2008) also found the inclusion of patient-relative representatives to be difficult in a consensus study which developed clinical practice guidelines for intensive care.

Attempts have been made to improve the guidelines on patient involvement (Staniszewska et al., 2011; INVOLVE, 2018). For example INVOLVE (2018), established in 1996, supports public involvement in social care, public health and NHS research. INVOLVE (2018) has produced guidelines to help researchers involve the public in research.

2.7.5 Analysing and Defining Consensus

The objective of consensus is to reach a final statement or set of statements, in this case a set of outcomes that most participants agree are core. It is an integral part of a Delphi study (Diamond et al., 2014). It is also concerned with within group agreement; the extent to which respondents agree with each other (Jones and Hunter, 1995; Murphy et al., 1998).

In the absence of all participants agreeing 100% on all elements within a consensus process, the researchers usually define, on the outset, the extent of agreement considered as consensus having been reached. A variety of ways to define consensus have been suggested but the majority do not justify their reasons (Williamson et al., 2017).

When analysing the levels of agreement participants have with an issue, cue, item or statement a measure of central tendency is required. To measure consensus both the central tendency (what people are clustering around) and dispersion (the extent to which participants' opinions are spread out away from

the central tendency) are needed. Because group views are seldom normally distributed the median should be used and not the mean (Black, 2006). The median is more robust to the effect of outliers (Murphy et al., 1998).

Within group agreement is analysed using the measure of dispersion. Black (2006) states that the interquartile range is an appropriate measure of dispersion. However, other methods have been used such as the mean absolute deviation from the median (MAD-M) and the RAND disagreement index (Fitch et al., 2001; Phillips et al., 2014). The MAD-M is the average distance of a participant's rating from the group's median rating, it is preferred compared to the standard deviation because it does not give extra weight to extreme observations and it measures variation about the medians (Hutchings et al., 2005). The MAD-M analyses the extent of disagreement for each cue, item or statement. It is the average distance (for example on a 9 point Likert scale) of the respondents' ratings from the group's median rating (Hutchings et al., 2005). Whilst Hutchings et al. (2005) argue that the MAD-M is the best method, Murphy et al. (1998) argue that the interquartile range is more robust. Fitch et al. (2001) point out that the MAD-M is rarely used other than as a guide on what to focus on during a panel meeting. Following the development of the RAND/UCLA Appropriateness Method which only allows a maximum of 9 people on a panel, Fitch et al (2001) developed the RAND disagreement index, which allows for larger group panels. The RAND disagreement index is a measure of dispersion using the interpercentile range and the interpercentile range adjusted for symmetry using the formula: IPRAS = IPRr + (AI * CFA). IPRAS stands for (Fitch et al., 2001, p.60):

> Interpercentile Range Adjusted for Symmetry required for disagreement; IPRr is the Interpercentile Range required for disagreement when perfect symmetry exists; AI is the Asymmetry Index; and CFA is the Correction Factor for Asymmetry

Fitch et al. (2001) state that when ratings are symmetric then the interpercentile range needed to label an indication as disagreement is smaller than when they are asymmetric.

Core outcome set developers have determined participants' agreement on an outcome for inclusion in the core outcome set by using the percentage of participants scoring each outcome, for example Loughlin and Moore (1979)

advocated a consensus level of at least 51% agreement amongst participants, whereas Rosenthal (2012) recommends a consensus level of at least 70%, while Green et al. (1999) suggests 80%. Alternatively, Schmitt et al. (2011) used a consensus level of 60% and Bennett et al. (2012) used 75%.

The use of a consensus level of at least 70% has been used by many core outcome set developers to define consensus (Potter et al., 2015; Coulman et al., 2016; Egan et al., 2017; Millar et al., 2017). Meaning that at least 70% of respondents agree that the outcome should be IN/OUT of the core outcome set for a consensus to be 'reached'.

Thresholds for inclusion in a core outcome set have been specified by some researchers for example Wylde et al. (2015) implemented a threshold of at least 70% or more of participants scoring an outcome 7 to 9 (indicating the outcome to be critically important) and 15% or less scoring an outcome 1 to 3 (having limited importance) by both clinician and patient groups or at least 90% or more scoring an outcome 7 to 9 from any single panel for it to be included in the core outcome set. The 70/15% (70% or more participants score the outcome 7 to 9, and 15% or less score it 1 to 3) consensus definition suggests that the majority believe that the item should be in the core outcome set and only a small minority think it is of little or no importance (Williamson et al., 2017).

Defining consensus criteria is an important part of developing a core outcome set because a too accommodating criteria can result in too many outcomes therefore creating a long list of outcomes whereas a too stringent criteria risks excluding fundamental outcomes that may have otherwise been included (Williamson et al., 2017).

2.8 Why the eDelphi Method was Chosen

The methodology and practice of developing a core outcome set is under developed compared to clinical trial methodology (Gargon et al., 2014; Gorst et al., 2016a; Gorst et al., 2016b; Davis et al., 2018; Kottner et al., 2018) but the field continues to improve guidance by addressing essential methodological questions and uncertainties (Williamson et al., 2017; Kottner et al., 2018; COMET, 2019).

To maximise content validity the eDelphi method was used to develop the core outcome set. The eDelphi method was favoured over the other types of consensus methods for the following reasons:

- Remote participants who are geographically dispersed can take part
- Relatively low costs
- Anonymity and confidentiality maintained
- Dominance of strong personalities and/or those with authority do not influence other's opinions

The eDelphi method enables the views of many to be equally heard and it allows people who are geographically dispersed to take part at a relatively low cost with feasible logistics which is crucial because reliability increases as the number of respondents increase (Keeney et al., 2011). The surveys can also be completed remotely, thus allowing and hard to reach stakeholders to take part and international involvement. In contrast, the Nominal Group Technique and RAND/UCLA Appropriateness Method only facilitates smaller groups and it can be costly to bring international participants together.

The Delphi method elicits responses that are more conducive to independent opinion but allows participants to see other peoples' opinions without the dominance of strong personalities and/or those with authority. The successive rounds of repeated questioning keeps participants focused and helps elicit reasoning behind participants' responses. The performance of two or more rating rounds, such as those used in the Delphi and the Nominal Group Technique, increases the likelihood that there will be a convergence of opinion (Murphy et al., 1998). They can consider other peoples' opinions without dominance of individuals, therefore if a participant chooses to change their opinion or retain their original answer it is not caused by their desire to be seen as agreeing with domineering individuals or someone that is senior (Sinha et al., 2011). Skvoretz (1988) suggested that those with a higher status attempt to dominate the group thus influencing others judgement on a topic. The non-face-to-face successive survey approach employed by the eDelphi method reduces conformity compared to techniques that involve only face-to-face discussions, such as the Nominal Group Technique, the consensus development conference and the RAND/UCLA Appropriateness method. The

method allows for anonymous responses thus encouraging ‘true’ opinions because participants do not have to present their opinions in front of others and they are free from the dominance of peers.
Participants do not need to interact directly during the survey rounds therefore maintaining anonymity is more straightforward.

The eDelphi method which is recommended by COMET (2017) has been used by other core outcome set developers (Taylor et al., 2008 (OMERACT team) ; Schmitt et al., 2011 (HOME team) ; Sinha et al., 2012; Gargon et al., 2014; Coulman et al., 2016; Gorst et al., 2016a; Gorst et al., 2016b; MacLennan et al., 2017; Millar et al., 2017; Davis et al., 2018).

Various aspects required consideration before the eDelphi consensus study was undertaken, such as the choice of stakeholders on the panel, the survey items, the number of rounds, whether a face-to-face discussion took place and the definition of consensus. The considerations are discussed further in chapter 4.

2.9 Summary

Consensus methods were chosen to establish common agreement on what outcome domains and outcomes are core for research evaluations of interventions used for venous leg ulceration.
Informal methods are not appropriate because they are at risk of fundamental flaws such as participants being influenced by dominant individuals with powerful, intimidating personalities or individuals with authority. They lack a structured approach to the consensus process, whereas formal methods provide a structure whilst encouraging participants to consider a range of options and they allow for the synthesising of opinions.
The eDelphi method was used to establish consensus on the outcome domains and outcomes identified during the scoping review. The method enables the views of many to be equally heard and it allows people who are geographically dispersed to take part at a relatively low cost with feasible logistics. The inclusion of a diverse population is important so that the consensus on the outcome domains and outcomes is representative of all stakeholders.

The next chapter describes and discusses how the scoping review identified the outcome domains and outcomes for the consensus process which is discussed in chapter 4 and 5.

Chapter 3 Scoping Review (Stage 1)

3.1 Introduction

A scoping review was performed to identify what outcome domains and outcomes have been reported in RCTs and qualitative research.
This chapter begins with an overview of the different types of reviews. A rationale to why a scoping review was chosen as the method for identifying outcome domains and outcomes reported in RCTs and qualitative research is then provided.
The chapter goes on to describe and discuss the methods used in the scoping review which generated a list of candidate outcome domains and outcomes for the consensus process. The results of the scoping review are then reported. Finally, the process of grouping the outcomes into outcome domains and condensing the list of outcomes is explained.

3.2 Why a Scoping Review was Performed

The aim of the scoping review was to identify what outcome domains and outcomes have been reported in venous leg ulceration research. There were a number of approaches that could have been used and the following section discusses these approaches.
Some core outcome set developers start with a blank page and generate a list of outcomes by asking open questions (Sinha et al., 2012), others have performed a literature review to identify outcomes for the list of outcomes (Al Wattar et al., 2017).
There are different types of literature reviews, such as scoping reviews, systematic reviews, critical reviews and rapid reviews, which address different types of questions, and feature different methods including data extraction and synthesis, and quality assessment. Systematic, critical and rapid reviews use focused research questions, whereas scoping reviews use broad research

questions. The aim of a scoping review is to assess the volume and/or characteristics of the available literature in a particular field, identifying any gaps therefore a broad research question is used to generate breadth of coverage. Whereas a systematic review seeks to collate all the evidence using pre-specified eligibility criteria to address a specific research question, and they can produce an overall effect or finding, for example treatment effect (Higgins and Green, 2011). A scoping review can be performed prior to a systematic review to explore the extent of the literature without describing the findings in detail (Armstrong et al., 2011), identify the potential costs of a systematic review (Arksey and O'Malley, 2005), and assist in defining a more precise research question and inclusion criteria (Joanna Briggs Institute, 2015). A critical review generates conclusions concerning the research question and a rapid review finds the quality of the literature and direction of effect. The inclusion and exclusion criteria for systematic reviews and rapid reviews is defined prior to the search whereas the inclusion and exclusion criteria in scoping reviews is defined a priori and post hoc. It is recommended that the criteria is refined post hoc once the researcher becomes familiar with the literature (Levac et al., 2010).

Summarised information on the types of literature reviews are presented in Table 5 (Carnwell and Daly, 2001; Petticrew and Roberts, 2006; Grant and Booth, 2009; Brien et al., 2010; Khangura et al., 2012).

	Scoping review	**Systematic review**	**Critical review**	**Rapid review**
Research question	Broad research question(s)	Focused research question	Research question can be focused depending on the topic	Focused research question
Inclusion/exclusion criteria	Inclusion/exclusion developed *a priori* and *post hoc*	Inclusion/exclusion defined prior to the search	Inclusion/exclusion developed *a priori* and *post hoc*	Inclusion/exclusion defined *a priori*
Search strategy	Determined by time and scope constraints	Exhaustive and comprehensive search	Identifies the most significant literature in the field	Time restraints determine completeness of search
Quality assessment	Quality of study not a priority. Option to include critical appraisal	Critical appraisal required	No formal quality assessment. Evaluation can be according to contribution	Critical appraisal required
Data synthesis	Usually tabular with narrative commentary	Narrative with tabular accompaniment	Normally narrative, perhaps conceptual or chronological	Narrative and tabular
Conclusions	Identifies extent and range of research in a the field of interest and identifies gaps in the literature	Generates estimates of effect. Meta-analysis or meta-synthesis may also be done	Generates conclusions concerning the research question	Finds the quantity of the literature and direction of effect

Table 5 Differences between types of reviews

A scoping review was chosen as the method to identify the outcome domains and outcomes for the consensus process because it enables concepts in a field of interest to be 'mapped' out and outlines the breadth and nature of the evidence (Arksey and O'Malley, 2005). It allows for a more rapid underpinning of the key concepts (Mays et al., 2001). A scoping review can also assess the types of existing studies and find where they are located in advance of a systematic review (Petticrew and Roberts, 2006), finding any gaps in the literature and locating any previous systematic reviews on the topic.

Scoping reviews are becoming increasingly popular (Daudt et al., 2013; Tricco et al., 2016). In spite of this there remains an uncertainty over the definition and terminology of a scoping review (Colquhoun et al., 2014). There are different names applied to this type of review including; scoping review, scoping study, scoping exercise, systematic scoping review, scoping project, scoping report and evidence mapping. For the purpose of this PhD it is referred to as a scoping review.

In a web-based survey involving various stakeholders and a consultation phase to explore others' experience and perspectives on scoping reviews O'Brien et al. (2016) conclude that participants' consider scoping reviews to be systematic and transparent. However the researchers highlight that the small sample size of 54 participants as a limitation to their study.

Weaknesses of a scoping review include the potential for bias due to limitations in the rigour and duration of a review (Grant and Booth, 2009), and interpretation of the subject due to reviewers' research interests (Anderson et al., 2008). Scoping reviews have been criticised for focusing on breadth instead of depth (Tricco et al., 2016), however this was not a concern because breadth of evidence was useful for identifying as many outcomes that have been reported in venous leg ulcer research as possible.

Because the aim of the scoping review was to identify as many outcomes that have been reported as possible the quality assessment of the RCTs and qualitative studies was not required. Critical appraisal is optional for scoping reviews, whereas it is mandatory for systematic reviews which assess the validity of the findings of studies for example the assessment of the risk of bias (Higgins and Green, 2011).

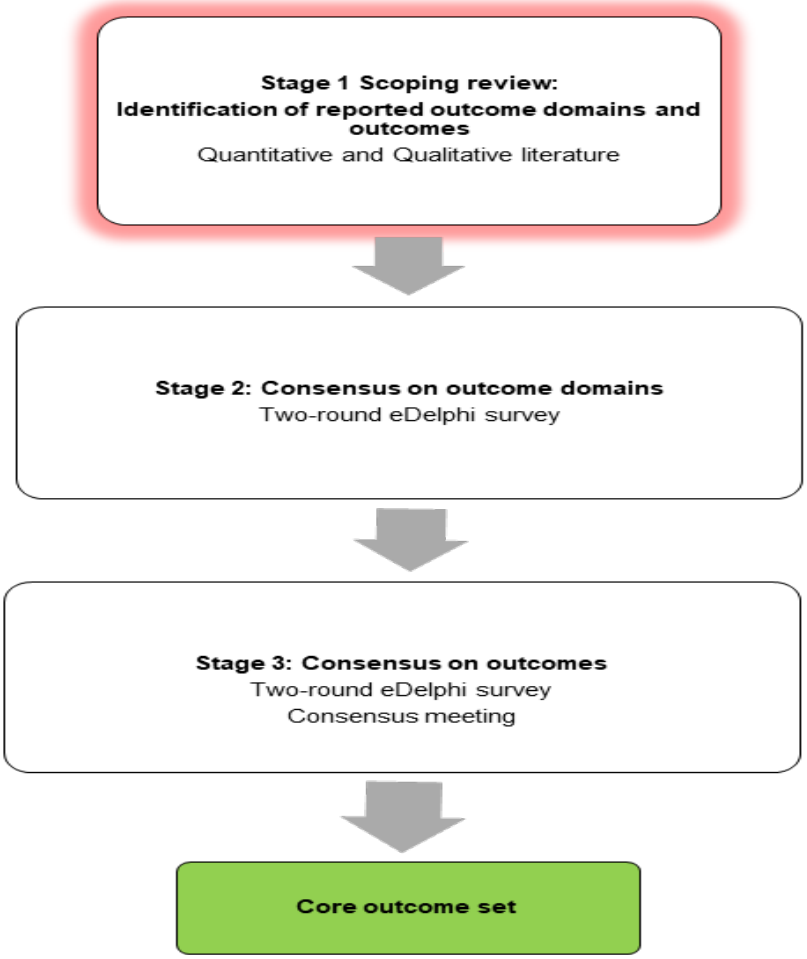
3.3 Aims

The aim of the scoping review was to identify what outcome domains and outcomes have been reported in RCTs evaluating treatments for people with venous leg ulceration. The scoping review also aimed to identify what outcomes have been identified by patients and carers in qualitative research. Both quantitative and qualitative research was searched to gain a broader insight into what outcome domains and outcomes have been reported. The definitions used in this PhD can be found in section 1.12.

3.4 Method

The overall methods used in this PhD are displayed in the flow chart below (Figure 4). The box highlighted in red is the stage that this chapter explains; the scoping review.

Figure 4 Methods flow chart.



Scoping reviews have been criticised for their lack of methodological guidance (O'Brien et al., 2016), therefore Levac et al's. (2010) adapted version of Arksey and O'Malley's (2005) framework for conducting a scoping review was utilised which provided a methodological structured approach to performing the review.

Levac et al's (2010) adapted version of Arksey and O'Malley's (2005) methodological framework contains six-steps:

- Step one: Identification of the research question
- Step two: Identification of relevant studies
- Step three: Study selection
- Step four: Charting the data
- Step five: Collating, summarising and reporting
- Step six: Consultation

Levac et al. (2010) updated and clarified areas of Arksey and O'Malley's (2005) framework. The adaptions made by Levac et al. (2010) are supported by Daudt et al. (2013) who concurrently evaluated Arksey and O'Malley's (2005) framework by performing a scoping review using the framework.

Levac et al. (2010) clarified step one of the framework on 'identification of the research question' by explaining that the question should be clearly explained, including its concept, population and health outcomes. The research question guides the search strategy, it can be broad but requires the inclusion of the study population, in this case people with venous leg ulcers. Using a broad question reduces the likelihood of appropriate articles being missed, however this can lead to an unmanageable number of articles (Arksey and O'Malley, 2005). If a large number of references are retrieved Arksey and O'Malley (2005) suggest that the parameters are changed once a sense of the volume and scope has been found. Additionally, Levac et al. (2010) suggest that the concept and health outcomes are specified in the research question.

Arksey and O'Malley (2005) state that the inclusion and exclusion criteria can be applied *post hoc* as the researcher becomes increasingly familiar with the literature. Levac et al. (2010) state that if limiting the scope of the search is unavoidable then justifications to why need to be provided and any limitations to the review should be acknowledged. Levac et al. (2010) state that the scope of the review should be guided by the research question and its purpose

therefore the team should have sufficient content and methodological expertise. When limiting the identification of the studies in step two is unavoidable, Levac et al. (2010) suggest that acknowledgment of any limitations and justifications is needed. Searching of the literature, refining the search strategy and reviewing the articles should be an iterative process. An iterative process is a process of repeated rounds or cycles to generate a final decision or result. Reviewers should meet at the beginning, during and in the final stages to discuss any challenges to the study selection and refine the search strategy if needed. Two reviewers should independently check the articles for inclusion, if any disagreements occur then a third reviewer will need to decide the final inclusion. The reviewing team should develop a charting form and decide which variables to extract. The data charting form should be continually updated. For the first five to ten included articles two reviewers should independently extract the data and compare the data charting forms to check for consistency. Qualitative content analysis is recommended for the charting of data.

The collating, summarising and reporting stage should be divided into three steps; analysis, reporting the results and finding meaning. Descriptive numerical summary analysis and qualitative thematic analysis should be used. The reported results should be related to the research question and meaning relating to the overall review purpose should be sought.

The consultation stage provides stakeholders with the opportunity to suggest additional insights. It allows for knowledge transfer and exchange by allowing additional sources of information and opinions to be offered by the stakeholders. The type of stakeholders involved in the consultation stage should be defined. How data will be collected, analysed, reported and integrated should be decided upon. Knowledge transfer and exchange with stakeholders should be facilitated.

The following sections describe the steps taken during the scoping review which were guided by Levac et al's. (2010) adapted version of Arksey and O'Malley's (2005) framework. The steps are broken into quantitative and qualitative research to show how the two types of research were searched, identified, charted and analysed.

3.4.1 Identification of the Research Question

The scoping review addressed the following questions:

Quantitative research search:

What outcomes have been reported in RCTs evaluating treatments for venous leg ulceration?

Qualitative research search:

What outcomes have been described in qualitative research on venous leg ulceration?

3.4.2 Identification of Relevant Studies

Because a large number of RCTs evaluating treatments for venous leg ulcers are included in the Cochrane Database of Systematic Reviews (CDSR) it was decided that RCTs within Cochrane reviews should produce an adequate number of articles. Cochrane reviews aim to collate all the evidence that suits the pre-specified eligibility criteria by regularly downloading from a variety of databases with sensitive search strategies (Higgins and Green, 2011), they search grey literature and hand searching is performed to optimise the collation of all the appropriate evidence. Unpublished studies are also assessed for inclusion in the Cochrane Review (Higgins and Green, 2011). Jadad et al. (1998) found Cochrane reviews to be more frequently updated and have greater methodological rigour compared to systematic reviews in paper-based journals. Jaded et al (1998) compared 36 Cochrane reviews with 39 systematic reviews and meta-analyses published in paper-based journals. Members of the research team and steering group were asked to identify additional relevant papers not identified through database searching. The members of the steering group have expertise in different aspects of leg ulceration and wound care research, including experience of consensus studies and core outcome set development. Their role in the research was to also support the development of the methods, verification of the interpreted results and support the development of the protocol and publications.

Quantitative research:

The Cochrane Database of Systematic Reviews (CDSR) was searched using the term 'venous leg ulcer*'.

Qualitative research:

The qualitative search strategy was updated post hoc because the first search generated a vast number (n=3259) of irrelevant articles therefore meaning the search strategy was too broad. The search strategy was then refined to include more specific concepts such as the different names given to venous leg ulcers and the types of qualitative literature e.g. interviews. The search strategy for the qualitative search can be found in appendix 1. The dates of the databases that were searched are as follows: Ovid MEDLINE 1946-2018, Scopus 1823- 2018, Ovid EMBASE 1980- 2018 and CINAHL 1960- 2018.
No date restrictions were applied to the searches but they were limited to English language publications due to lack of resources for translation services.
Articles not relevant to the review questions were excluded at this stage.
Potentially relevant articles were retrieved as full reports and checked against the selection criteria detailed in the next section.

3.4.3 Study Selection

RCTs recruiting people with open venous leg ulcers that assess the effectiveness of venous leg ulcer treatment were included. RCTs assessing interventions focusing on the primary or secondary prevention of venous leg ulcers were excluded.
Qualitative studies recruiting people with venous leg ulcers or their carers that include exploration of venous leg ulcer outcomes were included.
Date restrictions were not applied to the searches but they were limited to English language publications.
Levac et al. (2010) recommend that once the researcher is familiar with the literature then the inclusion/exclusion criteria is refined post hoc. The inclusion/exclusion criteria however did not need refining. When the RCTs were not available through the link on the Cochrane review reference section

the RCTs were searched using the University of Leeds' library database, Google scholar, and journal websites.

3.4.4 Charting the Data

The template shown in Table 6 was developed to chart the data extracted from RCTs. Data extracted from the RCTs was done before data was extracted from the qualitative studies. The template shown in Table 7 was developed to chart the data extracted from qualitative research. Tables 8 and 9 show examples of the extracted data from an RCT and a qualitative study using the templates.

Levac et al (2010) recommend that the charting of the data is an iterative process whereby the determination of which variables to collect is continually updated. Levac et al. (2010) also recommend that the charting form should be developed as a collective team which the team continually update. The data charting forms were developed with the research team, and continually updated to ensure that the correct variables were collected. The extracted data were inputted into Excel and then transferred to Microsoft Word.

In line with Levac et al's (2010) suggestion that two independent researchers should extract data from the first five to ten articles, data from the first 7 RCTs was independently extracted by two members of the research team (SH and SO'M), and then compared to check for consistency. An extract of the collected qualitative data was also checked by two members of the research team (SH and SO'M).

Table 6 Template for charting the data extracted from RCTs

Cochrane review identifier:	Author(s), year of publication, title of Cochrane review
RCT details:	RCT identifier (author(s), year of publication)
	Description of each outcome, verbatim as presented by the trial authors
	Reviewer interpretation (if different from the RCT's verbatim outcome) of the outcome was done to ensure it is understandable and demonstrates what it is that the RCT intended to measure in the context of the whole trial. Classification of the outcome into its outcome domain
	Whether the outcome was defined as primary or secondary by the RCT, or not clear
	Follow up period for each outcome
	Measurement instrument used to evaluate each outcome
	Unit of analysis measured e.g. ulcer or limb or person
	Comments including relevant information on the type of leg ulcer

Table 7 Template for charting the data extracted from qualitative research

Qualitative research identifier:	Author(s), year of publication
Details:	Description of each outcome, verbatim as presented by the authors
	Reviewer interpretation (if different from the article's verbatim outcome) of the outcome was done to ensure it is understandable and demonstrates what it is that the article intended in the context of the whole article. Classification of the outcome into its outcome domain
	Method e.g. semi-structured interview
	Comments including relevant information on type of leg ulcer and/or type of participant (carer/ patient)

RCT ID (year)	Outcomes (verbatim)	Outcomes (reviewer interpretation)	Primary or secondary	Follow up	Instrument [unit of analysis]	Comments
Armstrong et al (1997) *a*	**"Mean wear time"** "difference between the groups"	Wear time (number of days). Difference in the number of days worn between the groups.	1	6 weeks or until healing	Instrument not specified [patients randomised].	Mixed aetiology (venous= 36/44). Assessment periods not clear.
Armstrong et al (1997) *a*	"median decrease in ulcer area"	Decrease in ulcer area (mm^2 and percentage). (Relative decrease in ulcer area).	2	6 weeks or until healing	Photography and planimetry [patients]	Mixed aetiology (venous= 36/44). Assessed on enrolment, on days 14 and 28 and on completion.
Armstrong et al (1997) *a*	"achieved seven-day wear time" "estimated percentage difference"	Number and percentage of patients that achieved 7-day wear time. Percentage difference between groups for the achievement of 7-day wear.	2	6 weeks or until healing	Yes or no question	Mixed aetiology (venous= 36/44). Assessment periods not clear.
Armstrong et al (1997) *a*	"Patient comfort….on removal of dressing"	Level of pain on dressing removal.	2	6 weeks or until healing	6 point scale (0=none, 1= mild, 2= moderate, 3=severe, 4=excruciating, 5= unable to respond)	Mixed aetiology Mixed aetiology (venous= 36/44). Assessment periods not clear.
Armstrong et al (1997) *a*	"Level of pain on removal of dressing"	Level of pain on dressing removal.	2	6 weeks or until healing	6 point scale (0=none, 1= mild, 2= moderate, 3=severe, 4=excruciating, 5= unable to respond)	Mixed aetiology (venous= 36/44). Assessment periods not clear.

Table 8 Example of data extracted from an RCT

Study ID (year)	Outcomes (verbatim)	Outcomes (reviewer interpretation)	Method	Comments
Heinen et al 2007	“sleeping problem….itching of the wound”	Sleep deprivation Itching	Interview	Venous leg ulcers only. 141 patients.
Heinen et al 2007	“sleeping problem….wound leakage”	Sleep deprivation Leakage	Interview	Venous leg ulcers only. 141 patients.
Heinen et al 2007	“compression therapy….difficulties in putting-on and taking off elastic stockings”	Ease of applying stockings Ease of removing stockings	Interview	Venous leg ulcers only. 141 patients.
Heinen et al 2007	“compression therapy….painful”	Pain (related to compression)	Interview	Venous leg ulcers only. 141 patients.
Heinen et al 2007	“compression therapy….too tight or coming loose”	Comfort of compression	Interview	Venous leg ulcers only. 141 patients.
Heinen et al 2007	“compression therapy….warm and itching”	Itching (related to compression)	Interview	Venous leg ulcers only. 141 patients.

Table 9 Example of data extracted from a qualitative study

3.4.5 Collating, Summarising and Reporting

Arksey and O'Malley (2005) and Levac et al. (2010) state that a descriptive numerical summary and a thematic analysis should be used when collating and summarising the data. Arksey and O'Malley (2005) provide guidance on the numerical summary but stated it lacked adequate guidance on thematic analysis. Levac et al (2010) acknowledge this omission but do not provide further guidance other than stating that the analytical stage may require qualitative content analytical techniques. Levac et al. (2010 p. 6-7) go on to refer to a paper by Ehrich et al. (2002) and wrote "In our experience, this analytical stage resembled qualitative data analytical techniques, and researchers may consider using qualitative content analytical techniques [10]", 10 being a reference for Ehrich et al' s. (2002) paper but on investigation the paper does not appear to provide usable guidance on qualitative content analysis.

With Levac et al's (2010) recommendation to use qualitative content analysis in mind, it was decided that the framework approach would be adopted, therefore elements of Ritchie and Spencer's (1994) qualitative data analysis framework was used. Although Ritchie and Spencer's (1994) framework is initially for material collected through qualitative methods, for example interviews, it was used for guiding the identification of connections between data extracted from the RCTs and qualitative research. The framework contains five key stages:

1. Familiarisation
2. Identifying a thematic framework
3. Indexing
4. Charting
5. Mapping and interpretation

The key stages that were useful for the scoping review were 'identifying a thematic framework, 'charting', and 'mapping and interpretation'. The researcher identifies key concepts and themes during the 'identifying a thematic framework' stage producing a thematic framework. The researcher

needs logical and intuitive thinking whilst making decisions on the meaning of the data and if there are any connections between data. When the extracted data was identified during the scoping review the meaning of many outcomes had to be interpreted in the context of the papers because they were not consistently described and reported. The extracted outcomes from each paper were recorded verbatim and an interpretation in the context of the whole paper was included which was checked by every member of the research team to ensure the interpreted outcome reflected the outcome reported in the paper. Themes were constantly identified as data were extracted and charted.

Extracted data were rearranged during the 'charting' stage to build a picture as a whole and to identify the outcome domains. The outcome domains recommended by OMERACT (2014), see Figure 1 (p. 18), were used to guide the grouping of the outcomes under each outcome domain. Because the filter was applied to a different healthcare area compared to OMERACT's original use in rheumatology it meant some outcome domains were not included in the filter or they were worded differently compared to those outlined in the filter. For example 'healing' was identified as an outcome domain in venous leg ulceration research during the scoping review but it is not part of OMERACT's filer 2.0.

During the 'mapping and interpretation' stage the extracted data as a whole was sifted and charted according to the outcome domains. Ritchie and Spencer (1994) suggest the charts include headings and subheadings obtained from the thematic framework. Headings were included above each section to identify each outcome domain and the specific outcomes within it.
The list was continually sifted and rearranged to produce a workable document that could then be condensed into a more manageable list of outcome domains and outcomes ready for the consensus process.

3.4.6 Consultation

A session was held within the European Wound Management Association (EWMA) conference in May 2017. Patient organisation representatives, various healthcare professionals and researchers that attended the session

were consulted in the planning phase of the consensus methods (discussed in chapter 4).

Participants had the opportunity to provide qualitative comments and suggest additional outcomes during the consensus process in stages two and three of the research (discussed in chapters 4 and 5). Consultation with the participants built upon the outcomes extracted from the scoping review and offered greater meaning and context expertise.

3.5 Results

3.5.1 Scoping Review Results

The search of the Cochrane Database of Systematic Reviews identified 48 Cochrane reviews, of which 25 Cochrane reviews were relevant for inclusion. The search identified 23 Cochrane reviews that were not relevant for inclusion because they were either protocols, or they were not venous leg ulceration related. The 25 Cochrane reviews contained 535 RCTs.
The search for qualitative studies identified 667 studies and two studies were suggested for inclusion by members of the research team and steering group. After duplicated RCTs and qualitative studies were removed and records were screened, 308 records remained. Fifty non-venous leg ulcer related articles were then removed which resulted in 258 records for inclusion, of which 230 were RCTs and 28 were qualitative studies.

The results of the scoping review article search are displayed in Figure 5.

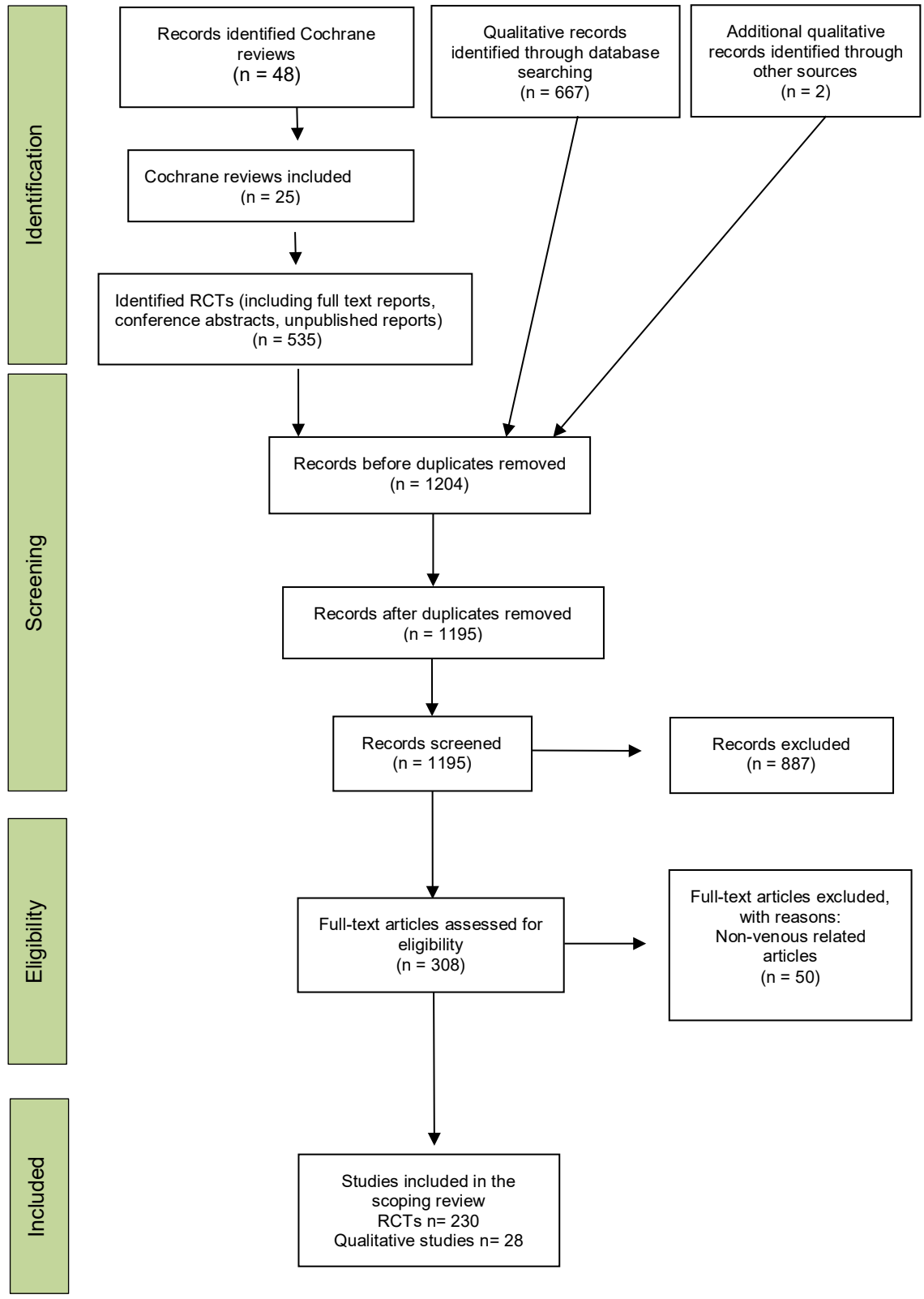


Figure 5 Results of the scoping review article search

The initial extraction of the outcomes yielded 1180 potential outcomes pre-deduplication. The first table in appendix 2 displays the outcomes that appeared more than once. It displays how many times they appeared across the RCTs. In addition to the outcomes in the table there were 460 outcomes that appeared once across the RCTs and 108 outcomes relating to adverse events, for example “digestive upset”. The outcomes that appeared once are not included in the appendix due to limits on the maximum length of the thesis.

Following deduplication 807 outcomes remained from 230 RCTs and 15 outcomes remained from 28 qualitative studies. The list in appendix 2 displays the outcomes extracted from qualitative studies. The references for the included RCTs and qualitative studies can be found in appendix 3.

Twenty-four percent (54/230) of the RCTs included in the scoping review stated an outcome or outcomes at the start of the paper but failed to report them in the results. Four percent (9/230) of the RCTs introduced an outcome in the discussion when it had not been stated in any other part of the paper. Further discussed in chapter 6.

Forty-five percent (63/140) of RCTs did not provide a definition of healing. Nineteen percent (44/230) of the RCTs failed to provide any information on the instruments used to measure outcomes. Seventy-four percent (83/112) of the RCTs that measured an outcome relating to quality of life, signs and symptoms (e.g. pain, discomfort and heavy leg sensation) used trial specific scales.

3.5.2 Grouping the Outcomes into Outcome Domains

The core areas of OMERACT’s filter 2.0 displayed in Figure 1, chapter 1 (Boers et al., 2014) was used to help guide the grouping of the outcomes into outcome domains. The core areas of the filter 2.0 include; death, life impacts resource use and pathophysiological manifestations. To begin with, the outcomes extracted during the scoping review were grouped under the filter 2.0’s four core areas. Once the outcomes were listed under the core areas with the addition of two outcome domains; healing and performance of the intervention, they were organised into outcome domains. The outcomes relating to

symptoms which were grouped under ‘pathophysiological manifestations’ were reorganised into three outcome domains; ‘patient reported symptoms’, ‘clinician reported symptoms’ and ‘carer reported symptoms’. The outcomes within the core area ‘pathophysiological manifestations’ were broken down into ‘clinical signs’ and ‘clinical measurement’. Resource use outcomes were separated into outcomes relating to supplies and outcomes relating to clinician time. The outcomes relating to healing were grouped together and the outcomes relating to performance of the intervention were also grouped together. The outcomes were classified into their outcome domains as they were charted (see Table 6), for example the outcome ‘time to complete healing’ was classified under the outcome domain ‘healing’. The 11 outcome domains are:

1. Healing
2. Patient reported symptoms
3. Clinician reported symptoms
4. Carer reported symptoms
5. Life impacts
6. Clinical signs
7. Clinical measurement
8. Performance of the intervention
9. Resource use: supplies
10. Resource use: clinician time
11. Adverse events

Although symptoms are things that are felt/perceived by the patient, the two outcome domains; ‘clinician reported symptoms’ and ‘carer reported symptoms’ were included. There are times when a clinician and/or carer will be required to report on a person’s symptoms, for example a person may not be able to articulate or express whether s/he has pain and to what extent, therefore a clinician or carer may need to report on the person’s pain.
The scoping review also identified that RCTs report on outcomes, such as pain, measured by clinicians and carers.

Outcome domains contain many different outcomes. This is highlighted by the outcome domain ‘healing’ which contained 111 different outcomes. The other outcome domains also contained a large number of outcomes. The outcome domain symptoms (including patient, clinician and carer reported symptoms)

contained 109 outcomes, life impacts contained 30 outcomes, clinical signs contained 88 outcomes, clinical measurement contained 184 outcomes, performance of the intervention contained 58 outcomes, resource use contained 52 outcomes and adverse events contained 190 outcomes.
The 111 outcomes on healing are presented in Table 10. All of the extracted outcomes that appeared more than once are presented in appendix 2.

Table 10 Outcomes within the outcome domain 'healing' identified during the scoping review

1. Number of patients that completely healed
2. Number of ulcers that completely healed
3. Number of healed ulcers in the case of multiple ulcers
Number of ulcers completely healed at… 4. 6 months 5. 12 months
6. Percentage of completely healed ulcers
Percentage of patients with healed legs 7. At 12 weeks 8. At 24 weeks 9. Per month
10. Percentage of patients completely healed
Percentage of healed ulcers…. 11. Per fortnight 12. Per month
13. Time to healing (not specified)
14. Number of weeks to complete healing
15. Cumulative healing times
16. Number of days to healing
Number of patients that achieved healing within each quintile: 17. "≤25 days" 18. ">25 days & ≤46 days" 19. ">46 days & ≤82 days" 20. ">82 days & ≤127 days" 21. ">127 days & ≤263 days"
22. Percentage of ulcers healed per week
23. Number of ulcer healed per week

24. Percentage healed at each visit
25. Number of limbs with complete healing
26. Percentage of limbs with complete healing
27. Relative risk of ulcer closure at any time point
Relative risk of healing at… 28. 12 weeks 29. 6 months
30. Residual area remaining
31. Percentage of the remaining area at the end
32. Proportion of healed ulcer within 90 days
33. Number of ulcers healed within 90 days
34. Proportion of healing within 180 days
35. Number of ulcers healed within 180 days
36. Number of ulcer free days
37. Number of weeks patients were free from ulcers
38. Number of ulcers that remained healed
39. Number of patients with an improvement in wound score/rating
40. Percentage reduction in ulcer area
41. Percentage reduction in ulcer area over time
42. Percentage reduction in ulcer area per week
43. Percentage decrease in ulcer size
Percentage reduction in ulcer size… 44. Per week 45. Per day
Percentage change in ulcer area….. 46. Per week 47. Over time
48. Reduction in ulcer diameter
49. Rate of healing cm^2 per day
50. Healing rate mm^2 per day
51. Rate of healing over time
52. Closure rate (cm^3) per day
Change in ulcer area…… 53. cm^2 54. mm^2

Change in ulcer area…
55. mm^2 per day
56. cm^2 per day
Reduction in ulcer area…
57. cm^2
58. mm^2
59. Reduction in ulcer area (cm^2) per week
60. Decrease in ulcer area per fortnight
61. Rate of healing per week cm^2
62. Rate of healing per week cm
63. Rate of healing per week cm^2
64. Rate of healing per week mm
65. Change in ulcer size per week
66. Change in surface area
67. mm^2
68. Reduction in ulcer area per week cm^2
69. Reduction in ulcer area per day
70. Relative change in total surface area
71. Relative rate of ulcer closure
72. Reduction in volume cm^3
73. Percentage reduction of ulcer volume per week
Relative change in…
74. Length
75. Width
76. Volume
77. Change in length cm^2
78. Change in width cm^2
79. Change in ulcer volume
80. Change in ulcer depth (cm)
Percentage of surface area healed
81. per week
82. Percentage of healing per week
At least 75% ulcer closure….
83. mm^2
84. Number of days till at least 75% reduction in ulcer area
85. Percentage of patients with 50% reduction in ulcer area
86. Number of days till at least 50% reduction in ulcer area

87. Incidence of at least 50% reduction in ulcer area
88. Reduction in daily ulcer radius (mm)
Linear healing rate per week…. 89. mm 90. cm 91. cm^2
92. Reduction in length of the ulcer
93. Reduction in width (cm) of the ulcer
94. Relative reduction in ulcer volume
95. Healing as a proportion of the baseline ulcer circumference
96. Number of patients showing a reduction in ulcer area relative to baseline
97. Reduction in the Gilman method result
98. Change in Gilman index score
99. Change in the healing index (mm)
100. Increase in the healing index
101. Percentage of healed ulcer area per fortnight
102. Percentage of ulcers that decreased by 40% or more
103. Number of days- percentage healed (i.e. 30% healed at day 70)
104. Percentage of patients that failed to heal/ remained unhealed
105. Number of patients whose ulcers were still open at 24 weeks
106. Number of days to at least 50% epithelialisation
107. Percentage of epithelializing tissue
108. Percentage of ulcers with an increase in epithelising tissue
109. Percentage change in epithelializing tissue
110. Percentage of ulcer surface covered with re-epithelialisation
111. Change in condition score: epithelialisation

3.5.3 Condensing the List of Outcomes

How to present the outcome data appropriately was considered because retaining each outcome would lead to an unmanageable list of potential outcomes for the consensus processes to follow. The 822 outcomes were condensed to produce a manageable list that could be entered into the consensus process.

Table 11 demonstrates how some of the outcomes within the healing outcome domain were condensed. The outcomes in column 1 are the outcomes extracted during the scoping review. The same outcomes were then rearranged into groups in column 2. The unit of randomisation was used for some of the healing outcomes, and other outcomes were grouped into binary/categorical, continuous or time to event. The condensing process also enabled the detection of any duplicated outcomes which were then removed from the list. The outcomes in column 3 contain the condensed outcomes for the consensus process.

The condensed list of outcomes was then reviewed and agreed by members of the steering group.

Although the list went through the condensing process, 120 outcomes still remained. Due to the vast number of extracted outcomes it made it difficult to reduce the list any further without making judgements on what should be removed which could have introduced researcher bias because a subjective decisions on which outcomes to remove from the list would have been made.

Column 1: Extracted outcomes from RCTs and qualitative research. Grouped under each outcome domain.	Column 2: Grouping process	Column 3: Candidate outcomes to be included in the eDelphi (dependent upon whether the outcome domain was rated as core in the stage 2 eDelphi)
	Unit of randomisation: patient	
1. Number of patients that completely healed	1.Number of patients that completely healed	Number of patients that completely healed
2. Number of ulcers that completely healed	7. Percentage of patients completely healed	Percentage of patients completely healed
	Unit of randomisation: leg	
3. Number of healed ulcers in the case of multiple ulcers	6. Percentage of patients with healed legs at a specified time point e.g. At 12 weeks At 24 weeks Per month	Percentage of limbs with complete healing
4. Number of ulcers completely healed at… 6 months 12 months	18. Percentage of limbs with complete healing 17. Number of limbs with complete healing	Number of limbs with complete healing
	Unit of randomisation: ulcer	
5. Percentage of completely healed ulcers	2. Number of ulcers that completely healed within the trial 4. Number of ulcers completely healed at specified trial time points: 6 months 12 months	Number of ulcers that completely healed

Column 1: Extracted outcomes from RCTs and qualitative research. Grouped under each outcome domain.	Column 2: Grouping process	Column 3: Candidate outcomes to be included in the eDelphi (dependent upon whether the outcome domain was rated as core in the stage 2 eDelphi)
6. Percentage of patients with healed legs At 12 weeks At 24 weeks Per month	15. Number of ulcers healed per week 13. Number of patients that achieved healing within each quintile: "≤25 days" ">25 days & ≤46 days" ">46 days & ≤82 days" ">82 days & ≤127 days" ">127 days & ≤263 days" 24. Number of ulcers healed within 90 days 26. Number of ulcers healed within 180 days 3. Number of healed ulcers in the case of multiple ulcers	Number of ulcers healed per week Percentage of completely healed ulcers

Table 11 Example: condensing the list of outcomes within the outcome domain 'healing'

3.6 Summary

The scoping review highlights the vast number and variety of outcomes that have been reported in RCTs on interventions to treat venous leg ulceration. The results of the review reinforce the need for the standardisation of outcomes in the form of a core outcome set for use in research evaluations of interventions used for venous leg ulceration

The scoping review provided the foundation to the development of a core outcome set by generating a comprehensive list of candidate outcome domains and outcomes for the consensus process. The consensus process is described and discussed in the next two chapters.

Chapter 4 Consensus Process for Identifying Core Outcome Domains (Stage 2)

4.1 Introduction

The purpose of the stage two consensus process was to identify which of the candidate outcome domains extracted during the scoping review are core to stakeholders for research evaluations of interventions for venous leg ulcers.

The chapter will begin by exploring the ways in which terms are defined by core outcome set developers and guideline initiatives before presenting the definitions in this PhD. It will then go on to explain the methods used to gain consensus on the outcome domains. Finally, the results of the consensus process will be presented.

4.2 Definitions

There is no consensus on the definitions to use in the development of core outcome sets (Boers et al., 2014; Prinsen et al., 2014). It appears that researchers are using different terminologies for the same concept. Table 12 presents the different ways in which people define core outcome sets, outcome domains, and outcomes. The table demonstrates how terms vary among core outcome set developers and guideline initiatives. The table contains verbatim quotes from a small sample of core outcome set developers and core outcome set guideline initiatives displaying their definitions and/or examples of outcome domains and outcomes.

Table 12 How terms have been defined and used by other core outcome set developers and guideline initiatives

	Definition and/or example			
Author	**Outcome domain/domain**	**Outcome**	**Outcome measurement**	**Set name**
Alkhaffaf et al. (2017)	"**Outcome domain**….A collection of 'outcomes' which share common features, e.g. the outcome domain 'respiratory complications' would include outcomes such as 'pleural effusion', 'hospital-acquired pneumonia' and 'atelectasis'" (p.3)	"A unique endpoint which attempts to describe health-related changes that occur secondary to a therapeutic intervention, e.g. hospital-acquired pneumonia" (p.3)	"A method or tool used to measure an 'outcome' or an 'outcome domain'" (p.3)	Core Outcome Set: "An agreed minimum set of outcomes that should be measured and reported in all trials in a specific condition"
OMERACT Boers et al. (2014)	"(Sub)**Domain**…Component of Core Area: a concept to be measured, a further specification of an aspect of health, categorized with a Core Area" (p.749). Example: quality of life, loss of ability to work, societal (resource use), individual (resource use), biomarkers and organ function. "Core Areas are broad concepts consisting of a number of more	"Any identified result in a (Sub)Domain arising from exposure to a causal factor or a health intervention…Generic word that has been used with different definitions; has often been used interchangeably with "Outcome Measure" and "Endpoint" (p.749)	"A measurement instrument chosen to assess Outcome. The result of measurement (recently termed 'specific metric' [33]) can be expressed as change, as end results, as cumulative results, or as "time to event" in a (Sub)Domain." (p.749) Example: "in pain measurement, the instrument could be a visual	Core Domain Set: "…minimum set of Domains and Subdomains necessary to adequately cover all Core Areas, that is, adequately measure all relevant concepts of a specific health condition within a specified setting. Describes what to measure. Currently, the COMET

	specific concepts called Domains." (p.749). Includes: Death, life impact, resource use/economical impact, pathophysiological manifestations.		analog scale, and outcome could be an improvement on that scale" (p.749) 33 (Zarin et al., 2011)	initiative uses the term "Core Outcome Set" for this concept, OMERACT has decided not to adopt this term, as there is no consensus on its technical definition." (p.749)
Williamson et al. (2017) columns 1 to 3 COMET (2019) column 4	"**outcome domains**, constructs which can be used to classify broad aspects of the effects of interventions, e.g. functional status." (p.11)	"Outcomes from multiple domains may be important to measure in trials, and several outcomes within a domain may be relevant or important. Initially researchers create outcome domains for each outcome to be grouped into" (p.11)	"Different outcomes may be measured by a single question, a questionnaire, a performance based test, a physical examination, a laboratory measurement, an imaging technique, and so forth. A variety of either definitions, measurement instruments or devices is often found to be used for the same outcome" (p.31)	"A "Core Outcome Set" is an agreed minimum set of outcomes or outcome measures. It is a recommendation of 'what' should be measured and reported in all trials in a specific area. Researchers also need to consider 'how' these outcomes should be measured, and work is ongoing to develop "Core Outcome Measurement Instrument Sets", which will include details on the

				instruments or tools to use to measure the outcomes in a Core Outcome Set." (http://www.comet-initiative.org/)
COSMIN (2018)	Not specified	"An outcome refers to what is being measured. It is also referred to as a construct or domain. In the context of a clinical trial it refers to what is being measured on trial participants to examine the effect of exposure to a health intervention."	"An outcome measurement instrument refers to how the outcome is being measured. It is a tool to measure a quality or quantity of the outcome. The tool can be a single question, a questionnaire, a score obtained through physical examination, a laboratory measurement, a score obtained through observation of an image, etcetera."	Core Outcome Set "A COS is a consensus-based agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population; it is a recommendation of what should be measured and reported in all clinical trials."
Egan et al. (2017)	**Domain** Example: "Measures of pregnancy preparation" (p.1193)	Example: "Healthcare professional review prior to conception" "Thyroid function at first antenatal visit"		Core Outcome Set "It represents a minimum that should be collected and reported, but does not restrict researchers from adding

		"BP at first antenatal visit First trimester HbA1c" (p.1193)		additional outcomes at their discretion." (p.1191)
Kirkham et al. (2016)	Not specified	Not specified	Not specified	Core Outcome Set "A COS describes what should be measured in a particular research or practice setting, with subsequent work needed to determine how each outcome should be defined or measured" (p.3)
Millar et al. (2017)	Example: "1. Medication appropriateness (potentially inappropriate prescribing)" (p.9) "7. Admissions to hospital (and associated costs)" (p.9)	"• Number of prescribed medicines" (p.9) (under the "outcome domain" Medication appropriateness) "• Accident and emergency (A&E) visits to hospital (and associated costs)" (p.9) (under the "outcome domain"	"'how' outcomes could be measured (i.e. the identification of different measurement instruments used to measure the same outcome)" (p.9)	Core Outcome Set "A COS is a list of outcomes which should be measured and reported, as a minimum, in all effectiveness trials pertaining to a specific health area, thereby facilitating comparisons of outcomes

		Admissions to hospital (and associated costs)"		between studies and evidence synthesis" (p.9)
Prinsen et al. (2014)	See column 2	"An outcome refers to what is being measured, also referred to as a concept, construct, or (sub)domain. In the context of a clinical trial it refers to any identified result in an outcome arising from exposure to a causal factor or a health intervention (the OMERACT definition refers to '(sub)domain' whereas the HOME definition refers to 'outcome domain')." (p.4)	"An outcome measurement instrument refers to how the outcome is being measured (the tool used to assess the outcome). An outcome measurement instrument can be a single question, a questionnaire, a performance-based test, a physical examination, a laboratory measurement, an imaging technique, and so forth (the HOME definition refers to 'outcome measure')." (p.4)	Core Outcome Set "A COS is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. A COS includes all relevant outcomes of a specific health condition within a specified setting (the OMERACT definition refers to 'core domain set' whereas the HOME definition refers to 'core outcome domains')." (p.4)
HOME Schmitt et al. (2011)	"Core sets of **outcome domains** (concepts to be measured) constitute an agreed minimum set of outcome domains to be measured. Outcome	Not defined	"Core sets of outcome measurement instruments constitute an agreed set of measurement instruments to	Core outcome set "consensus-derived minimum sets of outcomes to be assessed in a specific

Schmitt et al. (2015)	domains are aspects of disease, such as health-related quality of life, symptoms, clinical signs, productivity loss, or disability. Outcome domains relate to "what" should be measured" (p.25)		assess the core outcome domains. Outcome measurements relate to "how" to measure an outcome domain (measurement method, items, and quantification of response)." Example: "Psoriasis Area Severity Index (EASI) or the objective Scoring Atopic Dermatitis index for atopic eczema." (p.25)	situation" (Schmitt et al., 2015, p.1) "It was specified that outcomes included in the core set for eczema trials "should be assessed routinely in every clinical trial, but not necessarily as a primary outcome'' and that those outcomes included into the core set for clinical recordkeeping ''should be assessed routinely at every patient visit in routine practice''." (Schmitt et al., 2011, p.629)

Many core outcome set developers and guideline initiatives use the key concept ‘core outcome set’ (Sinha et al., 2012; Harman et al., 2013; Prinsen et al., 2014; Eleftheriadou et al., 2015; Hopkins et al., 2015; Potter et al., 2015; COMET, 2016; Kirkham et al., 2016; Alkhaffaf et al., 2017; Egan et al., 2017; Millar et al., 2017; Schaap et al., 2017; COSMIN, 2018; Sahnan et al., 2018; Van den Bussche et al., 2018). However, OMERACT (Boers et al., 2014) use the term “Core Domain Set” and state that they decided not to adopt the term “Core Outcome Set”. Whereas Turk et al. (2003, IMMPACT) use the term ‘core outcome domains’ in their study which developed core outcome domains for chronic pain in clinical trials. HOME (Schmitt et al., 2015) refer to core outcome sets stating that there are two levels that need to be differentiated; core sets of outcome domains and core sets of outcome measurement instruments. The definition of a core outcome set makes a distinction between ‘what to measure’ and ‘how to measure’. HOME (Schmitt et al., 2015) define a core set of outcome domains as a “minimum set of outcome domains that should be assessed” (p. 27). HOME also use the term ‘domain’ which they define as “The concept to measure…Example: clinical signs of atopic eczema” (p.27). Thus suggesting that the terms ‘outcome domain’ and ‘domain’ hold the same meaning.

Although there have been slight variations in the definitions (i.e. core domain set; core outcome domain set) between research studies, they all produce an agreed standardised set of outcomes which should be, as a minimum, measured and reported in all health related trials or other forms of research which evaluate treatment effectiveness for a given indication (COMET, 2016).

The different terminologies used by core outcome set developers and guideline initiatives posed challenges in the development of the definitions used in this PhD. As recommended by COMET (2019) who suggest that researchers should clearly define their terms; terms are defined in Table 1 (section 1.13) and in the following paragraphs. Many discussions took place amongst the research team to discuss how an outcome domain and outcome would be

defined. It was important to establish definitions that are not only relevant to core outcome set terminology but also to venous leg ulceration research.

A core outcome set in this PhD is defined as:

> An agreed standardised set of outcomes which should be, as a minimum, measured and reported in all RCTs or other forms of research which evaluate treatment effectiveness for a given indication (COMET, 2019). It includes *what* outcome domains and outcomes should be measured and *how* the outcome domains and outcomes should be measured.

An outcome domain has been defined by others as a collection of outcomes with common features (Alkhaffaf et al., 2017), and as a "Component of Core Area: a concept to be measured, a further specification of an aspect of health, categorized within a Core Area" (Boers et al., 2017, p. 29). The core areas being; Death, Life Impact, Resource Use/Economical Impact and Pathophysiological Manifestations (Boers et al., 2017). Schmitt et al. (2019) state that "An example of an outcome domain is Quality of Life, which would contain any outcome or measure that assessed quality of life, irrespective of the actual instrument used" (p. 5). The question of how broad or narrow an outcome domain should be remains problematic (Kottner et al., 2018).

An 'outcome domain' in this PhD is defined as:

> This relates to *what* is being measured. Outcome domains are broad, descriptive categories under which several, more specific, outcomes might be grouped. An example of an outcome domain is 'healing'.

The definition of an outcome domain was chosen because it reflects the groups of outcomes reported in venous leg ulceration RCTs which were identified during the scoping review. An outcome domain can contain many different outcomes (an example of this can be found in section 3.5.2).
The term 'outcome' has been defined as "Any identified result in a domain or Sub-domain arising from exposure to a causal factor or a health intervention" (Boers et al., 2017, p. 34), and as "a measurement or observation used to capture and assess the effect of treatment such as assessment of side effects

(risk) or effectiveness (benefits)" by Williamson et al. (2017, p. 1). Prinsen et al. (2014) state that an outcome refers to '*what* is being measured' and state that it can be referred to a concept, construct, or (sub) domain. However COSMIN (2018) states that a measurement instrument tool can also be a single question, thus suggesting a single outcome written as a single question, for example; Number of ulcers that completely healed in a trial period, is an outcome as well as an outcome measurement instrument. The outcome would, however, require a definition of what is meant by 'healed' and an accompanying measurement instrument (e.g. planimetry).

A single outcome domain may contain many defined outcomes because different methods of aggregation, time-points and measures are used (Mayo-Wilson et al., 2017). The method of aggregation for a given outcome is the procedure for estimating the treatment effect such as whether the outcome is regarded as categorical, continuous or a time-to-event variable. Time-point refers to the length of follow-up, and measures refer to the instrument used to measure an outcome domain, including the name of the instrument or questionnaire (e.g. Eczema Area and Severity Index) and the total score or subscale scores to be analysed (Mayo-Wilson et al., 2017). Mayo-Wilson et al. (2017) argue that core outcome sets may not have the intended impact if the outcomes are not completely defined, for example researchers need to completely define 'healed' in their trial. After analysing ClinicalTrials.gov data, Zarin et al. (2011. p. 858) recommend that four levels of specification are presented in the reporting of outcome measures, these being:

Level 1: Outcome domain (e.g. anxiety)

Level 2: Specific measurement (e.g. Hamilton Anxiety Rating Scale)

Level 3: Specific metric to characterize each participant's results (e.g. change from baseline at specified time)

Level 4: Method of aggregating data within each group (e.g. a categorical measure such as proportion of participants with a decrease greater than or equal to 50%)

An ‘outcome’ in this PhD is defined as:

> This also relates to *what* is being measured. An outcome should be a precisely defined method of assessing the effectiveness (benefit) or adverse effects (risk) of a healthcare intervention (Williamson et al., 2017). Where the outcome domain is defined as ‘healing’, examples of related outcomes could include: time to healing; the number of ulcers completely healed at 3 months, or; the change in ulcer surface area relative to baseline at 3 months.

4.3 Engaging with Potential Stakeholders

An open session was held at the EWMA conference in Amsterdam on the 4th May 2017. Information on the content of the session was made available in the programme handbook.

Fifty-two people attended the session, a show of hands indicated that the audience members included; patient organisation representatives, vascular surgeons, physicians, dermatologists, podiatrists, nurses, sociologists, and researchers.

The session aimed to inform delegates about the results of the scoping review and share information on the proposed consensus methods. An overview of core outcome sets, the research and its progress was presented to the audience. Presentation of the results of the scoping review, and the proposed consensus methodology was then delivered. The audience members were then invited to ask questions.

Questions and discussion points were raised by members of the audience. The questions and discussion points were taken away from the session and discussed with the research team. Responses to the questions and discussion points were published in a report in the EWMA journal (Hallas et al., 2017). The responses to the questions and discussion points are presented below:

It was discussed that the participants to be invited to take part in the consensus would include patients, carers, healthcare professionals, policy makers, researchers, and industry stakeholders.

The Delphi method, using an online survey tool (Bristol Online Survey), would be used to gain consensus on the outcome domains. The use of a 9 point Likert rating scale (1 being not important, and 9 being extremely important) was discussed and no concerns with its use arose (discussed further in section 4.4.7.1). Discussions took place over the number of rounds that the consensus process would use (i.e. two or three), the majority of the audience were in favour of using two-rounds.

An audience member raised a concern that an online format has methodological limitations and may limit the ability to reach the patient group. Due to funding restraints, it was decided that paper copies of the survey would not be sent out (discussed further in 6.5.10).

It was suggested that ulcer recurrence should be considered as an outcome domain. Ulcer recurrence was not initially included in the list of outcome domains because the focus of the core outcome set was the treatment of open venous leg ulcers. Ulcer recurrence was once again discussed by the research team in light of feedback at the meeting and it was concluded that it would not be included in the consensus because it is not possible for the scope of the research to cover all aspects of venous leg ulcer management. The scoping review of open ulceration revealed that this in itself (open ulceration) was a significant endeavour.

A number of people raised concerns and questions relating to methodological and statistical issues in venous leg ulcer trials more generally but not specifically associated to the core outcome set. It was highlighted that the research aimed to develop the core outcome set only and would not be advising on the conduct and reporting of trials, including; duration of follow up, baseline prognostic variables, and target number of trial participants. We emphasised the need for future research on the conduct and reporting in venous leg ulcer trials.

4.4 Methods

4.4.1 Aim

The aim of stage two was to gain consensus on the candidate outcome domains identified during the scoping review.

4.4.2 Design

A two-round electronic Delphi (eDelphi) was conducted to gain consensus on the outcome domains that were extracted from RCT's and qualitative research during the scoping review (stage 1). A two-round eDelphi was chosen instead of a three round eDelphi. Although more rounds increase the likelihood that there is a convergence of opinion, too many rounds can result in participant fatigue. Figure 6 displays the overall methods used in this PhD. It displays stage one which was the scoping review, stage two which was the eDelphi on the outcome domains (explained in this chapter), and stage three which was the eDelphi on the outcomes (explained in the next chapter). The box emphasised in red highlights the stage this chapter explains (stage 2). Figure 7 shows the eDelphi process used to gain consensus on the outcome domains.

Figure 6 Methods flow chart

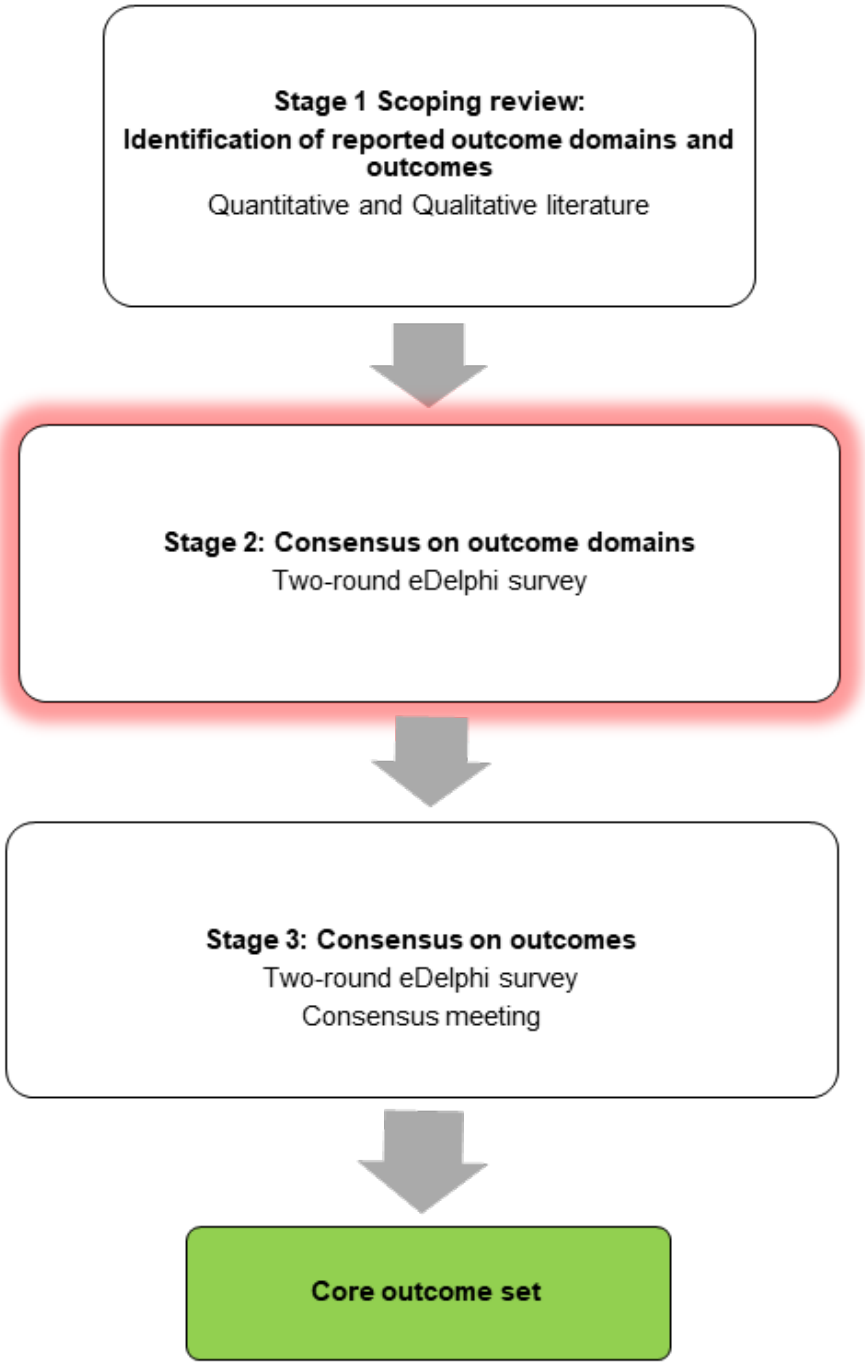
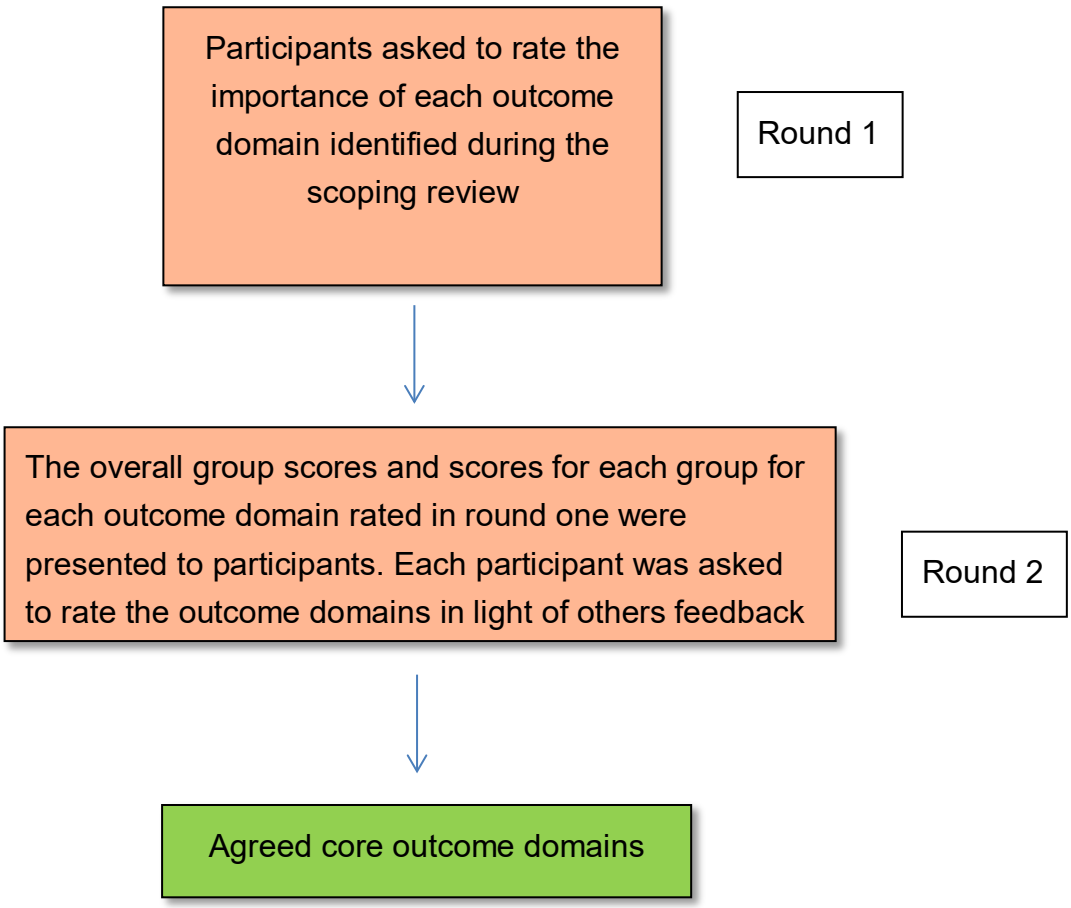
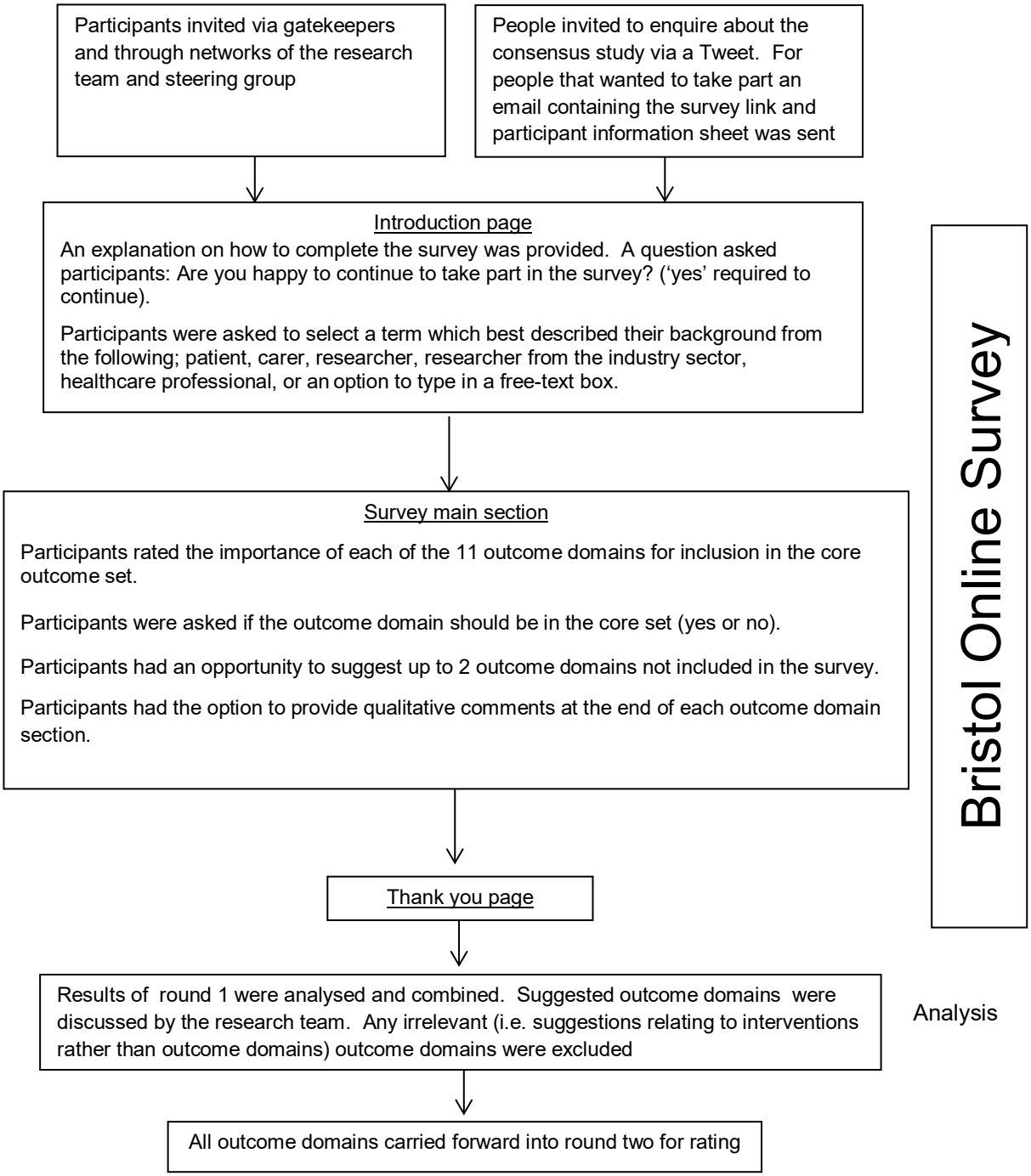


Figure 7 The eDelphi consensus process on the candidate outcome domains



The flow chart in Figure 8 displays how participants accessed the round one survey via a link on an email and through Twitter. Participants were shown an introduction page after they accessed the Bristol Online Survey. Participants were asked questions which sought their consent to take part and gain information on their background for example whether they were a patient, carer, healthcare professional or researcher. Once the questions were completed participants were directed to the main page which asked participants to rate the outcome domains. A thank you page was shown at the end on completion of the survey which included contact details for any questions.

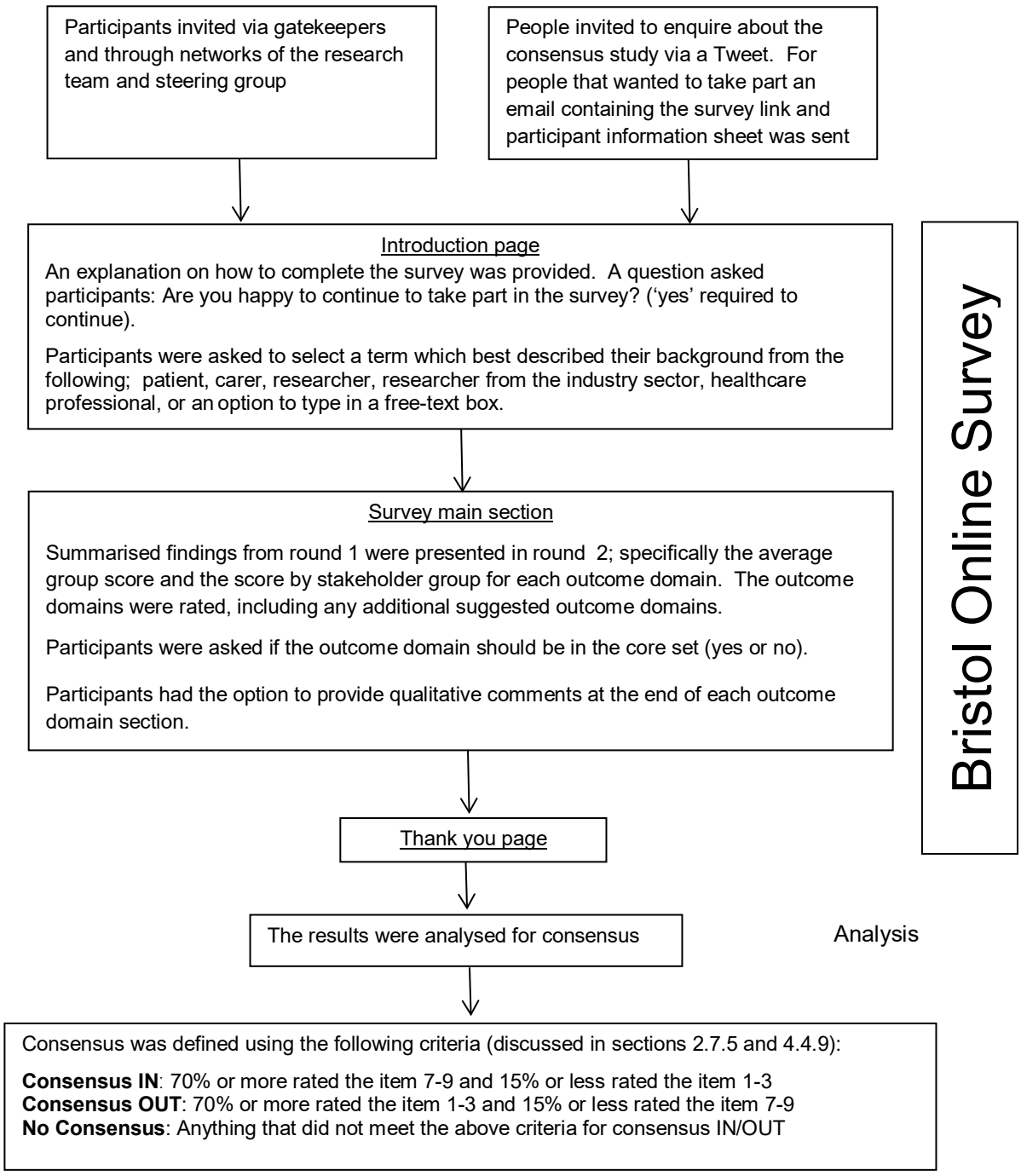
Figure 8 Flowchart: Methods for the round one eDelphi on the outcome domains



The flow chart in Figure 9 displays how participants accessed the round two survey via a link on an email. Participants were shown an introduction page after they accessed the Bristol Online Survey. Once participants completed information which sought their consent to take part and gain information on their background for example whether they were a patient, carer, healthcare professional or researcher they were directed to the main page which displayed

summarised findings from round one for each outcome domain. Participants were asked to rate each outcome domain in light of others feedback. A thank you page was shown at the end on completion of the survey which included contact details for any questions.

Figure 9 Flowchart: Methods for the round two eDelphi on the outcome domains



4.4.3 Participants

There are no set sample size requirements for a Delphi study (Powell, 2003; Boers et al., 2016). Instead, Powell (2003) states that the representativeness of a Delphi panel is based upon the qualities of the panel members and not the number on a panel. Similarly, Okoli and Pawlowski (2004) state that the size of the panel cannot be determined by a statistical power calculation but on the dynamics of the group. A heterogeneous panel ensures that all stakeholders affected by and involved in venous leg ulceration research are involved in the development of the core outcome set. When it can be demonstrated that the participants are representative of the area of interest then content validity can be assumed (Goodman, 1987). Participants from a variety of backgrounds were invited to take part in the two eDelphi's which included wound care researchers, researchers from industry, healthcare professionals, patients and carers. The composition of the panel is essential to ensure that the consensus reached is representative of all relevant stakeholders. The credibility of the core outcome set can be enhanced when the full range of participants reflect stakeholders. Venous leg ulceration affects people across the globe therefore involvement of international stakeholders was important. It is intended that the core outcome set will be used internationally so it was crucial that international stakeholders took part.

Purposive sampling was used to recruit participants. Purposive sampling is used to recruit participants with particular characteristics, or an interest in a particular field therefore it is a deliberate non-random method (Bowling, 2009). Participants were recruited internationally using the 'snowballing' technique, therefore it was not possible to predict the overall number of respondents. Snowball sampling is a form of purposive sampling which allows the selection of difficult to reach groups (Newell and Burnard, 2011). The 'snowballing' technique allows existing participants to recruit potential participants through their contacts (Vogt, 1999). An initial group of potential participants are asked to recruit other potential participants (Bowling, 2009). Participants were invited

to forward the survey invitations onto people they think may have been interested in taking part, and gatekeepers of organisations were asked to circulate the invitations to their members. This form of sampling was done to optimise the number of participants invited to take part in the consensus.

The stakeholder groups that were invited to take part in the consensus included:

(i) People with experience of venous leg ulcers

(ii) Carers of people with venous leg ulcers

(iii) Healthcare professionals whose practice included venous leg ulcer care

(iv) Researchers within wound care

(v) Wound care industry researchers

It was essential to invite as many stakeholders affected by venous leg ulcer research as possible, whether as a patient, carer, healthcare professional or researcher. By inviting a wide variety of stakeholders it increases the probability that the opinions of those who are affected or have expertise in venous leg ulceration are involved in the development of the core outcome set.

Potential participants were identified through network gatekeepers, and contacts of the research team and the steering group. A network gatekeeper was an appointed person (i.e. chairperson, secretariat, journal editor, clinical trial manager or committee member) who was asked to forward the recruitment emails and participant information sheet on to the members of their network, for example a wound care society. The gatekeepers of the following networks were approached and asked to invite their members to take part in the consensus:

- Patients and informal carers invited via the charity; the Lindsay Leg Club Foundation (https://www.legclub.org/), which has 30 Leg Clubs in the UK, 1 in Germany and 8 in Australia.
- Healthcare professionals; nurses, physicians, surgeons and physiotherapists were invited through steering group contacts. Healthcare professionals who are members of the networks (listed in the

next section) were also invited to take part (via gatekeepers of the networks).

- Leg ulcer researchers identified through the European Wound Management Association, Vascular Surgeons Imperial College, Society of Vascular Nurses, Alliance for Research and Innovation in Wounds and the Wounds Research Network were invited to participate.
- Leg ulcer researchers identified through wound care journals were invited to take part.

4.4.4 Recruitment Process

4.4.4.1 Round One

The following five recruitment routes were chosen to optimise the recruitment of people affected by venous leg ulceration across the globe whilst maintaining anonymity.

1. Gatekeepers of leg ulcer societies were sent an email which gave details about the study, and sought their permission to support the study by distributing recruitment emails, participant information sheets and reminders by email. The gatekeepers were asked to send a letter attached to an email or an email which included their organisational logo and official contact details, confirming that they are willing to support the project by forwarding the email invitations, participant information sheets and email reminders to the members of their organisation. All letters and emails were forwarded to the School of Healthcare Research Ethics Committee (SHREC), University of Leeds, UK. Ethics approval was granted providing the evidence of permission and support from the organisations' gatekeepers to send out the recruitment material was sent to the ethics committee.

   Once the gatekeepers provided evidence for their support of the study a covering email containing a recruitment email and participant information sheet was sent to the gatekeepers for circulation to their members.

The same recruitment email was sent to the members of the Lindsay Leg Club but included the following sentence: 'Your participation in this study will not affect any care you are receiving'. The same participant information sheet was sent to all participants.

2. Steering group members who are gatekeepers (i.e. committee members) of organisations including the Alliance for Research and Innovation in Wounds and the Wounds Research Network (WReN) were sent a permission request email. Once the gatekeepers provided evidence for their support of the study, a covering email containing a recruitment email and participant information sheet was sent to the gatekeepers for circulation to their members.

3. Gatekeepers (i.e. editors) of wound care journals were sent the permission request email. Once the gatekeepers provided evidence for their support of the study a covering email containing a recruitment email and participant information sheet was sent to the gatekeepers for circulation to their members.

4. The following tweet was shared on Twitter two to four times a day:

   @VLUcoreven Would you like to help **develop a core set of outcomes for venous leg ulceration?** Please contact us for more info by sending a direct message.

   A recruitment email and participant information sheet was sent to the potential participants who asked for more information via a direct message on Twitter.

5. Members of the steering group and research team (not including SH) sent out recruitment emails and participant information sheets to healthcare professionals and researchers. An accompanying covering letter was sent to the steering group explaining that is was not possible to send the recruitment emails and participant information sheets to

individuals identified because of their use of UK NHS services; carers of the latter, and; healthcare professionals identified because of their employment by the UK NHS.

Participants were invited to forward the recruitment email and participant information sheet onto people they thought might be interested in taking part.

A reminder was sent out approximately two weeks after the launch date via gatekeepers, members of the steering group and the research team.

An example recruitment email and participant information sheet can be found in appendix 4 and 5.

4.4.4.2 Round Two

The same recruitment processes detailed in the previous section (section 4.4.4.1) were used to recruit participants in round two. A recruitment email and participant information sheet were circulated using the same methods detailed in section 4.4.4.1.

4.4.5 Ethics

Ethical laws and regulations are designed to protect the rights and interests of all participants involved in research. Although the study was not of a highly sensitive nature, it was still essential to ensure all participants were safe, and the research was conducted in an ethical manner.

Ethics approval was obtained from the School of Healthcare Research Ethics Committee (SHREC), University of Leeds, UK [HREC16-031]. The ethics approval letter can be found in appendix 6. It was thought that the invitation of members of the Lindsay Leg Club, which is a charity, would recruit an adequate number of participants for the patient and carer group therefore NHS ethics approval was not sought.

Due to conditional ethics approval arrangements it was not permitted to recruit individuals identified because of their use of UK NHS services; carers of the latter, and; healthcare professionals identified because of their employment by the UK NHS. The steering group members and all gatekeepers were made aware of the ethics approval arrangements before they forwarded the recruitment emails.

4.4.5.1 Informed Consent and Right to Withdraw

Informed consent is the process of obtaining agreement from a participant who has received and understood all the relevant information to allow them to make an informed decision to take part in the research. An individual should be able to determine what participation entails especially what potential harms and benefits may arise (Moules et al., 2017). People should be informed of their right to withdraw and they should be made aware that withdrawal will not adversely affect their relationships (such as with care providers or researchers) or affect any care they may be receiving (General Medical Council, 2018).

All participants were fully informed what the research entailed on the recruitment email and participant information sheet. Participants were not under any obligation to take part and they were informed of this on the recruitment email.

Participants were informed that they would not be able to withdraw their responses after completing the survey because their responses were anonymous therefore their data could not be identified for it to be withdrawn. The participants were informed of this on the participant information sheet. Participants were able to withdraw at any point before submission of the survey. In order for the survey to be submitted, the participant was required to select “finish” at the end of the survey. Participants were informed of this on the survey introduction page.

Instructions on how to complete the survey was provided on the survey introduction page. Informed consent was gained by informing the participants that by continuing to complete the survey they will be consenting to taking part.

The question “Are you happy to continue to take part in this survey?” was also included at the beginning of the survey.

A contact email address and phone number was provided on the recruitment email, participant information sheet and at the end of the survey for any questions.

4.4.5.2 Confidentiality and Anonymity

The ethical principle of justice is concerned with confidentiality and anonymity (Keeney et al., 2011). Confidentiality should be maintained, meaning participants’ names are not ascribed to any comments or results in any report or publication (Keeney et al., 2011). Anonymity means that a participant’s data cannot be identified.

Self-administered questionnaires have the potential to maintain participant anonymity which is advantageous because participants can provide their opinions without being identified, providing the questionnaires are not coded or numbered (Parahoo, 2006).

All participants were informed that any information that they provided would be dealt with in the strictest of confidence and privacy. Participants were informed that their details would be anonymised and no details were passed on to third parties (i.e. name and email address). There were no questions requesting the participant’s personal details, other than a question asking participants about their background, for example whether they were a patient, carer, healthcare professional or researcher. Healthcare professionals were asked to type their role as a healthcare professional in a free text box. Participants were provided with a link and a password to access the Bristol Online Survey.

The Bristol Online Survey enables anonymity of participants to be maintained throughout. It does not use cookies for survey completion, external software is not supported and researchers cannot access the respondents IP addresses.

4.4.5.3 Privacy and Data Storage

Data was stored on the password protected Bristol Online Survey website which is fully compliant with UK data protection laws.

After completion of the survey data were exported and stored on a password protected university PC which is on a secure university system, using the network drive.

4.4.6 Software

The Bristol Online Survey (Bristol Online Bristol Online Survey, 2017) tool was used to collect data. Since the launch of the first eDelphi, the Bristol Online Survey has changed its name to 'Online Survey (formerly BOS)' https://www.onlinesurveys.ac.uk/ (Jisc, 2018). The change to the tool's name did not affect the research or software, for example the ways in which the survey tool collated and formatted data was the same, and it's security and data protection was not affected.

4.4.7 Rating of the Outcome Domains

4.4.7.1 Round One Survey

Participants accessed the first round online survey via a link on the recruitment email. Participants were directed to the survey's front page which requested the password that was provided on the recruitment email.

Once participants entered the survey they were shown an introduction page. To gain consent participants were asked if they were happy to continue to take part in the study. In order for participants to continue they needed to consent by selecting 'yes'. Participants were asked to select a term which best described their background which included; patient, carer, researcher from the industry sector, wound care researcher, healthcare professional, or an option to

type in a free-text box. Healthcare professionals were prompted to type their job role in a free-text box.

Participants were asked to rate each of the following 11 candidate outcome domains in terms of how important they are for inclusion in the core outcome set:

1. Healing
2. Patient reported symptoms
3. Clinician reported symptoms
4. Carer reported symptoms
5. Life impacts
6. Clinical signs
7. Clinical measurement
8. Performance of the intervention
9. Resource use: supplies
10. Resource use: clinician time
11. Adverse events

Examples of specific outcomes which may fall under each outcome domain were provided on the survey to give participants an idea of what the outcome domain represents, for example the outcomes; number of ulcers that completely healed, percentage of completely healed ulcers, and rate of reduction in ulcer area were provided for the 'healing' outcome domain.

The use of rating scales has been recommended when measuring preferences on health issues (Bowling, 2005; McDowell, 2006). A 9 point interval scale was chosen for use in the eDelphi surveys because attitudinal issues often lie on a continuum and are not easily dichotomised (Bowling, 2005). They have been used to measure attitudes, because attitudes are complicated and hold an array of properties it makes them difficult to capture, however if the evaluative property is measured, i.e. how positively or negatively a person feels towards an attitude then it makes it easier to measure (Ostrom et al., 1994; Jamieson, 2004).

The Likert rating scale of 1 to 9 where 1 indicated ‘not important’ and 9 indicated ‘extremely important’ which was used in the surveys is displayed in Figure 10.

Figure 10 Nine point Likert scale

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Nine point Likert scales are the most commonly used psychometric scales because smaller scales do not give as much information about the levels on consensus, and scale sensitivity is increased as the number of scale points increase (Cummins and Gullone, 2000; Keeney et al., 2011). A 9 point Likert scale has been used by many core outcome set developers such as Schmitt et al. (2011), Potter et al. (2015), van 't Hooft et al. (2016), MacLennan et al. (2017), and Millar et al. (2017).

A variety of labels have been applied to the 9 point Likert scales in core outcome set development studies for example HOME (Schmitt et al., 2011) used a scale with the labels ‘not important’ (1-3), ‘equivocal’ (4-6) and ‘important’ (7-9), Coulman et al. (2016) used a scale where 1 indicated ‘not important’ to 9 which indicated ‘extremely important’, Millar et al. (2017) labelled their scale ‘limited importance’ (1-3), ‘important but not critical’ (4-6) and ‘critical’ (7-9), Iorio et al. (2018) used a scale where 1 indicated ‘not important to include in the core set’ to 9 ‘essential to include’, and Meher et al. (2019) used ‘not important’ (1-3), ‘important but not critical’ (4-6) and ‘critically important’ (7-9).

Wildt and Mazis (1978) tested whether the labels on Likert scales affected responses. Four hundred and seventy-nine questionnaires were randomly assigned to undergraduate students. Six different scales were tested:

Scale 1: Extremely good ---------- Extremely poor

Scale 2: Extremely good- Good- Average- Moderately poor- Extremely poor

Scale 3: Extremely good- Average- Moderately poor- Quite poor- Extremely poor

Scale 4: Extremely good- Very good- Good- Average- Extremely poor
Scale 5: Extremely good- Very good- Average- Very poor- Extremely poor
Scale 6: Extremely good- Slightly good- Average- Mediocre- Extremely poor

Wildt and Mazis (1978) conclude their study by stating that there was no consensus in the results but that the scale labels and their position influenced responses. Wildt and Mazis (1978) found a greater reluctance for participants to move to the negative side of a scale compared to the positive side. The researchers do not indicate which of the scales is the best one to use. The researchers did not test whether the labels at the ends of the scale affected responses, for example if they are worded differently or if the ends were flipped.

The researchers do not explain how the questionnaires were randomised therefore subjective bias of the researchers cannot not be assessed, i.e. whether the participants were 'hand-picked' to receive the questionnaires containing a certain scale (Parahoo, 2006). Also, the researchers relationship with the undergraduates is not described therefore it cannot be determined whether the participants had an 'obligation' to take part which can affect results such as a desire to be seen as agreeing with someone that is senior (Sinha et al., 2011).

In a more recent study by Moors et al. (2014) concluded that end labelling evoked extreme response style than labelling each point on a scale. Extreme response style refers to a participant's tendency to choose the extreme end-point of a rating scale (Hurley, 1998). Thus supporting Wildt and Mavis's (1978) claim that participants are reluctant to move towards the negative side of a scale. An online questionnaire was distributed amongst a random sample of 5,351 participants from a Longitudinal Internet Studies for Social Sciences household panel. Five labelling formats were randomly allocated to a subsample of 3,266 participants using a split-ballot technique. The five formats were:

Format 1: full labelling with numerical values
Format 2: full labelling without numerical values
Format 3: end labelling with numerical values
Format 4: end labelling without numerical values

Format 5: end labelling with bipolar numerical values

The fully labelled scales used the labels “totally disagree”, “disagree”, “disagree somewhat”, “nether disagree or agree”, “agree somewhat”, “agree” and “totally agree”, and the end-labelled scales used “totally disagree” and “totally agree”. The numerical scales ranged from -3 to 3 in the bipolar scale and 1 to 7 in the numerical values. Moors et al. (2014) point out that extreme response style was consistently present despite the formatting of the scales and suggests that extreme response style is a personal style of participants rather than an issue with the scales. Again, the researchers did not test whether the labels at the ends of the scale affected responses, for example if they are worded differently or if the ends were flipped.

Evidence suggests that there is little difference in labelling the scales with adjectives under each rating number and end-anchored labels (labels at each end of the scale) (Dixon et al., 1984; Newstead and Arnold, 1989). However Frisbie and Brandenburg (1979) found that participants are influenced by the labels on the ends of the scales. Frisbie and Brandenburg (1979) tested various scales containing different labels which were randomly distributed to college freshman. Similarly to Wildt and Mazis (1978), Frisbie and Brandenburg (1979) did not provide adequate information on how the questionnaires were randomised.

The Likert scale used in the eDelphi surveys used end-anchored labels; ‘Not important’ and ‘Extremely important’ (Figure 10) to indicate how important the outcome domain was for inclusion in the core outcome set. Because international stakeholders were invited to take part it was thought that the wording ‘extremely important’ would be better understood compared to such wording as ‘critically important’ or ‘critical’. The labels were the same for each outcome domain as not to cause confusion.

Participants were asked to rate each outcome domain on the 9 point Likert scale or select ‘no opinion’. Comments relating to the outcome domains were invited using an optional free-text box. Participants were asked, on a separate page, whether they thought each outcome domain should be in the core set which required a yes or no answer.

Participants were given the opportunity to suggest up to two additional outcome domains which were not in the survey. The option to suggest two outcome domains instead of an unlimited amount was chosen because there was potential for a long list of outcome domains to be produced if participants were able to provide an unlimited amount. A free-text box was provided for any comments regarding the additional outcome domains.

The survey ended with a thank you page and contact details for any questions. The survey was in an online format, for reference purposes a facsimile of the survey can be found in MS Word format in appendix 7.

Participants had the option to download their responses (which could be saved to a computer or printed). Participants were advised to download their responses to remind them of their rating scores when completing the second round survey. Participants were advised to download their responses because their individualised data could not be presented in round two due to anonymised aggregation of data within Bristol Online Survey.

All outcome domains, including any relevant suggested outcome domains, were carried forward into round two to be rated. Many core outcome set developers have carried over all of the outcomes into round two (Waters et al., 2014; Harman et al., 2015; van 't Hooft et al., 2016; Byrne et al., 2017; Egan et al., 2017). Others have used pre-specified criteria for dropping outcomes between rounds for example Sahnan et al. (2018) carried outcomes forward between rounds if more than 70% of all participants scored them as ‘really important’ (7–9), and Potter et al. (2015) retained outcomes for round two if more than 50% of participants in either the patient or the professional group, or both groups combined scored the item 7-9, and less than 15% of either group or both combined scored the outcome as not important (1-3).
All outcome domains were carried forward into round two to enable participants to score the list of outcome domains as a whole. The dropping of outcome domains between rounds risked dropping outcome domains that are considered core by some participants who did not complete the survey in the round one. Duplicated outcome domains and any irrelevant suggestions, for

example any suggestions relating to interventions rather than outcome domains were not carried over into round two.

4.4.7.2 Round Two Survey

The link and password for the second round survey was provided on the recruitment emails which were circulated by the same gatekeepers detailed in section 4.4.4, the same participants that enquired about the research through Twitter and the same participants invited by the steering group members and the research team. Covering emails were sent to the gatekeepers and steering group members asking them to forward the recruitment email and participant information sheet.

Participants were reminded to look at their responses that they had downloaded or printed after completing the first round survey to assist them in re-rating the outcome domains in the second round survey.

A main characteristic of the Delphi method involves the feeding back of the 'collective' wisdom into the eDelphi. A table containing the median scores per stakeholder group and overall scores for each outcome domain were given to participants in round two of the eDelphi surveys. The overall group scores and scores for each group for each outcome domain were presented to participants in round two and participants were asked to rate each outcome domain in light of others feedback. Any suggested outcome domains were also rated. The percentage of participants who thought the outcome domain should be in the core set or should not be in the core set was provided along with the group scores.

The same 1 to 9 rating scale (1 being 'not important' and 9 being 'extremely important') was used to rate the outcome domains. The option to select 'no opinion' was not included. An optional free-text box was provided for comments relating to the outcome domains.

Once again, participants were asked, on a separate page, whether each outcome domain should be in the core set which required a yes or no answer.

Another optional free-text box was provided for comments relating to the outcome domains.

The survey ended with a thank you page and contact details for any questions.

4.4.8 Data Analysis

4.4.8.1 eDelphi Round One Analysis

Data were exported from each participant's response on the Bristol Online Survey and inputted into Excel.

The first round eDelphi survey responses were analysed using descriptive statistics IBM SPSS Statistics version 22.

Histograms displaying the distribution curve for each outcome domain were produced. Visual inspection of the histograms demonstrated that the data for every outcome domain was not normally distributed and negatively skewed. The histograms can be found in appendix 8.
Because the data was not normally distributed the median for each outcome domain per stakeholder group and groups overall was calculated for feedback purposes in round two. When data is not normally distributed the median should be used and not the mean (Black, 2006). The median can be used when outliers distort the data because the median is not skewed by outliers compared to the mean (Scott and Mazhindu, 2014).

The number of participants who selected 'no opinion' was calculated. The percentage of participants rating each outcome domain as 'yes' or 'no' to the question asking if the outcome domain should be in the core set was also calculated.

The suggested new outcome domains were reviewed by members of the research team to check for duplication with previously identified outcome domains and to exclude any irrelevant suggestions, for example any suggestions relating to interventions rather than outcome domains.

4.4.8.2 eDelphi Round Two Analysis

Data were exported from each participant's response on the Bristol Online Survey and inputted into Excel. An example of the data inputted into Excel for the researcher stakeholder group is presented in Figure 11. Researcher 1, 2, 3 etc. indicates participants' responses from the researcher stakeholder group.

Figure 11 Screen shot of data entered into excel

Outcome domain	Researcher 1	Researcher 1 should it be core yes or no	Researcher 2	Researcher 2 should it be core yes or no	Researcher 3	Researcher 3 should it be core yes or no	Researcher 4	Researcher 4 should it be core yes or no	Researcher 5	Researcher 5 should it be core yes or no
Healing	9	yes	9	yes	9	yes	9	yes	8	yes
Patient reported symptoms	9	yes	9	yes	9	no	7	no	9	yes
Clinician reported symptoms	6	no	5	no	6	no	9	yes	2	no
Carer reported symptoms	6	no	6	no	6	no	7	no	8	yes
Life impacts	7	yes	9	yes	9	yes	7	yes	9	yes
Clinical signs	6	no	9	yes	6	no	9	yes	7	yes
Clinical measurement	3	no	7	yes	9	yes	9	yes	8	yes
Performance of the intervention	7	yes	7	yes	7	no	9	yes	9	yes
Resource use: supplies	3	no	7	yes	7	no	5	no	8	yes
Resource use: clinician time	3	no	6	no	7	no	8	no	8	yes
Adverse events	7	yes	9	yes	8	yes	9	yes	8	yes

The second round eDelphi survey responses were analysed using descriptive statistics IBM SPSS Statistics version 22 and they were also analysed by calculating the percentage of participants rating each outcome domain as 7, 8 or 9 (extremely important), 4, 5, or 6, OR 1, 2 or 3 (not important).

The percentage of participants rating each outcome domain as 'yes' or 'no' to the question asking if the outcome domain should be in the core set was also calculated.

The following section explains how consensus was defined.

4.4.9 Consensus Definition

Defining the consensus criteria was important because a too accommodating criteria could have resulted in too many outcome domains therefore creating a long list of outcomes, whereas a too stringent criteria risked excluding fundamental outcome domains that may have otherwise been included (Williamson et al., 2017).

For any outcome domain to be included as core, one of the following three conditions was required:

The overall group (all stakeholders combined) reach consensus that the outcome domain is core,

OR

The 'patient and carer' sub-group ((i) Patients & (ii) Carers combined) deemed the outcome domain core,

OR

The 'professionals' sub-group ((iii) Healthcare professionals, (iv) Researchers within wound care, and (v) Other types of professionals combined) deemed the outcome domain core.

By using these three conditions it meant that there was not a group that did not have their opinions on what should be in the core outcome domain set included.

The consensus definition is outlined below:

Consensus IN: 70% or more rated the item 7-9 and 15% or less rated the item 1-3
Consensus OUT: 70% or more rated the item 1-3 and 15% or less rated the item 7-9
No Consensus: Anything else that did not meet the above criteria for consensus IN/OUT

Other ways to define consensus have been used by core outcome set developers, such as Schmitt et al. (2011) who stated that "at least 60% of all members of at least three stakeholder groups including consumers recommend including a domain" (p. 629) for the domain to be included. Whereas, Millar et al. (2017, p. 4) defined consensus as "≥70% of respondents scoring an outcome 7-9 and <15% scoring the outcome 1-3". Eleftheriadou et al. (2015)

stated at least 75% of participants from two stakeholder groups separately rated an outcome as being ‘very important’ or ‘important’ for it to be included.

The consensus definition of 70% of participants scoring the item 7 to 9 has been used by other core outcome set developers such as Wylde et al (2015), Potter et al (2015), Blazeby et al (2015) and Boers et al (2016). Williamson et al (2017) suggest that the 70/15% (70% or more rate the item 7-9 and 15% or less rate it 1-3) consensus definition means that the majority believe that the item should be in the core outcome set and only a small minority think it is of little or no importance.

4.5 Results

4.5.1 eDelphi Round One

Fifty-one participants took part in the first eDelphi round involving 2 carers, 7 researchers, 4 researchers from the industry, and 38 healthcare professionals. Of the 38 healthcare professionals that took part there were 14 nurses, 12 tissue viability nurses, 3 vascular surgeons, 3 nursing management personnel, 2 nurse consultants, 2 Doctors, 1 podiatrist and 1 microbiologist. Table 13 displays the overall number of participants, and participants per stakeholder group that participated in round one.

Table 13 Participant response numbers per stakeholder group in round one

Stakeholder group	Respondents in Round 1
Patients and Carers	2
Researchers and Healthcare professionals	49
Total number of participants	51

The first round was open between 5th October 2017 and 14th November 2017. Eleven outcome domains were rated by participants. The results from round one are presented in Table 14. The results are presented as median scores

per stakeholder group and the overall median scores for each outcome domain. All 11 outcome domains were rated extremely important (rated 7-9) overall. The median scores for 5 outcome domains; healing, carer reported symptoms, clinical measurement, resource use: supplies and resource use: clinician time rated by the researcher in industry group fell within 4-6 (thus classified as uncertain). The patient and carer, researcher, and healthcare professional group median scores all fell between 7-9 (extremely important) on the rating scale.

Table 14 also displays the percentage of stakeholders that selected either 'yes' or 'no' to whether they think the outcome domain should be in the core set. The number and percentage of participants that selected 'yes' when asked if each outcome domain should be in the core set are as follows (in descending order); clinical signs (n=50, 98%), healing (n= 48, 94%), patient reported symptoms (n= 48, 94%), life impacts (n= 48, 94%), performance of the intervention (n=46, 90%), adverse events (n=46, 90%), clinical measurement (n=43, 84%), clinician reported symptoms (n=38, 75%), resource use: clinician time (n=35, 69%), resource use: supplies (n=31, 61%), and carer reported symptoms (n=27, 53%).

Outcome domain	**Patient and carers** Median score (N)	**Researchers** Median score (N)	**Researchers (industry)** Median score (N)	**Healthcare professionals** Median score (N)	**Overall score** Median score (N)	**Percentage of participants who thought the outcome domain should be in the core set (selected yes)**	**Percentage of participants who thought the outcome domain should NOT be in the core set (selected no)**
Healing	9	7	6	8	9	94%	6%
Patient reported symptoms	9	9	7.5	8	8.5	94%	6%
Clinician reported symptoms	7.5	7	7.5	7	7.25	75%	25%
Carer reported symptoms	7.5	7.5	5.5	7	7.25	53%	47%
Life impacts	8.5	9	7	8	8.25	94%	6%
Clinical signs	8	7	7	8	7.5	98%	2%
Clinical measurement	7.5	8	5.5	8	7.75	84%	16%
Performance of the intervention	8.5	7	7	8	7.5	90%	10%
Resource use: supplies	7.5	7	6	7	7	61%	39%
Resource use: clinician time	8	7	6	7	7	69%	31%
Adverse events	7.5	9	9	8	8.5	90%	10%

Table 14 Results from round one of the eDelphi on the outcome domains: median scores and percentages

The number of participants that selected ‘no opinion’ when asked to rate each outcome domain is displayed in Table 15.

Table 15 Number of participants that selected ‘no opinion’

Outcome domain	Number of participants selecting ‘no opinion’	
	Researcher stakeholder group	Healthcare professional stakeholder group
Healing		1
Patient reported symptoms	1	3
Clinician reported symptoms	1	1
Carer reported symptoms	1	1
Clinical measurement		1
Performance of the intervention		1
Resource use: supplies		1
Adverse events		1

The following were suggested under the item asking if there were any additional outcome domains that participants thought should be considered for inclusion. All of the suggestions were already in the list of outcomes to be entered into the stage three consensus process.

Outcomes for inclusion in stage three:

Pain
Pain level
Sleep quality
Exudate management
Expenses to the patient- drug costs
Compliance
Concordance
Mobility

Patients' wellbeing
Clinical signs of infection
Mental health

Ulcer recurrence was again suggested as an outcome domain, however it was previously decided (discussed in section 4.3) that ulcer recurrence would not be included because it is not possible for the scope of the research to cover all aspects of venous leg ulcer management. Therefore the suggestions relating to ulcer recurrence were not included in the round two survey.

The qualitative comments and suggested outcome domains that participants provided in the round one survey are displayed in Table 16. The suggested outcome domains are the outcome domains that participants provided when asked if there were any additional outcome domains that should be considered other than what was listed in the survey. Some participants however suggested outcome domains in the free text comment box for qualitative comments; in this instance the suggested outcome domains were considered part of the suggested outcome domain list. The comments are discussed in chapter 6 section 6.2.2.1.

Table 16 Qualitative comments and suggested outcome domains in the round one survey

Participant number	**Comment (verbatim)**	**Suggested outcome domains (verbatim)**
1	The QOL measures are often very general and a specific measure such as veinesqol may be more appropriate	
	Combinations of outcomes presented	
2	Health economic would be very important given the current challenges in healthcare today. Patient and carer feedback is more significant that the nurse treating the ulcer as this impacts on the patients QOL	
	Location of treatment intervention i.e. at a specialist clinic or where treatment was/is received	

3		Clinical signs of infection NB
		Patient centred concerns
		Pain, sleep quality, exudate management. Expenses to patient- drg [drug] coats etc
4	The selection of domains compliment one another - some measures can be very subjective, even when using a validated scoring system (e.g. carer reported symptoms) but are worthwhile to include as often times the patient may not be telling the clinician the full story. In terms of chronic venous ulceration, healing should not be the overall objective, quality of life is paramount. Treatment options and costing are vital - empirical evidence is necessary to ensure treatment options are made available as "money talks" and clinicians need to be able to have the evidence to support the cost effectiveness of various treatment options. This empirical evidence may also support the fact that VLU in particular is a chronic illness and make these treatment options more easily available to all patients.	
	While there are a number of contemporaneous guidelines available to the clinicians of differing disciplines/professions caring for patients with leg ulceration, there is a paucity of evidence to demonstrate if these guidelines are being implemented and the outcomes related to same. There is very loose interpretation, adaption and implementation in certain areas meaning the standard of care differs across sectors.	
	Application of current guidelines across the disciplines caring for patients with leg ulceration	

5	I believe specific questions relating to compliance and concordance with treatment should be essential domains as they directly impact on outcomes and cost.	
		Psychological impacts from poverty, barriers to engagement, operational timings (out of hours/ patient travel, clinic availability, childcare issues etc)…mental health….and number one for venous improvement is client engagement and participation in their care package. Anything that improves this I believe will help outcomes
		Compliance
		Concordance
6	Important questions concerning trials: a) Inclusion and exclusion criteria, b) unblinded, single-blinded, double-blinded, c) statistical aspects (alpha-error adjustment, was a calculation of sample size done ahead of the beginning of the trial?)	
	Statistical aspects of the trial	
7	As they are all individually so important it is difficult to give priority to one over another	
	I think the domains above are all relevant. I'm not so sure about the relevance of clinical signs domain but I'm sure there are good reasons to keep it in but maybe it's one to seek more consensus on	
8	How about having patient adherence to treatment as a core domain?	Patient concordance

9	Concerning the severity of the wounds, it is more important as a Baseline data than as a final outcome. Concerning the pain of the patient, the evaluator should be specified but I do not know who would be the more relevant to answer. Too much evaluators may reduce the interest to the evaluation.	
10	Two problems - First, the survey tool doesn't allow one to deselect "no opinion" option once chosen. Second, it is not clear what is meant by Core Domain? It is not defined in PIS and it is not clear if one is being asked whether or not the domain must be included in all trials, or whether it should be included in trials as appropriate to the research question.	
11		Pain score is very important
12		Self efficacy
13		Management rather than healing
		Compliance
14	Recurrence should be able to capture long term effectiveness of treatment, as well as ensure trials include an adequate follow-up period	Recurrence
15		Mobility can be helpful
16		Has there been any imaging performed to aid diagnosis and treatments?
		Patient and clinicians expectations
17		Does a patient want to be healed?
18		Patient reported experience not only outcomes
19		Pain level
		Recurring ulceration
20		Comorbidities e.g. diabetes

21		Ulcer re occurrence rates following healing
		Whether the patient is being considered for surgical intervention
22		Clinician Competence ie; Bank Nurses
23		Systemic treatment
		Diagnostic
		Phlebotropic treatment. Antibiotics. Which tests should be performed before treatment.
24		Ulcer recurrence - time to ulcer recurrence
		Ulcer free time
25		Patients wellbeing
		Environment patient lives e.g. climate

All 11 outcome domains were carried over into round two to be rated by participants.

4.5.2 eDelphi Round Two

Forty-four participants took part in the second round involving 1 patient, 1 carer, 5 researchers, and 37 healthcare professionals. Of the 37 healthcare professionals that took part there were 8 tissue viability nurses, 7 nurse consultants, 6 nurses, 6 Doctors, 4 vascular surgeons, 4 nursing management personnel, 1 podiatrist and 1 microbiologist. Table 17 displays the overall number of participants, and participants per stakeholder group that participated in round two. Because participants were anonymised it could not be determined whether the same participants that took part in round one took part in round two.

Table 17 Participant response numbers per stakeholder group

Stakeholder group	Respondents in Round 1	Round 2
Patients and Carers	2	2
Researchers and Healthcare professionals	49	42
Total number of participants	51	44

The second round was open between 2nd January 2018 and 23rd February 2018. The results of round two are presented in Table 18. Table 19 displays the percentage of stakeholders that answered either 'yes' or 'no' to whether they think the outcome domain should be in the core set. There was no missing data.

Of the 11 outcome domains that were rated by participants, 10 outcome domains met the criteria for consensus IN (70% or more rate the item 7-9 and 15% or less rate the item 1-3):

1. Healing
2. Patient reported symptoms
3. Clinician reported symptoms
4. Life impacts
5. Clinical signs
6. Clinical measurement
7. Performance of the intervention
8. Resource use: supplies
9. Resource use: clinician time
10. Adverse events

The outcome domain 'carer reported symptoms' did not meet the criteria for consensus IN (70% or more rated the item 7-9 and 15% or less rated the item 1-3) or consensus OUT (70% or more rated the item 1-3 and 15% or less rated the item 7-9). 'Carer reported symptoms' was therefore reported to have 'no consensus'.

Outcome domain	**Patients and carers (N=2)** N (%)			**Professionals[a] (N= 42)** N (%)			**All[b] (N=44)** N (%)			**IN/OUT/No consensus**
Rating	**1-3[c]**	**4-6**	**7-9[d]**	**1-3[c]**	**4-6**	**7-9[d]**	**1-3[c]**	**4-6**	**7-9[d]**	
Healing	0	1 (50)	1 (50)	0	2 (5)	40 (95)	0	3 (7)	41 (93)	IN
Patient reported symptoms	0	0	2 (100)	0	4 (10)	38 (90)	0	4 (9)	40 (91)	IN
Clinician reported symptoms	0	1 (50)	1 (50)	1 (2)	10 (24)	31 (74)	1 (2)	11 (25)	32 (73)	IN
Carer reported symptoms	0	1 (50)	1 (50)	1 (2)	16 (38)	25 (60)	1 (2)	17 (39)	26 (59)	No consensus
Life impacts	0	0	2 (100)	0	2 (5)	40 (95)	0	2 (5)	42 (95)	IN
Clinical signs	0	0	2 (100)	0	3 (7)	39 (93)	0	3 (7)	41 (93)	IN
Clinical measurement	0	0	2 (100)	2 (5)	3 (7)	37 (88)	2 (5)	3 (7)	39 (89)	IN
Performance of the intervention	0	0	2 (100)	0	3 (7)	39 (93)	0	3 (7)	41 (93)	IN
Resource use: supplies	0	0	2 (100)	2 (5)	9 (21)	31 (74)	2 (5)	9 (20)	33 (75)	IN
Resource use: clinician time	0	0	2 (100)	2 (5)	6 (14)	34 (81)	2 (5)	6 (14)	36 (82)	IN
Adverse events	0	0	2 (100)	0	2 (5)	40 (95)	0	2 (5)	42 (95)	IN

Table 18 Results from round two: rating of the outcome domains stratified by stakeholder group

[a] Professionals: Healthcare professionals and researchers , [b] Patients and carers, and professionals combined, [c] 1-3= Not important, [d]7-9= Extremely important

Table 19 Percentage of stakeholders that selected either 'yes' or 'no' to whether they think the outcome domain should be in the core set

Outcome domain	Percentage of participants who thought it should be in the core set (selected yes) **Round 1**	Percentage of participants who thought it should NOT be in the core set (selected no) **Round 1**	Percentage of participants who thought it should be in the core set (selected yes) **Round 2**	Percentage of participants who thought it should NOT be in the core set (selected no) **Round 2**
	% (n)	**% (n)**	**% (n)**	**% (n)**
Healing	94% (48)	6% (3)	98% (43)	2% (1)
Patient reported symptoms	94% (48)	6% (3)	86% (38)	14% (6)
Clinician reported symptoms	75% (38)	25% (13)	84% (37)	16% (7)
Carer reported symptoms	53% (27)	47% (24)	50% (22)	50% (22)
Life impacts	94% (48)	6% (3)	98% (43)	2% (1)
Clinical signs	98% (50)	2% (1)	95% (42)	5% (2)
Clinical measurement	84% (43)	16% (8)	98% (43)	2% (1)
Performance of the intervention	90% (46)	10% (5)	93% (41)	7% (3)
Resource use: supplies	61% (31)	39% (20)	82% (36)	18% (8)
Resource use: clinician time	69% (35)	31% (16)	73% (32)	27% (12)
Adverse events	90% (46)	10% (5)	91% (40)	9% (4)

The data for each outcome domain in round two were negatively skewed indicating rare values were on the low side of the x axis towards the 'not important' end of the rating scale. The histograms displaying the distribution curve and tables displaying the degree of skewness are presented in appendix 9.

The percentage of participants that selected 'yes' to all but one outcome domain ('carer reported symptoms') when asked if the outcome domains should be in the core set was 73% or above. Only 50% of participants thought 'carer reported symptoms' it should be in the core set. The percentage of participants in round two that selected yes when asked if the outcome domains should be in the core set was similar to that in round one. However, the percentage of participants that thought the outcome domain 'resource use: supplies' should be in the core set increased from 69% in round one to 82% in round two. The percentage of participants that selected yes for the following outcome domains increased: 'clinician reported symptoms' which increased from 75% to 84%, and 'clinical measurement' which increased from 84% to 98%. The percentage of participants that thought the outcome domain 'patient reported symptoms' should be in the core set reduced slightly by 8%.

There were a number of outcome domains rated as extremely important but 'no' was selected when asked if the outcome domains should be in the core set, for example a participant scored adverse events an 8 (extremely important) but also selected 'no' when asked if the outcome domain should be in the core set.

The number of participants that rated the outcome domains extremely important (7, 8 or 9) but also selected no when asked if the outcome domain should be in the core set are as follows:

- 25% (11/44) selected 'no' when asked if the outcome domain 'Resource use: clinician time' should be in the core set despite rating it extremely important.

- 18% (8/44) selected ‘no’ when asked if the outcome domain ‘Carer reported symptoms’ should be in the core set despite rating it extremely important.
- 9% (4/44) selected ‘no’ when asked if the outcome domains ‘Patient reported symptoms’, ‘Resource use: supplies’ and ‘Adverse events’’ should be in the core set despite rating them extremely important.
- 5% (2/44) selected ‘no’ when asked if the outcome domain ‘Performance of the intervention’ should be in the core set despite rating it extremely important.
- 2% (1/44) selected ‘no’ when asked if the outcome domains; ‘Clinician reported symptoms’ and Life impacts’ should be in the core set despite rating them extremely important.

Two participants provided two qualitative comments, one being; “Expertise of the clinician is important factor influencing outcome” and the other participant said “Thank you”.

4.6 Summary

Ten out of the 11 outcome domains were rated core by participants in the stage two eDelphi:

1. Healing
2. Patient reported symptoms
3. Clinician reported symptoms
4. Life impacts
5. Clinical signs
6. Clinical measurement
7. Performance of the intervention
8. Resource use: supplies
9. Resource use: clinician time
10. Adverse events

The next stage was to gain consensus on the outcomes that fell within the outcome domains that were rated as core in stage two. The next chapter will describe the methods used to gain consensus on the outcomes.

Chapter 5 Consensus Process for Identifying Core Outcomes (Stage 3)

5.1 Introduction

The previous chapter described and discussed the method used to gain consensus on the outcome domains. It presented the outcome domains rated core by participants, which were; healing, patient reported symptoms, clinician reported symptoms, life impacts, clinical signs, clinical measurement, performance of the intervention, resource use: supplies, resource use: clinician time and adverse events.

This chapter will explain the methods used to gain consensus on the outcomes falling within the outcome domains rated as core in the previous eDelphi. Similar methods used in stage two were used in stage three, therefore to avoid repetition the rationale for the methods are explained in chapter 4. It will then go on to present the results from the consensus process.

5.2 Methods

5.2.1 Aim

The aim of stage three was to gain consensus on the candidate outcomes that fell within the outcome domains rated as core in stage two.

5.2.2 Design

A two-round eDelphi was conducted to gain consensus on the outcomes extracted during the scoping review (stage 1). Figure 12 shows the overall methods used in this PhD. The box emphasized in red highlights the stage this

chapter explains (stage 3). Figure 13 shows the eDelphi process used to gain consensus on the outcomes.

Figure 12 Methods flow chart

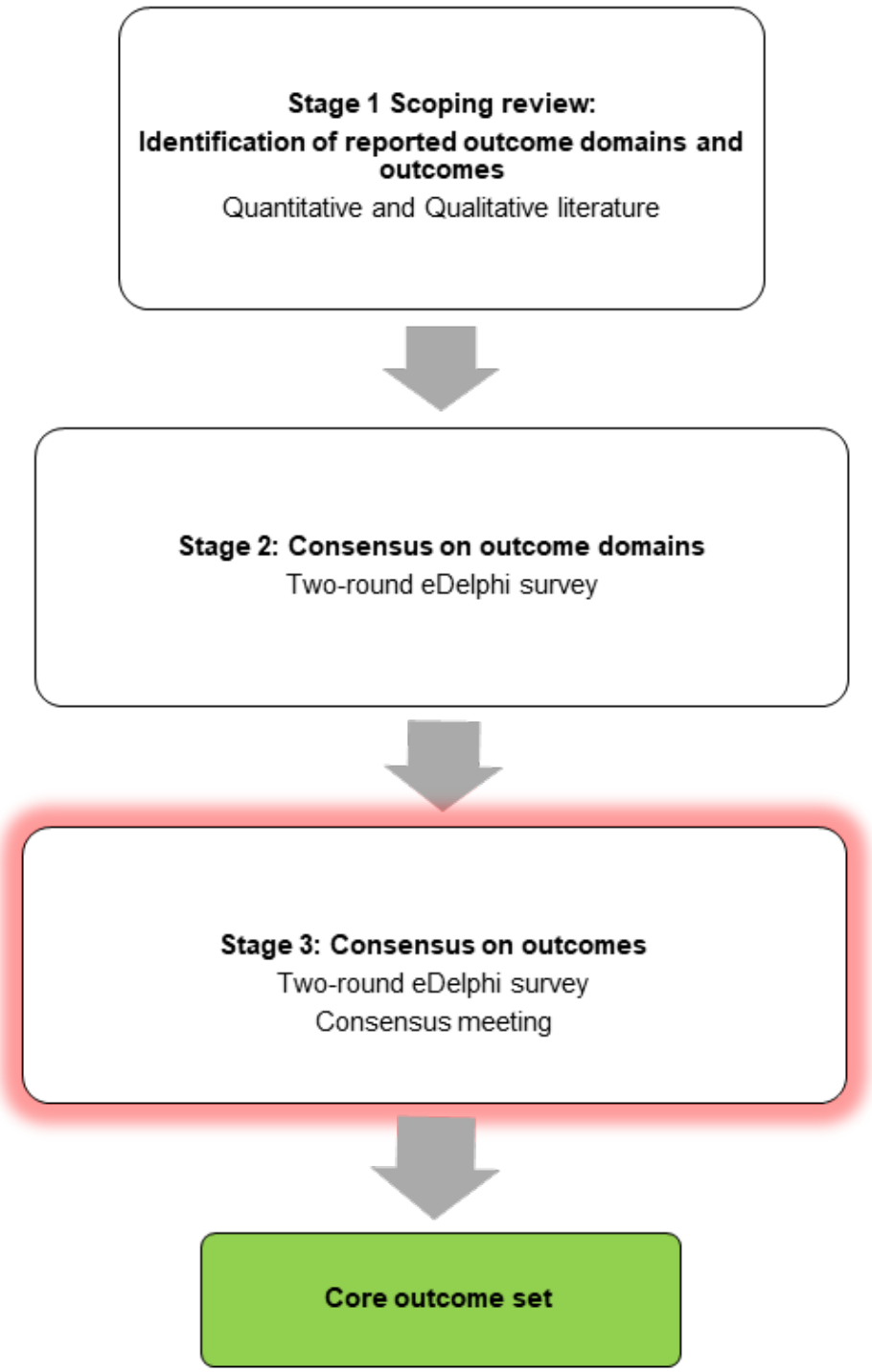
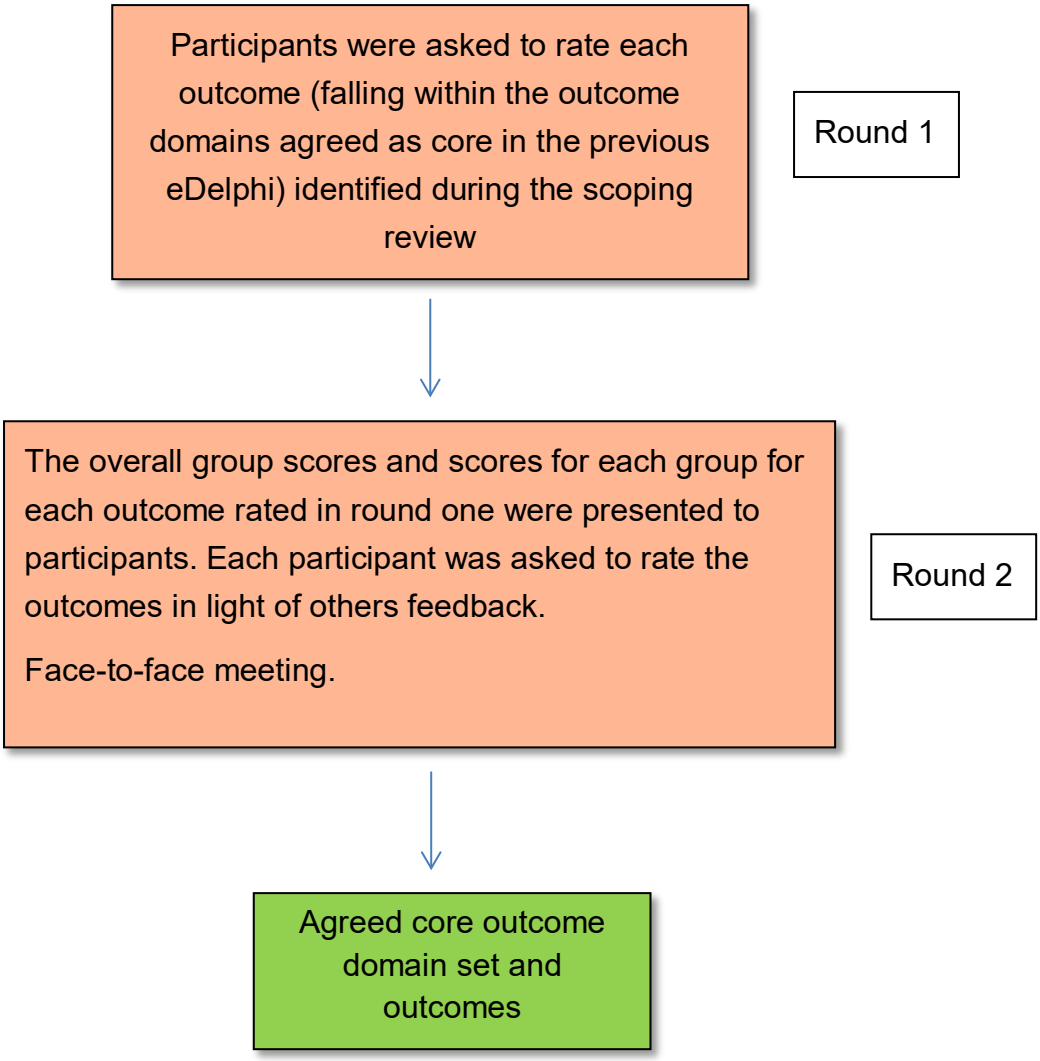


Figure 13 The eDelphi consensus process on the candidate outcomes



The flow charts in Figures 14 and 15 display how participants accessed the round one and round two surveys via the link on an email and a Tweet. Participants were shown an introduction page after they accessed the Bristol Online Survey. For the participants that accessed the survey via the Tweet the introduction page included the information that was on the participant sheet that other participants received via email. Participants were asked questions which sought their consent to take part and gain information on their background for example whether they were a patient, carer, healthcare professional or researcher. Once participants completed the information they were directed to the main page which asked participants to rate the outcomes. A thank you

page was shown at the end on completion of the survey which included contact details for any questions.

Figure 14 Flowchart: Methods for the round one eDelphi on the outcomes

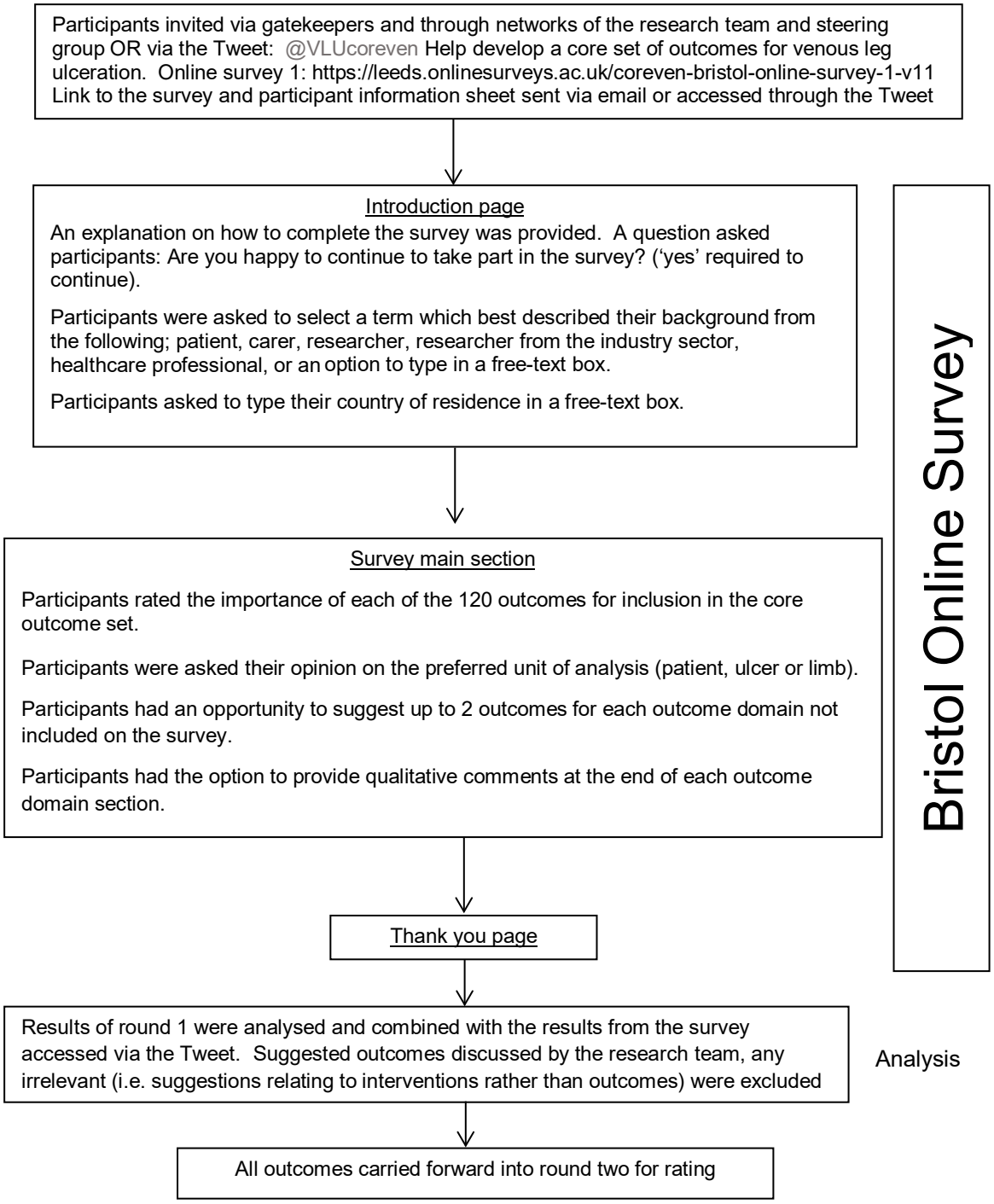
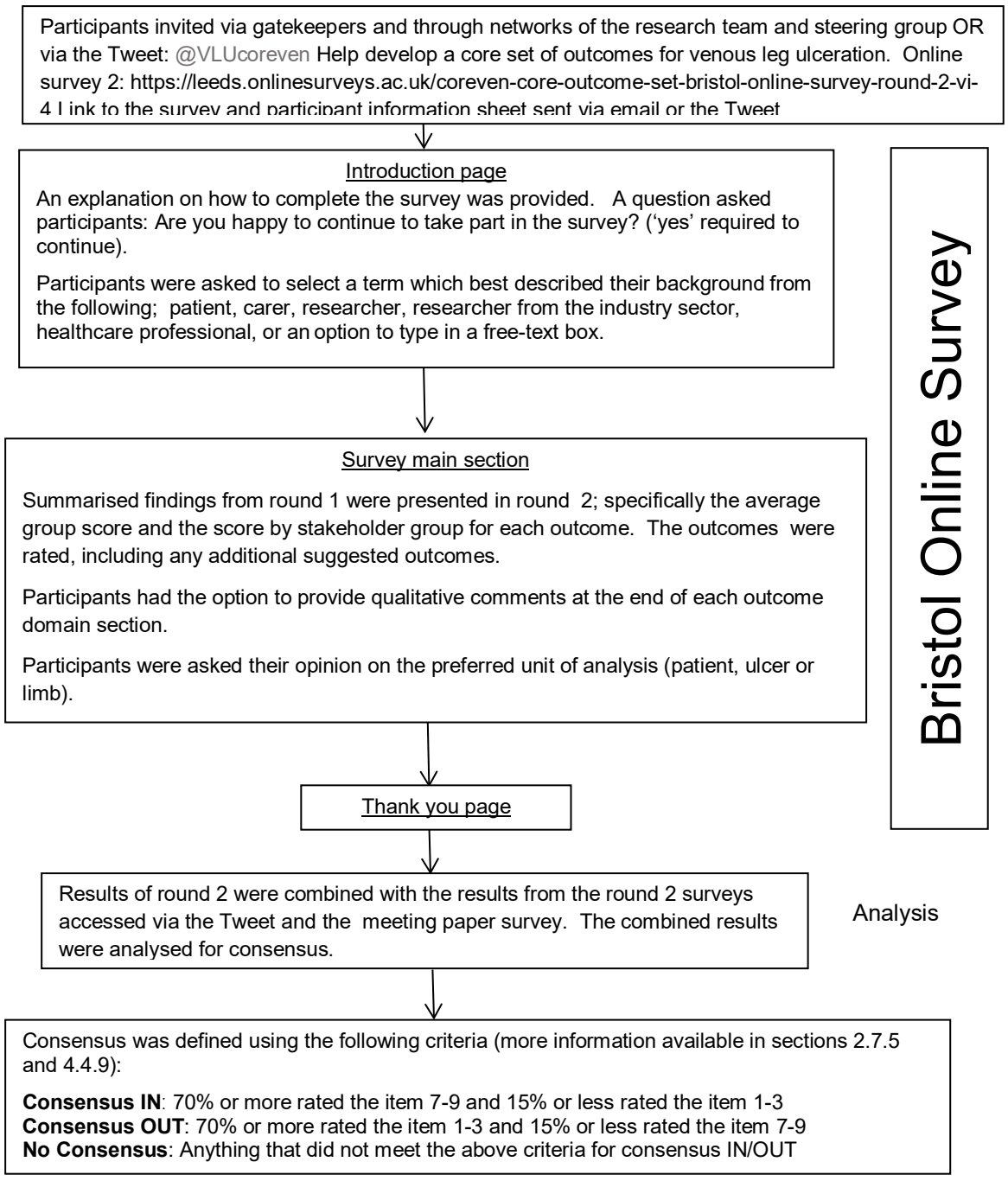


Figure 15 Flowchart: Methods for the round two eDelphi on the outcomes



5.2.3 Participants

The same strategy to identify participants used in stage two was used in stage three with the addition of the following:

- Leg ulcer researchers identified through national guideline development organisations were invited via editors.
- Stakeholders (healthcare professionals, wound care researchers and researchers from industry) attending the EWMA conference in Krakow, Poland on the 10th May 2018 were invited to take part in round two..

5.2.4 Recruitment Process

5.2.4.1 Round One

The same recruitment strategy that was used in stage two (section 4.4.4) was used in stage three, with the addition of the following:

1. Instead of asking people on Twitter to get in contact via a private Twitter message, the following tweet was shared two to four times a day:

   @VLUcoreven Help develop a core set of outcomes for venous leg ulceration. Online survey 1: https://leeds.onlinesurveys.ac.uk/coreven-bristol-online-survey-1-v11

   The information contained in the participant information sheet sent to participants who were recruited via email was included on the introduction page of the online survey.

   A Tweet with a direct link to the survey was used to make it easier for people to take part thus potentially increasing the number of participants.

2. A news item (appendix 10) was published on the Tissue Viability Society website. The news item contained information on the research and contact details for people wanting more information. Recruitment email and participant information sheets were sent to people who expressed their interest in taking part.

Again, participants were invited to forward the recruitment email and participant information sheet onto people they thought might be interested in taking part.

5.2.4.2 Round Two

The same recruitment processes detailed in the previous section (section 5.2.4.1) were used to recruit participants in round two.

The following Tweet was shared two to four times a day:

@VLUcoreven Help develop a core set of outcomes for venous leg ulceration. Online survey 2: https://leeds.onlinesurveys.ac.uk/coreven-core-outcome-set-bristol-online-survey-round-2-vi-4

Recruitment meeting at the EWMA conference

A permission request email was sent to the secretariat of EWMA to gain permission to recruit participants and collect data at the meeting held at the EWMA conference. The meeting was advertised in the EWMA handbook. More information on the meeting is available in section 5.2.5.1.

5.2.5 Ethics

Ethics approval was obtained from the School of Healthcare Research Ethics Committee (SHREC), University of Leeds, UK [HREC17-028]. The ethics approval letter can be found in appendix 11. An error occurred whereby the meeting at the EWMA conference was titled a consensus meeting in the ethics approval documentation titled ‘EWMA conference permission request email for

consensus meeting'. The aim of meeting which was to invite delegates to take part in the round two survey was however correctly described in the ethics review form and accompanying documentation for example the EWMA permission request email. Recruitment material for the surveys was sent prior to the launch of the EU General Data Protection Regulation (GDPR) which came into force on the 25th May 2018 (Information Commissioners Office, 2018).

Ethical considerations are outlined in chapter 4. Exceptions to the ethical considerations are detailed in the following sections.

5.2.5.1 Informed Consent and Right to Withdraw

Again, informed consent was gained by informing the participants that by continuing to complete the survey they will be consenting to taking part. The question "Are you happy to continue to take part in this survey?" was also included at the beginning of the survey.

For the participants that accessed the online survey via the Tweet, the participant information sheet was part of the text on the survey introduction page.

Participants were informed on the participant information sheet that they would not be able to withdraw their responses after completing the survey because their responses were anonymised therefore their data could not be identified for it to be withdrawn.

Meeting at the EWMA conference:

Participants at the meeting were asked to read a participant information sheet (appendix 12) and they were given an opportunity to ask questions and decide whether they wanted to take part. A PowerPoint slide was displayed at the beginning of the meeting explaining to the audience that by participating in the meeting they were consenting to taking part. Audience members were also informed on the PowerPoint slide "Once you have submitted data it cannot be withdrawn because it will be anonymised". Participants were also informed of

this verbally. A PowerPoint presentation was delivered which explained the purpose of the research and the meeting, and it went on to explain how to complete the survey. The PowerPoint presentation can be found in appendix 13.

5.2.5.2 Confidentiality and Anonymity

There were no questions requesting participant's personal details, other than a question asking for their country of residence and a question on their background, for example researcher. Healthcare professionals were asked to type, in a free text box, what their job role was.

5.2.6 Software

The Bristol Online Survey (Jisc, 2018) was used as the tool for data collection (https://www.onlinesurveys.ac.uk/).

5.2.7 Rating of the Outcomes

5.2.7.1 Round One

Once participants entered the survey either via the link on an email or via the Tweet, they were shown an introduction page.

Participants were asked to rate each of the 120 candidate outcomes (extracted during the scoping review) in terms of how important they are for inclusion in the core outcome set. The outcomes were presented under their outcome domains, for example the outcomes related to healing were listed within the section titled 'healing'.

A preamble for each outcome domain section was provided. The following text was the preamble to the outcomes in the 'healing' outcome domain section:

> We need to decide which outcomes are **core** and should be included in future trials on venous leg ulcer interventions. An outcome is a measurement to assess the effect of a treatment, for example, its effectiveness (benefit) or the assessment of adverse side effects (risks).
>
> You will see below a list of outcomes which can broadly be called 'healing'. Please rate each outcome in terms of how important, on a scale of 1 to 9 (1 being not important and 9 being extremely important). Remember to rate the outcome as extremely important if you think the outcome is core and should therefore be in the core outcome set.

Participants were asked to rate each outcome on a Likert rating scale of 1 to 9 where 1 indicated 'not important' and 9 indicated 'extremely important' (Figure 16). The option to select 'no opinion' and the yes/no question asking if the outcome should be in the core set used in stage two was not included in the eDelphi on the outcomes (stage three) as not to add to the length of the survey. The option to select 'no opinion' and the yes/no question did not generate data that was more useful than the 1 to 9 Likert rating scale and produced conflicting results. Comments relating to the outcomes in each outcome domain section were invited using an optional free-text box (an example is shown in Figure 17). Participants were given the opportunity to suggest up to two additional outcomes, for each outcome domain (Figure 18). A free-text box was provided for any comments regarding the additional outcomes. Towards the end of the survey, participants were asked to select their preferred unit of analysis (Figure 19) with an optional free text box for comments.

Figure 16 Example survey item from the first round survey

Number of patients/ulcers/limbs that completely healed in a trial period **Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Figure 17 Example of the free-text box for comments (no maximum number of characters)

Optional: Please write any comments relating to the outcomes for the healing domain

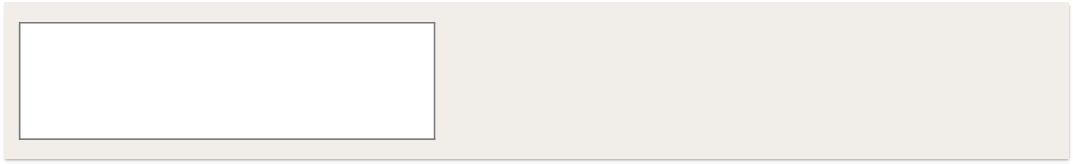


Figure 18 Example of the text box to suggest additional outcomes (no maximum number of characters)

Optional: Is there an outcome relating to healing that you think should be considered, other than what has been listed in this survey?. Please write the outcome in the box below.

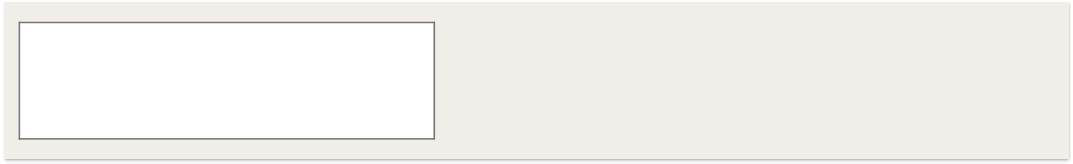
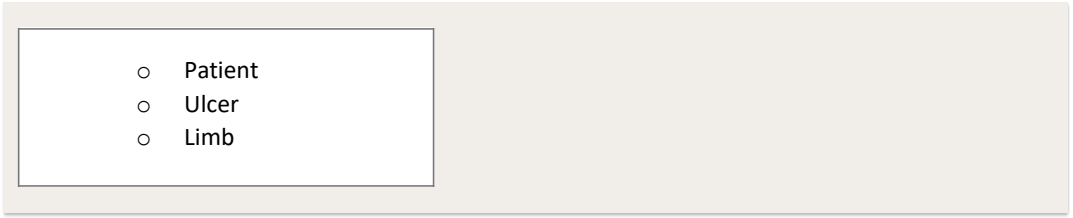


Figure 19 Survey item asking participants to select their preferred unit of analysis

Which unit of analysis do you think is the most important when measuring outcomes: **Required*



An explanation was provided for the outcomes that were ambiguous or where it was thought an explanation would be helpful, for example 'erythema' was described as 'redness of the skin caused by increased blood flow to the superficial capillaries'.

The survey ended with a thank you page and contact details for any questions.

The survey was in an online format. For reference purposes a facsimile of the survey section that asked participants to rate outcomes relating to healing can be found in MS Word format in appendix 14. It also contains the introduction pages, comment boxes to suggest additional outcomes and qualitative

comments, and the thank you page. The online survey also contained outcomes within the following outcome domain sections; adverse events, symptoms, life impacts, clinical signs, clinical measurement, performance of the intervention and concordance/compliance. It also contained a question on the preferred unit of analysis.

Participants were advised to download their responses (which could be saved to a computer or printed) to remind them of their responses when completing the second round survey.

All outcomes, including any relevant suggested outcomes, were carried forward into round two to be rated. Duplicated outcomes and any irrelevant suggestions, for example any suggestions relating to interventions rather than outcomes were not carried over into round two.

5.2.7.2 Round Two

Once participants entered the second round survey either via the link on an email or via the Tweet, they were shown the introduction page. The introduction page accessed by the link on the Tweet contained the information that was in the participant information sheet. Once again, to gain consent participants were asked if they were happy to continue to take part in the study. Participants had to select 'yes' to continue. Participants were asked the standard demographic questions as described in section 5.2.7.1

Participants were encouraged to look at their responses that they had downloaded or printed following completion of the first round survey to assist them in rating the outcomes in the second round survey.

Participants were asked to rate the 120 candidate outcomes on the same 1-9 Likert scale. A table containing the overall group scores and scores for each group for each outcome were presented to participants in round two and participants were asked to rate each outcome in light of others feedback. Any relevant (i.e. not intervention or trial specific) suggested outcomes were also rated.

A question on the preferred unit of analysis (patient, ulcer or limb) was once again presented to participants.

The survey ended with a thank you page and contact details for any questions.

5.2.7.2.1 Meeting at the EWMA conference

A meeting was held at the EWMA conference in Krakow, Poland, on the 10th May 2018 11:15-12:15.

The purpose of the meeting was to give stakeholders attending the conference an opportunity to rate the importance of the outcomes for inclusion in the core outcome set. The purpose of the meeting was explained to the attendees at the beginning of the session. It was explained that it would not be possible to withdraw the data collected at the meeting because it would be anonymised. Attendees were also informed that by participating in the meeting that they were consenting to take part. Attendees were given a participant information sheet (appendix 12). Attendees were able to ask questions and provide comments during the meeting.

A PowerPoint presentation was delivered, the PowerPoint slides can be found in appendix 13.

Participants were asked to rate each outcome on a paper copy of the online survey. Attendees were also provided with a link to access the survey online if they did not want to complete the paper survey during the meeting.

5.2.8 Data Analysis

5.2.8.1 eDelphi Round One Analysis

Data were exported from each participant's response on the Bristol Online Survey and inputted into Excel. An example of the extracted data can be seen in Table 20. HCP 1, 2, 3 etc. indicates an extract of participants responses from the healthcare professional group, were HCP indicates healthcare professional.

Table 20 Example of the data inputted into Excel from the round one eDelphi on the outcomes

	Rating score						
Outcome	**HCP 1 England**	**HCP 2 Finland**	**HCP 3 New Zealand**	**HCP 4 UK**	**HCP 5 UK**	**HCP 6 UK**	**HCP 7 Ireland**
Number of patients/ulcers/limbs that completely healed in a trial period	9	9	9	9	9	8	7
Time to complete healing - may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs	9	9	9	8	9	7	7
Change in size of ulcer, e.g. length, circumference, area, volume	6	6	9	6	9	9	8
Number of reference ulcers achieving a pre-defined ulcer area change (e.g. any reduction, at least 50% reduction, at least 75% reduction)	3	6	8	5	1	9	8
Time to achieving a pre-defined ulcer area change in a reference ulcer (e.g. any reduction, at least 50% reduction, at least 75% reduction)	3	6	8	5	1	8	8
Change in ulcer severity score	6	4	9	6	9	6	5

The first round eDelphi survey responses were analysed using descriptive statistics IBM SPSS Statistics version 22.

Histograms were produced displaying the displaying the distribution curve for each outcome. Visual inspection of the histograms demonstrated that the data for every outcome was not normally distributed and negatively skewed. Because the data was not normally distributed the median for each outcome per stakeholder group and groups overall was calculated for feedback purposes in round two.

The suggested new outcomes were reviewed by members of the research team to check for duplication with previously identified outcomes and to exclude any irrelevant suggestions, for example any suggestions relating to interventions rather than outcomes. All relevant suggested outcomes were carried forward into round two.

5.2.8.2 eDelphi Round Two Analysis

Data were exported from each participant's response on the Bristol Online Surveys and inputted into Excel. Data were extracted from the paper surveys completed at the meeting at the EWMA conference and inputted into Excel. Data extracted from the online surveys and the paper surveys was combined to produce an Excel spreadsheet containing all data from all surveys.

The second round eDelphi survey responses were analysed using descriptive statistics IBM SPSS Statistics version 22. Histograms displaying the distribution curve for each outcome were visually inspected and the degree of skewness was calculated using SPSS.

The second round eDelphi survey responses were analysed by calculating the percentage of participants rating each outcome as 7, 8 or 9 (extremely important), 4, 5, or 6, OR 1, 2 or 3 (not important).

The survey item asking participants what their preferred unit of analysis was analysed by calculating the number and percentage of participants selecting either patient, limb or ulcer.

5.2.9 Consensus Definition

The consensus definition and criteria that was applied in stage two (section 4.4.9) was applied in stage three.

5.3 Results

5.3.1 eDelphi Round One

Thirty-six participants from 16 countries took part in the first round involving 1 carer, 10 researchers, and 25 healthcare professionals. Of the 25 healthcare professionals that took part there were 10 nurses, 5 Doctors, 4 tissue viability nurses, 3 vascular surgeons, 2 nurse consultants and 1 nursing management. Table 21 displays the overall number of participants, and participants per stakeholder group that took part in round one. Table 22 displays the participants' countries of residence. Because participants were anonymised it was not possible to determine whether the same participants accessed both rounds.

Four participants accessed the survey via the Tweet and 32 participants accessed the survey via email.

The first round was open between 22nd March 2018 and 26th April 2018. One hundred and twenty outcomes were rated by participants.

Table 21 Participant response numbers per stakeholder group in round one

Stakeholder group	Respondents in Round 1
Patient and Carers	1
Researchers and Healthcare professionals	35
Total number of participants	36

Table 22 Participants' countries of residence (round one):

Country	**Number of participants**
Australia	1
Brazil	2
Czech Republic	1
Estonia	1
Finland	1
Ireland	5
Italy	1
New Zealand	2
Portugal	1
Spain	1
Sri Lanka	1
Sweden	1
Switzerland	1
United Kingdom	15
United States of America	2

The comments provided by participants and the suggested outcomes are displayed in Table 23. The suggested outcomes are the outcomes that participants' provided when asked if there were any outcomes that should be considered other than what was included in the survey. Many of the suggested outcomes were pre-emptive of the proceeding outcomes in the survey, for example the outcome 'measurement of pain' was suggested in the section on 'healing' and the outcomes on pain came after the section on healing. Therefore many of the suggested outcomes were already included but they

were further on in the survey. The qualitative comments are discussed in chapter 6, section 6.2.3.1.

Table 23 Comments and suggested outcomes

Participant number	Comments (verbatim)	Suggested outcomes (verbatim)
1	Time to healing and healing rates are much more important than reduction in surface area	Pain score / qol
	Many of the above appear too difficult to assess in a community setting [relating to the outcomes in the clinical measurement outcome domain]	Concordance
		Increase in pain [relating to adverse event]
		Limb distortion [relating to adverse event]
2	It is important that any adverse events are discussed with the whole clinical team to ensure learning from them	Not all ulcers are treated entirely in Leg Clubs so might be useful to know how often they attended for treatment at Leg Club
		Independent mobility
3	Hawthorne effect	QoL
	Important to treat whole patient hence my choice above [question on the preferred unit of analysis; patient, ulcer or limb]. However ulcer and limb are also important units of analysis	Pain at dressing change and overall pain score
		Reduction in ulcer size, area, etc. are surrogate outcomes. Ideal outcomes are number of ulcers healed. Feasibility of lengthening follow up time to capture these outcomes?
		Total time for visit, include travel to and from, waiting to be seen
		Length of time of adherence
		Pattern of adherence? Times and days occasions where device is used or not

4		Quality of life
		Who funds [relating to resource use]
5		Periwound edema/ border edema/ periwound inflammatory process
		Biofilm presence
6	The importance of outcomes will be determined by the research question- outcomes related granulating tissue or fibrin maybe important if the question is regarding debridement, for instance, but may otherwise be unimportant if the purpose of the trial is to evaluate efficacy of effectiveness of an intervention on healing	
	Adverse events are typically poorly reported in VLU trials ……What is also clear is not only are adverse events poorly reported, but the types of analysis vary considerably and guidance on the types of analysis would be useful eg how should adverse events be reported, not just what events should be reported. [This comment has been edited in order to maintain anonymity]	
	Again the importance of these outcomes [symptoms]	
	Again depends on the research question [life impacts]	
	I find this approach to establishing core outcomes less than useful - the outcomes should be driven by the research questions. A more useful approach might to have included scenarios with research questions so that in some circumstances some outcomes are core but in other circumstances they are.	
7	Outcome measure is highly dependent on nature of product evaluated	

	Some of these measures are required for cost-effectiveness valuations [performance of the intervention]	
8		Disability from adverse events
		Negligent events
		Time-trade-off specific to VLUs and QOL
		Compliance to care
		Cost of noncompliance compression
		Cost of pain medications
9		Sleep disturbance due to pain
		Maceration around the wound
10	Patients with leg ulcers are often experts on their condition and can provide valuable input to this topic	Patient factors impacting compliance eg allergy reaction, itch heat from bandage, discomfort/irritation, difficulty tolerating the treatment
11		% Epithelialisation tissue or increased new edge
12		Exudate
13		Reduction in pain
14		Measurement of pain
15		Relação tratamento vs custo [Relationship treatment vs cost]
16	Preferred unit depends on most appropriate to design and outcome of study and may be any of the 3 mentioned above	
17		Technical success or compliance (depending on intervention)
		Time to healing and recurrence but other than that patient opinion
18	The holistic care of the pt [patient] includes the ulcer and limb	Add question on patient wellbeing

No suggested outcomes were included in round two because the suggested outcomes had either been included further on in the round one survey, or they were intervention specific or trial specific and therefore not relevant to every research evaluation of interventions used for venous leg ulceration.
All outcomes were carried over into round two to be rated by participants.

5.3.2 eDelphi Round Two

Thirty participants from 15 countries took part in the second round involving 9 researchers, 4 researchers from industry, and 17 healthcare professionals. Of the 17 healthcare professionals that took part there were 8 nurses, 3 Doctors, 2 tissue viability nurses, 1 vascular surgeon, 1 pharmacist, 1 nursing management personnel and 1 nurse consultant. Table 24 displays the overall number of participants, and participants per stakeholder group that took part in round two. Table 25 displays the participants' countries of residence. Because participants were anonymised it was not possible to determine whether the same participants accessed both rounds.

Three participants accessed the survey via the Tweet, 12 participants accessed the survey via email and 15 participants completed the paper survey at the meeting at the EWMA conference.

The second round was open between 5th May 2018 and 5th June 2018.

Table 24 Participant response numbers per stakeholder groups in round one and two

Stakeholder group	Respondents in Round 1	Round 2
Patient and Carers	1	0
Researchers and Healthcare professionals	35	30
Total number of participants	36	30

Table 25 Participants' countries of residence (round two):

Country	**Number of participants**
Australia	1
Austria	3
Denmark	1
France	1
Finland	2
Germany	2
Greece	1
Ireland	3
Italy	1
Portugal	1
Sultanate of Oman	1
Sweden	1
Switzerland	2
United Kingdom	7
United States of America	1
Not specified (paper survey)	2

There was no missing data for the online surveys. One participant did not complete 13 items on a paper survey at the meeting at the EWMA conference meaning the ratings for the following outcomes were missing for that participant:

Time required for ulcer dressing changes

Change in the scoring/rating of tingling or pins and needles during the trial period

Percentage of the ulcer surface area covered with necrotic tissue

Change in necrotic tissue during the trial period

Number of patients with necrotic tissue

Change in the scoring/rating of exudate during the trial period

Time to cessation of exudate (e.g. number of days, weeks)

Rate of change in exudate

Number of ulcers with exudate

Change in the severity of malodourous exudate during the trial period

Number ulcers with lymphangitis (inflammation or infection of the lymphatic channels-part of the circulatory system)

Number of patients with abnormal skin changes

Number of patients with hyperpigmentation (darkening of an area of the skin) during the trial period

Another participant did not complete one item on a paper survey at the meeting:

Change in the scoring/rating of tingling or pins and needles during the trial period

Another participant did not complete one item on a paper survey at the meeting:

Number of reference ulcers achieving a pre-defined ulcer area change (e.g. any reduction, at least 50% reduction, at least 75% reduction)

The results of the round two survey are presented in Table 26 and Table 27. Forty-six outcomes met the criteria for consensus IN meaning 70% or more rated the outcomes 7-9 (extremely important) and 15% or less rated the outcomes 1-3 (not important). Table 26 displays the outcomes that met the criteria for consensus IN.

Seventy-four outcomes did not meet the criteria for consensus IN (70% or more rated the item 7-9 and 15% or less rated the item 1-3) or OUT (70% or more rated the item 1-3 and 15% or less rated the item 7-9), and were therefore deemed to have ‘no consensus’. Table 27 displays the outcomes with ‘no consensus’. There were no outcomes that met the criteria for consensus OUT.

Table 26 Outcomes that met the criteria for consensus IN

Outcome	**Rating 1-3** % (Nº of responses)	**Rating 4-6** % (Nº of responses)	**Rating 7-9** % (Nº of responses)
Healing (outcome domain)			
Number of patients/ulcers/limbs that completely healed in a trial period	7% (2)	13% (4)	80% (24)
Time to complete healing - may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs	3% (1)	10% (3)	87% (26)
Change in size of ulcer, e.g. length, circumference, area, volume	7% (2)	10% (3)	83% (25)
Adverse events (outcome domain)			
Number of adverse events (type of adverse event/s to be detailed in the paper)	3% (1)	3% (1)	93% (28)
Number of patients that experience an adverse event (type of adverse event/s to be detailed in the paper)	10% (3)	7% (2)	83% (25)
Number of patients that withdrew due to an adverse event (type of adverse event to be detailed in the paper)	10% (3)	7% (2)	83% (25)
Number of serious adverse events (type of adverse event/s to be detailed in the paper)	10% (3)	3% (1)	87% (26)
Number of patients that had episodes of clinically diagnosed infection	3% (1)	10% (3)	87% (26)
Number of patients with sepsis (also known as blood poisoning)	10% (3)	10% (3)	80% (24)
Number of patients with cellulitis	13% (4)	3% (1)	83% (25)
Change in the severity of cellulitis during the trial period	13% (4)	10% (3)	77% (23)
Pain (outcome domain)			
Number of patients/ulcers/limbs with pain	3% (1)	3% (1)	93% (28)
Number of patients reporting a pre-specified level of change in pain score during the trial period (e.g. any reduction, at least 50% relief)	10% (3)	3% (1)	87% (26)

Change in patient reported pain score/rating during the trial period	10% (3)	3% (1)	87% (26)
Life impacts (outcome domain)			
Change in the Quality of Life score during the evaluation period	0	3% (1)	97% (29)
Activities of living (outcome domain)			
Change in activities of daily living score	7% (2)	0	93% (28)
Ability to wear/find suitable clothes and shoes	10% (3)	17% (5)	73% (22)
Clinical signs / symptoms (outcome domain)			
Change in oedema during the trial period – on a trial leg / both legs	3% (1)	3% (1)	93% (28)
Number of patients with oedema	7% (2)	17% (5)	77% (23)
Number of patients with the presence of malodour of the ulcer	7% (2)	13% (4)	80% (24)
Number of patients/ulcers/limbs with a change in slough during the trial period	10% (3)	13% (4)	77% (23)
Percentage of ulcer surface covered in slough	10% (3)	20% (6)	70% (21)
Change in the scoring/rating of necrotic tissue during the trial period	7% (2)	17% (5)	77% (23)
Change in the scoring/rating of exudate during the trial period	10% (3)	7% (2)	80% (24)
Time to cessation of exudate (e.g. number of days, weeks)	7% (2)	20% (6)	70% (21)
Clinical measurement (outcome domain)			
Change in venous blood flow	10% (3)	10% (3)	80% (24)
Number of limbs with a pre-specified change in venous insufficiency (e.g. any improvement)	7% (2)	17% (5)	77% (23)
Change in venous pressure	13% (4)	13% (4)	73% (22)
Change in ankle/arm pressure ratio during the evaluation period	7% (2)	20% (6)	73% (22)

Resource use (outcome domain)			
Number of dressing changes (e.g. per week, to healing)	7% (2)	7% (2)	87% (26)
Time between dressing changes, in days	7% (2)	13% (4)	80% (24)
Time required for ulcer dressing changes	7% (2)	10% (3)	80% (24)
Number of debridements required to obtain a clean ulcer	7% (2)	20% (6)	73% (22)
Cost to heal patient/ulcer/limb completely	3% (1)	7% (2)	90% (27)
Cost per given time frame (e.g. week, month, year)	7% (2)	13% (4)	80% (24)
Total costs to the end of the study	7% (2)	10% (3)	83% (25)
Nursing or clinician time required per patient/ulcer/limb (cost and/or time)	13% (4)	3% (1)	83% (25)
Number of work days lost	7% (2)	13% (4)	80% (24)
Patient expenses	3% (1)	13% (4)	83% (25)
Performance of the intervention (outcome domain)			
Ease of application- Reported by the patient	3% (1)	7% (2)	90% (27)
Ease of removal - Reported by the patient	7% (2)	13% (4)	80% (24)
Patients scoring of satisfaction with the performance of the intervention	10% (3)	13% (4)	77% (23)
Healthcare professionals scoring of satisfaction with the performance of the intervention	10% (3)	20% (6)	70% (21)
Rating of exudate handling by dressing	13% (4)	17% (5)	70% (21)
Number of dressing changes with exudate leakage	10% (3)	13% (4)	77% (23)
OTHER			
Number of patients that adhered to treatment advice	7% (2)	3% (1)	90% (27)

Table 27 Outcomes with no consensus (did not meet the criteria for consensus IN or OUT)

Outcome	**Rating 1-3** % (Nº of responses)	**Rating 4-6** % (Nº of responses)	**Rating 7-9** % (Nº of responses)
Number of reference ulcers achieving a pre-defined ulcer area change (e.g. any reduction, at least 50% reduction, at least 75% reduction)	13% (4)	17% (5)	67% (20)
Time to achieving a pre-defined ulcer area change in a reference ulcer (e.g. any reduction, at least 50% reduction, at least 75% reduction)	10% (3)	30% (9)	60% (18)
Change in ulcer severity score	10% (3)	40% (12)	50% (15)
Number of ulcers with granulating tissue	20% (6)	40% (12)	40% (12)
Number of ulcers with: a. healthy granulation b. at least 75% clean granulation c. unhealthy granulation	20% (6)	37% (11)	43% (13)
Quantity of granulation tissue measured at a given time point	20% (6)	43% (13)	37% (11)
Time to a pre-specified level of granulation tissue (e.g. 50%, 75%, 100%)	17% (5)	40% (12)	43% (13)
Percentage change in granulating tissue during the trial period	13% (4)	33% (10)	53% (16)
Quantity of fibrin on the ulcer measured at a given time point	23% (7)	47% (14)	30% (9)
Percentage change in fibrin during the trial period	23% (7)	43% (13)	33% (10)
Investigator reported level of pain	20% (6)	60% (18)	20% (6)
Pain level during mobilisation	10% (3)	33% (10)	57% (17)
Change in ‘comfort’ score/rating during the trial period	10% (3)	33% (10)	57% (17)
Comfort rating during dressing change (e.g. dressing removal)	10% (3)	30% (9)	60% (18)
Change in ‘ache’ scores/rating during the trial period	17% (5)	43% (13)	40% (12)
Change in heavy legs sensation score/rating during the trial period	10% (3)	23% (7)	67% (20)

Change in the scoring/rating of tiredness of the lower limbs during the trial period	13% (4)	40% (12)	47% (14)
Number of patients reporting heavy leg sensation	10% (3)	40% (12)	50% (15)
Change in the scoring/rating of cramps during the trial period	17% (5)	40% (12)	43% (13)
Number of patients with cramps	20% (6)	40% (12)	40% (12)
Change in venous claudication severity score during the trial period	13% (4)	37% (11)	50% (15)
Change in the scoring/rating of skin tenseness around the ulcer during the trial period	13% (4)	30% (9)	57% (17)
Change in the scoring/rating of restless lower limbs during the trial period	17% (5)	37% (11)	47% (14)
Change in the scoring/rating of heat/burning during the trial period	13% (4)	23% (7)	63% (19)
Change in the scoring/rating of itching during the trial period	10% (3)	33% (10)	57% (17)
Number of patients reporting itching during the trial period	10% (3)	33% (10)	57% (17)
Change in the scoring/rating of tingling or pins and needles during the trial period	20% (6)	30% (9)	43% (13)
Change in the scoring/rating of tenderness (area i.e. limb or ulcer) during the trial period	17% (5)	37% (11)	47% (14)
Change in fatigue scores/rating during the trial period	23% (7)	43% (13)	33% (10)
Patients perception of their body image	13% (4)	20% (6)	67% (20)
Number of ulcers with suppuration (pus)	10% (3)	27% (8)	63% (19)
Absolute or relative change in pus during the trial period	10% (3)	30% (9)	60% (18)
Severity of odour (from the ulcer)	17% (5)	20% (6)	63% (19)
Change in the scoring/rating of erythema during the trial period	10% (3)	27% (8)	63% (19)
Number of ulcers that had a change in erythema (e.g. decreased, increased)	10% (3)	23% (7)	67% (20)
Number of ulcers with new areas of slough	13% (4)	20% (6)	67% (20)
Percentage of the ulcer surface area covered with necrotic tissue	7% (2)	27% (8)	63% (19)

Change in necrotic tissue during the trial period	7% (2)	30% (9)	60% (18)
Number of patients with necrotic tissue	7% (2)	27% (8)	63% (19)
Rate of change in exudate	10% (3)	33% (10)	53% (16)
Number of ulcers with exudate	7% (2)	23% (7)	67% (20)
Change in the severity of malodourous exudate during the trial period	10% (3)	20% (6)	67% (20)
Number ulcers with lymphangitis (inflammation or infection of the lymphatic channels-part of the circulatory system)	17% (5)	20% (6)	60% (18)
Number of patients with abnormal skin changes	13% (4)	20% (6)	63% (19)
Number of patients with hyperpigmentation (darkening of an area of the skin) during the trial period	23% (7)	33% (10)	40% (12)
Time to re-pigmentation (skin regains normal colour)	23% (7)	50% (15)	27% (8)
Change in the surface area of lipodermatosclerosis (inflammation of the layer of fat under the epidermis) during the trial period	20% (6)	40% (12)	40% (12)
Number of patients with denuded peri-wound skin (loss of the top layer of skin on the surrounding skin)	17% (5)	30% (9)	53% (16)
Changes in valvular competence	10% (3)	23% (7)	67% (20)
Number of limbs with superficial femoral incompetence	13% (4)	27% (8)	60% (18)
Diameter of the superficial femoral vein (mm)	17% (5)	50% (15)	33% (10)
Change in venous distensibility (swelling)	20% (6)	23% (7)	57% (17)
Change in transcutaneous partial pressure of oxygen (mmHg)	17% (5)	47% (14)	37% (11)
Change in pCO2 (partial pressure of carbon dioxide)	30% (9)	57% (17)	13% (4)
Change in blood biochemistry (e.g. Urea and electrolytes)	30% (9)	53% (16)	17% (5)
Change in a pre-specified haematological parameter (for example; Red blood cells, White blood cells, Erythrocyte sedimentation rate)	27% (8)	57% (17)	17% (5)

Change in glycaemia (blood glucose)	20% (6)	47% (14)	33% (10)
Change in cholesterol (blood test)	37% (11)	53% (16)	10% (3)
Change in systolic blood pressure	17% (5)	67% (20)	17% (5)
Change in diastolic pressure	17% (5)	63% (19)	20% (6)
Change in heart rate	30% (9)	57% (17)	13% (4)
Number of patients that had microbiologically determined presence of a particular pathogen/s on the ulcer bed (type of micro-organism to be specified by the trialist)	10% (3)	30% (9)	60% (18)
Change in mASEPSIS score (wound infection score)	13% (4)	20% (6)	67% (20)
Number of patients that achieved 7 day wear time	13% (4)	27% (8)	60% (18)
Ease of application- Reported by the researcher	10% (3)	27% (8)	63% (19)
Ease of removal - Reported by the researcher	10% (3)	33% (10)	57% (17)
Number with traumatic dressing removal (trauma to the ulcer bed or the surrounding skin)	10% (3)	23% (7)	67% (20)
Time required to debride the ulcer	13% (4)	27% (8)	60% (18)
Number of patients that required surgical debridement	10% (3)	33% (10)	57% (17)
Number of visits where debridement was needed	13% (4)	27% (8)	60% (18)
Cost per pre-specified reduction in ulcer area	13% (4)	33% (10)	53% (16)
Cost of dressings	13% (4)	23% (7)	63% (19)
Number of dressing treatments per group	13% (4)	23% (7)	63% (19)
Costs required to achieve debridement	17% (5)	33% (10)	50% (15)

A table displaying the degree of skewness for each outcome is presented in appendix 15. The data for each outcome in round two were negatively skewed indicating rare values were on the low side of the x axis towards the ‘not important’ end of the rating scale. There were however 17 outcomes that were approximately symmetric (skewness was between -0.5 and 0.5), these were:

Number of ulcers with granulating tissue

Number of ulcers with: a. healthy granulation b. at least 75% clean granulation c. unhealthy granulation
Quantity of granulation tissue measured at a given time point
Time to a pre-specified level of granulation tissue (e.g. 50%, 75%, 100%)
Quantity of fibrin on the ulcer measured at a given time point
Investigator reported level of pain
Number of patients with cramps
Change in fatigue scores/rating during the trial period
Number of patients with hyperpigmentation (darkening of an area of the skin) during the trial period
Time to re-pigmentation (skin regains normal colour)
Diameter of the superficial femoral vein (mm)
Change in blood biochemistry (e.g. Urea and electrolytes)
Change in a pre-specified haematological parameter (for example; Red blood cells, White blood cells, Erythrocyte sedimentation rate)
Change in glycaemia (blood glucose)
Change in cholesterol (blood test)
Change in diastolic pressure
Change in heart rate

Participants were asked what their preferred unit of analysis is; either patient, limb or ulcer. Sixty percent of participants chose the patient as their preferred unit of analysis, 27% chose ulcer and 10% chose limb (Table 28).

Table 28 Preferred unit of analysis

Question	**Unit of analysis**	**% (N)**
Which unit of analysis do you think is the most important when measuring outcomes	Patient Limb Ulcer	60% (18) 10% (3) 27% (8) 1 respondent selected all 3

The qualitative comments provided by participants in round two are displayed in Table 29. One participant suggested some outcomes but because round two was the last round the outcomes were not carried forward into a further round of rating. The qualitative comments are discussed in chapter 6, section 6.2.3.1.

Table 29 Qualitative comments provided by participants in round two

Participant number	**Comments (verbatim)**
1	Epithelialization
	Pain, eczema, itching
	Pain at night/ position changes/ pain from bandage
	Dependency on others, malodour, heavy secretion, leakage embarrassment
	Surgical debridement- unusual in venous leg ulcers
	Time off from work and travel costs for next of kins accompanying the patient and patient
	Healing time is most important
2	I suggest using a parameter that compares the center with respect to the edges of the skin lesion as an indicator of the healing trajectory
	Many symptoms are not related to Venous Leg Ulceration
	Some questions are related to infected or rheumatic ulcer. In fact the target of this survey are, mainly non-infected, Venous Leg or lymphatic stasis Ulcers
	Some questions are related to arterial or infected ulcer, in fact the target are mainly non-infected venous ulcers
	There is a need for robust health economics studies as a primary (non-secondary) endpoint

5.4 Steering Group Consultation

Forty-six outcomes met the criteria for consensus IN which is a large number of outcomes to have in a core outcome set. It would not be feasible to report on such a large number in every RCT evaluating venous leg ulceration

interventions. If 46 outcomes were to be included in the core outcome set then the inconsistency of reporting across trials would remain an issue because a large number of outcomes would still be reported on. Whereas if the core outcome set contained a more manageable number of outcomes, there would be a greater probability of the outcomes in the core outcome set being reported across trials thus facilitating treatment comparisons across different sources of evidence and expediting the production of systematic reviews, meta-analyses and evidence-based clinical guidelines. The option to perform another eDelphi round to refine the outcomes was an option however it would have required an ethics application delaying the research, and in the meantime participants may have forgotten about the project which risked lack of engagement. Another round also risked burdening participants, especially after they had completed the lengthy surveys in rounds one and two. An additional round did not guarantee that the outcomes would be refined, therefore it was decided that a third round would not be done, instead the findings were presented to the steering group who have experience in venous leg ulcer research.

A conference call was held with members of the steering group to discuss the results of the eDelphi on the outcomes. The aim of the conference call was to discuss the results, determine if the steering group agreed that the outcomes with 'no consensus' (Table 27) should not be considered for inclusion in the core outcome set and discuss how the list of 46 outcomes (that met the criteria for consensus IN) should be refined to produce a manageable list of outcomes. A discussion amongst the steering group and research team then took place. Each outcome in the consensus IN was discussed in turn.

In light of the results of the eDelphi the following was agreed by the steering group and research team in order to produce a feasible number of outcomes:

It was suggested that the outcomes; 'Change in activities of daily living score' and 'Ability to wear/find suitable clothes and shoes' are encompassed within the outcome 'Change in the Quality of Life score during the evaluation period', therefore it was proposed that the 'Change in the Quality of Life score during the evaluation period' was taken forward and the other two outcomes were not.

It was proposed that the following outcomes are sub-components of the outcome; ‘Cost to heal patient/ulcer/limb completely’ when a societal perspective is used:

Nursing or clinician time required per patient/ulcer/limb (cost and/or time)

Number of work days lost

Patient expenses

The three outcomes listed above are contributory factors to calculating the cost to heal a patient, ulcer or limb outcome therefore they are encompassed by the outcome ‘Cost to heal patient/ulcer/limb completely’.

The following outcomes on adverse events were condensed into one outcome; ‘Incidence and type of adverse event/s during the trial period (including number of events and number of people)’ because it captures all elements of the eight outcomes:

Number of adverse events (type of adverse event/s to be detailed in the paper)

Number of patients that experience an adverse event (type of adverse event/s to be detailed in the paper)

Number of patients that withdrew due to an adverse event (type of adverse event to be detailed in the paper)

Number of serious adverse events (type of adverse event/s to be detailed in the paper)

Number of patients that had episodes of clinically diagnosed infection

Number of patients with sepsis (also known as blood poisoning)

Number of patients with cellulitis

Change in the severity of cellulitis during the trial period

The following outcomes were considered to be intervention specific and therefore not core for every research evaluation of interventions used for venous leg ulceration, for example the outcome ‘Change in oedema during the trial period – on a trial leg / both legs’ only applies to research concerned with

measuring oedema. A trial on debridement may not be concerned with measuring oedema thus demonstrating that the outcome is not for use by every research evaluations of interventions used for venous leg ulceration. Also not everyone with venous leg ulceration has oedema. Another example includes 'Time between dressing changes, in days'; this outcome would only be relevant for research on dressings and would not be useful for a drug trial. It was therefore proposed that the following outcomes were not for inclusion:

Change in oedema during the trial period – on a trial leg / both legs

Number of patients with oedema

Number of patients with the presence of malodour of the ulcer

Number of patients/ulcers/limbs with a change in slough during the trial period

Percentage of ulcer surface covered in slough

Change in the scoring/rating of necrotic tissue during the trial period

Change in the scoring/rating of exudate during the trial period

Time to cessation of exudate (e.g. number of days, weeks)

Number of dressing changes (e.g. per week, to healing)

Time between dressing changes, in days

Time required for ulcer dressing changes

Number of debridement's required to obtain a clean ulcer

We noted that the outcomes within the outcome domains 'clinical signs/symptoms' and 'clinical measurement' were highly rated by respondents and given that they are in some cases interim outcome measures with the actual impact of patients being seen through healing and quality of life. The outcomes within 'clinical signs/symptoms' and 'clinical measurement' are:

Change in oedema during the trial period – on a trial leg / both legs

Number of patients with oedema

Number of patients with the presence of malodour of the ulcer

Number of patients/ulcers/limbs with a change in slough during the trial period

Percentage of ulcer surface covered in slough

Change in the scoring/rating of necrotic tissue during the trial period

Change in the scoring/rating of exudate during the trial period

Time to cessation of exudate (e.g. number of days, weeks)

Change in venous blood flow

Number of limbs with a pre-specified change in venous insufficiency (e.g. any improvement)

Change in venous pressure

Change in ankle/arm pressure ratio during the evaluation period

Given that some of the outcomes are population and/or intervention specific rather than applicable across all populations and all interventions, we were unable to reach consensus during the conference call to whether they should be in the core outcome set. It was decided by the research team that they would not be included in the core outcome set but we will recommend that trialist select them dependent upon their population and intervention type.

Inclusion of healing in the core outcome set may encourage its reporting in trials of interventions such as debridement which have not always reported healing. It was therefore agreed amongst the research team and the steering group that the following outcomes that met the consensus IN, within the healing outcome domain, are core:

Number of patients/ulcers/limbs that completely healed in a trial period

Time to complete healing - may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs

Change in size of ulcer, e.g. length, circumference, area, volume

It was agreed amongst the research team and steering group that the outcome domains ‘pain’ and the remaining outcomes within ‘resource use’ contain

outcomes that are core for reporting across all trials, therefore the following outcomes were retained:

Number of patients/ulcers/limbs with pain

Number of patients reporting a pre-specified level of change in pain score during the trial period (e.g. any reduction, at least 50% relief)

Change in patient reported pain score/rating during the trial period

Cost to heal patient/ulcer/limb completely

Cost per given time frame (e.g. week, month, year)

Total costs to the end of the study

It was suggested that the outcome domain 'life impacts' is ambiguous, therefore it was decided that it should be called 'quality of life'. Additionally, the majority of studies that report on quality of life and the tools that assess quality of life all use the term 'quality of life'.

Because adherence is part of the CONSORT guidelines, it was decided that it should not be in the core outcome set but trialists should be directed to the use of CONSORT (CONSORT, 2018). CONSORT gives an evidence-based, minimum set of recommendations for reporting RCTs with an aim to improve the reporting in RCTs. It provides guidelines on how to design and conduct an RCT; it provides advice on how to analyse and interpret results, and how to assess the validity of the results. Concerns were raised at the session at EWMA (section 4.3) over the methodological and statistical issues in venous leg ulceration trials, specifically baseline prognostic variables and number of participants. The CONSORT checklist provides guidance on such methodological and statistical issues including the specifying of primary and secondary outcomes.

5.5 Summary

To summarise, the consensus study on the outcomes helped refine the outcome domains for inclusion in the core outcome domain set for research

evaluations of interventions used for venous leg ulceration. The core outcome domain set comprises of five outcome domains:

1. Healing
2. Adverse events
3. Pain
4. Quality of life
5. Resource Use

The following candidate outcomes, which fell within the five outcome domains listed above, and met the consensus IN criteria now require a systematic appraisal of their performance characteristics i.e. whether the outcomes are reliable, valid and responsive (discussed further in section 6.9.3):

Number of patients/ulcers/limbs that completely healed in a trial period

Time to complete healing – may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs

Change in size of ulcer, e.g. length, circumference, area, volume

Incidence and type of adverse event/s during the trial period (including number of events and number of people)

Number of patients/ulcers/limbs with pain

Number of patients reporting a pre-specified level of change in pain score during the trial period (e.g. any reduction, at least 50% relief)

Change in patient reported pain score/rating during the trial period

Change in the Quality of Life score during the evaluation period

Cost to heal patient/ulcer/limb completely

Cost per given time frame (e.g. week, month, year)

Total costs to the end of the study

The primary use of CONSORT will be recommended for RCTs on interventions used for venous leg ulceration.

The next chapter will summarise the key findings of all three stages of the PhD. It will go on to outline the strengths of the PhD and then it will discuss the

challenges that arose and the limitations to the research. The chapter will then discuss dissemination of the core outcome domain set and recommendations for future research. Finally, the chapter will conclude with the implications of the PhD for research.

Chapter 6 Discussion

6.1 Introduction

The PhD set out to develop a core outcome set for use in research evaluations of interventions used for venous leg ulceration. A core outcome domain set and a set of candidate outcomes have been developed over three distinct stages comprising of a scoping review (stage one) which identified outcome domains and outcomes that have been reported in RCTs on venous leg ulceration interventions and qualitative research, a consensus study on the outcome domains (stage two) and a consensus study on the outcomes (stage three). A detailed account of each stage is provided in the previous chapters. This chapter will therefore summarise the key findings of this PhD and it will discuss the strengths and limitations to the methodological approaches. It will also discuss the challenges that arose. It will then go on to explain changes to the protocol. Finally, the chapter will discuss ideas for future research, including dissemination of the core outcome domain set, the development of the core set of measurement instruments and the systematic appraisal of the candidate outcomes.

6.2 Summary of Findings

6.2.1 Stage One: Scoping Review

In stage one, a scoping review was performed which provided the foundation for the consensus process. The scoping review identified the outcome domains and outcomes reported in RCTs and qualitative research on venous leg ulceration. The scoping review identified 258 eligible studies of which 230 were RCTs and 28 were qualitative studies. A total of 822 (following de-duplication) outcomes were identified, of which 807 outcomes were identified from 230 RCTs and 15 outcomes from 28 qualitative studies.

The 822 outcomes were grouped into 11 outcome domains which are presented below:

1. Healing
2. Patient reported symptoms
3. Clinician reported symptoms
4. Carer reported symptoms
5. Life impacts
6. Clinical signs
7. Clinical measurement
8. Performance of the intervention
9. Resource use: supplies
10. Resource use: clinician time
11. Adverse events

The 822 outcomes that were extracted during the scoping review were condensed into 120 outcomes, further information on the condensing process is available in chapter 3.

The findings of the scoping review support claims that the outcomes reported in venous leg ulceration RCTs are heterogeneous thus highlighting the need for standardisation of the outcomes (Franks et al., 2003; Dwan et al., 2008; Gottrup et al., 2010; Gethin et al., 2015b; Liu et al., 2017).

It is evident that there are a vast number of outcomes reported in RCTs posing difficulties for decision makers in recognising the trials purpose, identifying what outcomes have been reported, and collating usable information which is relevant to them. It also poses challenges in evidence synthesis. There is evidence of potential outcome reporting bias with 24% of the RCTs included in the scoping review stated an outcome or outcomes at the start of the paper but failed to report them in the results. Four percent of the RCTs introduced an outcome in the discussion when it had not been stated in any other part of the paper.

Deciphering what outcomes were reported in the RCTs was a challenge; in many cases the outcomes were worded in different ways in different parts of

the trial report making it unclear whether the outcome stated in the results was the same as the intended outcome that was stated in the methods.
When reading the trial report it was not always clear which outcomes were primary and secondary, which is not in keeping with the recommendations made by CONSORT (2010) which states that the primary and secondary outcomes should be pre-specified. When primary and secondary outcomes are not adequately reported it can cause ambiguity over the overall point of the study (Gethin et al., 2015b). In many cases there was not sufficient information on the outcomes making it difficult to fully understand what had been assessed. Nineteen percent of the RCTs failed to provide any information on the instruments used to measure the outcomes. Similarly to Gethin et al's (2015b) findings that the majority of venous leg ulcer trials (95%, 97/102) failed to make a reference to the reliability or validity of their measurement methods, the scoping review found that 74% (83/112) of the RCTs that measured an outcome relating to quality of life, signs and symptoms (e.g. pain, discomfort and heavy leg sensation) used trial specific scales. It is not clear if the trial specific scales were assessed for validity, reliability and sensitivity. Similarly to Gottrup et al. (2010) and Gethin et al. (2015b), the scoping review also found a lack of healing definitions; 45% (63/140) of RCTs included in the scoping review did not provide a definition of 'healing' or 'healed'. In addition, there was frequent use of un- defined outcomes such as 'acceptability' and 'tolerability'. These types of outcomes can be interpreted in many ways adding confusion to the meaning of the outcomes and the purpose of the trial. Many of the researchers who used these terms did not explain what they meant by them or how they were measured.

6.2.2 Stage Two: Consensus Process for Identifying Core Outcome Domains (eDelphi)

The second stage sought consensus on the outcome domains identified during the scoping review. Patients, carers, healthcare professionals, researchers from industry and wound care researchers were invited to take part in a two-

round eDelphi which aimed to identify which outcome domains are core for research evaluations of interventions used for venous leg ulceration.

A total of 95 participants took part in rounds one and two of the eDelphi, 51 in round one and 44 in round two. Patients, carers, healthcare professionals, researchers from industry and wound care researchers rated the outcome domains. Ten out of the 11 outcome domains were rated as core by participants. The outcome domain 'Carer reported symptoms' was not rated as core by participants. The outcome domains which were rated as core by participants are displayed below:

1. Healing
2. Patient reported symptoms
3. Clinician reported symptoms
4. Life impacts
5. Clinical signs
6. Clinical measurement
7. Performance of the intervention
8. Resource use: supplies
9. Resource use: clinician time
10. Adverse events

The data for each outcome domain in round two were negatively skewed indicating rare values were on the low side of the x axis towards the 'not important' end of the rating scale. Therefore the majority of ratings for each of the outcome domains were towards the 'extremely important' end of the rating scale. The histograms displaying the distribution curve can be found in appendix 9. All of the outcome domains, other than 'clinical signs', were highly skewed (less than -1). 'Clinical signs' was moderately skewed (between -1 and -0.5).

One carer and one healthcare professional rated healing '6' and life impacts '9' suggesting that quality of life is more important than healing. A participant suggested "…In terms of chronic venous ulceration, healing should not be the overall objective, quality of life is paramount…" thus emphasising why some participants rated 'life impacts' higher than 'healing'. The rating scores for each

outcome domains are displayed in Table 14 and Table 18, and the qualitative comments are displayed in Table 16, chapter 4.

The question asking if the outcome domain should be in the core set (yes or no) was not used to determine whether the outcome domain was included in the core outcome domain set because attitudinal issues often lie on a continuum and are not easily dichotomised (Bowling, 2005), and a dichotomous approach is related to a loss of information (Kottner et al., 2018). However, that said, it supported the decision not to include the outcome domain 'Carer reported symptoms' in the core set because the outcome domain had the highest percentage (50%) of participants selecting 'no' when asked if it should be in the core set, compared to the other outcome domains. This does not imply that the outcome domain is not important, but that the results of the eDelphi did not classify it as being 'core'.

The large number of outcome domains that met the consensus inclusion criteria meant that a very large number of outcomes were subjected to the subsequent consensus process.

6.2.2.1 Qualitative Comments

Some comments provided by participants in the round one survey reiterated the rating scores they gave, for example the following comment "Health economic would be very important given the current challenges in healthcare today. Patient and carer feedback is more significant that [than] the nurse treating the ulcer as this impacts on the patients QOL", was provided by a participant that rated resource use: supplies and clinician time, and patient and carer reported symptoms as extremely important and rated clinician reported symptoms as not important.

A participant suggested "The QOL measures are often very general and a specific measure such as veinesqol may be more appropriate" which is an important point, measurement instruments to assess the outcome domains now need to be established (further discussed in section 6.9.3).

One participant highlighted issues to be addressed in the conduct of trials:

> "Important questions concerning trials:
>
> a) Inclusion and exclusion criteria,
>
> b) unblinded, single-blinded, double-blinded,
>
> c) statistical aspects (alpha-error adjustment, was a calculation of sample size done ahead of the beginning of the trial?)"

However it was not in the scope of this PhD to address all aspects of venous leg ulceration research therefore the PhD was not able to address these issues but future research is needed on these.

A participant stated "…is not clear what is meant by Core Domain? It is not defined in PIS and it is not clear if one is being asked whether or not the domain must be included in all trials, or whether it should be included in trials as appropriate to the research question.". The introduction page to the survey included the following sentence "The purpose of this study is to determine what outcomes are essential for patients and their clinicians to make decisions and therefore must be reported for all trials of venous ulcer treatments.", the same sentence was included in the eDelphi on the outcomes but in light of feedback and the results of the eDelphi the following sentence was added at the start of each section to emphasise that the aim is for all outcomes in the core outcome set to be reported "We need to decide which outcomes are core and should be included in future trials on venous leg ulcer interventions.".

6.2.3 Stage Three: Consensus Process for Identifying Core Outcomes (eDelphi)

The third stage sought consensus on the outcomes that fell within the outcomes domains rated as core in stage two. The outcomes were those outcomes that were identified during the scoping review. Patients, carers, healthcare professionals, researchers from industry and wound care researchers were invited to take part in a two-round eDelphi which aimed to

identify which outcomes are core for research evaluations of interventions used for venous leg ulceration.

A total of 66 participants from 21 countries took part in rounds one and two of the eDelphi, 36 participants in round one and 30 participants in round two. Healthcare professionals, researchers from industry, wound care researchers and a carer rated 120 outcomes.
The majority of data (n=103/120) for each outcome in round two were negatively skewed indicating rare values were on the low side of the x axis towards the 'not important' end of the rating scale. As to be expected, the outcomes in the consensus IN category were highly skewed (less than -1), other than the outcome 'Change in ankle/arm pressure ratio during the evaluation period' which was moderately skewed (between -1 and -0.5). A table displaying the degree of skewness can be found in appendix 15.

The eDelphi on the outcomes refined the original set of 10 outcome domains that were rated as core in the stage two eDelphi to produce a set of five core outcome domains. The outcome domains which were agreed as core by participants and therefore comprise the core outcome domain set are displayed below:

Core outcome domain set:

1. Healing
2. Pain
3. Quality of Life
4. Resource use
5. Adverse events

Forty-six outcomes met the criteria for consensus IN (70% or more rated the item 7-9 and 15% or less rated the item 1-3) and 74 outcomes did not meet the criteria for consensus IN or OUT thus deemed 'no consensus'. No outcomes met the criteria for consensus OUT (70% or more rated the item 1-3 and 15% or less rated the item 7-9). The results of stage three are displayed in Table 26 and Table 27 in chapter 5.

Seventy-four outcomes did not meet the criteria for consensus IN or OUT, some core outcome set developers subject the 'no consensus' outcomes (rated 4-6) are subjected to another survey round, however the number of participants gradually declined since the start of the consensus process suggesting there may have been a further decline in participants if another round took place. The rating of such a large number of outcomes risked burdening participants resulting in fatigue. The 74 outcomes had no consensus thus suggesting they are unlikely to be appropriate for every trial and therefore they were deemed not suitable for the set of candidate outcomes.

An interesting observation was made; one healthcare professional rated the healing outcomes '2' and quality of life impact '8' suggesting that quality of life is more important than healing. Whereas one researcher rated the outcomes on quality of life '5' and the outcomes relating to healing a '9'.

Because it would not be feasible to report 46 outcomes in every trial a consultation meeting was held with the steering group to discuss the results (discussed in chapter 5). Each of the 46 outcomes were discussed in-turn and after consideration 35 outcomes were either formed to produce an outcome that incorporates other outcomes, for example the eight outcomes on adverse events were incorporated into the outcome 'Incidence and type of adverse event/s during the trial period (including number of events and number of people)', or the outcomes were excluded from inclusion because they are intervention/trial specific (discussed in section 5.4). This resulted in 11 outcomes which are proposed as candidate outcomes. The candidate outcomes now require a systematic appraisal of their performance characteristics i.e. whether the outcomes are reliable, valid and responsive. The 11 candidate outcomes are displayed in Table 30.

Table 30 Candidate outcomes

Number of patients/ulcers/limbs that completely healed in a trial period
Time to complete healing – may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs
Change in size of ulcer, e.g. length, circumference, area, volume
Incidence and type of adverse event/s during the trial period (including number of events and number of people)
Number of patients/ulcers/limbs with pain
Number of patients reporting a pre-specified level of change in pain score during the trial period (e.g. any reduction, at least 50% relief)
Change in patient reported pain score/rating during the trial period
Change in the Quality of Life score during the evaluation period
Cost to heal patient/ulcer/limb completely
Cost per given time frame (e.g. week, month, year)
Total costs to the end of the study

The results do not mean that the outcomes excluded from the list of candidate outcomes are not important or relevant but that the candidate outcomes (as displayed in Table 30) are agreed as core by stakeholders that took part in the eDelphi surveys. Trialists can report on additional intervention specific outcomes relevant to their trial (Schmitt et al., 2015).

Some of the candidate outcomes also require a suitable measurement instrument which is reliable, valid and responsive. Consensus is needed on what definition of healing is used in the core outcome set. There are existing definitions of 'healing' used in the literature for example, complete epithelialisation (Kerihuel, 2010), fully epithelized with the absence of drainage and without the need for a dressing (Alvarez et al., 2012), and complete epithelialization of the ulcer with no scab (Michaels et al., 2009). After a recent review by Gould and Li (2019) on how wound closure is determine in clinical trials and real-world wound literature, Gould and Li (2019) state that the widespread adoption of a wound healing definition and measurement method is needed for better comparisons of treatment effects across trials. Gould and Li's (2019) review included 64 RCTs (of which 21 were on venous leg ulcers),

and 9 real-world studies (studies based on electronic health records and patient/wound registry data). The review highlights the variance in the definition of 'healed'; five RCTs used the FDA definition of healing which is "skin reepithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart" (FDA, 2006, p. 12), four RCTs used a similar definition to the FDA's, 26 RCTs used a simpler definition (e.g. complete/full/100% (re)epithelialization or closure without discharge), 11 RCTs defined healing as complete epithelialization or closure, and 18 RCTs did not define healing. Only three out of nine real-world studies defined healing which included; 'complete epithelialization at 24 weeks', 'complete epithelialization of all wounds without any major amputations 1 year post treatment' and one study referred to an algorithm to determine whether an ulcer has healed but no further details were given.

After consultation with the steering group and research team the following is recommended for researchers planning and reporting on research evaluations of interventions for venous leg ulceration:

1. All trialists follow the CONSORT guidelines (http://www.consort-statement.org/)
2. All venous leg ulcer trialists report on the five outcome domains in the core outcome domain set which are; healing, pain, quality of life, resource use and adverse events.

Future research is now needed to systematically appraise the 11 candidate outcomes (displayed in Table 30). Once they have been appraised and an accompanying core set of measurement instruments has been developed the core outcome set (which includes *what* outcome domains and outcomes should be measured and *how* the outcome domains and outcomes should be measured) will be recommended. Future research on the development of a set of measurement instruments is discussed further in section 6.9.3.

6.2.3.1 Qualitative Comments

Many qualitative comments provided by participants in the surveys reiterated the rating scores given to the outcomes, for example one participant that rated 'Time to complete healing – may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs' extremely important and outcomes relating to the reduction in surface area not important commented "Time to healing and healing rates are much more important than reduction in surface area".

One participant included a comment which said "Reduction in ulcer size, area, etc. are surrogate outcomes. Ideal outcomes are number of ulcers healed. Feasibility of lengthening follow up time to capture these outcomes?". It was not in the scope of this PhD to address all aspects of venous leg ulceration research therefore the PhD was not able to address these issues, it does however highlight that future research is needed on minimum follow up time.

A participant stated "Adverse events are typically poorly reported in VLU trials……What is also clear is not only are adverse events poorly reported, but the types of analysis vary considerably and guidance on the types of analysis would be useful eg how should adverse events be reported, not just what events should be reported", the core outcome set has the potential to improve the reporting of adverse events in venous leg ulcer trials. The candidate outcome 'Incidence and type of adverse event/s during the trial period (including number of events and number of people)' has been proposed for inclusion in the core outcome set following a systematic appraisal of its performance characteristics thus if trialist report the outcome fully then both the incidence and type of adverse event/s will be reported.

A participant stated that many of the outcomes relating to symptoms are not related to venous leg ulceration however the outcomes included in the survey are those that have been reported in RCTs on venous leg ulceration therefore all of the outcomes in the eDelphi surveys were related to venous leg ulceration.

6.3 Validity and Reliability

A ‘good’ judgement cannot be determined therefore the use of a rigorous method can increase the likelihood that a ‘good’ judgement is derived (Murphy et al., 1998). The principles of a rigorous method were applied in the planning and deliverance of the consensus process. Patient organisation representatives, various healthcare professionals and researchers were consulted in the planning phase of the consensus methods at the session at the EWMA conference (see section 4.3). The careful preparation of the methods through the development of a protocol strengthened the principles of good research practice.

Threats to external validity include the selection of the sample, and threats to internal validity include the situation (i.e. number of rounds and type of feedback provided), attrition and researcher bias (Keeney et al., 2011). Rowe et al. (1991) suggest that the validity of a study is influenced by the number of participants and their relative expertise. By involving participants with expert knowledge, the content validity can be enhanced (Goodman, 1987). The snowballing technique was used to optimise recruitment of participants with different expertise from various countries. The sample size and characteristics of a sample impact the generalisability of the findings to venous leg ulceration research (Parahoo, 2006). The findings however cannot be generalised to the wider context (outside of venous leg ulceration research) because the purpose of the research is to gain consensus on venous leg ulcer outcome domains and outcomes. The eDelphi panel was composed of ‘experts’ in venous leg ulceration and thus may not be typical of the general population outside of this context.

Consideration was given to the number of survey rounds because reliability increases as the number of rounds increase, however too many rounds can result in participant fatigue (Hasson et al., 2000), and successive rounds can lead to an increased number of drop outs (Simoens, 2006). It was decided that the survey would involve two rounds so that participants would not become fatigued which would have increased attrition. The audience members at the EWMA session (discussed in section 4.3) were also in favour of two rounds.

The opportunity to provide participants with explicit input ensures face and content validity by identifying any gaps in what has been measured (Kirwan et al., 2007). Participants who took part in the eDelphi surveys were able to suggest outcome domains and outcomes, and qualitative comments on the surveys, thus providing participants with an opportunity to give explicit input whilst identifying any missing outcome domains and outcomes.

While reliability was not assessed in this PhD, one way of assessing the Delphi method for reliability is to compare two or more Delphi studies which are on the same subject. The results are than analysed for intra-group agreement using Pearson correlation coefficient (Kastein et al., 1993). However, Kastein et al. (1993) highlight that although a study may demonstrate reliability, it cannot be generalised to an "Ideal Delphi". Future research is needed on the reliability of the Delphi method, however variations in Delphi studies will always exist therefore every Delphi study will be different, for example the level of expertise, size of the panel, clarity of the survey items and the number of rounds will be different, posing difficulties in assessing reliability.

6.4 Strengths of the PhD

6.4.1 Scoping Review

The scoping review generated a comprehensive list of outcomes which were extracted from RCTs on venous leg ulceration interventions and qualitative research. The scoping review enabled the breadth of the literature to be searched in a relatively time efficient way. Many (n=358) of the outcomes extracted from the RCTs and qualitative research papers were duplicated suggesting the extraction of the outcomes became saturated, implying that further searching may not have led to the retrieval of further outcomes. Some core outcome set developers recommend asking open questions to generate the list of outcomes (Sinha et al., 2011). Evidently the number of patients and carers that participated in both eDelphi's was low thus meaning if the list of outcomes had been generated by only using open questions then

some outcomes and outcome domains important to this stakeholder group may have been missed. Trials have been criticized for not including outcomes that are important to patients and carers (Gandhi et al., 2008; Chalmers and Glasziou, 2009; Sinha et al., 2009). Therefore, solely relying on the outcomes reported in RCTs to generate the list risked missing outcomes that are important to patients and carers. It was therefore essential to include outcomes that are important to this stakeholder group. It was hypothesised that the inclusion of outcomes identified in qualitative research would capture the outcomes regarded as important to patients and carers. The inclusion of qualitative studies reporting on outcomes expressed by patients and carers in the scoping review, and by including an option to suggest two additional outcome domains and outcomes in the surveys it was intended that the eDelphi surveys included outcomes that have been identified by patients and carers. The identification of patients' perspectives by including outcomes reported in qualitative research to inform the 'list' of outcomes is supported by Gorst et al. (2019). Gorst et al. (2019) carried out a rapid review on qualitative research. MEDLINE was searched for qualitative studies on type 2 diabetes with no date restrictions. The rapid review identified 458 individual outcomes from 26 studies which either involved qualitative interviews (69%) or focus groups (31%). The identified outcomes contributed to the development of the 'long list' of outcomes to be entered into a consensus process for the development of a core outcome set (Gorst et al., 2019). Gorst et al. (2019) demonstrated that a large number of outcomes which are important to patients can be identified through a review of qualitative studies.

6.4.2 International Involvement

Participants from 22 different countries took part in the eDelphi on the outcomes (stage three). International involvement is important because venous leg ulceration is a condition which is experienced world-wide and research on venous leg ulceration is carried out in various countries. International involvement increases the probability that the core outcome domain set is implemented and recognised worldwide, also the generalisability

and validity of the results is increased by the involvement of stakeholders from different cultures (Boers et al., 2017). The external validity of the core outcome domain set and candidate outcomes is increased by the involvement of international participants that took part in the eDelphi surveys. External validity is concerned with the extent to which the findings can be applied to the wider population (Creswell and Plano Clark, 2011). In a systematic review by Hutchings and Raine (2006) it was found that there were international differences in the overall and chance-corrected agreement on healthcare interventions between different countries (Switzerland, US, UK, Israel, Netherlands). Hutchings and Raine (2006) suggested that the difference may have been due to differences in healthcare resources between the countries, thus highlighting the importance of international involvement in the development of a core outcome set because there are potential differences in healthcare between countries. However cultural differences in the rating of the outcomes for research evaluations of interventions for venous leg ulceration are not evident.

6.4.3 Anonymity

The anonymity of participants was maintained throughout. Being able to inform participants that their responses would be anonymous potentially increased the likelihood of open and honest opinions in the rating of the outcome domains and outcomes, and in the qualitative feedback. One characteristic of the Delphi method is anonymity which is advantageous because it encourages true opinions which are not affected by peer pressure (Goodman, 1987). Subject bias is eliminated when participants are not known to each other (Jeffery et al., 1995). Subject bias, also known as participant bias or social desirability bias, occurs when participants want to respond in a socially acceptable way (Bowling, 2009). Therefore by maintaining anonymity it potentially meant that participants did not give responses they thought it were expected from them, eliciting true opinions.

The following example demonstrates that participants were potentially able to express open and honest opinions.

> I find this approach to establishing core outcomes less than useful - the outcomes should be driven by the research questions. A more useful approach might to have included scenarios with research questions so that in some circumstances some outcomes are core but in other circumstances they are [not]. [Participants number 6]

The participant raised a useful suggestion, however it was decided that scenarios would not be included for each outcome because the survey was already very long, adding scenarios for participants to read would have added to it length thus risking participant burden.

6.4.4 Opportunity for Participants to Suggest Outcome Domains and Outcomes

Consultation with stakeholders provides the opportunity to gain additional insights and allows for knowledge transfer and exchange by allowing additional sources of information and opinions to be offered (Levac et al., 2010). Participants were given an opportunity to suggest additional outcome domains and outcomes not included in the eDelphi surveys, and provide qualitative comments thus adding to the comprehensive list of outcomes.

Some outcomes were suggested in the eDelphi on the outcome domains (stage two) but they were already included on the list of outcomes to be subjected to the consensus process in stage three. There were no outcomes suggested in the eDelphi on the outcomes (stage three) that were relevant for inclusion i.e. suggestions that were not related to interventions or they were trial specific, or they were duplicated outcomes. This suggests that because there were no outcome domains or outcomes that participants suggested in addition to those that were already on the survey, that the survey captured the outcome domains and outcomes that are core to the stakeholders involved in the consensus.

6.5 Summary of the Strengths of the PhD

The scoping review generated a comprehensive list of outcomes for the consensus process, which included outcomes that have been reported in venous leg ulceration RCTs and qualitative research. There was international involvement in the consensus to develop the core outcome domain set and candidate outcomes. Participants had an opportunity to suggest outcome domains and outcomes that were not included in the eDelphi surveys. Anonymity was maintained throughout the consensus process.

The next section will discuss the methodological challenges that arose in the development of the core outcome domain set and set of candidate outcomes, and the limitations to the findings of the PhD.

6.6 Challenges and Limitations of the PhD

6.6.1 Terminology

The different terminology used by core outcome set developers posed challenges in the development of the definitions used in this PhD. Table 12 in section 4.2 displays examples of how the different terminology has been used.

Many discussions took place amongst the research team to discuss how an outcome domain and outcome would be defined. It was important to establish definitions that are not only relevant to core outcome set terminology but also to venous leg ulceration research. After many discussions and re-iterations the definitions presented in Table 1 (section 1.13) were decided upon.

Although the option of titling this PhD ‘the development of a core outcome domain set’ was possible, the term ‘core outcome set’ is well-recognised and therefore people are more likely to search for this term, which is crucial for its dissemination and implementation. Therefore the title of this PhD uses ‘core outcome set’ and it will be used for future publications.

Conceptual frameworks and guidance on core outcome set development has continued to grow and develop since the start of this PhD, for example the OMERACT filter 2.0 which was used to help guide the grouping of the outcomes into outcome domains has now been updated to filter 2.1. The filter was updated by OMERACT in order to address ambiguous wording and terminology (Boers et al., 2019). The OMERACT handbook has also been updated since the start of the PhD and they have developed a workbook (OMERACT, 2019). The COMET handbook (Williamson et al., 2017) was published towards the end of the planning phase for the stage two consensus process. The continual development of core outcome set guidance is positive and crucial for developers but the evolving guidance during the time this PhD has been carried out was challenging. The changing goal posts made them difficult to meet because the methods and ethics applications had already been developed and submitted.

6.6.2 Scoping Review Search Strategy

The search strategy retrieved 258 studies of which 230 were RCTs and 28 were qualitative studies. Two of the retrieved qualitative studies (Cullum et al., 2016; Burke, No date) were identified by members of the research team. The qualitative study by Cullum et al (2016) was part of a larger 5 year funded programme of research. Cullum et al's (2016) programme of research was not retrieved during the database searches which led to an investigation into whether the search strategy was sufficient in identifying relevant studies. A search (strategy can be found in appendix 16) was run to find out if the research by Cullum et al. (2016) was indexed in any of the four databases; MEDLINE, Scopus, Embase and CINAHL searched during the scoping review. The search did not locate Cullum et al's (2016) research thus suggesting the reason for not retrieving it in the scoping review was because the research is not indexed in the databases that were searched rather than the search strategy (appendix 1).

6.6.3 Language Bias

Language bias arises when researchers and readers only use scientific studies reported in English (Egger et al., 1997). Egger et al. (1997) found that RCTs with statistically significant results are more likely to be published in English. However Jüni et al. (2002) found that non-English trials produced significant results ($p<0.05$) and the estimates of effects were 16% more beneficial compared to English-language trials. Jüni et al. (2002) looked at 303 meta-analyses of which 50 included at least one published non-English trial. However, Jüni et al. (2002) point out that non-English trials included fewer participants compared to trials in English and the methodological quality of the trials was lower.

Due to lack of funding for translation services it meant English only RCTs and qualitative studies were included in the scoping review therefore language bias is a limitation to this PhD.
There were no additional outcomes or outcome domains suggested by participants from countries where English is not their first language suggesting the outcomes and outcome domains considered to be core to international stakeholders that took part in the consensus were captured.

6.6.4 Grouping of Outcomes into Outcome domains

The grouping of a large number of outcomes into outcome domains was challenging. There were many outcomes that had high degrees of overlap with other reported outcomes therefore making the grouping process challenging. Outcome domains contain many different outcomes, such as the 111 outcomes contained within the outcome domain ‘healing’ which the scoping review identified. The 111 outcomes are displayed in Table 10 (section 3.5.2). The 111 outcomes demonstrate that there can be a large number of outcomes within an outcome domain. By only recommending core outcome domains in a core outcome set it does not solve the problem that outcomes cannot be

combined to facilitate systematic reviews and meta-analyses. Trialist's can report on any outcome within an outcome domain, for example one trial may choose to report on 'Number of patients with the presence of malodour of the ulcer' as their primary outcome and another trial may choose 'Severity of odour (from the ulcer)' as their primary outcome, the two outcomes cannot be combined for a meta-analysis, whereas if trials report on the same outcomes in the same way they can be combined.

Taxonomy can facilitate the grouping of the outcomes into outcome domains. Taxonomy is a controlled vocabulary. It is a classification scheme to control the naming of groups within a hierarchical structure (American Society for Indexing, 2019). Since the launch of the consensus process a taxonomy was developed by Dodd et al. (2018) for outcomes in medical research. Conceptual models on taxonomy or classification schemes are not new; models exist such as Wilson and Cleary's (1995) conceptual model which groups health related quality of life outcomes into five areas: biological and physiological, symptoms, functioning, general health perceptions and overall quality of life. Wilson and Cleary's (1995) model was later revised by Ferrans et al. (2005). Ferrans et al. (2005) expanded the explanation of the five areas outlined in Wilson and Cleary's model. The areas depicted by Wilson and Cleary's (1995), and Ferrans et al's (2005) models are similar to the areas in the OMERACT filter 2.0 (Boers et al., 2014), which was used to guide the grouping of the outcomes extracted during the scoping review into outcome domains.

However, the new taxonomy by Dodd et al. (2018) provides a more detailed approach. The taxonomy contains 38-categories for classifying trial and systematic review outcomes. It was developed following a literature review by Dodd et al. (2018) who found that there was not a suitable outcome taxonomy for trial outcomes. The taxonomy was tested by applying it to the classification of outcomes recorded within 299 published core outcome sets on the COMET database, 3,515 Cochrane reviews and 30 studies identified from a search of US National Institutes of Health clinical trials registry (Dodd et al., 2018). The outcome taxonomy can be used to annotate core outcome sets. The COMET initiative promotes the use of Dodd et al's (2018) 38-category scale taxonomy in the development of a core outcome set, and provides explanations to each of

the 38 outcome domains on their website (http://www.comet-initiative.org/OutcomeClassification/Taxonomy).
Dodd et al's (2018) 38-category taxonomy would have been useful for the grouping of the outcomes into outcome domains but the taxonomy was not available at that time.

6.6.5 Rating of the Outcome Domains

Ten out of 11 outcome domains were rated as core by participants in the eDelphi on the outcome domains (stage two). One reason for this may have been because outcome domains containing many different, more specific outcome domains and outcomes within them, for example the outcome domain 'clinical signs' contains 14 outcome domains of which contains 28 specific outcomes. The 14 outcome domains and specific outcomes are displayed in Table 31.

Table 31 List of outcome domains and their specific outcomes within 'clinical signs'

Outcome domain	**Outcome**
Oedema	Change in oedema during the trial period – on a trial leg / both legs
	Number of patients with oedema
Pus	Number of ulcers with suppuration (pus)
	Absolute or relative change in pus during the trial period
Odour	Number of patients with the presence of malodour of the ulcer
	Severity of odour (from the ulcer)
Erythema	Change in the scoring/rating of erythema during the trial period
	Number of ulcers that had a change in erythema (e.g. decreased, increased)
Cellulitis	Number of patients with cellulitis

	Change in the severity of cellulitis during the trial period
Slough	Number of patients/ulcers/limbs with a change in slough during the trial period
	Number of ulcers with new areas of slough
	Percentage of ulcer surface covered in slough
Necrotic tissue	Change in the scoring/rating of necrotic tissue during the trial period
	Percentage of the ulcer surface area covered with necrotic tissue
	Change in necrotic tissue during the trial period
	Number of patients with necrotic tissue
Exudate	Change in the scoring/rating of exudate during the trial period
	Time to cessation of exudate (e.g. number of days, weeks)
	Rate of change in exudate
	Number of ulcers with exudate
	Change in the severity of malodourous exudate during the trial period
Lymphangitis	Number ulcers with lymphangitis (inflammation or infection of the lymphatic channels-part of the circulatory system)
Abnormal skin changes	Number of patients with abnormal skin changes
Hyperpigmentation	Number of patients with hyperpigmentation (darkening of an area of the skin) during the trial period
Re-pigmentation	Time to re-pigmentation (skin regains normal colour)
Lipodermatosclerosis	Change in the surface area of lipodermatosclerosis (inflammation of the layer of fat under the epidermis) during the trial period
Denuded peri-wound skin	Number of patients with denuded peri-wound skin (loss of the top layer of skin on the surrounding skin)

The refinement of the list of outcome domains in the eDelphi on the outcomes (stage three) proved to be more effective at gaining consensus on the outcome domains. One reason for this could have been because participants were able to see which specific outcomes are contained within each of the outcome domains.

On reflection, it may have been better to have included more specific outcome domains in the first eDelphi on the outcome domains, rather than the 11 broad outcome domains.

6.6.6 Rating of the Long List of Outcomes

There was a loss of 29 participants between the consensus study on the outcome domains (stage two) and the consensus study on the outcomes (stage three). One reason for this may have been due to the length of the online surveys in the eDelphi on the outcomes (stage three). Participants were asked to rate 120 outcomes; meaning it was a long survey for participants to complete. This could therefore have resulted in participant fatigue. Participant fatigue can arise when participants get tired of completing a survey (Lavrakas, 2008).

Edwards et al. (2002) performed a systematic review on RCTs of any method to influence response to postal questionnaires and found that the shorter the questionnaire, the more likely the response (odds ratio 1.86; confidence interval 1.55 to 2.24). The review included 292 trials of which 40 reported on the effect of questionnaire length.

Meta-analyses of published studies suggest lower response rates are associated with longer surveys (Heberlein and Baumgartner, 1978; Yammarino et al., 1991). However, the studies included in the meta-analyses are based on paper-based mail surveys. A meta-analysis by Sheehan (2001) was carried out on 31 studies that used e-mail surveys. Sheenan (2001) reported on; number of questions in the survey, number of pre-survey notifications, year of study, follow ups and topic salience but did not report on whether the studies

informed participants of how long the survey would take to complete. Sheenan (2001) did not find a correlation between survey length and response rate. Galesic and Bosnjak (2009) tested whether the information given to participants on the length of a survey affected response rates. They found that the longer the stated length of time to complete the survey the less respondents took part compared to a quicker survey.

In the stage two and stage three eDelphi surveys participants were given an approximate length of time each survey would take on the survey introduction page and participant information sheet. Participants were informed of the length of time in order to make an informed decision whether to take part, thus reducing participant burden. Efforts went into making the eDelphi surveys as succinct as possible, for example the outcomes were grouped under their outcome domains i.e. the outcomes related to healing were displayed under the title 'healing'. The same Likert scale was used for each outcome to make it more straight forward for participants to use.

6.6.7 Ordering of Survey Items

The ordering of the questions which asked participants to rate each outcome domain on a Likert scale of 1 to 9 was considered. Research suggests that the ordering of questions can influence response rate and participant's responses to questions (Bradburn et al., 2004; Galesic and Bosnjak, 2009; Krosnick and Presser, 2010; Brookes et al., 2018). The questions at the start of the survey can influence whether a person decides to take part or not because the initial questions give the participant an idea of what the survey entails (Krosnick and Presser, 2010).

Brookes et al. (2018) carried out a study on the impact of question order on the prioritisation of outcomes for a core outcome set. A parallel RCT, nested within a Delphi survey to test three hypotheses; the ordering of items impacts on the following: response rates, participants' responses and influences the items retained at the end of the first Delphi round (Brookes et al., 2018). One hundred and eighty seven participants took part, of which 116 were patients who had undergone an oesophagectomy, and 71 were healthcare

professionals who were members of the Association of Upper Gastro Intestinal Surgeons of Great Britain and Ireland. Participants were randomised to receive a survey with clinical and patient-reported outcomes, where patient-reported outcomes appeared either first or last. Participants rated a 68-item survey. Brookes et al. (2018) found that the ordering of the questions did not impact on response rates for the surveys sent to patients, but fewer healthcare professionals participated when the survey gave clinical items first and patient-reported items last. The importance of patient-reported outcomes were rated higher by patients when patient-reported outcomes came last in the survey, whereas healthcare professionals rated clinical outcomes higher when they appeared last on the survey. Brookes et al. (2018) also found that the order of questions impacted upon the number of outcomes retained at the end of round one. Discrepancy was found in the items retained by one stakeholder group and not by the other stakeholder group. Brookes et al. (2018) conclude that the ordering of outcomes in a Delphi survey can affect participants' ratings.

Galesic and Bosnjak (2009) found that questions posed later on in a survey were given shorter response times. Because the nature of the questions in the eDelphi surveys were the same throughout it may have meant participants spent less time on the questions posed later on in the survey as they became fatigued with completing the rating scales for each outcome. Alternatively, participants may have become accustomed to the framing of the items and thus did not need to spend as much time reading the questions. The length of time participants spent on each item is not known as the Bristol Online Survey did not time how long participants spent completing the surveys.

Guidance on question order in Delphi studies developing core outcome sets is lacking. Brookes et al. (2018) point out that further research is needed on the area of question order in core outcome set development and that there is little guidance on the best way to structure Delphi surveys.

The option to select 'no opinion' and the yes/no question asking if the outcome should be in the core outcome set which was asked in stage two was not included in the eDelphi on the outcomes (stage three) as not to add to the length of the survey. The option to select 'no opinion' and the yes/no question

did not generate data that was more useful than the 1 to 9 Likert rating scale (explained in chapter 4).

In order to make the survey shorter it would have meant omitting outcomes from the survey which would have introduced subjective bias of the researchers, whereby the researchers would have made judgements on which outcomes to omit. A shorter survey would have meant there was less possibility that people were put off from starting it or participants becoming fatigued completing it. The number of participants starting but not finishing the survey was not recorded by the Bristol Online Survey tool.

6.6.8 Selection of 'Experts'

The selection of participants was important because reliability can be affected by the judgements made by 'experts' taking part in an eDelphi. What makes an 'expert' has been debated over the years (discussed in chapter 2). Experts for the eDelphi surveys were thought of as being those that have either experienced a venous leg ulcer, cared for a person that has experienced a venous leg ulcer, decision makers, guideline developers or those involved in research on venous leg ulceration. Therefore recruitment aimed to invite these groups of stakeholders to take part in the development of the core outcome set because they have an in-depth understanding of which outcomes should be reported in research.

Purposive sampling was used to recruit participants belonging to venous leg ulcer and wound care networks, for example Alliance for Research and Innovation in Wounds and the European Wound Management Association. There is potential for subjective bias of the researchers as the participants were purposefully selected. The subjectivity of researchers selecting the type of participant is a potential for bias (Jones and Hunter, 1995), and threatens validity of the conclusions (Jupp, 2006). In an attempt to minimise subjective bias, the uptake of the eDelphi surveys was promoted through gatekeepers of the venous leg ulcer and wound care networks. Nevertheless, for the core

outcome set to be representative of venous leg ulceration, it was important to involve people who hold knowledge in this area.

6.6.9 Patient and Carer Participation

Two carers participated in round one of the eDelphi on the outcome domains, and one patient and one carer took part in round two of the eDelphi on the outcome domains. One carer took part in round one of the eDelphi on the outcomes, and no patients or carers took part in round two. The inclusion of five participants from the patient and carer group may limit its representation of patients' and carers' perspectives on the outcomes.

Low numbers for patient and carer participation have been reported in core outcome set development. In a systematic review by Davis et al. (2018) which included the findings from three previous systematic reviews (Gargon et al., 2014; Gorst et al., 2016a; Gorst et al., 2016b), it was found that of the 225 studies that provided details on the stakeholder groups that participated in 259 studies to develop a core outcome set, only 28% (62/225) included public representatives (i.e. patients, carers, service users and patient support group representatives). There are various reasons for this; public representatives were not recruited, public representatives did not respond to invitations, only a small number responded, and because of attrition. Attrition is the loss of participants over time (Bowling and Ebrahim, 2005). Attrition bias can occur in core outcome set development when the participants that do not take part in subsequent rounds have different views to other participant groups that continued to take part (Williamson et al., 2017). Attrition bias can lead to an over-estimation of the degree of consensus (Mullen, 1983; Bardecki, 1984; Williamson et al., 2017). However Harman et al. (2015) found that attrition bias did not affect the results in their Delphi study. One hundred and four healthcare professionals took part in round one of Harman et al's (2015) study, 85 completed round two and 74 completed round three. Participants in Harman et al's (2015) study were asked to rate outcomes (n=49). Harman et al (2015) calculated the average scores for round one then compared the average

scores for participants completing Delphi rounds one and two. Round three scores were compared with round two scores in the same manner. Harman et al (2015) found that the people that did not take part in round two or three did not represent extreme views therefore stating that bias was not an issue caused by attrition. However, no parents of children with cleft palate, or adults or children with cleft palate took part in the eDelphi's instead 35 parents, eight adults and eight children were interviewed.

Williamson et al. (2017) suggest that core outcome set developers should examine the presence of potential attrition bias. Because no patients or carers took part in round two of the eDelphi on the outcomes (stage three), the consensus in round two was dependent upon the participants within the 'professionals' stakeholder group (researchers, researchers from industry and healthcare professionals).

Attempts were made to recruit patients and carers by inviting members of the Lindsay Leg Club Society which has 39 clubs (30 Leg Clubs in the UK, 1 in Germany and 8 in Australia), and through a Tweet which was Tweeted two to four times a day. The use of Twitter increased the opportunity for public involvement.

Some core outcome set developers have used a combination of a systematic review or a literature review with interviews and/or focus groups to generate the list of outcomes (Millar et al., 2017; Sahnan et al., 2018). The use of interviews or focus groups may have generated a richer insight into the outcomes that are core to patients and carers and is worth considering in future core outcome set development. However that said, the scoping review identified a large number of outcomes that have been reported in RCTs and it identified outcomes that have been expressed by patients and carers in qualitative research which were included in the consensus. Therefore the inclusion of interviews or focus groups may not have generated outcomes that were not already identified during the scoping review, in which case interviews or focus groups may result in a waste of resources and patient's and carer's time.

6.6.10 Online Surveys Only

The surveys were only available to complete online, other than at the meeting at the EWMA conference where paper surveys were also available. The surveys were in English therefore only people literate in English could take part and those with access to the internet. A limitation to the research is therefore that the surveys were only available in English and mainly in an online format. In addition to the online surveys, paper versions of the surveys may have reached more participants. A meta-analysis by Manfreda et al. (2008) found that web surveys had an 11% lower response rate than other modes (e.g. mail, telephone, face to face survey or fax), suggesting paper surveys may generate better response rates than online surveys. The meta-analysis included 24 studies, but because some studies contained more than one comparison between the questionnaire modes there were 45 comparisons in total. Members of the Lindsay Leg Club were invited to take part in the eDelphi surveys. There are 30 Leg Clubs in the UK, 1 in Germany and 8 in Australia therefore it was thought that by inviting Lindsay Leg Club members to take part online it would capture a large sample of people who have had experience of having a venous leg ulcer or carers of people with venous leg ulceration. It also meant that an equal opportunity to participate was given to all members of the Lindsay Leg Club rather than a select few being offered paper versions of the surveys which were also not guaranteed to recruit participants.

An error in the formatting of the online survey arose which was identified by one participant who provided the following qualitative comment on the online survey; “the survey tool doesn't allow one to deselect "no opinion" option once chosen”. In this instance the score on the Likert scale was included in the data analysis.

6.6.11 Tracking of Survey Responses

All participants received the same link to each survey sent via gatekeepers of organisations meaning participants’ responses could not be identified on the

Bristol Online Survey. Therefore because participant's responses could not be linked to an individual it meant it was not possible to track whether the same participant took part in each round of the eDelphi studies. It also meant that attrition rates could not be accurately calculated. An advantage of this approach, however, was that anonymity was maintained throughout. Because participant's responses could not be identified it also meant that participant's responses could not be presented to them in the second round survey. To help overcome this participants were recommended to download or print their responses after completing the first survey so that they could see their ratings when completing the second survey. They were able to see how other stakeholder groups (i.e. patients and carers, researchers, and healthcare professionals) rated the outcome domains and outcomes in the first round. Participants were able to view a statistical summary of the stakeholder groups' views before rating the outcome domains and outcomes in round two.

6.6.12 Important Versus Core

All outcome domains were rated extremely important (7-9) apart from one ('carer reported symptoms') in stage two which meant all 120 outcomes were entered into the eDelphi on the outcomes (stage three). The large number of outcome domains rated as core could be due to the labelling on the Likert scale. The labelling of the Likert scale may have influenced participants rating; studies by Wildt and Mazis (1978), Frisbie and Brandenburg (1979) and Moors et al. (2014) found that adjective on the ends of the scales are more influencing than the labels in between. Therefore participants are more likely to be pulled towards the ends of end-anchored scales (Streiner and Norman, 2008), thus suggesting participants who took part in the eDelphi surveys may have been influenced by the extreme end of the scale. Acquiescence bias is the tendency of participants to endorse a survey item without considering its opposite (Watson, 1992), often called 'yes-saying' to items (Bowling and Ebrahim, 2005). Thus participants may have been pulled towards the positive end of the scale ('extremely important'). Bowling and Ebrahim (2005) suggest a solution to acquiescence bias is to switch the survey scale so that the end

labels are swapped. Reversed-scored items have been used in surveys in an attempt to overcome acquiescence (Cronbach, 1950; Paulhus, 1991). Conversely, Barnette (2000) found that reversing response options became too confusing for participants and therefore recommended against it. Barnette (2000) conducted a study to assess what the effects of wording on item and item response direction had on consistency reliability. Reversing response direction, for example instead of 1 indicating 'not important' it would indicate 'extremely important', was not tested in the eDelphi surveys because it was thought that it would be confusing for participants, especially with the number of outcomes that they were asked to rate in stage three. In addition, continually changing the scales throughout a lengthy survey risked participants selecting the wrong rating score, however further research on reversing response options in core outcome set development using the eDelphi is required. Conversely, end- aversion bias, also called central tendency bias, is the reluctance of a participant to use the extreme categories of a scale (Streiner and Norman, 2008). End-aversion bias is one explanation to why many outcomes (74/120) were defined as 'no consensus' (Anything else that did not meet the criteria for consensus IN/OUT) in the eDelphi on outcomes (stage three) instead of falling within the consensus OUT category (70% or more rated the item 1-3 and 15% or less rated the item 7-9).

Additionally, attitudes towards questions on a survey can be influenced by the fact that participants are being asked to answer that question, sometimes called 'reactivity'. Reactivity is concerned with the degree to which the act of measuring something changes the thing that is being measured (Punch, 2005). Therefore the fact that a participant was asked to rate an outcome domain or outcome may have influenced their rating score, changing it in some way.

Another explanation to why the majority of outcome domains and a large number of outcomes were rated as core could be because the difference in the concepts 'important' and 'core' were not clear to participants. The majority of outcomes rated extremely important (7-9) were by healthcare professionals and carers whereas researchers were more selective to which outcomes they rated as extremely important. The difference between healthcare professionals and researchers selective nature of which outcomes were rated extremely important

suggests that researchers are more familiar with the concept of core outcome sets and the implications of reporting many outcomes in a trial. Alternatively, researchers by nature of their job may be more critical and also more familiar with ratings scales thus taking longer to consider the options.

The development of a core outcome set in leg ulcer research is new for its discipline therefore healthcare professionals who took part in the consensus may have not been familiar with its concept. The findings of this PhD suggests more information on core outcome sets in nursing based journals would be useful, especially since core outcome sets are on the increase in various healthcare fields meaning healthcare professionals may be invited to take part in the development of core outcome sets.

In a qualitative comment provided in the round one eDelphi on the outcome domains, a participant highlighted “As they are all individually so important it is difficult to give priority to one over another” and “I think the domains above are all relevant…” thus emphasising that participants struggled to differentiate between which outcome domains were core versus those that were important but not core.

6.7 How the Findings Compare to Previous Research

This PhD supports findings reported by other researchers who have highlighted that multiple outcomes are reported in venous leg ulcer research. Gethin et al. (2015b) concluded in their systematic review that the outcomes reported in RCTs on venous leg ulceration are highly heterogeneous with 79 of the 102 RCTs reporting different outcomes. Liu et al. (2017) also found a variation in the reported outcomes in trials. Liu et al (2017) analysed outcomes pre-specified in Cochrane Wounds systematic reviews and found a large number (n=126) of different outcome domains were specified. The scoping review in this PhD found that 230 RCTs had reported 807 different outcomes thus supporting Gethin et al’s (2015b) conclusion that the outcomes reported in RCTs on venous leg ulceration interventions are highly heterogeneous. When outcomes are heterogeneous it means they cannot be compared and synthesised, therefore hindering systematic reviews and meta-analyses. As a

result, the findings from this body of research might not always reliably inform clinical decision making.

Gethin et al. (2015b) found that 39% (40/102) of RCTs did not report any outcomes in the methods section. Dwan et al. (2008) found that 40-62% (16 included studies in their systematic review) of wound care studies had a primary outcome that was either changed, omitted or introduced in the studies publication compared to the protocol. Similarly, Kirkham et al. (2010) found that only 55% (157/283) of trials in a cohort of Cochrane reviews included full data for primary outcomes. As previously reported in chapter 3, the scoping review found 24% (54/230) of the RCTs on venous leg ulceration stated an outcome or outcomes in the introduction and/or methods but failed to report them in the results. Also, 4% (9/230) of the RCTs introduced an outcome in the discussion when it had not been stated in any other part of the paper. Such issues suggest that RCTs on venous leg ulcer interventions are at risk of outcome reporting bias.

Gethin et al. (2015b) found that only 5% (5/102) of the RCTs made a reference to the reliability or validity of the measurement methods. Gottrup et al. (2010) found that 76% (134/176) of the studies that defined their measurement instruments did not meet the reproducibility criteria defined as (p.262);

> the inclusion of a verifiable source of data, e.g. photos, to secure the possibility of validation from an external source by reproducing the study, or the involvement of an external validation source as part of the study design

Gottrup et al. (2010) also found that 30% (53/176) of instruments were not robust (the adequacy of information on the measurement method used in order for another to replicate the data collection). In this scoping review it was found that 19% (44/230) of the RCTs failed to provide any information on the instruments used to measure outcomes. Also, 74% (83/112) of the RCTs that measured an outcome relating to quality of life, signs and symptoms (e.g. pain, discomfort and heavy leg sensation) used trial specific scales therefore it is not clear if the scales were assessed for validity, reliability and sensitivity.

The scoping review found a lack of wound healing definitions with 45% (63/140) of RCTs not providing a definition of healing, similarly Gethin et al (2015b) found that 61% (62/102) of the RCTS did not provide a definition of healing. Likewise, Gottrup et al. (2010) found that 45% of 176 articles in a literature review on chronic wounds and ulcer endpoints did not predefine their endpoints or their definition was not sufficient; for example of the 53 articles whose endpoint included wound closure, 36% did not define what was meant by wound closure.

6.8 Changes to the Protocol

To increase recruitment potential in the eDelphi on the outcomes, a news item (appendix 10) was published on the Tissue Viability Society website. The news item contained information on the research and contact details for people wanting to take part. Viewers of the news item were able to request more details via email before deciding to participate.

The option for participants to select 'no opinion' in round one of the eDelphi on the outcome domains (stage two) was not used in the second round eDelphi on the outcome domains and in the eDelphi on the outcomes (stage three). It's inclusion in the first eDelphi did not prove to be useful because it was unclear how its use could contribute to the consensus; did no opinion mean that it is not thought of enough and therefore should not be in the core outcome set? And did it hold the same weight as the outcomes in the 'uncertain' category (4-6 on the Likert scale)?. The option to select 'no opinion' did not generate data that was more useful than the 1 to 9 Likert rating scale (discussed in chapter 4). The yes/no question asking if the outcomes should be in the core set was not asked in the eDelphi on the outcomes (stage three). There were conflicting results when the ratings for the outcome domains were compared to the results of the yes/no question; for example 25% (11/44) selected 'no' when asked if the outcome domain 'Resource use: clinician time' should be in the core set despite rating it as extremely important (further information can be found in section 4.5). Because a dichotomous approach can be related to a loss of information (Kottner et al., 2018), the question provided conflicting results and

because the eDelphi survey on the outcomes was already very long it was decided that the yes/no question would not be included in the eDelphi on the outcomes.

Because a large number of outcomes (46/120) remained in the consensus IN group (70% or more rated the item 7-9 and 15% or less rated the item 1-3) following the second round eDelphi on the outcomes (stage three), consultation with the steering group to refine the number of outcomes took place. The steering group consultation was not in the protocol because it was done ad hoc following the large number of outcomes that remained after round two. Generally, when outcomes remain in the 'no consensus' category another round to rate the outcomes for a third time is done (COMET, 2017). However it was decided that another round would not be justifiable. An additional round may have caused participant burden because four rounds (two for the eDelphi on the outcome domains and two for the eDelphi on the outcomes) had already taken place. Also, gradual attrition rates had occurred since the first eDelphi survey suggesting the number of participants may have reduced further. An amendment or another ethics application would have been required creating a time gap between the last eDelphi survey and the additional eDelphi survey potentially leading to a loss participant engagement. A large number of outcomes in the consensus IN category and no outcomes in the consensus OUT category suggested that the likelihood of participants rating a substantial number of outcomes so that they were in the consensus OUT category would have been unlikely.

6.9 Future Research

6.9.1 Patient and Carer Validation of the Core Outcome Domain Set and Candidate Outcomes

Because a low number of patients and carers took part in the eDelphi studies, future research on the validation of the core outcome domain set and set of candidate outcomes would be useful to ensure that no outcomes believed to be

core to patients and carers are missing. However detailed planning of this is essential as not to burden patients and carers.

6.9.2 Dissemination and Implementation

Dissemination of the core outcome domain set is now needed so that it is accessible. It is essential that trialists and researchers can access the core outcome domain set so it can be used for research evaluations of interventions for venous leg ulceration. Knowledge of the recommendations becomes more widespread as the usage of the core outcome set increases (Copsey et al., 2016), thus highlighting the importance of dissemination.
Engagement with clinical guideline developers, journal editors, Cochrane Review Groups, research funders, regulators and trial registries is needed to increase the uptake of the core outcome domain set. Publication of the results will be promoted through social media, for example Twitter, and uploaded to the COMET database. Considerations need to be given to potential barriers and cost implications in its implementation.

Kirkham et al's. (2016) Core Outcome Set- STAndards for Reporting (COS-STAR) will be utilised so that a clear and transparent presentation of the results is provided. Kirkham et al. (2016) have produced a checklist for the reporting of core outcome set development. The checklist will be used when a publication of the results is composed. Kirkham et al. (2016) performed a two-round Delphi and a consensus meeting involving core outcome set developers, methodologists, journals editors, core outcome set users, and patient representatives. One hundred and eighty-three international participants were involved in the development of an 18 item checklist comprising of standards for reporting a core outcome set.

The core outcome domain set will need to be periodically reviewed to check that the outcome domains in the set are still relevant and core to stakeholders. Audits are then required to assess the uptake and adherence to the core outcome domain set recommendations. This can be done by means of a scoping review. The uptake of the core outcome domain set overtime will also

needs to be tracked. By assessing uptake it indicates if the promotion of the core outcome domain set has been effective and if more needs to be done to promote it.

6.9.3 Development of a Core Set of Measurement Instruments

Some core outcome set developers gain consensus on the outcome domains (sometimes called domains) then perform a systematic review on the measurement instruments (Boers et al., 2014). A systematic review on all of the measurement instruments available to measure the outcome domains rated as core in this case would be unnecessarily lengthy and would waste resources.

It is evident from the second eDelphi on the outcomes (stage three) that not all the outcomes within each outcome domain are core to stakeholders, for example the outcome 'Time to achieving a pre-defined ulcer area change in a reference ulcer (e.g. any reduction, at least 50% reduction, at least 75% reduction)' falls within the outcome domain 'healing' which was agreed as core by participants but the specific outcome was not deemed core. The eDelphi surveys identified which of the outcomes are core to stakeholders who took part.

The development of a core outcome domain set alone may not solve the problems that exist, for example the inability to combine results for a meta-analysis. Schmitt et al. (2019) found that there is agreement amongst trialists at the outcome domain level but there is still a lack of reporting on specific outcomes. Schmitt et al. (2019) systematically assessed concordance on outcomes between 220 dermatology trials and 10 Cochrane Skin systematic reviews. They conclude that there is a low degree of overlap in outcomes between trials and reviews which facilitates weaknesses in conclusions of systematic reviews because of insufficient data.

Even if the core outcome domain set went to the level of sub-outcome domains, for example odour (sub-outcome domain in clinical signs) it still contains different ways of reporting that sub-outcome domain such as 'Number

of patients with the presence of malodour of the ulcer' or 'Severity of odour (from the ulcer)'. Therefore specific outcomes are needed along with their accompanying measurement instrument.

The specific outcomes (candidate outcomes) which were rated as core by stakeholders in the eDelphi on the outcomes (stage three) now require a systematic appraisal of their performance characteristics. Once appraised, consideration over how the outcomes are defined and measured will be required, for example two of the 11 candidate outcomes require definitions and five require an accompanying measurement instrument (Table 32). A core outcome set is comprised of *what* to measure and *how* to measure, therefore the next step in the development of the core outcome set requires the development of a core set of outcome measurements.

Table 32 Requirement for each candidate outcome

Candidate outcome	**Definition or measurement instrument required**
Number of patients/ulcers/limbs that completely healed in a trial period	Definition of 'healed'
Time to complete healing – may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs	Definition of 'complete healing'
Change in size of ulcer, e.g. length, circumference, area, volume	Measurement instrument needed
Number of patients/ulcers/limbs with pain	Pain measurement instrument needed
Number of patients reporting a pre-specified level of change in pain score during the trial period (e.g. any reduction, at least 50% relief)	Pain measurement instrument needed
Change in patient reported pain score/rating during the trial period	Pain measurement instrument needed
Change in the Quality of Life score during the evaluation period	Quality of life measurement instrument needed

The scoping review identified some of the measurement instruments which have been used to measure the outcomes reported in the RCTs. Many of the RCTs used trial specific instruments which is problematic because it is not clear if they were assessed for validity, reliability and feasibility, and they can be a source of bias (Marshall et al., 2000). When the reliability, validity and feasibility of measurement instruments are low or not clear it is a barrier to evidence based decision making (Chalmers and Glasziou, 2009).
OMERACT and HOME state that when there is no applicable (i.e. truthful, discriminative and feasible) instrument then a new one needs to be developed (Boers et al., 2014; Schmitt et al., 2015). Once the instrument is developed it requires a validation study to test whether it is valid and reliable.
Measurement instruments may need to be developed for the core outcome set if there are no applicable existing instruments.
There is published guidance on assessing measurement instruments in the development of the core set of measurement instruments. Mokkink et al. (2010b) have developed taxonomy on measurement properties. The taxonomy was developed following a lack of consensus in the literature on which measurement proprieties are relevant. The taxonomy contains three quality domains on measurement properties; reliability, validity and responsiveness (ability of an outcome measure to detect change over time). Reliability contains the measurement properties; measurement error, internal consistency and reliability (test-retest, inter-rater and intra-rater). Validity contains content validity, criterion validity and construct validity. The COSMIN checklist is a tool to assess the methodological qualities of studies on measurement properties (outlined on the previous page), and it can also be used when designing a study on measurement properties (Mokkink et al., 2010a).

6.9.4 Recurrence

Recurrence is an outcome domain that audience members at the EWMA conference suggested for inclusion in the core outcome domain set. Because the scoping review revealed that the outcome domains and outcomes relating to open ulceration was a significant endeavour in itself it was decided that

recurrence would not be in the scope of this PhD. Future research is needed to investigate how recurrence in venous leg ulceration research is investigated.

6.9.5 Methodological and Statistical Issues in Venous Leg Ulceration Research

There are issues on the methodological and statistical issues in venous leg ulceration research that arose at the session at the EWMA conference and in the comments provided on the eDelphi surveys. It was not in the scope of this PhD to address all aspects of venous leg ulceration research therefore the PhD was not able to address these issues but future research is needed. The methodological and statistical issues are outlined in the following paragraphs.

The Cochrane handbook (Higgins and Green, 2011) points out that the data on the change from baseline measures and final measurements can be missing due to missed visits and withdrawals. Therefore causing problems for systematic reviews because it is difficult to identify the subset of participants from whom they can compute the change scores from. A fully specified outcome requires a specific metric (i.e. change from baseline at a specific time), therefore the candidate outcomes that will be included in the core outcome set following a systematic appraisal of their performance characteristics will require a specific metric.

The minimum follow up times varied in the RCTs included in the scoping review (for example 8 weeks, 12 weeks, 1 year). Follow up time is an important part of a fully specified outcome (Zarin et al., 2011). A study with short duration of follow-up risks missing outcome events and can be underpowered (Hodgson et al., 2014). Future research is needed on the minimum follow up duration.

The target number of trial participants in venous leg ulceration research requires investigation. It is recommended that CONSORT guidelines are used in the reporting of venous leg ulceration trials.

The majority of participants chose the ‘patient’ as their preferred unit of analysis (N=18, 60%), a full report of the results is presented in section 5.3.2. The unit

of analysis may be intervention specific. Further research is needed on the unit of analysis reported in RCTs on venous leg ulcer interventions.

6.10 Conclusion and Implications of the PhD for Research

The aim of this PhD was to develop a core outcome set for use in research evaluations of interventions used for venous leg ulceration. To date, no core outcome set exists for venous leg ulceration research. This PhD has developed a core outcome domain set and candidate outcomes through three stages. In stage one a scoping review generated a comprehensive list of outcomes for the two consensus processes (stage two and three). Stage two gained consensus from stakeholders on the outcome domains, and stage three gained consensus from stakeholders on the outcomes.

The scoping review supports claims that the outcomes reported in RCTs on venous leg ulceration interventions are heterogeneous and outcome reporting bias is a problem in the RCTs. It also highlights the lack of 'healing' definitions and the lack of valid and reliable measurement instruments used to measure the outcomes reported in the RCTs.

The work of this PhD makes an important contribution to venous leg ulceration research, however there are limitations to the methodological approaches used in the PhD, which are outlined earlier on in this chapter. It has begun work on developing a core set of outcomes by identifying which candidate outcomes are considered to be core by stakeholders that took part in the eDelphi surveys. The candidate outcomes now require a systematic appraisal of their performance characteristics. Once appraised they will form part of the core outcome set along with an accompanying set of measurement instruments. The implementation of a core outcome set has the potential to improve the utility of RCTs, reduce outcome reporting bias, increase the consistency of outcomes reported in research, and facilitate treatment comparisons across different sources of evidence. The reporting of appropriate outcomes which are core to stakeholders has the potential to reduce research waste. Providing the core outcome set has good uptake, it will also expedite the production of systematic reviews, meta-analyses and evidence-based clinical guidelines.

References

Abbade, L.P.F., Lastória, S., De Almeida, R. and Stolf, H.O. 2005. A sociodemographic, clinical study of patients with venous ulcer. *International Journal of Dermatology.* **44**(12), pp.989-992.

Adderley, U.J. 2013. *Community Nurses' Judgement and Decision Making for the Management of Venous Leg Ulceration* Doctor of Philosophy thesis, University of York

Al Wattar, B., Tamilselvan, K., Khan, R., Kelso, A., Sinha, A., Pirie, A., McCorry, D., Khan, K. and Thangaratinam, S. 2017. Development of a core outcome set for epilepsy in pregnancy (E-CORE): a national multi-stakeholder modified Delphi consensus study. *BJOG: An International Journal of Obstetrics & Gynaecology.* **124**(4), pp.661-667.

Alkhaffaf, B., Glenny, A.-M., Blazeby, J.M., Williamson, P. and Bruce, I.A. 2017. Standardising the reporting of outcomes in gastric cancer surgery trials: protocol for the development of a core outcome set and accompanying outcome measurement instrument set (the GASTROS study). *Trials.* **18**(1), pp.1-9.

Allegra, C., Cariotti, R., Bonadeo, P., Cataldi, R., Polignano, R. and Andriessen, A. 2001. Four-layer compared with Unna's Boot in venous leg ulcer management. In: *11th Annual Meeting of the European Tissue Repair Society*, *Cardiff UK*. Wound Repair and Regeneration.

Alvarez, O.M., Patel, M., Booker, J. and Markowitz, L. 2004. Effectiveness of a biocellulose wound dressing for the treatment of chronic venous leg ulcers: results of a single centre randomised study involving 24 patients. *Wounds: A compendium of Clinical Research and Practice.* **16**(7), pp.224-233.

Alvarez, O.M., Phillips, T.J., Menzoian, J.O., Patel, M. and Andriessen, A. 2012. An RCT to compare a bio-cellulose wound dressing with a non-adherent dressing in VLUs. *Journal of Wound Care.* **21**(9), pp.448-453.

American Society for Indexing. 2019. *Taxonomies & Controlled Vocabularies SIG.* [Online]. Available from: http://www.taxonomies-sig.org/about.htm

Anderson, S., Allen, P., Peckham, S. and Goodwin, N. 2008. Asking the right questions: Scoping studies in the commissioning of research on the organisation and delivery of health services. *Health Research Policy and Systems.* **6**, pp.7-7.

Arksey, H. and O'Malley, L. 2005. Scoping Studies: Towards a Methodological Framework. *International Journal of Social Research Methodology.* **8**(1), pp.19-32.

Armstrong, R., Hall, B.J., Doyle, J. and Waters, E. 2011. 'Scoping the scope' of a Cochrane review. *Journal of Public Health.* **33**(1), pp.147-150.

Arnold, L.M., Crofford, L.J., Mease, P.J., Burgess, S.M., Palmer, S.C., Abetz, L. and Martin, S.A. 2008. Patient perspectives on the impact of fibromyalgia. *Patient Education and Counseling.* **73**(1), pp.114-120.

Bajracharya, S.M. 2006. An Assessment of the Perceived Barriers and Strategies to Promoting Early Detection of Colorectal Cancer: A Practitioners' Perspective. *International Quarterly of Community Health Education.* **26**(1), pp.23–44.

Bardecki, M.J. 1984. Participants' response to the Delphi method: An attitudinal perspective. *Technological Forecasting and Social Change.* **25**(3), pp.281-292.

Barnette, J. 2000. Effects of Stem and Likert Response Option Reversals on Survey Internal Consistency: If You Feel the Need, There is a Better Alternative to Using those Negatively Worded Stems. *Educational and Psychological Measurement.* **60**(3), pp.361-370.

Beech, B. 2001. The Delphi approach: recent applications in health care. *Nurse Researcher.* **8**(4).

Beers, M.H., Ouslander, J.G., Rollingher, I., Reuben, D.B., Brooks, J. and Beck, J.C. 1991. Explicit criteria for determining inappropriate medication use in nursing home residents. *Archives of Internal Medicine.* **151**(9), pp.1825-1832.

Bennett, W.L., Robinson, K.A., Saldanha, I.J., Wilson, L.M. and Nicholson, W.K. 2012. High priority research needs for gestational diabetes mellitus. *Journal of Women's Health.* **21**(9), pp.925-932.

Beretta, R. 1995. A critical review of the Delphi technique. *Nurse Researcher.* **3**(4), pp.79-89.

Black, N. 2006. Consensus Development Methods. In: Pope, C. and Mays, N. eds. *Qualitative Research in Health Care.* Molden, Massachusetts: Blackwell Publishing.

Black, N., Murphy, M., Lamping, D., McKee, M., Sanderson, C., Askham, J. and Marteau, T. 1999. Consensus development methods: A review of best practice in creating clinical guidelines. *Journal of Health Services Research & Policy.* **4**(4), pp.236-248.

Bland, J.M. and Altman, D.G. 1997. Statistics notes: Cronbach's alpha. *BMJ.* **314**(7080), p572.

Blecken, S.R., Villavicencio, J.L. and Kao, T.C. 2005. Comparison of elastic versus nonelastic compression in bilateral venous ulcers: A randomized trial. *Journal of Vascular Surgery.* **42**(6), pp.1150-1155.

Boers, M., Beaton, D.E., Shea, B.J., Maxwell, L.J., Bartlett, S.J., Bingham, C.O., Conaghan, P.G., D'Agostino, M.A., de Wit, M.P., Gossec, L., March, L., Simon, L.S., Singh, J.A., Strand, V., Wells, G.A. and Tugwell, P. 2019. OMERACT Filter 2.1: Elaboration of the Conceptual Framework for Outcome Measurement in Health Intervention Studies. *The Journal of Rheumatology.* pjrheum.181096.

Boers, M., Brooks, P., Strand, V. and Tugwell, P. 1998. The OMERACT filter for Outcome Measures in Rheumatology. *Journal of Rheumatology.* **25**(2), pp.198-199.

Boers, M., Kirwan, J.R., Tugwell, P., Beaton, D., Bingham III, C.O., Conaghan, P.G., D'Agostino, M.-A., de Wit, M., Gossec, L., March, L., Simon, L.S., Singh, J.A., Strand, V. and Wells, G. 2017. The OMERACT handbook. [Online]. [Accessed 02 June 2018]. Available from: https://omeract.org/resources

Boers, M., Kirwan, J.R., Tugwell, P., Beaton, D., Bingham III, C.O., Conoghan, P.G., D'Agostino, M.-A., de Wit, M., Gossec, L., March, L., Simon, L.S., Singh,

J.A., Strand, V. and Wells, G. 2016. *The OMERACT Handbook.* [Online]. Available from: http://www.omeract.org/pdf/OMERACT_Handbook.pdf

Boers, M., Kirwan, J.R., Wells, G., Beaton, D., Gossec, L., d'Agostino, M.-A., Conaghan, P.G., Bingham, C.O., Brooks, P., Landewé, R., March, L., Simon, L.S., Singh, J.A., Strand, V. and Tugwell, P. 2014. Developing Core Outcome Measurement Sets for Clinical Trials: OMERACT Filter 2.0. *Journal of Clinical Epidemiology.* **67**(7), pp.745-753.

Bowling, A. 2005. *Measuring Health: A review of quality of life measurement scales.* 3rd ed. Maidenhead: Open University Press.

Bowling, A. 2009. *Research Methods in Health: Investigating Health and Health Services.* 3rd ed. Maidenhead: Open University Press.

Bowling, A. and Ebrahim, S. 2005. *Handbook of health research methods : investigation, measurement and analysis.* Maidenhead: Open University Press.

Bradburn, N.M., Sudman, S. and Wansink, B. 2004. *Asking Questions: The Definitive Guide to Questionnaire Design -- For Market Research, Political Polls, and Social and Health Questionnaires.* San Francisco: Jossey-Bass.

Brien, S.E., Lorenzetti, D.L., Lewis, S., Kennedy, J. and Ghali, W.A. 2010. Overview of a formal scoping review on health system report cards. *Implementation Science.* **5**(2), pp.1-12.

Briggs, M. and Flemming, K. 2007. Living with leg ulceration: a synthesis of qualitative research. *Journal of Advanced Nursing.* **59**(4), pp.319-328.

Bristol Online Survey. 2017. *Bristol Online Survey.* [Online]. [Accessed 22 September 2017]. Available from: https://www.onlinesurveys.ac.uk/

Brizzio, E., Amsler, F., Lun, B. and Blättler, W. 2010. Comparison of low-strength compression stockings with bandages for the treatment of recalcitrant venous ulcers. *Journal of Vascular Surgery.* **51**(2), pp.410-416.

Brookes, S.T., Chalmers, K.A., Avery, K.N.L., Coulman, K., Blazeby, J.M., Barham, C.P., Berrisford, R., Donovan, J., Elliott, J., Falk, S., Goldin, R., Hanna, G., Hollowood, A., Noble, S., Sanders, G. and Wheatley, T. 2018. Impact of question order on prioritisation of outcomes in the development of a core outcome set: a randomised controlled trial. *Trials.* **19**(1), p66.

Browse, N.L., Gray, L., Jarrett, P.E. and Morland, M. 1977. Blood and vein-wall fibrinolytic activity in health and vascular disease. *British Medical Journal.* **1**(6059), pp.478-481.

Buckley, B., Grant, A.M., Firkins, L., Greene, A.C. and Frankau, J. 2007. Influencing the research agenda: establishing and evaluating a partnership of patients, carers and clinicians to identify research priorities–a protocol. *BMJ.* **9**(4), pp.222-231.

Buckley, B.S., Grant, A.M., Tincello, D.G., Wagg, A.S. and Firkins, L. 2010. Prioritizing research: Patients, carers, and clinicians working together to identify and prioritize important clinical uncertainties in urinary incontinence. *Neurourology and Urodynamics.* **29**(5), pp.708-714.

Buetow, S.A. and Coster, G.D. 2000. New Zealand and United Kingdom experiences with the RAND modified Delphi approach to producing angina and heart failure criteria for quality assessment in general practice. *BMJ Quality & Safety* **9**(4), pp.222- 231.

Burke, M. No date. *Venous Leg Ulcer Treatment Outcomes: Perspectives of Patients*. Unpublished.

Burnand, K.G., Clemenson, G., Whimpster, I. and Browse, N.L. 1976. Extravascular fibrin deposition in response to venous hypertension- the cause of venous ulcers. *British Journal of Surgery.* **63**(8), pp.655-670.

Burnand, K.G., Whimster, T.L.I., Clemenson, G., Thomas, M.L. and Browse, N.L. 1981. The relationship between the number of capillaries in the skin of the venous ulcer-bearing area of the lower leg and the fall in foot vein pressure during exercise. *British Journal of Surgery.* **68**(5), pp.297-300.

Byrne, M., O'Connell, A., Egan, A.M., Dinneen, S.F., Hynes, L., O'Hara, M.C., Holt, R.I.G., Willaing, I., Vallis, M., Hendrieckx, C. and Coyne, I. 2017. A core outcome set for clinical trials of interventions for young adults with type 1 diabetes: an international, multi-perspective Delphi consensus study. *Trials.* **18**(1), p602.

Callam, M.J., Harper, J., Dale, J., Brown, B., Gibson, R., Prescott, J. and Ruckley, C.V. 1992. Lothian and forth valley leg ulcer healing trial, part 1: Elastic versus non-elastic bandaging in the treatment of chronic leg ulceration. *Phlebology.* **7**, pp.142-145.

Campbell, S.M. and Cantrill, J.A. 2001. Consensus methods in prescribing research. *Journal of Clinical Pharmacy and Therapeutics.* **26**(1), pp.5-14.

Carnwell, R. and Daly, W. 2001. Strategies for the construction of a critical review of the literature. *Nurse Education in Practice.* **1**(2), pp.57-63.

Chalmers, I. and Glasziou, P. 2009. Avoidable waste in the production and reporting of research evidence. *The Lancet.* **374**(9683), pp.86-89.

Charles, H. 1991. Compression healing of ulcers. *Journal of District Nursing.* **10**(3), pp.4-8.

Charles, H. 1995. The impact of leg ulcers on patients' quality of life. *Professional Nurse.* **10**(9), pp.571-574.

Chasens, E.R. and Olshansky, E. 2008. Daytime sleepiness, diabetes, and psychological well-being. *Issues in Mental Health Nursing.* **29**(10), pp.1134-1150.

Chin, J., Sato, P.A. and Mann, J.M. 1990. Projections of HIV infections and AIDS cases to the year 2000. *Bulletin of the World Health Organization.* **68**(1), pp.1-11.

Clarke-Moloney, M., O'Brien, J.F., Grace, P.A. and Burke, P.E. 2005. Health-related quality of life during four-layer compression bandaging for venous ulcer disease: a randomised controlled trial. *Irish Journal of Medical Science.* **174**(2), pp.21-25.

Clarke, M. 2007. Standardising outcomes for clinical trials and systematic reviews. *Trials.* **8**(1), p39.

Colgan, M.-P., Teevan, M., McBride, C., O'Sullivan, L., Moore, D. and Shanik, G. 1995. Cost comparisons in the management of venous ulceration. In: *Preceedings of the 5th European Conference on Advances in Wound Management, Harrogate UK*. Macmillan Magazines, pp.21-24.

Colquhoun, H.L., Levac, D., O'Brien, K.K., Straus, S., Tricco, A.C., Perrier, L., Kastner, M. and Moher, D. 2014. Scoping reviews: time for clarity in definition, methods, and reporting. *Journal of Clinical Epidemiology.* **67**(12), pp.1291-1294.

COMET. 2016. *COMET initiative.* [Online]. [Accessed 01 June 2018]. Available from: http://www.comet-initiative.org/

COMET. 2017. *Delphi Plain Language Summary.* [Online]. [Accessed 20th August 2018]. Available from: http://www.comet-initiative.org/resources/PlainLanguageSummary

COMET. 2019. *COMET initiative.* [Online]. Available from: http://www.comet-initiative.org/

CONSORT. 2018. *Transparent reporting of trials.* [Online]. [Accessed 15th August 2018]. Available from: http://www.consort-statement.org/

Copsey, B., Hopewell, S., Becker, C., Cameron, I.D. and Lamb, S.E. 2016. Appraising the uptake and use of recommendations for a common outcome data set for clinical trials: a case study in fall injury prevention. *Trials.* **17**(1), pp.131-131.

Cordts, P.R., Hanrahan, L.M., Rodriguez, A.A., Woodson, J., LaMorte, W.W. and Menzoian, J.O. 1992. A prospective, randomized trial of Unna's boot versus Duoderm CGF hydroactive dressing plus compression in the management of venous leg ulcers. *Journal of Vascular Surgery.* **15**(3), pp.480-486.

COSMIN. 2018. *COSMIN* [Online]. [Accessed 02nd October 2018]. Available from: https://www.cosmin.nl/

Coulman, K.D., Hopkins, J., Brookes, S.T., Chalmers, K., Main, B., Owen-Smith, A., Andrews, R.C., Byrne, J., Donovan, J.L., Mazza, G., Reeves, B.C., Rogers, C.A., Thompson, J.L., Welbourn, R., Wordsworth, S. and Blazeby, J.M. 2016. A Core Outcome Set for the Benefits and Adverse Events of Bariatric and Metabolic Surgery: The BARIACT Project. *PLOS Medicine.* **13**(11), pe1002187.

Council, G.M. 2018. *Consent to research.* [Online]. Available from: https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent-to-research/consent-to-research#paragraph-3

Creswell, J.W. and Plano Clark, V.L. 2011. *Designing and Conducting Mixed Methods Research.* London: Sage.

Cronbach, L.J. 1950. Further evidence on response sets and test design. *Educational and Psychological Measurement.* **10**(1), pp.3-31.

Cullum, N., Buckley, H., Dumville, J., Hall, J., Lamb, K., Madden, M., Morley, R., O'Meara, S., Saramago Goncalves, P., Soares, M. and Stubbs, N. 2016. Wounds research for patient benefit: a 5 year programme of research. *Health Technology Assessment.* pp.1-334.

Cullum, N. and Liu, Z. 2017. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database of Systematic Reviews.* [Online]. CD001180. (5). Available from: https://doi.org//10.1002/14651858.CD001180.pub4

Cummins, R.A. and Gullone, E. 2000. Why we should not use 5-point Likert scales: The case for subjective quality of life measurement. In: *Second International Conference on Quality of Life in Cities*, *National University of Singapore*. pp.74-93.

Dalkey, N. 1967. Delphi. [Online]. [Accessed 26th August 2018]. Available from: https://www.rand.org/pubs/papers/P3704.html

Dalkey, N. and Helmer, O. 1963. An Experimental Application of the DELPHI Method to the Use of Experts. *Management Science.* **9**(3), pp.458-467.

Danielsen, L., Madsen, S. and Henriksen, L. 1998a. Venous leg ulcer healing: a randomized prospective study of long-stretch versus short-stretch compression bandages. *Phlebology.* **13**(2), pp.59-63.

Danielsen, L., Madsen, S.M., Henriksen, L., Sindrup, J. and Petersen, L.J. 1998b. Subbandage pressure measurements comparing a long-stretch with a short-stretch compression bandage. *Acta Dermatovenereologica Stockholm* **78**, pp.201-204.

Daudt, H.M., van Mossel, C. and Scott, S.J. 2013. Enhancing the scoping study methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. *BMC Medical Research Methodology.* **13**(1), p48.

Davis, K., Gorst, S.L., Harman, N., Smith, V., Gargon, E., Altman, D.G., Blazeby, J.M., Clarke, M., Tunis, S. and Williamson, P.R. 2018. Choosing important health outcomes for comparative effectiveness research: An updated systematic review and involvement of low and middle income countries. *Plos ONE.* **13**(2), pp.1-14.

Dealey, C. 2012. *The Care of Wounds: A Guide for Nurses.* [Online]. 4th ed. Oxford: Wiley-Blackwell. [Accessed 18 December 2017]. Available from: https://www.dawsonera.com/readonline/9781118276174

Deeks, J.J., Higgins, J.P.T. and Altman, D.G. 2011. Analysing data and undertaking meta-analyses. In: Higgins, J.P.T. and Green, S. eds. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0.* [Online]. The Cochrane Collaboration. [Accessed 01 June 2018]. Available from: http://handbook-5-1.cochrane.org/

Delbacq, A.L. and Van de Ven, A.H. 1971. A Group Process Model for Problem Identification and Program Planning. *Journal of Applied Behavioural Science.* **7**(4), pp.466-492.

DePalma, R.G., Kowallek, D., Spence, R.K., Caprini, J.A., Nehler, M.R., Jensen, J., Goldman, M.P. and Bundens, W.P. 1999. Comparison of Costs and Healing Rates of Two Forms of Compression in Treating Venous Ulcers. *Vascular and Endovascular Surgery.* **33**(6), pp.683-690.

Diamond, I.R., Grant, R.C., Feldman, B.M., Pencharz, P.B., Ling, S.C., Moore, A.M. and Wales, P.W. 2014. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. *Journal of Clinical Epidemiology.* **67**(4), pp.401-409.

Dixon, P.N., Bobo, M. and Stevick, R.A. 1984. Response Differences and Preferences for All-Category-Defined and End-Defined Likert Formats. *Educational and Psychological Measurement.* **44**(1), pp.61-66.

Dodd, S., Clarke, M., Becker, L., Mavergames, C., Fish, R. and Williamson, P.R. 2018. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. *Journal of Clinical Epidemiology.* **96**, pp.84-92.

Donohoe, H., Stellefson, M. and Tennant, B. 2012. Advantages and Limitations of the e-Delphi Technique. *American Journal of Health Education.* **43**(1), pp.38-46.

Doughty, D.B. and Holbrook, R. 2007. Lower-extremity ulcers of vascular aetiology. In: Bryant, R.A. and Nix, D.P. eds. *Acute and Chronic Wounds: Current Management Concepts.* 3rd ed. St Louis, Missouri: Mosby.

Duffield, C. 1993. The Delphi technique: a comparison of results obtained using two expert panels. *International Journal of Nursing Studies.* **30**(3), pp.227-237.

Dumville, J.C., Land, L., Evans, D. and Peinemann, F. 2015. Negative pressure wound therapy for treating leg ulcers. *Cochrane Database of Systematic Reviews.* [Online]. CD011354. (7). Available from: https://doi.org//10.1002/14651858.CD011354.pub2

Dwan, K., Altman, D.G., Arnaiz, J.A., Bloom, J., Chan, A.-W., Cronin, E., Decullier, E., Easterbrook, P.J., Von Elm, E., Gamble, C., Ghersi, D., Ioannidis, J.P.A., Simes, J. and Williamson, P.R. 2008. Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. *Plos One.* **3**(8), pp.1-31.

Edwards, P., Clarke, M. and Pratap, S. 2002. Increasing response rates to postal questionnaires: systematic review. *BMJ.* **324**.

Egan, A.M., Galjaard, S., Maresh, M.J.A., Loeken, M.R., Napoli, A., Anastasiou, E., Noctor, E., de Valk, H.W., van Poppel, M., Todd, M., Smith, V., Devane, D. and Dunne, F.P. 2017. A core outcome set for studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes. *Diabetologia.* **60**(7), pp.1190-1196.

Egger, M., Zellweger-Zähner, T., Schneider, M., Junker, C., Lengeler, C. and Antes, G. 1997. Language bias in randomised controlled trials published in English and German. *The Lancet.* **350**(9074), pp.326-329.

Ehrich, K., Freeman, G., Richards, S., Robinson, I. and Shepperd, S. 2002. How to do a scoping exercise: continuity of care. *Research Policy and Planning.* **20**(1), pp.25-29.

Eleftheriadou, V., Thomas, K., Geel, N., Hamzavi, I., Lim, H., Suzuki, T., Katayama, I., Anbar, T., Abdallah, M., Benzekri, L., Gauthier, Y., Harris, J., Silva de Castro, C.C., Pandya, A., Goh, B.K., Lan, C.-C.E., Oiso, N., Al Issa, A., Esmat, S., Le Poole, C., Lee, A.-Y., Parsad, D., Taieb, A., Picardo, M. and Ezzedine, K. 2015. Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment Cell & Melanoma Research.* **28**(3), pp.363-369.

Equator Network. 2018. *Enhancing the Quality and Transparency Of health Research.* [Online]. [Accessed 15th August 2018]. Available from: http://www.equator-network.org/

Eriksson, G. 1986. Comparison of two occlusive bandages in the treatment of venous leg ulcers. *British Journal of Dermatology.* **114**(2), pp.227-230.

Eysenck, H.J. 1994. Systematic Reviews: Meta-analysis and its problems. *BMJ.* **309**(6957), pp.789-792.

Falanga, V., Moosa, H.H., Nemeth, A.J., Alstadt, S.P. and Eaglstein, W.H. 1987. Dermal pericapillary fibrin in venous disease and venous ulceration. *Archives of Dermatology.* **123**(5), pp.620-623.

FDA. 2006. *Guidance for Industry Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment* US: Department of Health and Human Services.

Ferrans, C.E., Zerwic, J.J., Wilbur, J.E. and Larson, J.L. 2005. Conceptual Model of Health-Related Quality of Life. *Journal of Nursing Scholarship.* **37**(4), pp.336-342.

Fink, A., Kosecoff, J., Chassin, M. and Brook, R.H. 1984. Consensus methods: characteristics and guidelines for use. *American Journal of Public Health.* **74**(9), pp.979-983.

Firth, J., Nelson, E.A., Hale, C., Hill, J. and Helliwell, P. 2010. A review of design and reporting issues in self-reported prevalence studies of leg ulceration. *Journal of Clinical Epidemiology.* **63**(8), pp.907-913.

Fitch, K., Bernstein, S.J., Aguilar, M.D., Burnand, B., LaCalle, J.R., Lazaro, P., van het Loo, M., McDonnell, J., Vader, J. and Kahan, J.P. 2001. The RAND/UCLA Appropriateness Method User's Manual. [Online]. [Accessed 05 September 2018]. Available from: https://www.rand.org/pubs/monograph_reports/MR1269.html

Franks, P., Moffatt, C., Ellison, D., Connolly, M., Fielden, S., Groarke, L. and McCollum, C. 1999a. Quality of life in venous ulceration: A randomized trial of two bandage systems. *Phlebology.* **14**(3), pp.95-99.

Franks, P.J., Barker, J., Collier, M., Gethin, G., Haesler, E., Jawien, A., Laeuchli, S., Mosti, G., Probst, S. and Weller, C. 2016. Management of Patients With Venous Leg Ulcers: Challenges and Current Best Practice. *Journal of Wound Care.* **25**(Sup6), pp.S1-S67.

Franks, P.J., Bosanquet, N., Brown, D., Straub, J., Harper, D.R. and Ruckley, C.V. 1999b. Perceived Health in a Randomised Trial of Treatment for Chronic Venous Ulceration. *European Journal of Vascular and Endovascular Surgery.* **17**(2), pp.155-159.

Franks, P.J., Moody, M. and Moffat, C.J. 2003. Randomised trial of four-layer and cohesive short stretch compression in venous ulceration. In: *Tissue Viability Society Conference*. Journal of Tissue Viability, p.170.

Franks, P.J., Moody, M., Moffatt, C.J., Martin, R., Blewett, R., Seymour, E., Hildreth, A., Hourican, C., Collins, J. and Heron, A. 2004. Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration. *Wound Repair and Regeneration.* **12**(2), pp.157-162.

Franks, P.J., Stevens, J., Hourican, C., Doherty, D.C. and O'Connor, T. 2002. Quality of life in venous ulceration: use of the SF-36 in a randomized trial of two bandage systems (abstract only). *Ostomy/Wound Management.* **48**(4), p73.

Fries, J.F., Spitz, P.W. and Young, D.Y. 1982. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *Journal of Rheumatology.* **9**, pp.789-793.

Frisbie, D.A. and Brandenburg, D.C. 1979. Equivalence of Questionnaire Items with Varying Response Formats. *Journal of Educational Measurement.* **16**(1), pp.43-48.

Galesic, M. and Bosnjak, M. 2009. Effects of Questionnaire Length on Participation and Indicators of Response Quality in a Web Survey. *Public Opinion Quarterly* **73**(2), pp.349-360.

Gandhi, G.Y., Murad, M., Fujiyoshi, A., Mullan, R.J., David N. Flynn, D.N., Mohamed B. Elamin, M.B., Swiglo, B.A., Isley, W.L., Guyatt, G.H. and Montori, V.M. 2008. Patient-important outcomes in registered diabetes trials. *JAMA.* **299**(21), pp.2543-2549.

Gardon-Mollard, C., Junger, M., Patsch, H., Zuccarelli, F. and Taupin, V. 2003. Efficacy of a tubular compression orthosis compared to a SSB in the treatment of venous leg ulcers. *Phlebology.* **18**(3), p152.

Gargon, E., Gurung, B., Medley, N., Altman, D.G., Blazeby, J.M. and Clarke, M. 2014. Choosing important health outcomes for comparative effectiveness research: a systematic review. *PLoS One.* **9**(6), pp.1-12.

Gethin, G. and Cowman, S. 2008. Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: an RCT. *Journal of Wound Care.* **17**(6), pp.241-247.

Gethin, G. and Cowman, S. 2009. Manuka honey vs. hydrogel – a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. *Journal of Clinical Nursing.* **18**(3), pp.466-474.

Gethin, G., Cowman, S. and Kolbach, D.N. 2015a. Debridement for venous leg ulcers. *Cochrane Database of Systematic Reviews.* [Online]. CD008599. (9). Available from: https://doi.org//10.1002/14651858.CD008599.pub2

Gethin, G., Killeen, F. and Devane, D. 2015b. Heterogeneity of wound outcome measures in RCTs of treatments for VLUs: a systematic review. *Journal of Wound Care.* **24**(5), pp.211-226.

Ghauri, A.S.K. and Nyamekye, I.K. 2010. Leg ulceration: the importance of treating the underlying pathophysiology. *Phlebology.* **25** pp.42-51.

Gohel, M.S. and Poskitt, K.R. 2009. Venous ulceration. In: Donnelly, R. and London, N.J.M. eds. *ABC of arterial and venous disease.* [Online]. 2nd ed. Oxford ; Chichester, West Sussex ; Hoboken, NJ: BMJ/Wiley-Blackwell,, pp.ix, 104 p. [Accessed 26 May 2018]. Available from: http://site.ebrary.com/lib/yale/Doc?id=10307805

Goodman, C.M. 1987. The Delphi technique: a critique. *Journal of Advanced Nursing.* **12**(6), pp.729-734.

Gordon, T.J. and Helmer, O. 1964. *Report on a Long-Range Forcasting Study.* New York: The RAND Corporation.

Gorst, S.L., Gargon, E., Clarke, M., Blazeby, J.M., Altman, D.G. and Williamson, P.R. 2016a. Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and User Survey. *Plos ONE.* **11**(1), pp.1-12.

Gorst, S.L., Gargon, E., Clarke, M., Smith, V. and Williamson, P.R. 2016b. Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and Identification of Gaps. *Plos ONE.* **11**(12), pp.1-14.

Gorst, S.L., Young, B., Williamson, P.R., Wilding, J.P.H. and Harman, N.L. 2019. Incorporating patients' perspectives into the initial stages of core outcome set development: a rapid review of qualitative studies of type 2 diabetes. *BMJ Open Diabetes Research and Care* **7**(1), pp.1-12.

Gottrup, F., Apelqvist, J. and Price, P. 2010. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. *Journal of Wound Care.* **19**(6), pp.237-268.

Gould, D.J., Campbell, S. and Harding, E.F. 1993. Short stretch vs. long stretch bandages in the management of chronic venous leg ulcers. In. Phlebology, p.43.

Gould, D.J., Campbell, S., Newton, H., Duffelen, P., Griffin, M. and Harding, E., F. 1998. Setopress vs Elastocrepe in chronic venous ulceration. *British Journal of Nursing.* **7**(2), pp.66-73.

Gould, L. and Li, W.W. 2019. Defining complete wound closure: Closing the gap in clinical trials and practice. *Wound Repair and Regeneration.* **27**(3), pp.201-224.

Graham, I.D., Harrison, M.B., Nelson, E.A., Lorimer, K. and Fisher, A. 2003. Prevalence of Lower-Limb Ulceration: A Systematic Review of Prevalence Studies. *Advances in Skin & Wound Care.* **16**(6), pp.305-316.

Grant, M.J. and Booth, A. 2009. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Information & Libraries Journal.* **26**(2), pp.91-108.

Green, B., Jones, M., Hughes, D. and Williams, A. 1999. Applying the Delphi technique in a study of GPs' information requirements. *Health & Social Care in the Community.* **7**(3), pp.198-205.

Guest, J.F., Ayoub, N., McIlwraith, T., Uchegbu, I., Gerrish, A., Weidlich, D., Vowden, K. and Vowden, P. 2017. Health economic burden that different wound types impose on the UK's National Health Service. *International Wound Journal.* **14**(2), pp.322-330.

Gulati, S., Qureshi, A., Srivastava, A., Kataria, K., Kumar, P. and Ji, A.B. 2014. A Prospective Randomized Study to Compare the Effectiveness of Honey Dressing vs. Povidone Iodine Dressing in Chronic Wound Healing. *Indian Journal of Surgery.* **76**(3), pp.193-198.

Hall, J., Buckley, H.L., Lamb, K.A., Stubbs, N., Saramago, P., Dumville, J.C. and Cullum, N.A. 2014. Point prevalence of complex wounds in a defined United Kingdom population. *Wound Repair Regeneration.* **22**(6), pp.694-700.

Hallas, S., Nelson, A., O' Meara, S. and Gethin, G. 2017. Meeting Report: Core outcome set for Venous leg ulceration "CoreVen". *European Wound Management Association* **18**(2), pp.27-31.

Hansson, C. 1998. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. *International Journal of Dermatology.* **37**(5), pp.390-396.

Harding, K., Dowsett, C., Fias, L., Jelnes, R., Mosti, G., Oien, R., Partsch, H., Reeder, S., Senet, P., Soriano, J.V. and Vanscheidt, W. 2015. Simplifying venous leg ulcer management: Consensus recommendations. *Wounds International.* p3.

Harley, J., Harcourt, D., Hutchinson, B., McLean, M. and Long, M. 2004. A comparative trial of long stretch compression bandaging versus multi-layer compression bandaging in the treatment of chronic venous ulcers. *Primary Intention: The Australian Journal of Wound Management.* **12**(1), p6.

Harman, N.L., Bruce, I.A., Callery, P., Tierney, S., Sharif, M.O., O'Brien, K. and Williamson, P.R. 2013. MOMENT – Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials.* **14**(1), p70.

Harman, N.L., Bruce, I.A., Kirkham, J.J., Tierney, S., Callery, P., O'Brien, K., Bennett, A.M.D., Chorbachi, R., Hall, P.N., Harding-Bell, A., Parfect, V.H., Rumsey, N., Sell, D., Sharma, R. and Williamson, P.R. 2015. The Importance of Integration of Stakeholder Views in Core Outcome Set Development: Otitis Media with Effusion in Children with Cleft Palate. *PLOS ONE.* **10**(6), pe0129514.

Hasson, F. and Keeney, S. 2011. Enhancing rigour in the Delphi technique research. *Technological Forecasting and Social Change.* **78**(9), pp.1695-1704.

Hasson, F., Keeney, S. and McKenna, H. 2000. Research guidelines for the Delphi survey technique. *Journal of Advanced Nursing.* **32**(4), pp.1008-1015.

Heberlein, T.A. and Baumgartner, R. 1978. Factors Affecting Response Rates to Mailed Questionnaires: A Quantitative Analysis of the Published Literature. *American Sociological Review.* **43**(4), pp.447-462.

Herber, O.R., Schnepp, W. and Riegger, M. 2007. A systematic review on the impact of leg ulceration on patients' quality of life. *Health and Quality of Life Outcomes.* **5**(44), pp.1-12.

Higgins, J., Altman, D.G. and Sterne, J.A. 2011. Chapter 8: Assessing risk of bias in included studies. In: JPT, H. and S, G. eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* [Online]. The Cochrane Collaboration. [Accessed 01 June 2018]. Available from: http://handbook-5-1.cochrane.org/

Higgins, J.P.T. and Green, S. 2011. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [Online]. The Cochrane Collaboration. [Accessed 29 May 2018]. Available from: http://handbook-5-1.cochrane.org/

Hirsch, M., Duffy, J.M.N., Barker, C., Hummelshoj, L., Johnson, N.P., Mol, B., Khan, K.S. and Farquhar, C. 2016. Protocol for developing, disseminating and implementing a core outcome set for endometriosis. *BMJ Open.* **6**(12), pp.1-5.

Hodgson, R., Allen, R., Broderick, E., Bland, J.M., Dumville, J.C., Ashby, R., Bell-Syer, S., Foxlee, R., Hall, J., Lamb, K., Madden, M., O'Meara, S., Stubbs, N. and Cullum, N. 2014. Funding source and the quality of reports of chronic wounds trials: 2004 to 2011. *Trials.* **15**(1), pp.1-10.

Hopkins, J.C., Howes, N., Chalmers, K., Savovic, J., Whale, K., Coulman, K.D., Welbourn, R., Whistance, R.N., Andrews, R.C., Byrne, J.P., Mahon, D. and Blazeby, J.M. 2015. Outcome reporting in bariatric surgery: an in-depth analysis to inform the development of a core outcome set, the BARIACT Study. *Obesity Reviews.* **16**(1), pp.88-106.

Howell, D., Fitch, M., Bakker, D., Green, E., Sussman, J., Mayo, S., Mohammed, S., Lee, C. and Doran, D. 2013. Core Domains for a Person-Focused Outcome Measurement System in Cancer (PROMS-Cancer Core) for Routine Care: A Scoping Review and Canadian Delphi Consensus. *Value in Health.* **16**(1), pp.76-87.

Huang, H.-C., Lin, W.-C. and Lin, J.-D. 2008. Development of a fall-risk checklist using the Delphi technique. *Journal of Clinical Nursing.* **17**(17), pp.2275-2283.

Hurley, J.R. 1998. Timidity as a Response Style to Psychological Questionnaires. *The Journal of Psychology.* **132**(2), pp.201-210.

Hutchings, A. and Raine, R. 2006. A systematic review of factors affecting the judgments produced by formal consensus development methods in health care. *Journal of Health Services Research & Policy.* **11**(3), pp.172-179.

Hutchings, A., Raine, R., Sanderson, C. and Black, N. 2005. An experimental study of determinants of the extent of disagreement within clinical guideline development groups. *Quality and Safety in Health Care.* **14**(4), pp.240-245.

Idzerda, L., Rader, T., Tugwell, P. and Boers, M. 2014. Can We Decide Which Outcomes Should Be Measured in Every Clinical Trial? A Scoping Review of the Existing Conceptual Frameworks and Processes to Develop Core Outcome Sets. *The Journal of Rheumatology* **41**(5), pp.986-993.

Ieran, M., Zaffuto, S., Bagnacani, M., Annovi, M., Moratti, A. and Cadossi, R. 1990. Effect of low frequency pulsing electromagnetic fields on skin ulcers of venous origin in humans: A double-blind study. *Journal of Orthopaedic Research.* **8**(2), pp.276-282.

Iglesias, C.P., Nelson, E.A., Cullum, N. and Torgerson, D.J. 2004a. Economic analysis of VenUS I, a randomized trial of two bandages for treating venous leg ulcers. *British Journal of Surgery.* **91**(10), pp.1300-1306.

Iglesias, U., C., Nelson, A., Cullum, N. and Torgerson, D. 2004b. VenUS1: a randomised controlled trial of two types of bandage for treating venous leg ulcers. *Health Technology Assessment.* **8**(29), p120.

Information Commissioners Office. 2018. *Guide to the General Data Protection Regulation (GDPR).* [Online]. Available from: https://www.gov.uk/government/publications/guide-to-the-general-data-protection-regulation

Institute, J.B. 2015. *The Joanna Briggs Institute Reviewers' Manual 2015: Methodology for JBI Scoping Reviews.* [Online]. [Accessed 04 June 2018]. Available from: http://joannabriggs.org/assets/docs/sumari/Reviewers-Manual_Methodology-for-JBI-Scoping-Reviews_2015_v2.pdf

INVOLVE. 2018. *Involve resources.* [Online]. [Accessed 10 September 2018]. Available from: http://www.invo.org.uk/resource-centre/

Iorio, A., Skinner, M.W., Clearfield, E., Messner, D., Pierce, G.F., Witkop, M. and Tunis, S. 2018. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. *Haemophilia.* **24**(4), pp.e167-e172.

Jackson, S. ed. 1992. *Team composition in organizational settings: Issues in managing an increasingly diverse work force.* Newby Park; London: Sage.

Jadad, A.R., Cook, D.J., Jones, A., Klassen, T.P., Tugwell, P., Moher, M. and Moher, D. 1998. Methodology and reports of systematic reviews and meta-analyses: A comparison of Cochrane reviews with articles published in paper-based journals. *JAMA.* **280**(3), pp.278-280.

Jadad, A.R. and Enkin, M. 2007. *Randomized controlled trials: Questions, answers, and musings.* Oxford: Blackwell.

Jaeschke, R., Guyatt, G.H., Dellinger, P., Schünemann, H., Levy, M.M., Kunz, R., Norris, S. and Bion, J. 2008. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ.* **337**.

James Lind Alliance. 2019. *About Priority Setting Partnerships.* [Online]. [Accessed 14 March 2019]. Available from: http://www.jla.nihr.ac.uk/about-the-james-lind-alliance/about-psps.htm

Jamieson, S. 2004. Likert scales: how to (ab)use them. *Medical Education.* **38**(12), pp.1217-1218.

Jeffery, G., Hache, G. and Lehr, R. 1995. A Group Based Delphi application: a Defining Rural and Career Counselling Needs. *Measurement and Evaluation in Counselling and Development.* **28**, pp.45-60.

Jisc. 2018. *Bristol Online Survey.* [Online]. [Accessed 22 January 2018]. Available from: https://www.onlinesurveys.ac.uk/about/

Jones, J. and Hunter, D. 1995. Consensus methods for medical and health services research. *British Medical Journal.* **311**(7001), pp.376-380.

Jull, A. 2007. *Honey and venous leg ulceration: a systematic review & randomised controlled trial*. thesis, The University of Auckland.

Jull, A., Walker, N., Parag, V., Molan, P. and Rodgers, A. 2008. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *British Journal of Surgery.* **95**(2), pp.175-182.

Jünger, M., Partsch, H., Ramelet, A.A. and Zuccarelli, F. 2004a. Efficacy of a ready-made tubular compression device versus short-stretch compression bandages in the treatment of venous leg ulcers. *Wounds: A compendium of Clinical Research and Practice.* **2004**(10), pp.313-320.

Jünger, M., Wollina, U., Kohnen, R. and Rabe, E. 2004b. Efficacy and tolerability of an ulcer compression stocking for therapy of chronic venous ulcer compared with a below-knee compression bandage: results from a prospective, randomized, multicentre trial. *Current Medical Research and Opinion.* **20**(10), pp.1613-1623.

Jüni, P., Holenstein, F., Sterne, J., Bartlett, C. and Egger, M. 2002. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *International Journal of Epidemiology.* **31**, pp.115-123.

Jupp, V. 2006. *The SAGE Dictionary of Social Research Methods.* London.

Kaplan, A., Skogstad, A.L. and Girshick, M.A. 1950. The Prediction of Social and Technological Events. *The Public Opinion Quarterly.* **14**(1), pp.93-110.

Kastein, M.R., Jacobs, M., van der Hell, R.H., Luttik, K. and Touw-Otten, F.W.M.M. 1993. Delphi, the issue of reliability: A qualitative Delphi study in

primary health care in the Netherlands. *Technological Forecasting and Social Change.* **44**(3), pp.315-323.

Keeney, S., Hasson, F. and McKenna, H. 2011. *The Delphi Technique in Nursing and Health Research.* Chichester: Wiley-Blackwell.

Kenkre, J., Hobbs, F., Carter, Y., Holder, R. and Holmes, E. 1996. A randomized controlled trial of electromagnetic therapy in the primary care management of venous leg ulceration. *Family Practice.* **13**(3), pp.236-241.

Kerihuel, J.C. 2010. Effect of activated charcoal dressings on healing outcomes of chronic wounds. *Journal of Wound Care.* **19**(5), pp.208-214.

Khangura, S., Konnyu, K., Cushman, R., Grimshaw, J. and Moher, D. 2012. Evidence summaries: the evolution of a rapid review approach. *Systematic Reviews.* **1**(1), p10.

Kikta, M.J., Schuler, J.J., Meyer, J.P., Durham, J.R., Eldrup-Jorgensen, J., Schwarcz, T.H. and Flanigan, D.P. 1988. A prospective, randomized trial of Unna's boots versus hydroactive dressing in the treatment of venous statis ulcers. *Journal of Vascular Surgery.* **7**(3), pp.478-486.

Kirkham, J.J., Davis, K., Altman, D.G., Blazeby, J.M., Clarke, M., Tunis, S. and Williamson, P.R. 2017. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. *PLOS Medicine.* **14**(11), pe1002447.

Kirkham, J.J., Dwan, K.M., Altman, D.G., Gamble, C., Dodd, S., Smyth, R. and Williamson, P.R. 2010. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ.* **340**.

Kirkham, J.J., Gargon, E., Clarke, M. and Williamson, P.R. 2013. Can a core outcome set improve the quality of systematic reviews? – a survey of the Co-ordinating Editors of Cochrane review groups. *Trials.* **14**(1), p21.

Kirkham, J.J., Gorst, S., Altman, D.G., Blazeby, J.M., Clarke, M., Devane, D., Gargon, E., Moher, D., Schmitt, J., Tugwell, P., Tunis, S. and Williamson, P.R. 2016. Core Outcome Set–STAndards for Reporting: The COS-STAR Statement. *PLOS Medicine.* **13**(10), pe1002148.

Kirwan, J.R. 1992. A theoretical framework for process, outcome and prognosis in rheumatoid artritis. *Journal of Rheumatology.* **19**(3), pp.333-336.

Kirwan, J.R., Minnock, P., Adebajo, A., Bresnihan, B., Choy, E., de Wit, M., Hazes, M., Richards, P., Saag, K., Suarez-Almazor, M., Wells, G. and Hewlett, S. 2007. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *The Journal of Rheumatology.* **34**(5), pp.1174-1177.

Koksal, C. and Bozkurt, A.K. 2003. Combination of hydrocolloid dressing and medical compression stocking versus Unna's boot for the treatment of venous leg ulcers. *Swiss medical weekly.* **133**(25/26), pp.364-368.

König, M., Vanscheidt, W., Augustin, M. and Kapp, H. 2005. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. *Journal of Wound Care.* **14**(7), pp.320-323.

Kottner, J., Jacobi, L., Hahnel, E., Alam, M., Balzer, K., Beeckman, D., Busard, C., Chalmers, J., Deckert, S., Eleftheriadou, V., Furlan, K., Horbach, S.E.R., Kirkham, J., Nast, A., Spuls, P., Thiboutot, D., Thorlacius, L., Weller, K., Williams, H.C. and Schmitt, J. 2018. Core outcome sets in dermatology: report from the second meeting of the International Cochrane Skin Group Core Outcome Set Initiative. *British Journal of Dermatology.* **178**(4), pp.e279-e285.

Krosnick, J.A. and Presser, S. 2010. Question and questionnaire design. In: Marsden, P.V. and Wright, J.D. eds. *Handbook of Survey Research.* Bingley, UK: Emerald Group.

Lavrakas, P.J. 2008. *Encyclopedia of Survey Research Methods.* California: Thousand Oaks.

Lazarus, G., Valle, F., Malas, M., Qazi, U., Maruthur, N., Zenilman, J., Boult, C., Doggett, D., Fawole, O.A. and Bass, E.B. 2013. Chronic Venous Leg Ulcer Treatment: Future Research Needs. [Online]. [Accessed 24 June 2017]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK184808/pdf/Bookshelf_NBK184808.pdf

Lelkes, Y., Krosnick, J.A., Marx, D.M., Judd, C.M. and Park, B. 2012. Complete anonymity compromises the accuracy of self-reports. *Journal of Experimental Social Psychology.* **48**(6), pp.1291-1299.

Levac, D., Colquhoun, H. and O'Brien, K.K. 2010. Scoping studies: advancing the methodology. *Implementation Science.* **5**, pp.1-9.

Liao, X.H. and Cheater, F. 2000. The management of patients with venous leg ulcers: Audit protocol. [Online]. [Accessed 08 November 2017]. Available from: https://www.rcn.org.uk/professional-development/publications/pub-001269

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J. and Moher, D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* **339**.

Lim, C.S., Baruah, M. and Bahia, S.S. 2018. Diagnosis and management of venous leg ulcers. *BMJ.* **362**.

Linstone, H.A. and Turoff, M. 1975. The Delphi Method: Techniques and Applications

Liu, Z., J., S.I., David, M., C., D.J. and A., C.N. 2017. Outcomes in Cochrane systematic reviews related to wound care: An investigation into prespecification. *Wound Repair and Regeneration.* **25**(2), pp.292-308.

Lomas, J. 1991. Words Without Action? The Production, Dissemination, and Impact of Consensus Recommendations. *Annual Review of Public Health.* **12**(1), pp.41-65.

Lord, S.J., Gebski, V.J. and Keech, A.C. 2004. Multiple analyses in clinical trials: sound science or data dredging?. *Medical Journal of Australia.* **181**(8), p452.

Loughlin, K.G. and Moore, L.F. 1979. Using Delphi to achieve congruent objectives and activities in a pediatrics department. *Journal of Medical Education.* **54**(2), pp.101-106.

MacLennan, S., Williamson, P.R., Bekema, H., Campbell, M., Ramsay, C., N'Dow, J., MacLennan, S., Vale, L., Dahm, P., Mottet, N. and Lam, T. 2017. A core outcome set for localised prostate cancer effectiveness trials. *BJU International.* **120**(5B), pp.E64-E79.

Madden, M. and Morley, R. 2016. Exploring the challenge of health research priority setting in partnership: reflections on the methodology used by the James Lind Alliance Pressure Ulcer Priority Setting Partnership. *Research Involvement and Engagement.* **2**(1), p12.

Manfreda, K.L., Berzelak, J., Vehovar, V., Bosnjak, M. and Haas, I. 2008. Web Surveys versus other Survey Modes: A Meta-Analysis Comparing Response Rates. *International Journal of Market Research.* **50**(1), pp.79–104.

Mariani, F., Mattaliano, V., Mosti, G., Gasbarro, V., Bucalossi, M., Blattler, W., Amsler, F. and Mancini, S. 2008. The treatment of venous leg ulcers with a specifically designed compression stocking kit- Comparison with bandaging. *Phlebologie.* **37**, pp.191-197.

Marshall, M., Lockwood, A., Bradley, C., Adams, C., Joy, C. and Fenton, M. 2000. Unpublished Rating Scales: a Major Source of Bias in Randomised Controlled Trials of Treatments for Schizophrenia. . *British Journal of Psychiatry.* **176**, pp.249-252.

Mason, J. 2002. *Qualitative Researching.* 2nd ed. London: Sage Publications.

Mayo-Wilson, E., Fusco, N., Li, T., Hong, H., Canner, J.K. and Dickersin, K. 2017. Multiple outcomes and analyses in clinical trials create challenges for interpretation and research synthesis. *Journal of Clinical Epidemiology.* **86**, pp.39-50.

Mays, N., Roberts, E. and Popay, J. 2001. Synthesising research evidence. In: Fulop, N., et al. eds. *Studying the organisation and delivery of health services: Research methods.* London: Routledge.

McDowell, I. 2006. *Measuring health : a guide to rating scales and questionnaires* Oxford: Oxford University Press.

McKenna, H.P. 1994. The Delphi technique: a worthwhile research approach for nursing? *Journal of Advanced Nursing.* **19**(6), pp.1221-1225.

Meher, S., Cuthbert, A., Kirkham, J., Williamson, P., Abalos, E., Aflaifel, N., Bhutta, Z., Bishop, A., Blum, J., Collins, P., Devane, D., Ducloy-Bouthors, A.-S., Fawole, B., Gülmezoglu, A., Gutteridge, K., Gyte, G., Homer, C., Mallaiah, S., Smith, J., Weeks, A. and Alfirevic, Z. 2019. Core outcome sets for prevention and treatment of postpartum haemorrhage: an international Delphi consensus study. *BJOG: An International Journal of Obstetrics & Gynaecology.* **126**(1), pp.83-93.

Meyer, F.J., Burnand, K.G., Lagattolla, N.R.F. and Eastham, D. 2002. Randomized clinical trial comparing the efficacy of two bandaging regimens in the treatment of venous leg ulcers. *British Journal of Surgery.* **89**(1), pp.40-44.

Meyer, F.J., McGuinness, C.L., Lagattolla, N.R.F., Eastham, D. and Burnand, K.G. 2003. Randomized clinical trial of three-layer paste and four-layer bandages for venous leg ulcers. *British Journal of Surgery.* **90**(8), pp.934-940.

Michaels, J.A., Campbell, B., King, B., Palfreyman, S.J., Shackley, P. and Stevenson, M. 2009. Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial). *British Journal of Surgery.* **96**(10), pp.1147-1156.

Milic, D.J., Zivic, S.S., Bogdanovic, D.C., Jovanovic, M.M., Jankovic, R.J., Milosevic, Z.D., Stamenkovic, D.M. and Trenkic, M.S. 2010. The influence of different sub-bandage pressure values on venous leg ulcers healing when treated with compression therapy. *Journal of Vascular Surgery.* **51**(3), pp.655-661.

Milic, D.J., Zivic, S.S., Bogdanovic, D.C., Perisic, Z.D., Milosevic, Z.D., Jankovic, R.J., Visnjic, A.M. and Jovanovic, B.M. 2007. A randomized trial of the Tubulcus multilayer bandaging system in the treatment of extensive venous ulcers. *Journal of Vascular Surgery.* **46**(4), pp.750-755.

Millar, A.N., Daffu-O'Reilly, A., Hughes, C.M., Alldred, D.P., Barton, G., Bond, C.M., Desborough, J.A., Myint, P.K., Holland, R., Poland, F.M. and Wright, D. 2017. Development of a core outcome set for effectiveness trials aimed at optimising prescribing in older adults in care homes. *Trials.* **18**(1), p175.

Miller, C., McGuiness, W., Wilson, S., Cooper, K., Swanson, T., Rooney, D., Piller, N. and Woodward, M. 2017. Venous leg ulcer healing with electric stimulation therapy: a pilot randomised controlled trial. *Journal of Wound Care.* **26**(3), pp.88-98.

Mills, J.L. and Armstrong, D.G. 2018. *Chronic Venous Insufficiency.* [Online]. [Accessed 15th August 2018]. Available from: https://0-bestpractice-bmj-com.wam.leeds.ac.uk/topics/en-gb/507

Mobily, P.R., Herr, K.A. and Kelley, L.S. 1993. Cognitive-behavioral techniques to reduce pain: a validation study. *International Journal of Nursing Studies.* **30**(6), pp.537-548.

Moffatt, C., Martin, R. and Smithdale, R. 2007. *Leg Ulcer management: Essential clinical skills for nurses.* Oxford: Blackwell Publishing.

Moffatt, C., Simon, D., Franks, P., Connolly, M., Fielden, S., Groarke, L. and McCollum, C. 1999. Randomised trial comparing two four-layer bandage systems in the management of chronic leg ulceration. *Phlebology.* **14**(4), pp.139-142.

Moffatt, C.J. and Dorman, M.C. 1995. Recurrence of leg ulcers within a community ulcer service. *Journal of Wound Care.* **4**(2), pp.57-61.

Moffatt, C.J., Edwards, L., Collier, M., Treadwell, T., Miller, M., Shafer, L., Sibbald, G., Brassard, A., McIntosh, A., Reyzelman, A., Price, P., Kraus, S.M., Walters, S.-A. and Harding, K. 2008. A randomised controlled 8-week crossover clinical evaluation of the 3M™ Coban™ 2 Layer Compression System versus Profore™ to evaluate the product performance in patients with venous leg ulcers. *International Wound Journal.* **5**(2), pp.267-279.

Moffatt, C.J. and Franks, P.J. 2004. Epidemiology and Health Services Research: Implementation of a Leg Ulcer Strategy. *British Journal of Dermatology.* **151**(4), pp.857-867.

Moffatt, C.J., McCullagh, L., O'Connor, T., Doherty, D.C., Hourican, C., Stevens, J., Mole, T. and Franks, P.J. 2003. Randomized trial of four-layer and two-layer bandage systems in the management of chronic venous ulceration. *Wound Repair and Regeneration.* **11**(3), pp.166-171.

Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gøtzsche, P.C., Devereaux, P.J., Elbourne, D., Egger, M. and Altman, D.G. 2010. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ.* **340**.

Mokkink, L.B., Terwee, C.B., Patrick, D.L., Alonso, J., Stratford, P.W., Knol, D.L., Bouter, L.M. and de Vet, H.C.W. 2010a. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Quality of Life Research.* **19**(4), pp.539-549.

Mokkink, L.B., Terwee, C.B., Patrick, D.L., Alonso, J., Stratford, P.W., Knol, D.L., Bouter, L.M. and de Vet, H.C.W. 2010b. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of

measurement properties for health-related patient-reported outcomes. *Journal of Clinical Epidemiology.* **63**(7), pp.737-745.

Monk, B.E. and Sarkany, I. 1982. Outcome of treatment of venous stasis ulcers. *Clinical and Experimental Dermatology.* **7**(4), pp.397-400.

Moody, M. 1999. Comparison of Rosidal K and SurePress in the treatment of venous leg ulcers. *British Journal of Nursing.* **8**(6), pp.345-355.

Moors, G., Kieruj, N. and Vermunt, J. 2014. The Effect of Labelling and Numbering of Reponse Scales on the Likelihood of Reponse Bias. *Sociological Methodology* **44**, pp.369-399.

Morgan, P.J., Lam-McCulloch, J., Herold-McIlroy, J. and Tarshis, J. 2007. Simulation performance checklist generation using the Delphi technique. *Canadian Journal of Anaesthesia.* **54**(12), pp.992-997.

Morison, M. and Moffat, C.J. 1997. *Leg ulcers.* London: Mosby.

Morrell, C.J., Walters, S.J., Dixon, S., Collins, K.A., Brereton, L.M.L., Peters, J. and Brooker, C.G.D. 1998. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ.* **316**(7143), p1487.

Moules, P., Aveyard, H. and Goodman, M. 2017. *Nursing Research: An Introduction.* 3rd ed. Los Angeles: SAGE Publications.

Mphande, A.N.G., Killowe, C., Phalira, S., Wynn Jones, H. and Harrison, W.J. 2007. Effects of honey and sugar dressings on wound healing. *Journal of Wound Care.* **16**(7), pp.317-319.

Mullen, B. 1983. Egocentric Bias in Estimates of Consensus *The Journal of Social Psychology.* **121**(1), pp.31-38.

Murphy, E., Black, N., Lamping, D., Mckee, C. and Sanderson, C. 1998. Consensus development methods, and their use in clinical guideline development: a review. *Health Technology Assessment.* **2**(3), pp.1-90.

Nair, R., Aggarwal, R. and Khanna, D. 2011. Methods of Formal Consensus in Classification/Diagnostic Criteria and Guideline Development. *Seminars in Arthritis and Rheumatism.* **41**(2), pp.95-105.

Nanus, B., Leland, M., Wooten, M. and Borko, H. 1973. *The Social Implications of the Use of Computers Across National Boundries.* New Jersey: AFIPS Press.

Nelson, A. 2004. 3 layer paste bandages were more effective than 4 layer bandages for healing venous leg ulcers. *Evidence Based Nursing.* **7**(1), pp.21-21.

Nelson, E.A., Iglesias, C.P., Cullum, N. and Torgerson, D.J. 2004. Randomized clinical trial of four-layer and short-stretch compression bandages for venous leg ulcers (VenUS I). *British Journal of Surgery.* **91**(10), pp.1292-1299.

Nelson, E.A., Prescott, R.J., Harper, D.R., Gibson, B., Brown, D. and Ruckley, C.V. 2007. A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydrocolloid dressings for venous ulcers. *Journal of Vascular Surgery.* **45**(1), pp.134-141.

Nelzen, O., Bergqvist, D. and Lindhagen, A. 1994. Venous and non-venous leg ulcers: clinical history and appearance in a popular study. *British Journal Surgery.* **81**(2), pp.182-187.

Newell, R. and Burnard, P. 2011. *Research Evidence-Based Practice in Healthcare.* Chichester: Wiley- Blackwell Publishing.

Newstead, S.E. and Arnold, J. 1989. The Effect of Response Format on Ratings of Teaching. *Educational and Psychological Measurement.* **49**(1), pp.33-43.

NHS. 2016. *Leading Change, Adding Value.* [Online]. [Accessed 01 June 2018]. Available from: https://www.england.nhs.uk/wp-content/uploads/2016/05/nursing-framework.pdf

NHS RightCare. 2017. *NHS RightCare scenario: The variation between sub-optimal and optimal pathways.* [Online]. [Accessed 28 May 2018]. Available from: https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2017/01/nhs-rightcare-bettys-story-narrative-full.pdf

NICE. 2015. *Leg ulcer- venous.* [Online]. [Accessed 08 November 2016]. Available from: https://cks.nice.org.uk/leg-ulcer-venous#!diagnosissub:3

NICE. 2017. *Compression stockings.* [Online]. [Accessed 24 December 2018]. Available from: https://cks.nice.org.uk/compression-stockings#!scenario

NMC. 2018. *The Code: Professional standards of practice and behaviour for nurses and midwives.* [Online]. [Accessed 28 May 2018]. Available from: https://www.nmc.org.uk/globalassets/sitedocuments/nmc-publications/nmc-code.pdf

Norman, G., Westby, M., J, Stubbs, N., Dumville, J., C and Cullum, N. 2016. A 'Test and Treat' Strategy for Elevated Wound Protease Activity for Healing Venous Leg Ulcers *Cochrane Database of Systematic Reviews.* [Online]. CD011753. (1). Available from: https://doi.org//10.1002/14651858.CD011753.pub2

O'Brien, J.F., Grace, P.A., Perry, I.J., Hannigan, A., Clarke Moloney, M. and Burke, P.E. 2003. Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. *British Journal of Surgery.* **90**(7), pp.794-798.

O'Meara, S., Al-Kurdi, D., Ologun, Y., Ovington, L.G., Martyn-St James, M. and Richardson, R. 2014. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database of Systematic Reviews.* [Online]. CD003557. (1). [Accessed 26 May 2018]. Available from: http://dx.doi.org/10.1002/14651858.CD003557.pub5

O'Brien, K.K., Colquhoun, H., Levac, D., Baxter, L., Tricco, A.C., Straus, S., Wickerson, L., Nayar, A., Moher, D. and O'Malley, L. 2016. Advancing scoping study methodology: a web-based survey and consultation of perceptions on terminology, definition and methodological steps. *BMC Health Services Research.* **16**(1), p305.

O'Meara, S., Cullum, N., Nelson, E.A. and Dumville, J.C. 2012. Compression for venous leg ulcers (Review). *Cochrane Database for Systematic Reviews.* [Online]. CD000265. (11). [Accessed 18 December 2017]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000265.pub3/full

Okoli, C. and Pawlowski, S.D. 2004. The Delphi method as a research tool: an example, design considerations and applications. *Information & Management.* **42**(1), pp.15-29.

OMERACT. 2019. *OMERACT Core Domain Set Selection Workbook.* [Online]. [Accessed 21 March 2019]. Available from: https://omeracthandbook.org/workbooks-%26-resources

Orbai, A.-M., de Wit, M., Mease, P., Shea, J.A., Gossec, L., Leung, Y.Y., Tillett, W., Elmamoun, M., Callis Duffin, K., Campbell, W., Christensen, R., Coates, L., Dures, E., Eder, L., FitzGerald, O., Gladman, D., Goel, N., Grieb, S.D., Hewlett, S., Hoejgaard, P., Kalyoncu, U., Lindsay, C., McHugh, N., Shea, B., Steinkoenig, I., Strand, V. and Ogdie, A. 2017. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Annals of the Rheumatic Diseases.* **76**(4), pp.673-680.

Ostrom, T.M., Bond Jr, C.F., Krosnick, J.A. and Sedikides, C. 1994. Attitude scales: How we measure the unmeasurable. *Persuasion: Psychological insights and perspectives.* Needham Heights, MA, US: Allyn & Bacon, pp.15-42.

Palmer, N. and Batchelor, P. 2006. Informing Research in Primary Dental Care: Setting Priorities. *Primary Dental Care.* **13**(3), pp.85-90.

Parahoo, K. 2006. *Nursing Research: Principles, Process and Issues.* 2nd ed. Basingstoke: Palgrave Macmillan.

Partsch, H., Damstra, R.J., Tazelaar, D.J., Schuller-Petrovic, S., Velders, A.J., de Rooij, M.J.M., Tjon Lim Sang, R.R.M. and Quinlan, D. 2001. Mulitcentre, randomised controlled trial of four-layer bandaging versus short-stretch bandaging in the treatment of venous leg ulcers. *Vasa.* **30**(2), pp.108-113.

Paulhus, D.L. 1991. CHAPTER 2 - Measurement and Control of Response Bias. In: Robinson, J.P., et al. eds. *Measures of Personality and Social Psychological Attitudes.* Academic Press, pp.17-59.

Persoon, A., Heinen, M.M., Van Der Vleuten, C.J.M., De Rooij, M.J., Van De Kerkhof, P.C.M. and Van Achterberg, T. 2004. Leg ulcers: a review of their impact on daily life. *Journal of Clinical Nursing.* **13**(3), pp.341-354.

Petticrew, M. and Roberts, H. 2006. *Systematic Reviews in the Social Sciences: A practical guide.* Oxford: Blackwell publishing.

Phillips, A.C., Lewis, L.K., McEvoy, M.P., Galipeau, J., Glasziou, P., Hammick, M., Moher, D., Tilson, J.K. and Williams, M.T. 2014. A Delphi survey to

determine how educational interventions for evidence-based practice should be reported: Stage 2 of the development of a reporting guideline. *BMC Medical Education.* **14**(1), p159.

Pocock, S.J. 1983. *Clinical trials: a practical approach.* Chichester: Wiley.

Polignano, R., Boneado, P., Gasbarro, S. and Allegra, C. 2004a. A randomised controlled study of four-layer compression versus Unna's Boot for venous ulcers. *Journal of Wound Care.* **13**(1), pp.21-24.

Polignano, R., Guarnera, G. and Boneado, P. 2004b. Evaluation of SurePress Comfort: a new compression system for the management of venous leg ulcers. *Journal of Wound Care.* **13**(9), pp.387-391.

Polit, D.F. and Beck, C.T. 2006. The content validity index: Are you sure you know what's being reported? critique and recommendations. *Research in Nursing & Health.* **29**(5), pp.489-497.

Porta, M. 2016. *A Dictionary of Epidemiology.* Oxford: Oxford University Press.

Posnett, J. and Franks, P.J. eds. 2007. *The cost of skin breakdown and ulceration in the UK.* Smith and ɴewphew Foundation.

Potter, S., Holcombe, C., Ward, J.A. and Blazeby, J.M. 2015. Development of a core outcome set for research and audit studies in reconstructive breast surgery. *BJS.* **102**(11), pp.1360-1371.

Powell, C. 2003. The Delphi technique: myths and realities. *Journal of Advanced Nursing.* **41**(4), pp.376-382.

Prinsen, C.A.C., Vohra, S., Rose, M.R., King-Jones, S., Ishaque, S., Bhaloo, Z., Adams, D. and Terwee, C.B. 2014. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. *Trials.* **15**(1), p247.

PRISMA. 2015. *PRISMA checklist.* [Online]. [Accessed 24 November 2018]. Available from: http://www.prisma-statement.org/PRISMAStatement/Checklist

Prowse, R.L., Dalbeth, N., Kavanaugh, A., Adebajo, A.O., Gaffo, A.L., Terkeltaub, R., Mandell, B.F., Suryana, B.P.P., Goldenstein-Schainberg, C., Diaz-Torne, C., Khanna, D., Lioté, F., Mccarthy, G., Kerr, G.S., Yamanaka, H.,

Janssens, H., Baraf, H.F., Chen, J.-H., Vazquez-Mellado, J., Harrold, L.R., Stamp, L.K., Van De Laar, M.A., Janssen, M., Doherty, M., N, B.M., Edwards, L., Gow, P., Chapman, P., Khanna, P., Helliwell, P.S., Grainger, R., Schumacher, R.H., Neogi, T., Jansen, T.L., Louthrenoo, W., Sivera, F. and Taylor, W.J. 2013. A Delphi Exercise to Identify Characteristic Features of Gout — Opinions from Patients and Physicians, the First Stage in Developing New Classification Criteria. *Journal of Rheumatology.* **40**(4), pp.498-505.

Punch, K.F. 2005. *Introduction to social research : quantitative and qualitative approaches.* 2nd ed. London: Sage.

Rabe, E. and Pannier, F. 2010. Societal costs of chronic venous disease in CEAP C4, C5, C6 disease. *Phlebology.* **25**(1_suppl), pp.64–67.

Raine, R., Sanderson, C. and Black, N. 2005. Developing clinical guidelines: a challenge to current methods. *BMJ.* **331**(7517), p631.

RAND Cooperation. 2018. *RAND at a Glance.* [Online]. Available from: https://www.rand.org/about/glance.html

Richardson, F.M.D. 1972. Peer Review of Medical Care. *Medical Care.* **10**(1), pp.29-39.

Ritchie, J. and Spencer, L. 1994. Qualitative data analysis for applied policy research. In: Bryman, A. and Burgess, R.G. eds. *Analyzing qualitative data.* London: Routledge, pp.173-194.

Robson, V., Dodd, S. and Thomas, S. 2009. Standardized antibacterial honey (Medihoney™) with standard therapy in wound care: randomized clinical trial. *Journal of Advanced Nursing.* **65**(3), pp.565-575.

Rolls, K.D. and Elliott, D. 2008. Using consensus methods to develop clinical practice guidelines for intensive care: The Intensive Care Collaborative project. *Australian Critical Care.* **21**(4), pp.200-215.

Rosenthal, R.J. 2012. International Sleeve Gastrectomy Expert Panel Consensus Statement: best practice guidelines based on experience of >12,000 cases. *Surgery for Obesity and Related Diseases.* **8**(1), pp.8-19.

Rowe, G., Wright, G. and Bolger, F. 1991. Delphi: A reevaluation of research and theory. *Technological Forecasting and Social Change.* **39**(3), pp.235-251.

Rubin, J.R., Alexander, J., Plecha, E.J. and Marman, C. 1990. Unna's boot vs polyurethane foam dressings for the treatment of venous ulceration: A randomized prospective study. *Archives of Surgery.* **125**(4), pp.489-490.

Ruckley, C.V., Callam, M.J., Harper, D.R., Dale, J.J., Gibson, B. and Prescott, R.J. 2002. Randomized clinical trial comparing the efficacy of two bandaging regimens in the treatment of venous leg ulcers *British Journal of Surgery.* **89**(6), pp.810-810.

Sackett, D., I, Rosenberg, W., M. C, Gray, J.A., Muir, Haynes, R.B. and Richardson, W.S. 1996. Evidence based medicine: what it is and what it isn't. *BMJ.* **312**.

Sackman, H. 1975. *Delphi critique: expert opinion, forecasting, and group process.* Lexington, Mass: Lexington Books.

Sahnan, K., Tozer, P.J., Adegbola, S.O., Lee, M.J., Heywood, N., McNair, A.G.K., Hind, D., Yassin, N., Lobo, A.J., Brown, S.R., Sebastian, S., Phillips, R.K.S., Lung, P.F.C., Faiz, O.D., Crook, K., Blackwell, S., Verjee, A., Hart, A.L. and Fearnhead, N.S. 2018. Developing a core outcome set for fistulising perianal Crohn's disease. *Gut.* **68**(2), pp.226-238.

Sanderson, T., Morris, M., Calnan, M., Richards, P. and Hewlett, S. 2010. What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. *Arthritis Care & Research.* **62**(5), pp.640-646.

Saust, L.T., Bjerrum, L., Arpi, M. and Hansen, M.P. 2017. Quality indicators for the diagnosis and antibiotic treatment of acute respiratory tract infections in general practice: a RAND Appropriateness Method. *Scandinavian Journal of Primary Health Care.* **35**(2), pp.192-200.

Schaap, T., Bloemenkamp, K., Deneux-Tharaux, C., Knight, M., Langhoff-Roos, J., Sullivan, E. and Akker, T. 2017. Defining definitions: a Delphi study to develop a core outcome set for conditions of severe maternal morbidity. *BJOG: An International Journal of Obstetrics & Gynaecology.* **126**(3), pp.394-401.

Schmitt, J., Apfelbacher, C., Spuls, P.I., Thomas, K.S., Simpson, E.L., Furue, M., Chalmers, J. and Williams, H.C. 2015. The Harmonizing Outcome Measures for Eczema (HOME) Roadmap: A Methodological Framework to

Develop Core Sets of Outcome Measurements in Dermatology. *Journal of Investigative Dermatology.* **135**(1), pp.24-30.

Schmitt, J., Langan, S., Stamm, T. and Williams, H.C. 2011. Core Outcome Domains for Controlled Trials and Clinical Recordkeeping in Eczema: International Multiperspective Delphi Consensus Process. *Journal of Investigative Dermatology.* **131**(3), pp.623-630.

Schmitt, J., Lange, T., Kottner, J., Prinsen, C.A.C., Weberschock, T., Hahnel, E., Apfelbacher, C., Brandstetter, S., Dreher, A., Stevens, G., Burden-Teh, E., Rogers, N., Spuls, P., Grainge, M.J., Williams, H.C. and Jacobi, L. 2019. Cochrane Reviews and Dermatological Trials Outcome Concordance: Why Core Outcome Sets Could Make Trial Results More Usable. *Journal of Investigative Dermatology.* **139**(5), pp.1045-1053.

Schneider, P., Evaniew, N. and Rendon, J.S. 2016. Moving forward through consensus: protocol for a modified Delphi approach to determine the top research priorities in the field of orthopaedic oncology. *BMJ Open.* **6**(5).

Scott, I. and Mazhindu, D. 2014. *Statistics for Healthcare Professionals: An introduction.* Second ed. London: Sage.

Scriven, J., Taylor, L., Wood, A., Bell, P., Naylor, A. and London, N. 1998. A prospective randomised trial of four-layer versus short stretch compression bandages for the treatment of venous leg ulcers. *Annals of the Royal College of Surgeons of England.* **80**(3), p215.

Sheehan, K.B. 2001. E-mail Survey Response Rates: A Review. *Journal of Computer-Mediated Communication.* **6**(2), pp.0-0.

Shekelle, P.G., Kahan, J.P., Bernstein, S.J., Leape, L.L., Kamberg, C.J. and Park, R.E. 1998. The Reproducibility of a Method to Identify the Overuse and Underuse of Medical Procedures. *New England Journal of Medicine.* **338**(26), pp.1888-1895.

Simoens, S. 2006. Using the Delphi technique in economic evaluation: time to revisit the oracle? *Journal of Clinical Pharmacy and Therapeutics.* **31**(6), pp.519-522.

Sinha, I.P., Gallagher, R., Williamson, P.R. and Smyth, R.L. 2012. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. *Trials.* **13**(1), p103.

Sinha, I.P., Smyth, R.L. and Williamson, P.R. 2011. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS Medicine.* **8**(1), pe1000393.

Sinha, I.P., Williamson, P.R. and Smyth, R.L. 2009. Outcomes in Clinical Trials of Inhaled Corticosteroids for Children with Asthma Are Narrowly Focussed on Short Term Disease Activity. *PLOS ONE.* **4**(7), pe6276.

Skog, E., ArnesjÖ, B., TroËNg, T., GjÖRes, J.E., Bergljung, L., Gundersen, J., HallbÖÖK, T., Hessman, Y., HillstrÖM, L., MÅNsson, T., Eilard, U., EklÖFf, B., Plate, G. and Norgren, L. 1983. A randomized trial comparing cadexomer iodine and standard treatment in the out-patient management of chronic venous ulcers. *British Journal of Dermatology.* **109**(1), pp.77-83.

Skvoretz, J. 1988. Models of Participation in Status-Differentiated Groups. *Social Psychology Quarterly.* **51**(1), pp.43-57.

Smith, D.M. and Murphy, W.M. 1994. Histologic changes in prostate carcinomas treated with leuprolide (luteinizing hormone–-releasing hormone effect). Distinction from poor tumor differentiation. *Cancer.* **73**(5), pp.1472-1477.

Smith, P.D.C., Thomas, P., Scurr, J.H. and Dormandy, J.A. 1988. Causes Of Venous Ulceration: A New Hypothesis. *British Medical Journal (Clinical Research Edition).* **296**(6638), pp.1726-1727.

Snape, D., Kirkham, J., Preston, J., Popay, J., Britten, N., Collins, M., Froggatt, K., Gibson, A., Lobban, F., yatt, K. and Jacoby, A. 2014. Exploring areas of consensus and conflict around values underpinning public involvement in health and social care research: a modified Delphi study. *BMJ Open.* **4**(1), pp.1-10.

Song, F., Parekh, S., Hooper, L., Loke, Y.K., Ryder, J., Sutton, A.J., Hing, C., Kwok, C.S., Pang, C. and Harvey, I. 2010. Dissemination and publication of research findings: an updated review of related biases. *Health Technology Assessment* **14**(8), pp.1-220.

Stacey, M.C., Burnand, K.G., Bhogal, B.S. and Black, M.M. 2000. Pericapillary Fibrin Deposits and Skin Hypoxia Precede the Changes of Lipodermatosclerosis in Limbs at Increased Risk of Developing a Venous Ulcer. *Cardiovascular Surgery.* **8**(5), pp.372-380.

Staines, K. 2018. Safe compression and accurate ABPI – overcoming barriers. *Wounds UK.* **14**(1), pp.64-67.

Staniszewska, S., Brett, J., Mockford, C. and Barber, R. 2011. The GRIPP checklist: Strengthening the quality of patient and public involvement reporting in research. **27**(4), pp.391-399.

Stiller, M.J., Pak, G.H., Shupack, J.L., Thaler, S., Kenny, C. and Jondreau, L. 1992. A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial. *British Journal of Dermatology.* **127**(2), pp.147-154.

Strauss, H.J. and Zeigler, L.H. 1975. Delphi, political philosophy and the future. *Futures.* **7**(3), pp.184-196.

Streiner, D.L. and Norman, G.R. 2008. *Health Measurement Scales: a Practical Guide to Their Development and Use.* Oxford: Oxford University Press.

Sullivan, G.M. and Feinn, R. 2012. Using Effect Size-or Why the P Value Is Not Enough. *Journal of Graduate Medical Education.* **4**(3), pp.279-282.

Szewczyk, M.T., Jawień, A., Cierzniakowska, K., Cwajda-Białasik, J. and Mościcka, P. 2010. Comparison of the effectiveness of compression stockings and layer compression systems in venous ulceration treatment. *Archives of Medical Science.* **6**(5), pp.793-799.

Tan, C., Treasure, T., Browne, J., Utley, M., Davies, C.W.H. and Hemingway, H. 2007. Seeking consensus by formal methods: a health warning. *Journal of the Royal Society of Medicine.* **100**(1), pp.10-14.

Taradaj, J., Franek, A., Brzezinska-Wcislo, L., Blaszczak, E. and Polak, A. 2009. Randomized trial of medical compression stockings versus two-layer short-stretch bandaging in the management of venous leg ulcers. *Phlebologie.* **38**(4), pp.157-163.

Taylor, A., Taylor, R. and Marcuson, R. 1998. Prospective comparison of healing rates and therapy costs for conventional and four-layer high-compression bandaging treatments of venous leg ulcers. *Phlebology.* **13**(1), pp.20-24.

Taylor, A.E.M., Taylor, R. and Marcuson, R. 1995. Comparative healing rates and cost of conventional and four-layer treatment of venous ulcers. *Phlebology.* **10**, p85.

Taylor, W.J., Schumacher, H.R., Baraf, H.S.B., Chapman, P., Stamp, L., Doherty, M., McQueen, F., Dalbeth, N., Schlesinger, N., Furst, D.E., Mellado, J.V., Becker, M.A., Kavanaugh, A., Louthrenoo, W., Bardin, T., Khanna, D., Simon, L.S., Yamanaka, H., Choi, H.K., Zeng, X., Strand, V., Grainger, R., Clegg, D., Singh, J.A., Diaz-Torne, C., Boers, M., Gow, P. and Barskova, V.G. 2008. A modified Delphi exercise to determine the extent of consensus with OMERACT outcome domains for studies of acute and chronic gout. *Annals of the Rheumatic Diseases.* **67**(6), pp.888-891.

To, T., Guttmann, A., Lougheed, M.D., Gershon, A.S., Dell, S.D., Stanbrook, M.B., Wang, C., McLimont, S., Vasilevska-Ristovska, J., Crighton, E.J. and Fisman, D.N. 2010. Evidence-based performance indicators of primary care for asthma: a modified RAND Appropriateness Method. *International Journal for Quality in Health Care.* **22**(6), pp.476-485.

Tomasik, T. 2010. Reliability and validity of the Delphi method in guideline development for family physicians. *Quality in Primary Care.* **18**(5), pp.317-326.

Tomkins-Lane, C., Melloh, M., Lurie, J., Smuck, M., Battie, M., Freeman, B., Samartzis, D., Hu, R., Barz, T., Stuber, K., Schneider, M., Haig, A., Schizas, C., Cheung, J.P.Y., Mannion, A.F., Staub, L., Comer, C., Macedo, L., Ahn, S.-H., Takahashi, K. and Sandella, D. 2016. Consensus on the clinical diagnosis of lumbar spinal stenosis: Results of an International Delphi Study. *Spine.* **41**(15), pp.1239-1246.

Torgerson, D.J. and Torgerson, C. 2008. *Designing Randomised Trials in Health, Education and the Social Sciences: An Introduction.* [Online]. Springer Nature. [Accessed 28 May 2018]. Available from: https://www.dawsonera.com:443/abstract/9780230583993

Travers, J., Dalziel, K. and Makin, G. 1992. Assessment of a new one-layer adhesive bandaging method in maintaining prolonged limb compression and effects on venous ulcer healing. *Phlebology.* **7**(2), pp.59-63.

Trial Forge. 2018. *A systematic approach to making trials more efficient.* [Online]. [Accessed 15th August 2018]. Available from: https://www.trialforge.org/

Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K., Colquhoun, H., Kastner, M., Levac, D., Ng, C., Sharpe, J.P., Wilson, K., Kenny, M., Warren, R., Wilson, C., Stelfox, H.T. and Straus, S.E. 2016. A scoping review on the conduct and reporting of scoping reviews. *BMC Medical Research Methodology.* **16**(1), p15.

Tucker, J.A. 2008. A prospective, multi-site, randomized, cross-over, clinical trial of a two-layer and a four-layer compression bandage system in the treatment of venous leg ulcers. In: *40th Annual Wound, Ostomy and Continence Nurses Annual Conference*. Journal of Wound, Ostomy and Continence, p.S71.

Turk, D.C., Dworkin, R.H., Allen, R.R., Bellamy, N., Brandenburg, N., Carr, D.B., Cleeland, C., Dionne, R., Farrar, J.T., Galer, B.S., Hewitt, D.J., Jadad, A.R., Katz, N.P., Kramer, L.D., Manning, D.C., McCormick, C.G., McDermott, M.P., McGrath, P., Quessy, S., Rappaport, B.A., Robinson, J.P., Royal, M.A., Simon, L., Stauffer, J.W., Stein, W., Tollett, J. and Witter, J. 2003. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain.* **106**(3), pp.337-345.

Uhl, N.P. 1975. *Consensus and the Delphi Process.* ERIC: Institute of Education Services.

Ukat, A., Konig, M., Vanscheidt, W. and Münter, K.-C. 2003. Short-stretch versus multilayer compression for venous leg ulcers: a comparison of healing rates. *Journal of Wound Care.* **12**(4), pp.139-143.

van 't Hooft, J., Duffy, J.M.N., Daly, M., Williamson, P.R., Meher, S., Thom, E., Saade, G.R., Alfirevic, Z., Mol, B.W.J. and Khan, K.S. 2016. A Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth. *Obstetrics & Gynecology.* **127**(1), pp.49-58.

van 't Hooft, J., Alfirevic, Z., Asztalos, E.V., Biggio, J.R., Dugoff, L., Hoffman, M., Lee, G., Mol, B.W., Pacagnella, R.C., Pajkrt, E., Saade, G.R., Shennan,

A.H., Vayssière, C. and Khan, K.S. 2018. CROWN initiative and preterm birth prevention: researchers and editors commit to implement core outcome sets. *BJOG: An International Journal of Obstetrics & Gynaecology.* **125**(1), pp.8-11.

Van de Ven, A.H. and Delbecq, A.L. 1972. The nominal group as a research instrument for exploratory health studies. *American Journal of Public Health.* **62**(3), pp.337-342.

Van den Bussche, K., Kottner, J., Beele, H., De Meyer, D., Dunk, A.M., Ersser, S., Lange, T., Petrovic, M., Schoonhoven, L., Smet, S., Van Damme, N., Verhaeghe, S., Van Hecke, A. and Beeckman, D. 2018. Core outcome domains in incontinence-associated dermatitis research. *Journal of Advanced Nursing.* **74**(7), pp.1605-1617.

Vogt, W.P. 1999. *Dictionary of statistics and methodology: A nontechnical guide for the social sciences.* 2nd ed. Newbury Park: Sage.

Vowden, K. and Vowden, P. 2001. Doppler and the ABPI: how good is our understanding? *Journal of Wound Care.* **10**(6), pp.197-202.

Vowden, K.R., Barker, A. and Vowden, P. 1997. Leg ulcer management in a nurse-led, hospital-based clinic. *Journal of Wound Care.* **6**(5), pp.233-236.

Vowden, K.R., Mason, A., Wilkinson, D. and Vowden, P. 2000. Comparison of the healing rates and complications of three four-layer bandage regimens. *Journal of Wound Care.* **9**(6), pp.269-272.

Vowden, K.R. and Vowden, P. 2009. The prevalence, management and outcome for patients with lower limb ulceration identified in a wound care survey within one English health care district. *Journal of Tissue Viability.* **18**(1), pp.13-19.

Waters, A.M.I., Tudur, S., Catrin, Young, B. and Jones, T.M. 2014. The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer. *Trials.* **15**(1), p168.

Watson, D. 1992. Correcting for Acquiescent Response Bias in the Absence of a Balanced Scale: An Application to Class Consciousness *Sociological Methods and Research.* **21**(1), pp.52-88.

Wayman, J., Nirojogi, V., Walker, A., Sowinski, A. and Walker, M.A. 2000. The cost effectiveness of larval therapy in venous ulcers. *Journal of Tissue Viability.* **10**(3), pp.91-94.

Weinstein, B.D. 1993. What is an expert? *Theoretical Medicine.* **14**(1), pp.57-73.

Westerhof, W., van Ginkel, C.J.W., Cohen, E.B. and Mekkes, J.R. 1990. Prospective Randomized Study Comparing the Debriding Effect of Krill Enzymes and a Non-Enzymatic Treatment in Venous Leg Ulcers. *Dermatology.* **181**(4), pp.293-297.

Wild, T., Eberlein, T. and Andriessen, A. 2010. Wound cleansing efficacy of two cellulose-based dressings. *Wounds UK.* **6**(3), pp.14-21.

Wildt, A.R. and Mazis, M.B. 1978. Determinants of Scale Response: Label versus Position. *Journal of Marketing Research.* **15**(2), pp.261-267.

Williams, P.L. and Webb, C. 1994. The Delphi technique: a methodological discussion. *Journal of Advanced Nursing.* **19**(1), pp.180-186.

Williamson, P.R., Altman, D.G., Bagley, H., Barnes, K.L., Blazeby, J.M., Brookes, S.T., Clarke, M., Gargon, E., Gorst, S., Harman, N., Kirkham, J.J., McNair, A., Prinsen, C.A.C., Schmitt, J., Terwee, C.B. and Young, B. 2017. The COMET Handbook: Version 1.0. *Trials.* **18** (suppl 3), pp.1-50.

Wilson, I.B. and Cleary, P.D. 1995. Linking Clinical Variables With Health-Related Quality of Life: A Conceptual Model of Patient Outcomes. *JAMA.* **273**(1), pp.59-65.

Wylde, V., MacKichan, F., Bruce, J. and Gooberman-Hill, R. 2015. Assessment of chronic post-surgical pain after knee replacement: Development of a core outcome set. *European Journal of Pain.* **19**(5), pp.611-620.

Yammarino, F.J., Skinner, S.J. and Childers, T.L. 1991. Understanding Mail Survey Response Behavior: A Meta-Analysis. *The Public Opinion Quarterly.* **55**(4), pp.613-639.

Zarin, D.A., Tse, T., Williams, R.J., Califf, R.M. and Ide, N.C. 2011. The ClinicalTrials.gov Results Database — Update and Key Issues. *New England Journal of Medicine.* **364**(9), pp.852-860

Appendices

Appendix 1 Scoping Review Qualitative Search Strategy

Ovid MEDLINE

1. exp Varicose Ulcer/ or venous leg ulcer*.mp.
2. crural ulcer*.tw.
3. stasis ulcer*.tw.
4. ulcus cruris*.tw.
5. ulcer cruris*.tw.
6. outcome*.tw.
7. quality of life.tw.
8. exp "Quality of Life"/ or QoL.mp.
9. expert patient.tw.
10. (((patient$ or consumer$ or parent$ or famil$ or spouse$) adj attitude$) or involvement or desir$ or perspective$ or activation or view$).mp. or preference$.tw.
11. experience*.tw.
12. perspective*.tw.
13. feeling*.tw.
14. insight*.tw.
15. descripti*.tw.
16. explorat*.tw.
17. impact.tw.
18. exp QUALITATIVE RESEARCH/ or qualitative.mp.
19. interview*.mp.
20. narrative.mp.
21. ethnograph*.mp.
22. phenomenolog*.mp.
23. grounded theor*.mp.
24. case study.mp.
25. focus group*.mp.

26. survey*.mp.

27. 1 or 2 or 3 or 4 or 5

28. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

29. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

30. 27 and 28 and 29

31. limit 30 to (english language and humans)

Scopus

((ABS (qualitative) OR ABS (interview*) OR ABS (narrative) OR ABS (ethnograph*) OR ABS (phenomenolog*) OR ABS (grounded AND theor*) OR ABS (case AND study) OR ABS (focus AND group*) OR ABS (survey*))) AND ((ABS (outcome*) OR ABS (quality AND of AND life) OR ABS (expert AND patient) OR ABS (experience*) OR ABS (patient) OR ABS (perspective*) OR ABS (feeling*) OR ABS (insight*) OR ABS (descripti*) OR ABS (explorat*) OR ABS (impact))) AND ((ABS (varicose AND ulcer) OR ABS (crural AND ulcer*) OR ABS (stasis AND ulcer*) OR ABS (ulcus AND cruris*) OR ABS (ulcer AND cruris*) OR ABS (venous AND leg AND ulcer))) AND (LIMIT-TO (LANGUAGE , "English"))

Ovid Embase

1. exp Varicose Ulcer/ or venous leg ulcer*.mp.

2. crural ulcer*.tw.

3. stasis ulcer*.tw.

4. ulcus cruris*.tw.

5. ulcer cruris*.tw.

6. outcome*.tw.

7. quality of life.tw.

8. exp "Quality of Life"/ or QoL.mp.

9. expert patient.tw.

10. (((patient$ or consumer$ or parent$ or famil$ or spouse$) adj attitude$) or involvement or desir$ or perspective$ or activation or view$).mp. or preference$.tw.

11. experience*.tw.

12. perspective*.tw.

13. feeling*.tw.

14. insight*.tw.
15. descripti*.tw.
16. explorat*.tw.
17. impact.tw.
18. exp QUALITATIVE RESEARCH/ or qualitative.mp.
19. interview*.mp.
20. narrative.mp.
21. ethnograph*.mp.
22. phenomenolog*.mp.
23. grounded theor*.mp.
24. case study.mp.
25. focus group*.mp.
26. survey*.mp.
27. 1 or 2 or 3 or 4 or 5
28. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
29. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
30. 27 and 28 and 29
31. limit 30 to (english language and humans)

CINAHL

- S1. AB (Varicose Ulcer/ or venous leg ulcer*) OR AB crural ulcer* OR AB stasis ulcer* OR AB ulcus cruris* OR AB ulcer cruris*

- S2. AB outcome* OR AB quality of life OR AB expert patient OR AB (patient$ or consumer$ or parent$ or famil$ or spouse$) adj attitude$) or involvement or desir$ or perspective$ or activation or view$ or) OR AB preference$ OR AB experience* OR AB perspective* OR AB feeling* OR AB insight*

- S3. AB descripti* OR AB explorat* OR AB impact OR AB QUALITATIVE OR AB interview* OR AB narrative OR AB ethnograph* OR AB phenomenolog* OR AB grounded theor*v OR AB case study OR AB focus group* OR AB survey*

- S1 AND S2 AND S3

English Language; Exclude MEDLINE records; Human

Appendix 2 Outcomes Extracted from RCTs and Qualitative Research

The information in the tables below display the outcomes extracted from RCTs. The outcomes are grouped by the number of times they appeared in descending order from 10+ appearances. The outcomes written in red appeared once in the RCTs but because they related to the outcome above it they were placed in that group, for example “Number of healed ulcers in the case of multiple ulcers” appeared once but it relates to the outcome “Number of ulcers that completely healed” which appeared 38 times :

Number of ulcers that completely healed	**38**
Number of healed ulcers in the case of multiple ulcers	1

10+ appearances

Outcome	**Number of appearances**
Number of patients that completely healed	**42**
Number of ulcers that completely healed	**38**
Number of healed ulcers in the case of multiple ulcers	1
Number of ulcers completely healed at…	
6 months	1
12 months	1
Percentage of completely healed ulcers	**36**
Percentage of patients with healed legs	1
At 12 weeks	2
At 24 weeks	2
Per month	1
Percentage of patients completely healed	**34**
Percentage of the group that had completely healed	1
Percentage of patients completely healed over weeks	1
Percentage of ulcer free patients over time	1
Number of days to healing	**30**
Number of days to healing quintiles	1
Percentage reduction in ulcer area	**28**
Percentage reduction in ulcer area over time	1
Percentage of healed ulcer area	1
Percentage reduction in ulcer area per week	2
Number of patients that did not heal	**20**
Number of weeks to complete healing	**14**
Percentage change in ulcer area	**13**
Per week	**2**
Over time	**1**
Reduction in ulcer size	**12**
Percentage of patients that had recurrent ulceration	**11**

Ulcer healing rates	**10**
Reduction in ulcer diameter	1

Compliance (not specific)	**26**
Change in pain score/rating	**25**
Percentage of patients that experienced the difference ratings of levels of pain relief during wear	1
Change in Quality of Life scores/rating	**19**
Change in Philadelphia Geriatric Morale Scale scores	1
Change in Geriatric Depression scale scores	1
Change in Rosenbergs Self-esteem scale scores	1
Changes in Medical Outcomes Study support scale scores	1
Changes in Medical Outcomes Study Pain Measures scores	1
Pain (not specific)	**16**
Percentage of ulcers with pain	1
Tolerability (not specific)	**13**
Reduction in pain	**12**
Percentage of patients with a disappearance of pain	1
Proportion of patients with a pain score of >50% of the total maximum pain relief score	1
Proportion of patients that reported >50% of the maximum daily pain relief	1
Proportion of patients that reported a reduction in pain intensity of >50% of the pain intensity at baseline	1
Number of patients that reported slight or more pain relief	1
Change score for pain reduction	1
Percentage reduction in pain	1
Number of patients pain free at the end of treatment	1
Number of patients where pain between dressing changes decreased	1
Percentage of patients with improvement in pain	1
Patient comfort	**11**

Ease of application…	**19**
Reported by researcher	**1**
Reported by patient	**1**
Ease of removal…	**15**
Reported by researcher	**1**
Reported by patient	**1**

Number of adverse events/ patients that experienced adverse events:	
Ulcer infection	**21**
Pain	**27**

Number of patients that withdrew and number of events causing withdrawal:	
Pain	**15**
Poor compliance	**18**
Allergy	**11**
Infection	**13**

5-9 appearances

Time to healing (not specified)	**9**
Cumulative healing times	1
Reduction in the time to complete healing	1
Rate of healing cm^2 per day	**9**
Healing rate mm^2 per day	1
Rate of healing over time	1
Closure rate (cm^3) per day	1
Percentage decrease in ulcer size	**8**
Percentage reduction in ulcer size…	
Per week	1
Per day	1
Percentage improvement in ulcer size	1
Change in ulcer area……	**2**
cm^2	**8**
mm^2	**2**
Change in ulcer area…	
Mm^2 per day	1
Cm^2 per day	1
Change in ulcer area…	
Per day	1
Complete healing (not specific)	**7**
Percentage of patient that failed to heal/ remained unhealed	**7**
Number of patients whose ulcers were still open at 24 weeks	1
Remained unhealed (not clear)	1
Percentage of healed ulcers over time	**7**
Percentage of healed ulcers….	
Per fortnight	1
Per month	1
Reduction in ulcer surface	**7**
Per week	**1**
Percentage reduction in ulcer surface area	2
Reduction in ulcer area…	**5**
Cm^2	**6**
Mm^2	**1**
Reduction in ulcer area (cm^2) per week	1
Decrease in ulcer area per fortnight	1
Number of days in the study	**6**
Number of recurrences	**5**
Number of extremities that showed recurrence	1
Number of patients that reported a skin break	1
Number of patients that had recurrent ulceration	**5**

Pain score/rating at dressing change	**7**
Change in pain severity score/rating	**5**
Frequency of severity scores	1
Relative change in pain severity	1
Percentage of patients with a reduction in pain intensity	
Intensity of pain	1
Change in pain intensity score	1
Change in comfort score/rating	**7**

Reduction in oedema	**6**
Reduction in the score/rating of oedema	1
Percentage decrease in oedema	1
Cm per week	1
Number of ulcers where oedema decreased	1
Percentage of patients with improvement in oedema	1
Change in ankle circumference	**6**
Rate of change in pus	**5**
Rate of suppurate area percentage reduction per week	1
Relative ulcer suppurate area after treatment	1
Percentage of ulcers with suppuration	
Decrease in pus	1
Relative change in pus covered area	1
Percentage change in granulating tissue	**6**
Quality of Life (not specific)	**7**
Percentage of patients reporting an improvement in quality of life	1
Quality of life score for patients with unhealed ulcers	**5**
Change in haematology blood test	**6**
Number of patients with haematological abnormalities	1
Reduction in heavy legs sensation score/rating	**5**
Percentage reduction in heavy legs	1
Improvement in the heavy leg sensation	1
Percentage of patients with the disappearance of heaviness	1
Change in heavy legs sensation score/rating	**9**
Percentage reduction in the scoring of heavy legs sensation	1
Change in severity	1
Reduction in tiredness of lower extremities/ limbs score/rating	**5**

Number of days (wear time)	**5**
Number of dressing changes	**8**
Number of dressing changes per patient	1
Frequency of dressing changes	1
Total cost per patient	**7**
Cost of dressings	**5**

Number of adverse events/ patients that experienced adverse events:	
Maceration	**7**
Eczema	**6**
Deterioration of the ulcer	**5**
Erythema	**7**
Allergy	**5**
Burning	**7**
Itching	**6**
Dermatitis	**7**
New ulceration	**5**
Nausea	**6**
Abdominal pain	**5**
Cellulitis	**5**
Rash	**5**
Headache	**8**
Affecting gastrointestinal system	**7**

Number of patients that withdrew and number of events causing withdrawal:	
Eczema	**5**
Increase in ulcer size	**6**
Deterioration in the ulcer	**7**
Number of deaths	**7**

2- 4 appearances

Rate of healing per week cm^2 **cm**	**4** **1**
Rate of healing per week cm^2 **mm**	**3** **1**
Change in ulcer size cm^2 **Cm**	**2** **1**
Change in ulcer size per week	1
Change in surface area **Mm^2**	**3** **1**
Reduction in ulcer area per week cm^2	**3**
Reduction in ulcer area per day	**2**
Reduction in limb volume	**4**
Percentage reduction in leg volume	1
Change in limb volume	**3**
Absolute difference in total lower leg volume (ml)	1
Difference in the lower leg volume change per patient (ml)	1
Lower leg volumes	1
Absolute change in leg volume (cm^3)	1
Percentage change in leg volume	1
Relative change in total surface area	**2**
Change in ulcer depth (cm)	**2**
Improvement in the depth of the ulcer	1
Percentage of surface area healed **Per week**	**2** **1**
Percentage change in ulcer area	**2**
Percentage of healing per week	**4**
Percentage of ulcers healed per week	**3**
Number of ulcer healed per week	1
Percentage healed per week (not specific)	**4**
Percentage healed at each visit	**1**
Reduction in ankle circumference	**2**
Number of limbs with complete healing	**2**
Percentage of limbs with complete healing	1
Change in calf circumference	**3**
Change in leg circumference	1
Decrease in the leg circumference	1
Percentage of ulcer area regression	**2**
Relative risk of ulcer closure at any time point	**2**
Relative risk of healing at… 12 weeks 6 months	 1 1

Relative rate of ulcer closure	1
Relative chance of healing	1
Ability to accelerate healing (not specific)	**2**
Number with rapid healing	1
Percentage with rapid healing	1
Increased healing (not clear)	1
Number of ulcers that improved	**4**
Number of patients that improved	1
Improvement in the ulcer	1
Number of patients that showed clinical improvement	1
Percentage of patients that showed clinical improvement	1
Percentage of ulcers that improved	**2**
Percentage that reported improvement (not specific)	**2**
Predicted healing (not specific)	**2**
Predictor of healing at 24 weeks	**2**
Predictor of healing after 1 year	1
Probability (%) that ulcers will be healed	**4**
Number of patients with no varicose veins recurrence	**2**
Number of patients with varicose veins	1
Percentage of patients that had recurrence of varicose veins	1
Percentage of patients with no varicose veins recurrence	**2**
Number of patients with varicose veins recurrence <5mm	**2**
Number of patients with varicose veins recurrence >5mm	**2**
No change in ulcer area	**4**
Increase in ulcer area cm^2	**2**
Reduction in volume cm^3	**2**
Percentage reduction of ulcer volume per week	1
Relative change in…	
Length	**2**
Width	**2**
Volume	**2**
Change in length cm^2	1
Change in width cm^2	1
Change in ulcer volume	1
Number of days spent in hospital	**4**
Number of patients that were hospitalised	1
Residual area remaining	**2**
Percentage of the remaining area at the end	1
Change in foot volumes (ml/100ml + refilling rate ml/min x 100ml)	**2**

Pain on dressing removal	**4**
Level of pain on dressing removal	1
Pain post dressing change	1
Pain on dressing application	1
Percentage of patients with pain	**2**
Number of patients with pain	**2**
Number of patients that complained of pain	1
Pain during debridement	**2**
Percentage decrease in pain scores for debridement	1
Number of patients that interrupted debridement due to pain	1
Pain between dressing changes	**4**
Reduction in intensity (not specific)	**3**

Decrease in pain intensity over time	1
Percentage of total visits with pain	**2**
Percentage of pain scores/rating	**2**
Difference in pain scores/rating between groups	**2**
Number of patients experienced a decrease in pain	**2**
Percentage of patients experienced a decrease in pain	**3**
Percentage reduction in pain	**4**
Reduction in the scoring/rating of pain	**2**
Change in aching scores/rating	**2**
Improvement in aching score	1
Reduction in aching scores	1
Percentage of patients reporting heavy leg sensation	**2**
Number of patients reporting leg heaviness	1
Discomfort	**2**
Comfort during wear	**3**
Levels of comfort	**2**
Comfort during removal	**3**
Satisfaction… **Patients** **Nurse**	**1** **3** **1**
Number of patients that were satisfied aesthetically	1
Number of patients that were not satisfied	1
Change in the rating of oedema (not specific)	**3**
Percentage reporting the severity of oedema	1
Change in the severity of pitting oedema	**2**
Change in the extent of oedema	**2**
Percentage of patients with oedema	**2**
Number of patients with oedema	**2**
Oedema (not specific)	**4**
Acceptability… **Nurse** **Patient**	 **2** **2**
Acceptability of the dressing	**4**
Acceptance (not clear)	1
Convenience (not specific)	**2**
Convenience at dressing changes	1
Dressing performance (not specific)	**2**
Exudation score	**2**
Decrease in exudate	**2**
Number of ulcers where heavy exudation decreased	1
Percentage of patients that had no exudate	1
Decrease in score/rating for exudation	1

Improvement in exudates	1
Type of exudate	**2**
Percentage of visits with purulent or serosanguineous exudate	1
Amount of exudate	**4**
Percentage of visits with medium-large amount of exudate	1
Change in the extent of exudate	**2**
Ability to contain exudate	**2**
Containment of ulcer drainage	1
Number that rated the dressing absorbency as excellent	1
Percentage that rated the dressing absorbency as excellent	1
Exudate handling capacity	**3**
Exudate absorption	**3**
Reason for removal prior to visit: exudate strike through	1
Number of days to achieve lack of exudation	**2**
Time taken to cease exudation	1
Percentage of ulcers that ceased exudation	**2**
Number of patients whose exudate resolved	1
Rate of change in exudation	**4**
Odour (not specific)	**2**
Levels of odour	1
Percentage levels of odour	1
Severity of odour	1
Percentage of ulcer area affected by odour	1
Effect of odour on general well-being	1
Number of ulcers where foul odour decreased	1
Number of ulcers with malodour	1
Difference in odour scores/rating	1
Time to no odour	1
Percentage of patients with the presence of foul odour	**2**
Number of ulcers where odour was present	**3**
Change in the reporting of odour (not specific)	**2**
Condition of surrounding skin	**3**
Number of patients showing signs of abnormal or normal… Skin condition Skin tropism Skin colour	 1 1 1
Improvement in the condition of peri ulcer skin	1
Percentage of patients with normal peri wound skin	1
Rate of change in debris	**4**
Extent of debridement	**2**
Rating of the debridement procedure in terms of difficulty	1
Quality of debridement (percentage of rating responses)	1
Duration of debridement (mins)	1
Number of patients that required surgical debridement	1
Nursing time (mins) required to achieve debridement	1
Required more weekly debridement (not clear)	1
Percentage of visits which required debridement	1

Percentage reduction of debrided tissue	1
Improvement in tissue debridement	1
Number of debridement's required to obtain a clean ulcer	**2**
Number of days to achieve cleaning	1
Cleaning effect (not specific)	**2**
Percentage of area covered in residue following irrigation	1
Number of patients with a clean ulcer at the end of the study	1
Percentage of patients with a clean ulcer at the end of the study	1
Number of patients with the appearance of granulation tissue	**2**
Number of ulcers with unhealthy granulation	**2**
Number of ulcers with healthy granulation	**4**
Appearance of healthy granulation	1
Percentage of healthy granulation tissue	1
Number of weeks to healthy red granulation	1
Percentage of patients with granulating tissue	**2**
Amount of granulation tissue	**3**
Change in granulation tissue (not clear)	1
Percentage of ulcers with changes in granulation tissue	1
Weekly growth of granulation tissue	1
Number of days required to achieve a clean granulating ulcer	1
Frequency of ulcers with at least 75% clean and granulating ulcer bed	1
Increase in granulation tissue	**2**
Formation of granulation tissue	1
Percentage increase in granulation tissue	**2**
Number of days to at least 75% granulation	**2**
Number of days to 100% granulation	1
Decrease in score/rating of granulation	**2**
Change in condition score: granular tissue	1
Percentage of granulating tissue	**3**
Rate of change in granulation	**2**
Percentage of ulcer surface covered with granulation	**2**
Amount of slough	**3**
Percentage of ulcer surface covered in slough	1
Slough	1
Percentage of ulcers with a decrease in slough	1
Change in the amount of slough	1
Change in the amount of ulcers with slough	**2**
Percentage of slough	**2**
Reduction in the percentage area of slough	**2**
Reduction of at least 50% slough	**3**
Reduction in slough	1
Number of patients with a decrease in slough	1
Percentage reduction in slough	**3**
Percentage change in slough	**2**
Number of days to at least 50% epithelialisation	**2**
Presence of epithelial tissue	**2**
Epithelialisation	1
Levels of epithelial (not clear)	1
Increase in epithelial tissue	1

Percentage of epithelializing tissue	**3**
Percentage of ulcers with an increase in epithelising tissue	1
Percentage change in epithelializing tissue	1
Percentage of ulcer surface covered with re-epithelialisation	**2**
Re-epithelialized to at least 90% of the initial area	1
Number of patients that developed eczema	**3**
Eczema (not specific)	1
Reduction in erythema	**3**
Number of ulcers where perilesional skin erythema decreased	1
Change in the scoring/rating of erythema	**2**
Erythema	1
Change in the extent of erythema	1
Rate of change in erythema	1
Number that reported severe erythema	1
Percentage that reported severe erythema	1
Percentage of dressing changes where erythema was observed	1
Percentage of the ulcer surface area covered with necrotic tissue	**2**
Percentage of fibrin	**2**
Percentage change in fibrin	1
Percentage reduction in fibrin	1
Maceration	**3**
Percentage of patients that developed maceration	1
Percentage of patients with maceration of the skin	1
Extent of maceration (number and percentage of each rating)	1
Percentage in the reporting of maceration of the surrounding skin	1
Percentage of visits with maceration of the peri-wound skin	**2**
Reduction in the scoring/rating of cramps	**4**
Change in the scoring/rating of cramps	**3**
Change in the severity of cramps	**2**
Change in venous claudication score	**2**
Change in tenseness score	**2**
Change in severity of swelling	**3**
Reduction in swelling	1
Reduction in the scoring/rating of swelling	**4**
Percentage reduction in the scoring of swelling	1
Percentage of patients with a disappearance of swelling	1
Change in the scoring/rating of swelling	**3**
Change in the scoring/rating of tiredness of the lower extremities	**3**
Reduction in the scoring/rating of restless lower limbs	**3**
Change in the scoring of restless lower limbs	1
Severity of restless lower limbs	1

Change in the scoring/rating of paraesthesia	**4**
Improvement in the scoring/rating of paraesthesia	1
Reduction in the scoring of paraesthesia	1
Paraesthesia (not specific)	**1**
Reduction in the scoring/rating of nocturnal cramps	**2**
Percentage reduction in night cramps	1
Change in the scoring/rating of nocturnal cramps	**2**
Severity of nocturnal cramps	1
Presence of night cramps	1
Reduction of the severity of heavy legs	**2**
Number of patients-heavy legs severity score	1
Change in the scoring/rating of heat/burning	**4**
Burning	1
Improvement in the burning score/rating	1
Change in the scoring/rating of itching	**3**
Itching	1
Number of patients that complained of itching	1
Improvement in the itching score/rating	1
Reduction of itching (not clear)	1
Number of patients that experienced stinging sensation	**2**
Change in the scoring/rating of tingling	**3**
Improvement in the tingling score/rating	1
Improvement in quality of life	**2**
Quality of life scores/rating for patients with healed ulcers	**4**
Change in quality of life score/rating… **Social functioning** **Emotional** **Energy/vitality**	 **2** **2** **2**
Improvement in functional ability	1
Change in the number of patients reporting being less sociable	1
Percentage of the patients reporting being less sociable	1
Change in the number of patients reporting going out to visit less frequently	1
Percentage in the number of patients reporting going out to visit less frequently	1
Change in the Comprehensive Classification System for Chronic Venous Disorders (CEAP) score	**4**
Variations in Laser Doppler flowometry (flux units)	**2**
Change in systolic blood pressure	**2**
Change in diastolic pressure	**2**
Change in heart rate	**2**
Change in venous pressure	**2**
Change in blood flow	**2**

Healing by secondary intention (not specific)	**2**
Number of patients with skin staining	**2**
Change in transcutaneous O_2 ($TcPO_2$) measurements	**4**
Variation in transcutaneous partial pressure of oxygen (mmHg)	1
Relative change in transcutaneous O_2 ($TcPO_2$)	1
Capillary filtration (ml/100ml/min/mmHg)	**2**
Capillary filtration rate (ml/100ml per min)	1
Change in capillary filtration coefficient (ml/100ml/min)	1
Number of patients that had….reduced or eliminated **Staphylococcus** **Pseudomonas aeruginosa**	 **2** **2**
Incidence of infection	**3**
Number of patients that had episodes of infection	**2**
Number of isolated bacteriological species	**4**
Frequency distribution of isolated bacteria	1
Percentage of ulcers that developed a clinical infection	1
Change in the severity of pruritus	**2**
Percentage of patients reporting the severity of pruritus	1
Pruritus severity score improved	1
Pruritus (not specific)	**3**
Number of patients that developed pruritus	1
Cellulitis (not specific)	**3**
Change in the severity of cellulitis	1
Number of patients with indications of cellulitis	1
Percentage of patients with cellulitis	1
Percentage of dressing changes where cellulitis was observed	1
Number of bacterial burden signs present in the ulcer	**2**
Change in half refilling times (seconds)	**2**
Change in refilling time (seconds)	**3**
Number of patients that were compliant	**2**
Percentage of patients that were non-compliant	**2**
Percentage of patients that were compliant	**3**
Number of patients that were not compliant	**4**
Occurrence of pinhead bleeding	**2**
Change in plasma fibrinogen level	**3**
Number of patients that experienced micro bleeding	1
Thyroid stimulating hormone levels	**3**
Number of patients that developed abnormal thyroid hormone levels	1
Changes in thyroid function	1
Change in white cell count	**2**

Change in growth factors	**2**
Change in biochemistry	**3**
Number of patients with biochemical abnormalities	1

Number of days compression devices were worn	**2**
Number of patients that wore the stockings for at least 8 hours	1
Percentage of patients that wore the stockings for at least 8 hours	1
Frequency of dressing changes	**4**
Number of days between dressing changes	**2**
Number of unscheduled dressing changes	**2**
Number of dressing changes needed per week	**2**
Number of dressing changes to healing	1
Time required to apply	**4**
Time spent on ulcer care (mins)	1
Time spent on a typical dressing change	1
Time taken to apply bandages	1
Shorter wound bed preparation time (not specific)	1
Percentage of patients taking less time to change a dressing	1
Number of hours per day patients wore stockings	**2**
Bandage slippage	**2**
Reason for removal prior to visit: slippage	1
Ease of handling	**2**
Ease of use	**2**
Wound re-injury on dressing removal	**2**
Trauma on dressing removal	**2**
Non-traumatic dressing removal	1
Conformability to ulcer site	**2**
Percentage of dressing changes reporting adhesion to the ulcer bed on removal	**2**
Adhesion of the dressing to the ulcer bed	1
Number of dressing changes where the dressing had adhered to the ulcer bed	1
Cost of dressings per patient	**2**
Costs per percentage ulcer reduction	**2**
Cost to heal ulcer completely	**2**
Total costs to the end of the study	**2**
Total mean costs for patients with healed ulcers compared to patients with unhealed ulcers	1
Total direct costs per group	1
Total indirect costs per group	1
Total cost per group	1
Cost per healed patient	1
Incremental costs	**2**
Incremental Quality-adjusted life years gain	1
Incremental cost-effectiveness ratios per Quality-adjusted life years gained	1
Total annual cost	**2**
Cost per week	**3**
Material costs per week	1
Weekly costs for healed ulcers	1

Weekly costs for unhealed ulcers	1
Number of work days lost	**2**
Number of days patients had working difficulties	1
Nursing time (cost)	**2**
Nursing time required per ulcer (cost)	1
Cost- nurse costs	1
Cost of nursing time to dress each patient	1
Cost of nursing time spent doing administration per patient	1
Nursing time spent doing administration (hours) per group (cost)	1
Cost of nursing time spent travelling	1
Nursing time spent travelling (hours)	1
Nursing time spent dressing the ulcers per group (cost)	1
Total time (hours) spent by nurses per group (cost)	1
Distance (miles) travelled by the nurse per group (cost)	1

Number of adverse events/ patients that experienced adverse events:	
Bleeding	**4**
Pruritus	**2**
Oedema	**4**
Increased	**2**
Vomiting	**3**
Diarrhoea	**4**
Epigastric pain	**3**
Gastralgia	**2**
Excoriation	**2**
Slippage	**2**
Dryness	**2**
Restriction of tightness	**2**
Exudate	**2**
Redness	**3**
Pallor	**2**
Over granulation	**2**
Skin irritation	**4**
Increased ulcer size	**4**
DVT	**3**
Urticarial	**2**
Erysipelas	**2**
Gastrointestinal haemorrhage	**2**

Number of patients that withdrew and number of events causing withdrawal:	
Ulcer aggravation	**2**
Skin irritation	**2**
Nausea	**3**
Diarrhea	**2**
Erythema	**2**
Burning	**2**
No progress	**2**
Phlebitis	**2**
Mild cutaneous event	**2**

Urticarial	**2**
Pruritus of the scalp	**2**
Headaches	**3**
Exudate	**2**
Development of a new ulcer	**2**
Maceration	**2**
Vomiting	**2**
Sensitivity	**2**

Adverse drug reactions (not specific)	**2**

The list below displays the outcomes extracted from qualitative research.

Effect on family

Limited choice of shoes

Ability to wear clothes and shoes

Limited choice of clothes

Throbbing

Body image

Self image

Avoiding trauma to the leg

Personal hygiene

Ability to self care

Personal expenses e.g. laundry costs

Loss of identity

Worry [about the ulcer not healing]

Fixed ankle [support stockings/mobility]

Social embarrassment

Appendix 3 Scoping Review Included References

The references included in the scoping review are displayed below. For the full reference please see the reference section in the thesis.

RCTs and secondary references:

Interventions for helping people adhere to compression treatments for venous leg ulceration Cochrane Systematic Review

Baquerizo Nole, K.L., Yim, E., Van Driessche, F., Lamel, S.A., Richmond, N.A., Braun, L.R. and Kirsner, R.S. 2015.

Edwards, H., Courtney, M., Finlayson, K., Lewis, C., Lindsay, E. and Dumble, J. 2005a.

Edwards, H., Courtney, M., Finlayson, K., Lindsay, E., Lewis, C., Shuter, P. and Chang, A. 2005b.

Heinen, M., Borm, G., van der Vleuten, C., Evers, A., Oostendorp, R. and van Achterberg, T. 2012.

Compression for venous leg ulceration Cochrane Systematic Review

Allegra, C., Cariotti, R., Bonadeo, P., Cataldi, R., Polignano, R. and Andriessen, A. 2001.

Blecken, S.R., Villavicencio, J.L. and Kao, T.C. 2005.

Brizzio, E., Amsler, F., Lun, B. and Blättler, W. 2010.

Callam, M.J., Harper, J., Dale, J., Brown, B., Gibson, R., Prescott, J. and Ruckley, C.V. 1992.

Charles, H. 1991. Compression healing of ulcers. *Journal of District Nursing.* **10**(3), pp.4-8.

Clarke-Moloney, M., O'Brien, J.F., Grace, P.A. and Burke, P.E. 2005.

Colgan, M.-P., Teevan, M., McBride, C., O'Sullivan, L., Moore, D. and Shanik, G. 1995.

Cordts, P.R., Hanrahan, L.M., Rodriguez, A.A., Woodson, J., LaMorte, W.W. and Menzoian, J.O. 1992.

Danielsen, L., Madsen, S. and Henriksen, L. 1998a.

Danielsen, L., Madsen, S.M., Henriksen, L., Sindrup, J. and Petersen, L.J. 1998b.

DePalma, R.G., Kowallek, D., Spence, R.K., Caprini, J.A., Nehler, M.R., Jensen, J., Goldman, M.P. and Bundens, W.P. 1999.

Eriksson, G. 1986.

Franks, P., Moffatt, C., Ellison, D., Connolly, M., Fielden, S., Groarke, L. and McCollum, C. 1999a.

Franks, P.J., Bosanquet, N., Brown, D., Straub, J., Harper, D.R. and Ruckley, C.V. 1999b.

Franks, P.J., Moody, M. and MOFFAT, C.J. 2003.

Franks, P.J., Moody, M., Moffatt, C.J., Martin, R., Blewett, R., Seymour, E., Hildreth, A., Hourican, C., Collins, J. and Heron, A. 2004.

Franks, P.J., Stevens, J., Hourican, C., doherty, D.C. and O'Connor, T. 2002.

Gardon-Mollard, C., Junger, M., Patsch, H., Zuccarelli, F. and Taupin, V. 2003.

Gould, D.J., Campbell, S. and Harding, E.F. 1993.

Gould, D.J., Campbell, S., Newton, H., Duffelen, P., Griffin, M. and Harding, E., F. 1998.

Harley, J., Harcourt, D., Hutchinson, B., McLean, M. and Long, M. 2004.

Iglesias, C.P., Nelson, E.A., Cullum, N. and Torgerson, D.J. 2004a.

Iglesias, U., C., Nelson, A., Cullum, N. and Torgerson, D. 2004b.

Jünger, M., Partsch, H., Ramelet, A.A. and Zuccarelli, F. 2004.

Jünger, M., Wollina, U., Kohnen, R. and Rabe, E. 2004.

Kikta, M.J., Schuler, J.J., Meyer, J.P., Durham, J.R., Eldrup-Jorgensen, J., Schwarcz, T.H. and Flanigan, D.P. 1988.

Koksal, C. and Bozkurt, A.K. 2003.

Mariani, F., Mattaliano, V., mosti, G., Gasbarro, V., Bucalossi, M., Blattler, W., Amsler, F. and Mancini, S. 2008.

Meyer, F.J., Burnand, K.G., Lagattolla, N.R.F. and Eastham, D. 2002.

Meyer, F.J., McGuinness, C.L., Lagattolla, N.R.F., Eastham, D. and Burnand, K.G. 2003.

Milic, D.J., Zivic, S.S., Bogdanovic, D.C., Jovanovic, M.M., Jankovic, R.J., Milosevic, Z.D., Stamenkovic, D.M. and Trenkic, M.S. 2010a.

Milic, D.J., Zivic, S.S., Bogdanovic, D.C., Perisic, Z.D., Milosevic, Z.D., Jankovic, R.J., Visnjic, A.M. and Jovanovic, B.M. 2007.

Moffatt, C., Simon, D., Franks, P., Connolly, M., Fielden, S., Groarke, L. and McCollum, C. 1999.

Moffatt, C.J., Edwards, L., Collier, M., Treadwell, T., Miller, M., Shafer, L., Sibbald, G., Brassard, A., McIntosh, A., Reyzelman, A., Price, P., Kraus, S.M., Walters, S.-A. and Harding, K. 2008.

Moffatt, C.J., McCullagh, L., O'Connor, T., Doherty, D.C., Hourican, C., Stevens, J., Mole, T. and Franks, P.J. 2003.

Moody, M. 1999.

Morrell, C.J., Walters, S.J., Dixon, S., Collins, K.A., Brereton, L.M.L., Peters, J. and Brooker, C.G.D. 1998.

Nelson, A. 2004.

Nelson, E.A., Iglesias, C.P., Cullum, N. and Torgerson, D.J. 2004.

Nelson, E.A., Prescott, R.J., Harper, D.R., Gibson, B., Brown, D. and Ruckley, C.V. 2007.

O'Brien, J.F., Grace, P.A., Perry, I.J., Hannigan, A., Clarke Moloney, M. and Burke, P.E. 2003.

Partsch, H., Damstra, R.J., Tazelaar, D.J., Schuller-Petrovic, S., Velders, A.J., de Rooij, M.J.M., Tjon Lim Sang, R.R.M. and Quinlan, D. 2001.

Polignano, R., Boneado, P., Gasbarro, S. and Allegra, C. 2004a.

Polignano, R., Guarnera, G. and Boneado, P. 2004b.

Rubin, J.R., Alexander, J., Plecha, E.J. and Marman, C. 1990.

Ruckley, C.V., Callam, M.J., Harper, D.R., Dale, J.J., Gibson, B. and Prescott, R.J. 2002.

Scriven, J., Taylor, L., Wood, A., Bell, P., Naylor, A. and London, N. 1998.

Szewczyk, M.T., Jawień, A., Cierzniakowska, K., Cwajda-Białasik, J. and Mościcka, P. 2010.

Taradaj, J., Franek, A., Brzezinska-Wcislo, L., Blaszczak, E. and Polak, A. 2009.

Taylor, A., Taylor, R. and Marcuson, R. 1998.

Taylor, A.E.M., Taylor, R. and Marcuson, R. 1995.

Travers, J., Dalziel, K. and Makin, G. 1992.

Tucker, J.A. 2008.

Ukat, A., Konig, M., Vanscheidt, W. and Münter, K.-C. 2003.

Vowden, K.R., Mason, A., Wilkinson, D. and Vowden, P. 2000.

Antibiotics and antiseptics for venous leg ulcers Cochrane Systematic Review

Belcaro, G., Cesarone, M.R., Errichi, B.M., Di Renzo, A., Errichi, S., Ricci, A., Gizzi, G., Dugall, M., Cacchio, M., Ruffini, I., Fano, F., Vinciguerra, G. and Grossi, M.G. 2007.

Belcaro, G., Cesarone, M.R., Nicolaides, A.N., Geroulakos, G., Di Renzo, A., Milani, M., Ricci, A., Brandolini, R., Dugall, M., Ruffini, I., Cornelli, U. and Griffin, M. 2003.

Binic, I., Jankovic, A., Jankovic, D., Jankovic, I. and Vrucinic, Z. 2010.

Bishop, J.B., Phillips, L.G., Mustoe, T.A., VanderZee, A.J., Wiersema, L., Roach, D.E., Heggers, J.P., Hill, D.P., Jr., Taylor, E.L. and Robson, M.C. 1992.

Blair, S.D., Backhouse, C.M., Wright, D.D.I., Riddle, E. and McCollum, C.N. 1988.

Daróczy, J. 2006.

Dimakakos, E.P., Katsenis, K., Kalemikerakis, J., Arkadopoulos, N., Mylonas, S. and Arapoglou, V. 2009.

Gethin, G. and Cowman, S. 2008.

Gethin, G. and Cowman, S. 2009.

Hansson, C. 1998.

Holloway, G.A., Johansen, K.H., Barnes, R.W. and Pierce, G.E. 1989.

Jørgensen, B., Price, P., Andersen, K.E., Gottrup, F., Bech-Thomsen, N., Scanlon, E., Kirsner, R., Rheinen, H., Roed-Petersen, J., Romanelli, M., Jemec, G., Leaper, D.J., Neumann, M.H., Veraart, J., Coerper, S., Agerslev, R.H., Bendz, S.H., Larsen, J.R. and Sibbald, R.G. 2005.

Jull, A., Walker, N., Parag, V., Molan, P. and Rodgers, A. 2008.

Kerihuel, J.C. 2010.

Laudansk, H. and Gustavson, B. 1988.

Lazareth, I., Mcaume, S., Sigal-Grinberg, M.L., Combemale, P., Le Guyadec, T., Zagnoli, A., Perrot, J.-L., Sauvadet, A. and Bohbot, S. 2008.

Meaume, S., Vallet, D., Nguyen Morere, M. and Téot, L. 2005.

Michaels, J.A., Campbell, B., King, B., Palfreyman, S.J., Shackley, P. and Stevenson, M. 2009a.

Michaels, J.A., Campbell, W.B., King, B.M., MacIntyre, J., Palfreyman, S.J., Shackley, P. and Stevenson, M.D. 2009b.

Miller, C.N., Carville, K., Newall, N., Kapp, S., Lewin, G., Karimi, L. and Santamaria, N. 2011b.

Miller, C.N., Newall, N., Kapp, S.E., Lewin, G., Karimi, L., Carville, K., Gliddon, T. and Santamaria, N.M. 2010.

Morias, C.N., Peremans, W., Campaert, H. and Mertens, R.I. 1979.

Moss, C., Taylor, A. and Shuster, S. 1985.

Moss, C., Taylor, A.E.M. and Shuster, S. 1987.

Munter, K.-C., Beele, H., Russel, L., Gröchenig, E., Basse, P., Crespi, A., Alikadic, M., Fraulin, F., Dahl, C.A. and Jemma, A.P. 2006.

Ormiston, M.C., Seymour, M.T., Venn, G.E., Cohen, R.I. and Fox, J.A. 1985.

Skog, E., ArnesjÖ, B., TroËNg, T., GjÖRes, J.E., Bergljung, L., Gundersen, J., HallbÖÖK, T., Hessman, Y., HillstrÖM, L., MÅNsson, T., Eilard, U., EklÖFf, B., Plate, G. and Norgren, L. 1983.

Smith, J., Dore, C., Charlett, A. and Lewis, J. 1992.

Steele, K., Irwin, G. and Dowds, N. 1986.

Foam dressings for venous leg ulcers Cochrane Systematic Review

Andersen, K.E., Franken, C.P.M., Gad, P., Larsen, A.M., Larsen, J.R., van Neer, P.A.F.A., Vuerstaek, J.D.D., Wuite, J. and Martino, H.A. 2002.

Andriessen, A., Polignano, R. and Abel, M. 2009.

Bowszyc, J., Silny, W., Bowszyc-Dmochowska, M., Kazmierowski, M., Ben-Amer, H.M., Garbowska, T. and Harding, E. 1995.

Callam, M.J., Harper, J., Dale, J., Brown, B., Gibson, R., Prescott, J. and Ruckley, C.V. 1992.

Charles, H., Callicot, C., Mathurin, D., Ballard, K. and Hart, J. 2002.

Franks, P.J., Moody, M., Moffatt, C.J., Hiskett, G., Gatto, P., Davies, C., Furlong, W.T., Barrow, E., Thomas, H. and On behalf of the Wound Healing Nursing Research, G. 2007.

Franks, P.J., Moody, M., Moffatt, C.J., Martin, R., Blewett, R., Seymour, E., Hildreth, A., Hourican, C., Collins, J. and Heron, A. 2004.

Norkus, A., Dargis, V., Thomsen, J.K., Harding, K.G., Ivins, N., Serra, N., Torres de Castro, O.G., Galindo, A., Andersen, K.E., Roed-Peterseon, J., Gottrup, F., Blanco, J.L., A, d.M.M., Hauschild, A., Moll, I., Svensson, A. and Cart, K. 2005.

Thomas, S., Banks, V., Fear-Price, M., Hagelstein, S., Harding, K.G., Orpin, J., Bale, S. and Thomas, N. 1997.

Vanscheidt, W., Sibbald, R.G. and Eager, C.A. 2004.

Oral aspirin for treating venous leg ulcers Cochrane Systematic Review

Agrifoglio, G., Domanin, M., Baggio, E., Cao, P., Alberti, A.N., Borin, F., Todini, A.R., Becchi, G. and Caserini, M. 2000.

del Rio Sola, M.I., Antonio, J., Fajardo, G. and Vaquero Puerta, C. 2012.

Layton, A.M., Goodfield, M.J.D., Ibbotson, S. and Davies, J.A. 1994.

Topical agents or dressings for pain in venous leg ulcers Cochrane Systematic Review

Agrifoglio, G., Domanin, M., Baggio, E., Cao, P., Alberti, A.N., Borin, F., Todini, A.R., Becchi, G. and Caserini, M. 2000.

Arapoglou, V., Katsenis, K., Syrigos, K.N., Dimakakos, E.P., Zakopoulou, N., Tsoutsos, D., Gjødsbøl, K., Glynn, C., Schäfer, E. and Petersen, B. 2011.

Domenech, R.P., Romanelli, M., Tsiftsis, D.D., Slonkov, V., Jortikka, A., Johannesen, N., Ram, A., Persson, L.M., Altindas, M., Orsted, H. and Schäfer, E. 2008.

Gottrup, F., Jørgensen, B., Karlsmark, T., Sibbald, R.G., Rimdeika, R., Harding, K., Price, P., Venning, V., Vowden, P., Jünger, M., Wortmann, S., Sulcaite, R., Vilkevicius, G., Ahokas, T.-L., Ettler, K. and Arenbergerova, M. 2007.

Gottrup, F., Jørgensen, B., Karlsmark, T., Sibbald, R.G., Rimdeika, R., Harding, K., Price, P., Venning, V., Vowden, P., Jünger, M., Wortmann, S., Sulcaite, R., Vilkevicius, G., Ahokas, T.-L., Ettler, K. and Arenbergerova, M. 2008.

Lok, C., Paul, C., Amblard, P., Bessis, D., Debure, C., Faivre, B., Guillot, B., Ortonne, J.P., Huledal, G. and Kalis, B. 1999.

Rosenthal, D., Murphy, F., Gottschalk, R., Baxter, M., Lycka, B. and Nevin, K. 2001.

Therapeutic Ultrasound for venous leg ulcers Cochrane Systematic Review

Callam, M.J., Dale, J.J., Harper, D.R., Ruckley, C.V. and Prescott, R.J. 1987.

Dolibog, P., Franek, A., Tardaj, J., Blaszczak, E. and Cierpka, L. 2008.

Eriksson, S., Lundebergz, T. and Malrn, M. 1991.

Franek, A., Chmielewska, D., Brzezinska-Wcislo, L., Slezak, A. and Blaszczak, E. 2004.

Peschen, M. and Vanscheidt, W. 1997.

Taradaj, J., Franek, A., Brzezinska-Wcislo, L., Cierpka, L., Dolibog, P., Chmielewska, D., Blaszczak, E. and Kusz, D. 2008.

Sulodexide for treating venous leg ulcers Cochrane Systematic Review

Coccheri, S., Scondotto, G., Agnelli, G., Aloisi, D., Palazzini, E. and Zamboni, V. 2002.

Scondotto, G., Aloisi, D., Ferrari, P. and Martini, L. 1999.

Flavonoids for treating venous leg ulcers Cochrane Systematic Review

Guilhou, J.-J., Dereure, O., Marzin, L., Ouvry, P., Zuccarelli, F., Debure, C., Van Landuyt, H., Gillet-Terver, M.-N., Guillot, B., Levesque, H., Mignot, J., Pillion, G., Février, B. and Dubeaux, D. 1997.

Gliński, W., Chodynicka, B., Roszkiewicz, J., Bogdanowski, T., Lecewicz-Toruń, B., Kaszuba, A., Bowszyc, J., Nowak, A., Wnorowski, J. and Wąsik, F. 1999.

Roztocil, K., Stvrtinova, V. and Strejcek, J. 2003.

Alginate dressings for venous leg ulcers Cochrane Systematic Review

Armstrong, S.H. and Ruckley, C.V. 1997.

Armstrong, S.H., Brown, D.A., Hill, E., Ruckley, C.V., Pucheault, M. and Hofman, D. 1995

Harding, K.G., Price, P., Robinson, B., Thoma, S.S. and Hofman, D. 2001.

Limova, M. 2003.

Moffatt, C.J., Oldroyd, M.I. and Franks, P.J. 1992.

Robinson, B., Harding, K., Thomas, S. and Cherry, G. 1997.

Smith, B.A. 1994.

Oral zinc for arterial and venous leg ulcers Cochrane Systematic Review

Clayton, R.J. 1972.

Greaves, M.W. and Ive, F.A. 1972.

Hallböök, T. and Lanner, E. 1972.

Phillips, A., Maureen, D. and Greaves, M.W. 1977.

Pentoxifylline for treating venous leg ulcers Cochrane Systematic Review

Barbarino, C. 1992.

Colgan, M.-P., Dormandy, J.A., Jones, P.W., Schraibman, I.G., Shanik, D.G. and Young, R.A.L. 1990.

Dale, J.J., Ruckley, C.V., Harper, D.R., Gibson, B., Nelson, E.A. and Prescott, R.J. 1999.

Falanga, V., Fujitani, R.M., Diaz, C., Hunter, G., Jorizzo, J., Lawrence, P.F., Lee, B.Y., Menzoian, J.O., Tretbar, L.L., Holloway, G.A., Hoballah, J., Seabrook, G.R., McMillan, D.E. and Wolf, W. 1999.

Debridement for venous leg ulcers Cochrane Systematic Review

Alvarez, O.M., Patel, M., Booker, J. and Markowitz, L. 2004.

Alvarez, O.M., Phillips, T.J., Menzoian, J.O., Patel, M. and Andriessen, A. 2012b.

Gethin, G. and Cowman, S. 2009.

Hansson, C. 1998.

König, M., Vanscheidt, W., Augustin, M. and Kapp, H. 2005.
Skog, E., ArnesjÖ, B., TroËNg, T., GjÖRes, J.E., Bergljung, L., Gundersen, J., HallbÖÖK, T., Hessman, Y., HillstrÖM, L., MÅNsson, T., Eilard, U., EklÖFf, B., Plate, G. and Norgren, L. 1983.

Wayman, J., Nirojogi, V., Walker, A., Sowinski, A. and Walker, M.A. 2000.

Westerhof, W., van Ginkel, C.J.W., Cohen, E.B. and Mekkes, J.R. 1990.

Wild, T., Eberlein, T. and Andriessen, A. 2010.

Skin grafting for venous leg ulcers Cochrane Systematic Review

Burdge, J., Cope, F., Abbruzze, B. and Wille, J. 2001.

Duhra, P., Blight, A., Mountford, E., Cheshire, I., Withers, A. and Ilchyshyn, A. 1992.

Falanga, V. and Sabolinski, M. 1999.

Falanga, V., Margolis, D., Alvarez, O. and et al. 1998.

Jankunas, V., Bagdonas, R., Samsanavicius, D. and Rimdeika, R. 2007.

Krishnamoorthy, L., Harding, K., Griffiths, D., Moore, K., Leaper, D., Poskitt, K., Sibbald, R.G., Brassard, A., Dolynchuk, K., Adams, J. and Whyman, M. 2003.

Lindgren, Marcusson and ToftgÅrd. 1998

Liu, J.Y., Hafner, J., Dragieva, G., Seifert, B. and Burg, G. 2004.

Navrátilová, Z., Slonková, V., Semrádová, V. and Adler, J. 2004.

Omar, A.A., Mavor, A.I.D., Jones, A.M. and Homer-Vanniasinkam, S. 2004.

Paquet, P., Quatresooz, P., Braham, C. and Gérald, P.E. 2005.

Poskitt, K.R., James, A.H., Lloyd-Davies, E.R., Walton, J. and McCollum, C. 1987.

Sabolinski, M.L., Alvarez, O., Auletta, M., Mulder, G. and Parenteau, N.L. 1996.

Schonfeld, W.H., Villa, K.F., Fastenau, J.M., Mazonson, P.D. and Falanga, V. 2000.

Tausche, A.-K., Skaria, M., Böhlen, L., Liebold, K., Hafner, J., Friedlein, H., Meurer, M., Goedkoop, R.J., Wollina, U., Salomon, D. and Hunziker, T. 2003.

Warburg, F., Danielsen, L., Madsen, S., Raaschou, H., Munkvad, S., Jensen, R. and al, e. 1994.

Compression for preventing recurrence of venous ulcers Cochrane Systematic Review

Franks, P.J., Oldroyd, M.I., Dickson, D., Sharp, E.J. and Moffatt, C.J. 1995.

Harper, D.R., Ruckley, C.V., Gibson, B., Brown, D. and Prescott, R.J. 1999.

Milic, D.J., Zivic, S.S., Bogdanovic, D.C., Pejic, M., Roljic, Z. and Jovanovic, M. 2010b.

Nelson, E.A., Harper, D.R., Prescott, R.J., Gibson, B., Brown, D. and Ruckley, C.V. 2006.

Vandongen, Y.K. and Stacey, M.C. 2000.

Intermittent pneumatic compression for treating venous leg ulcers Cochrane Systematic Review

Alvarez, O., Wendelken, M., Markowitz, L., Parker, R. and Comfort, C. 2012a.

Dolibog, P., Franek, A., Taradaj, J., Polak, A., Dolibog, P., Blaszczak, E., Wcislo, L., Hrycek, A., Urbanek, T. and Ziaja, J. 2013.

Kumar, S., Samraj, K., Nirujogi, V., Budnik, J. and Walker, M.A. 2002.

Kumar, S., Walker, A., Gates, S. and Walker, M. 2001.

McCulloch, J.M., Marler, K.C., Neal, M.B. and Phifer, T.J. 1994.

Nikolovska, S., Arsovski, A., Damevska, K., Gocev, G. and Pavlova, L. 2005.

Rowland, J. 2000.

Schuler, J., Maibenco, T., Megerman, J., Ware, M. and Montalvo, J. 1996.

Smith, P.C., Sarin, S., Hasty, J. and Scurr, J.H. 1990.

Electromagnetic therapy for treating venous leg ulcers Cochrane Systematic Review

Ieran, M., Zaffuto, S., Bagnacani, M., Annovi, M., Moratti, A. and Cadossi, R. 1990.

Kenkre, J., Hobbs, F., Carter, Y., Holder, R. and Holmes, E. 1996.

Stiller, M.J., Pak, G.H., Shupack, J.L., Thaler, S., Kenny, C. and Jondreau, L. 1992.

Negative pressure wound therapy for treating leg ulcers Cochrane Systematic Review

Vuerstaek, J.D.D., Vainas, T., Wuite, J., Nelemans, P., Neumann, M.H.A. and Veraart, J.C.J.M. 2006.

Surgery for deep venous incompetence Cochrane Systematic Review

Belcaro, G., Nicolaides, A.N., Ricci, A., Laurora, G., Errichi, B.M., Christopoulos, D., Cesarone, M.R., De Sanctis, M.T., Incandela, L. and Belcaro, G. 1999.

Makarova, N.P., Lurie, F. and Hmelniker, S.M. 2001.

Wang, S.M., Hu, Z.J., Li, S.Q., Huang, X.L. and Ye, C.S. 2005.

Wang, S.-M., Hu, Z.-J., Li, S.-Q., Huang, X.-L. and Ye, C.-S. 2006.

Autologous platelet-rich plasma for treating chronic wounds Cochrane Systematic Review

Anitua, E., Aguirre, J.J., Algorta, J., Ayerdi, E., Cabezas, A.I., Orive, G. and Andia, I. 2008.

Knighton, D.R., Ciresi, K., Fiegel, V.D., Schumerth, S., Butler, E. and Cerra, F. 1990.

Senet, P., Bon, F.-X., Benbunan, M., Bussel, A., Traineau, R., Calvo, F., Dubertret, L. and Dosquet, C. 2003.

Stacey, M.C., Mata, S.D., Trengove, N.J. and Mather, C.A. 2000b.

Weed, B., Davis, M.D., Felty, C.L., Liedl, D.A., Pineda, A.A., Moore, S. and Rooke, T. 2004.

Phlebotonics for venous insufficiency Cochrane Systematic Review

Arcangeli, P. 2000.

Belczak, S.Q., Sincos, I.R., Campos, W., Beserra, J., Nering, G. and Aun, R. 2014.

Burnand, K., Powell, S., Bishop, C., Stacey, M. and Pulvertaft, T. 1989.

Casley-Smith, J.R. 1988.

Cesarone, M.R., Incandela, L., DeSanctis, M.T., Belcaro, G., Griffin, M., Ippolito, E. and Acerbi, G. 2002.

Cloarec, M., Clement, R. and Griton, P. 1996.

Danielsson, G., Jungbeck, C., Peterson, K. and Norgren, L. 2002.

Dominguez, C., Brautigam, I., Gonzilez, E., Gonzalez, J.A., Nazco, J., Valiente, R. and Boada, J. 1992.

Fermoso, J., Legido, A.G., Del Pino, J. and Valiente, R. 1992.

Flota-Cervera, F., Flota-Ruiz, C., Treviño, C. and Berber, A. 2008.

Gilly, R., Pillion, G. and Frileux, C. 1994.

Guilhou, J.-J., Dereure, O., Marzin, L., Ouvry, P., Zuccarelli, F., Debure, C., Van Landuyt, H., Gillet-Terver, M.-N., Guillot, B., Levesque, H., Mignot, J., Pillion, G., Février, B. and Dubeaux, D. 1997.

Hachen, H.J. and Lorenz, P. 1982.

Ihme, N., Kiesewetter, H., Jung, F., Hoffmann, H.K., Birk, A., Müller, A. and Grützner, I.K. 1996.

Labs, K.-H., Degischer, S., Gamba, G. and Jaeger, K.A. 2004.

MacLennan, W.J., Wilson, J., Rattenhuber, V., Dikland, W.J., Vanderdonckt, J. and Moriau, M. 1994.

Martínez-Zapata, M.J., Moreno, R.M., Gich, I., Urrútia, G. and Bonfill, X. 2008.

Parrado, F. and Buzzi, A. 1999.

Petrassi, C., Mastromarino, A. and Spartera, C. 2000.

Pointel, J.P. 1986.

Pointel, J.P., Boccalon, H., Cloarec, M., Ledevehat, C. and Joubert, M. 1987.

Přerovský, I., Roztočil, K., Hlavová, A., Koleilat, Z., Rázgová, L. and Oliva, I. 1972.

Rabe, E., Jaeger, K.A., Bulitta, M. and Pannier, F. 2011.

Vanscheidt, Rabe, Naser-Hijazi, Ramelet, Partsch, Diehm, Schultz-Ehrenburg, Spengel, Wirsching, Götz, Schnitker and Zepelin, H.-v. 2002.

Vin, F., Chabanel, A., Taccoen, A., Ducros, J., Gruffaz, J., Hutinel, B., Maillet, P. and Samama, M. 1994.

Honey as a topical treatment for wounds Cochrane Systematic Review

Gethin, G. and Cowman, S. 2008.

Gethin, G. and Cowman, S. 2009a.

Gulati, S., Qureshi, A., Srivastava, A., Kataria, K., Kumar, P. and Ji, A.B. 2014.

Jull, A. 2007.

Jull, A., Walker, N., Parag, V., Molan, P. and Rodgers, A. 2008.

Mphande, A.N.G., Killowe, C., Phalira, S., Wynn Jones, H. and Harrison, W.J. 2007.

Robson, V., Dodd, S. and Thomas, S. 2009.

CHIVA method for the treatment of chronic venous insufficiency Cochrane Systematic Review

Carandina, S., Mari, C., De Palma, M., Marcellino, M.G., Cisno, C., Legnaro, A., Liboni, A. and Zamboni, P. 2008.

Carandina, S., Mari, C., De Palma, M., Marcellino, M.G., Legido, A.G. and Liboni, A. 2006.

Iborra, E., Linares, P., Hernández, E., Vila, R. and Cairols, M.A. 2000.

Pares, J.O., Juan, J., Moreno, C., Tellez, R., Codony, I., Mata, A. and al, e. 2008.

Pares, J.O., Juan, J., Tellez, R., Mata, A., Moreno, C. and Quer, F.X. 2010.

Zamboni, P., Cisno, C., Marchetti, F., Mazza, P., Fogato, L., Carandina, S., De Palma, M. and Liboni, A. 2003.

Hyperbaric oxygen therapy for chronic wounds Cochrane Systematic Review

Hammarlund, C.M.D. and Sundberg, T.M.D. 1994.

Kaur, S., Pawar, M., Banerjee, N. and Garg, R. 2012.

Non-pharmalogical interventions for preventing venous insufficiency in a standing worker population Cochrane Systematic Review

Weiss, R.A. and Duffy, D. 1999.

Qualitative studies

Brown, A. 2005.

Brown, A. 2010.

Burke, M. No date.

Chase, S.K., Melloni, M. and Savage, A. 1997.

Cullum, N., Buckley, H., Dumville, J., Hall, J., Lamb, K., Madden, M., Morley, R., O'Meara, S., Saramago Goncalves, P., Soares, M. and Stubbs, N. 2016.

de Sousa Azevedo Aguiar, A.C., Sadigursky, D., Martins, L.A., de Oliva Meneze, T.M., de Souza Santos, A.L. and dos Reis, L.A. 2016.

Douglas, V. 2001.

Ebbeskog, B. and Ekman, S.L. 2001.

Flaherty, E. 2005.

Green, J., Jester, R., McKinley, R. and Pooler, A. 2013.

Green, J., Jester, R., McKinley, R. and Pooler, A. 2017.

Hareendran, A., Bradbury, A., Budd, J., Geroulakos, G., Hobbs, R., Kenkre, J. and Symonds, T. 2005.

Heinen, M.M., Persoon, A., van de Kerkhof, P., Otero, M. and van Achterberg, T. 2007.

Hopkins, A. 2004.

Madden, M. 2015.

Mapplebeck, L. 2008.

McCaughan, D., Cullum, N. and Dumville, J. 2015.

Morgan, P.A. and Moffatt, C.J. 2008.

Mudge, E., Holloway, S., Simmonds, W. and Price, P. 2006.

O'Brien, J., Finlayson, K., Kerr, G. and Edwards, H. 2014.

Palfreyman, S., Michaels, J. and Brazier, J. 2007.

Renner, R., Gebhardt, C., Simon, J.C. and Seikowski, K. 2009.

Rich, A. and McLachlan, L. 2003.

Salomé, G.M., de Almeida, S.A., de Jesus Pereira, M.T., Massahud, M.R.J., de Oliveira Moreira, C.N., de Brito, M.J.A. and Ferreira, L.M. 2016.

Silva, M.H.d., Jesus, M.C.P.d., Oliveira, D.M.d. and Merighi, M.A.B. 2017.

Spilsbury, K., Cullum, N., Dumville, J., O'Meara, S., Petherick, E. and Thompson, C. 2008.

Upton, D., Andrews, A. and Upton, P. 2014.

Walshe, C. 1995.

Appendix 4 Recruitment Email eDelphi on the Outcome Domains (stage 2) Round One

Dear Sir/Madam

You are being invited to participate in a research study titled '**Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration'**. This study is being led by members of the CoreVen (Core outcome set for Venous leg ulceration) project team who are researchers from the University of Leeds, UK and the National University of Ireland, Galway. The project team includes Sarah Hallas (PhD student on the CoreVen project, University of Leeds), Professor Andrea Nelson (University of Leeds), Dr Susan O'Meara (University of Leeds) and Dr Georgina Gethin (National University of Ireland Galway).

Further information about the project is provided below and on the participant information sheet attached to this email.

We apologise if you have already received this from another source, please ignore this email if you have already received it.

As part of this project we are seeking to include views from all people who are affected by venous leg ulcers whether as a patient, carer, nurse, doctor, other health professional or researcher. You have been asked to participate so that we can learn more about peoples' views on which domains should be included in future trials.

The study is broken down into 2 rounds. At each round an online survey will be presented to you. It will take you approximately 20 minutes to complete the round 1 survey and approximately 15 minutes to complete the round 2 survey. Details of the round 2 survey will be sent via email once the results from the round 1 survey have been analysed. A summary of the group responses will be visible on the round 2 survey.

Following on from the surveys which look at which domains are important we will need to gain agreement on the domains' associated outcomes. So please look out for communication from us regarding the next stage of the study when

we will be inviting your views on the importance of specific outcomes falling within the domains.

We believe there are no known risks associated with this research study. Your participation in this study is entirely voluntary and all results will be anonymous. We have been granted ethics approval [HREC16-031] from the University of Leeds. If you wish to receive a copy of the approval please send your request to *********@leeds.ac.uk.

By completing the Bristol Online Survey you are consenting to take part in the study. If you decide to participate it would be greatly appreciated if you could complete the survey within the next three weeks from the date this email was sent. The survey will take approximately 20 minutes to complete. You will have the opportunity to download the responses you have submitted at the end of the survey, we recommend that you do this to allow you to see your previous responses when completing the round 2 survey.

Please feel free to forward this email onto others that may be interested in participating in this study. But please note that in order to comply with the project's ethics approval conditions, ***please DO NOT forward the invitations to the following: individuals identified because of their use of UK NHS services; carers of the latter, and; healthcare professionals identified because of their employment by the UK NHS.***

If you have any questions please do not hesitate to contact Sarah Hallas by email *********@leeds.ac.uk or contact Dr Susan O'Meara by email *********@leeds.ac.uk or telephone **********.

In order to help you decide whether or not to take part in the study please read the participant information sheet attached to this email. If you do decide to take part, a Bristol Online Survey has been created for you and can be accessed from the following link: https://leeds.onlinesurveys.ac.uk/coreven-brsitol-online-survey-core-domains. You will need to enter the password:**********, as directed on the Bristol Online Survey website.

With many thanks for your consideration,

Kind regards [Name of research team member, gate keeper or steering group to be inserted]

Appendix 5 Participant Information Sheet eDelphi on the Outcome Domains (stage 2)

CoreVen (Core outcome set for Venous leg ulceration**)**

Participant Information Sheet

Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration

We would like to invite you to take part in the above named study but before you decide it is important for you to understand why the research is being carried out and what it will involve. Please ask if there is anything that is not clear or if you would like more information before deciding whether to take part, contact details are shown at the end of this document. Please read the following information carefully.

Purpose of this study

This study is part of a project called CoreVen (Core outcome set for Venous leg ulceration), which aims to determine what outcomes are essential for patients and their clinicians to make decisions and therefore must be reported for all venous ulcer treatments. By doing this we will be able to see over time how different interventions impact on these outcomes.

An outcome is any identifiable consequence of the exposure to a health care intervention, for example a dressing. Clinical trials aim to determine how effective a new product, device, drug or other intervention is in helping to manage venous leg ulceration. The problem is that each trial can focus on a different outcome and as a result it is very difficult to see which interventions work. There is evidence that the number of outcomes measured in trials is so large that it is difficult to compare the results, meaning decision making on interventions used for venous leg ulcers can be challenging. A list of core outcomes to be measured in trials will help future decision making, making it

easier for the results of trials to be compared. This in turn will improve the information available to clinicians and patients.

Before determining which outcomes are important we need to decide which domains are important. Domains are broad, descriptive categories under which several, more specific, outcomes might be grouped. For venous leg ulcers, domains might include:

- Healing
- Patient reported symptoms
- Clinician reported symptoms
- Carer reported symptoms
- Life impacts
- Clinical signs
- Clinical measurement
- Performance of the intervention
- Resource use: supplies
- Resource use: clinician time
- Adverse events

These examples of domains have been derived from a thorough review of the research literature.

We would like to invite you to contribute to a two-round online survey on the importance of different domains in evaluations of treatments for venous leg ulcers. Later on we will launch a follow-up survey to explore the importance of different outcomes and will circulate more details in due course; but for now we are inviting your views on the importance of different domains.

Who is doing the study?

This study is being undertaken by Miss Sarah Hallas as part of a PhD in the School of Healthcare at the University of Leeds, UK. Professor Andrea Nelson and Dr Susan O'Meara from the School of Healthcare, University of Leeds are supervising this research. Dr Georgina Gethin from the School of Nursing and Midwifery, National University of Ireland Galway will also be supervising the study as a founder of the CoreVen project. Further details on the CoreVen project can be found on:

http://www.comet-initiative.org/studies/details/680?result=true

Why have I been asked to participate?

As part of this project we are seeking to include views from all people who are affected by venous leg ulcers whether as a patient, carer, nurse, doctor, researcher or other professional related to healthcare. You have been invited to participate in this study because you have been identified as belonging to one of these groups.

What will be involved if I take part in this study?

Your participation in this study is entirely voluntary. If you choose to take part, we will ask you to complete online surveys which can be accessed via a link and login details shown in the email sent with this attachment. On entering the surveys you will be asked to confirm whether you are willing to participate. There will be 2 rounds to the study.

On the first survey (round 1) you will be presented with a list of potential domains along with a rating scale below each one. You will be asked to rate each domain in terms of importance on a scale of 1 to 9 (1 being not important and 9 being extremely important). You will also be given an option to suggest 2 domains that have not been included on the list. If you decide to take part we would appreciate that the survey is completed within 3 weeks from the date of sending this email.

You will also be asked whether each domain should be included in the core domain set; yes or no. If you are uncertain, then please tick the answer closest to your opinion, for example if you think it probably shouldn't be then select no.

Following on from the first survey (round 1) you will be presented with a summary of the results from round 1 via a link on the invitation email. You will have an opportunity to rate each domain once more on the Bristol Online Survey (round 2), allowing the list of domains to be refined. You will also be asked to rate the additional domains suggested on the first survey.

Please note that by completing the Bristol Online Survey you are consenting to take part in the study.

What are the advantages and disadvantages of taking part?

Your participation in this study will inform the design of future research addressing the effectiveness of treatments for venous leg ulcers. In turn, this research will provide useful information to assist clinical decision making in terms of identifying the best treatment options for patients. It is foreseen that by having a minimum core set of outcomes in trials it will make it easier and more efficient for the reader to compare and contrast the evaluations of interventions. The first survey should take approximately 20 minutes to complete and we estimate the second survey will take 15 minutes to complete.

Can I withdraw from the study at any time?

You are under no obligation to take part in the study. Once you start the online survey you may withdraw at any point provided you have not clicked on 'Finish' at the end. This will mean that your responses will not be used for analysis or any other purpose. You do not need to give a reason for discontinuing with the survey.

If you complete the survey and click on 'Finish' at the end your responses will be merged with those from other participants and used as part of our analysis of data. Once you click on 'Finish' it will not be possible withdraw your responses because they are anonymised.

If you wish you can enter responses for part of the survey on one occasion and then select the 'Finish later' option on the survey pages in order to return to it later. If you choose to do this you will be asked to provide an email address so that a link can be sent to you to enable you to return to the survey. In this instance, your responses will still be anonymised as your email address will not be linked to your finished set of responses.

If you do not click on 'Finish' at the end your responses will not be included in the analysis. The questions on the survey that require a response will be highlighted with *'*Required'* next to it. There are some responses that are optional, you will be informed that it is optional at the beginning of the question.

Will the information I give be kept confidential?

The survey will be conducted using the Bristol Online Survey which is fully compliant with all current UK data protection laws. All information obtained

from you will be kept confidential at all times. No personal data will be stored other than your name and email address but this cannot be linked to the responses you make on the Bristol Online Survey. Your name and email address have been required to enable the emails with the link for the Bristol Online Surveys to be sent to you. Your name and email address will not be passed onto third parties.

All data will be password protected on the Bristol Online Survey and on the password protected secure network of the University of Leeds. Other members of the CoreVen project that may have access to your name and email address are Professor Andrea Nelson (University of Leeds), Dr Susan O'Meara (University of Leeds) and Dr Georgina Gethin (National University of Ireland Galway).

What will happen to the results of the study?

Your responses from the Bristol Online Surveys will be analysed, along with other participant's responses. An email containing a password protected attachment showing the scores for the domains on clearly marked bar charts will be sent after the study. We anticipate that it will take approximately 4 weeks for the results of the study to be sent to you.

Who has reviewed this study?

Ethical approval has been granted by the University of Leeds School of Healthcare Research Ethics Committee reference: HREC16-031.

If you would like more information or have any questions or concerns about the study please contact:

Sarah Hallas, [University contact details were provided
Dr Susan O'Meara (PhD supervisor), [University contact details were provided]

Thank you for taking the time to read this information sheet

Appendix 6 Ethics Approval Letter [HREC16-031]

Faculty of Medicine and Health
Research Office

University of Leeds
Worsley Building
Clarendon Way
Leeds LS2 9NL
United Kingdom

T +44 (0) 113 343 31642
12 April 2017

UNIVERSITY OF LEEDS

Miss Sarah Hallas
PhD student
School of Healthcare
Faculty Medicine and Health
Baines Wing
University of Leeds
LEEDS LS2 9JT

Dear Saran

Ref no: HREC16-031

Title: Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration

Thank you for submitting your documentation for the above project. Following review by the School of Healthcare Research Ethics Committee (SHREC), I can confirm a favourable ethical opinion based on the documentation received at date of this letter and subject to the following conditions *which must be confirmed as being fulfilled prior to the study commencing:*

- **Evidence of permission and support from the organisations' gatekeepers to send the recruitment material should be submitted**

Document Received	*Version*	*Date Submitted*
Ethical_Review_Form_V3 version 1.2	1.2	15/02/2017
1. new email invitation domains for non patients version 2.1 updated	2.1	17/03/2017
2. new email invitation domains for patients version 2.1 updated	2.1	17/03/2017
3. new recruitment email domains non patients v 1.5 updated	1.5	17/03/2017
4. new recruitment email domains patients v 1.5 updated	1.5	17/03/2017
5. new participant information sheet version 2.0 updated	2.0	17/03/2017
6. new Bristol Online Survey introduction page updated version 1.3	1.3	17/03/2017
steering group gatekeepers email template version 1.2	1.2	17/03/2017
Bristol Online Survey results word doc np	1.0	18/01/2017
Fieldwork_Assessment_Form_medium_risk_final_protected_nov_15	1.0	18/01/2017

Please notify the committee if you intend to make any amendments to the original research as submitted at date of this approval. This includes recruitment methodology and all changes must be ethically approved prior to implementation. Please contact the Faculty Research Ethics Administrator for further information FMHUniEthics@leeds.ac.uk

Ethical approval does not infer you have the right of access to any member of staff or student or documents and the premises of the University of Leeds. Nor does it imply any right of access to the premises of any other organisation, including clinical areas. The SHREC takes no responsibility for you gaining access to staff, students and/or premises prior to, during or following your research activities.

Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, any risk assessments and other documents relating to the study. This should be kept in your study file, and may be subject to an audit inspection. If your project is to be audited, you will be given at least 2 weeks notice.

It is our policy to remind everyone that it is your responsibility to comply with Health and Safety, Data Protection and any other legal and/or professional guidelines there may be.

Appendix 7 eDelphi on the Outcome Domains Round One Survey

The next pages display a facsimile of the online survey in MS Word format.

CoreVen Bristol Online Survey 1

Page 1: Introduction

Dear Participant,

You are being invited to participate in a research study called ‘Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration’. The purpose of this study is to determine what outcomes are essential for patients and their clinicians to make decisions and therefore must be reported for all trials of venous ulcer treatments. Your participation in this study is entirely voluntary.

On the following pages you will see a series of areas which have been described as 'domains'. A domain is the overarching name for a group of outcomes that have been measured in venous leg ulcer trials.

We will ask you to rate how important you consider each domain to be in venous leg ulcer trials using a numerical rating scale of 1 to 9 (‘1’ means ‘not important’ and ‘9’ means ‘extremely important’).
Below each domain we have shown examples of associated outcomes. For example, for the domain of ‘Healing’ we have suggested ‘Number of ulcers completely healed’ as a specific outcome.

Once the survey is started you will be able to leave it and return to it at a later time by selecting the ‘finish later’ option at the end of the page. If you decide to use this option, you will be asked to enter your email address so that a link can be sent to you for returning to the survey. Your responses will be anonymous throughout the study, regardless of whether you use the ‘finish later’ option.

We believe that there are no known risks associated with this research study; however, as with any online activity the risk of a breach is always possible. We have minimised risks by using the Bristol Online Survey which is fully compliant with all UK data protection laws and is password protected. All results will be anonymous.

By continuing onto the survey you are consenting to take part in the study. You are under no obligation to take part and you can withdraw from the study until you click on ‘Finish’ at the end. You do not need to provide a reason for withdrawal. You can stop at any point in the survey. In order for your responses to be used in the analysis you must answer all the questions and click on ‘Finish’ at the end. Once you do this, your responses cannot be withdrawn and will be included in the analysis. The questions on the survey that require a response will be highlighted with ‘*Required’ next to it. There are some responses that are optional, you will be informed that it is optional at the beginning of the question.

Please do not provide any personal details on the survey, other than stating your role (for example patient, researcher, nurse) on the question included on the first page of the survey.

We anticipate that the survey will take approximately 20 minutes to complete. We very much appreciate you taking time to complete the survey.

1. Are you happy to continue to take part in this survey? *Required*

- ○ Yes

2. Which term best describes your background? (please select only one response that best describes your role) *Required*

Please select exactly 1 answer(s).

- ☐ Patient
- ☐ Carer
- ☐ Researcher
- ☐ Researcher from the industry sector
- ☐ Healthcare professional
- ☐ Other

2.a. If you are a healthcare professional, please state your job role:

2.b. If you selected Other, please specify:

Page 2: Core domains

3. Research studies often refer to healing as an outcome in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **HEALING** as a core domain in future research trials?

Examples of outcome measures in this domain: Number of ulcers that completely healed, Percentage of completely healed ulcers, Rate of reduction in ulcer area. *Required

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

3.a. Select below if you do not have an opinion on whether healing should be a core domain:

○ No opinion

4. Research studies often refer to various patient reported symptoms as outcomes in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **PATIENT REPORTED SYMPTOMS** as a core domain in future research trials? Examples of outcome measures in this domain include: Pain score/rating (rated by the patient), Heavy legs sensation score/rating (rated by the patient).

*Required

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

4.a. Select below if you do not have an opinion on whether patient reported symptoms should be a core domain:

○ No opinion

3. Research studies often refer to symptoms that have been reported by the clinician, for example a nurse, as an outcome in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **CLINICIAN REPORTED SYMPTOMS** as a core domain in future research trials? An example of an outcome measure in this domain includes: Pain score at dressing removal (rated by the clinician). *Required

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

5.a. Select below if you do not have an opinion on whether clinician reported symptoms should be a core domain:

○ No opinion

6. Research studies often refer to symptoms of the patient reported by carers as an outcome in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **CARER REPORTED SYMPTOMS** as a core domain in future research trials? An example of an outcome measure in this domain includes: Pain score/rating (rated by the carers) . *Required

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

6.a. Select below if you do not have an opinion on whether carer reported symptoms should be a core domain:

○ No opinion

7. Research studies often refer to outcomes relating to life impacts in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **LIFE IMPACTS** as a core domain in future research trials?

The life impact domain contains outcomes that measure the patients' ability to function. It covers quality of life, loss of ability to work, secondary impact on their family, and social interactions. It also encompasses what impact the leg ulcer and the treatments required to treat the leg ulcer has on the patient. Examples of outcome measures in this domain include: Quality of Life scores/rating, Percentage of patients reporting an improvement in quality of life. **Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

7.a. Select below if you do not have an opinion on whether life impacts should be a core domain:

○ No opinion

8. Research studies often refer to various clinical signs as outcomes in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **CLINICAL SIGNS** as a core domain in future research trials? The clinical signs domain contains outcomes that measure the bodily function and structure, including reversible and irreversible symptoms such as oedema. Examples of outcome measures in this domain include: Severity of pitting oedema, Severity of odour. **Required*

Table 1

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

8.a. Select below if you do not have an opinion on whether clinical signs should be a core domain:

○ No opinion

9. Research studies often refer to various clinical measurement outcomes in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **CLINICAL MEASUREMENT** as a core domain in future research trials? The clinical measurement domain contains outcomes that measure the bodily function including organ function and biomarkers (measurable indicator of the presence or severity of venous ulceration). Examples of outcome measures in this domain include: Deep vein reflux, Maximal venous outflow (ml/100ml/min). *Required

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

9.a. Select below if you do not have an opinion on whether clinical measurement should be a core domain:

○ No opinion

10. Research studies often refer to the performance of an intervention as an outcome in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **PERFORMANCE OF THE INTERVENTION** as a core domain in future research trials? The performance of the intervention domain contains outcomes that measure how well the intervention, such as a dressing, has worked and performed. Examples of outcome measures in this domain include: Ease of application, Number of days between dressing changes. *Required

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

10.a. Select below if you do not have an opinion on whether performance of the intervention should be a core domain:

○ No opinion

11. Research studies often refer to resource use, such as supplies, as an outcome in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **RESOURCE USE: SUPPLIES** as a core domain in future research trials? The resource use: supplies domain contains outcomes that measure supply costs for example the cost of a dressing. Examples of outcome measures in this domain include: Material costs per week, Total single treatment cost per group. **Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

11.a. Select below if you do not have an opinion on whether resource use: supplies should be a core domain:

- ○ No opinion

12. Research studies often refer to resource use, such as clinician time, as an outcome in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **RESOURCE USE: CLINICIAN TIME** as a core domain in future research trials? The resource use: clinician time domain contains outcomes that measure costs related to clinician time for example nursing time. Examples of outcome measures in this domain include: Nursing time required per ulcer (cost), Cost of clinician contact per patient. **Required*

Table 1

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

12.a. Select below if you do not have an opinion on whether resource use: clinician time should be a core domain:

- ○ No opinion

13. Research studies often record adverse events in clinical trials of treatments for venous leg ulcers. We would like to know how important it is, in your opinion, to have **ADVERSE EVENTS** as a core domain in future research trials? Examples of outcome measures in this domain include: Number of patients that experienced ulcer infection, Number of patients that withdrew due to an allergic reaction. *Required

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

13.a. Select below if you do not have an opinion on whether adverse events should be a core domain:

○ No opinion

14. Optional: Please write any comments relating to the domains below.

Page 3: Core domains

Should the following domains be included in the core domain set for venous leg ulceration?. *If you are uncertain, then please tick the answer closest to your opinion for example 'Probably not' = 'No'

15. Healing *Required*

Please select exactly 1 answer(s).

- [ ] Yes
- [ ] No

16. Patient reported symptoms *Required*

Please select exactly 1 answer(s).

- [ ] Yes
- [ ] No

17. Clinician reported symptoms *Required*

Please select exactly 1 answer(s).

- [ ] Yes
- [ ] No

18. Carer reported symptoms *Required*

Please select exactly 1 answer(s).

- [ ] Yes
- [ ] No

19. Life impacts □ *Required*

Please select exactly 1 answer(s).

- ☐ Yes
- ☐ No

20. Clinical signs □ *Required*

Please select exactly 1 answer(s).

- ☐ Yes
- ☐ No

21. Clinical measurement □ *Required*

Please select exactly 1 answer(s).

- ☐ Yes
- ☐ No

22. Performance of the intervention □ *Required*

Please select exactly 1 answer(s).

- ☐ Yes
- ☐ No

23. Resource use: supplies □ *Required*

Please select exactly 1 answer(s).

- ☐ Yes
- ☐ No

24. Resource use: clinician time *Required*

Please select exactly 1 answer(s).

- [ ] Yes
- [ ] No

25. Adverse events *Required*

Please select exactly 1 answer(s).

- [ ] Yes
- [ ] No

Page 4: Additional core domains

26. Optional: Is there a domain that you think should be considered, other than what has been listed in this survey?.

Please write the domain in the box below.

27. Optional: Is there a domain that you think should be considered, other than what has been listed in this survey?.

Please write the domain in the box below.

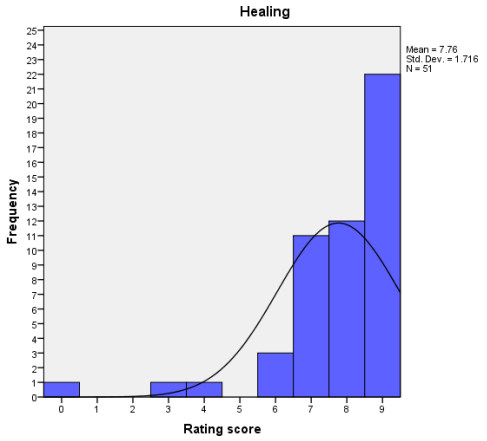
28. Optional: Please write any comments relating to the suggested domains below.

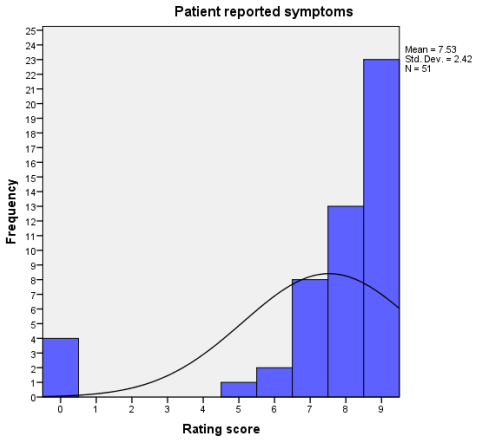
Page 5: Thank you

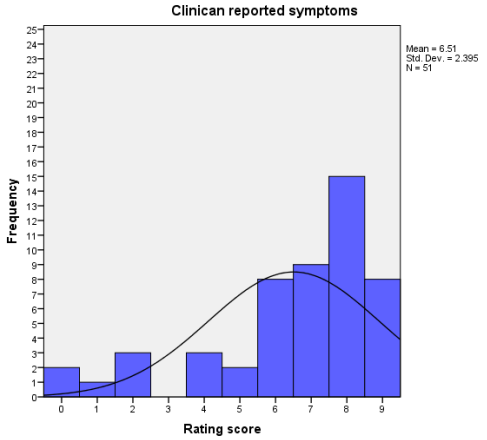
Thank you for the time you have taken to complete this survey. Your opinion is important to us and your assistance in producing the minimum list of outcomes for future effectiveness evaluations on venous leg ulcer treatments is invaluable.

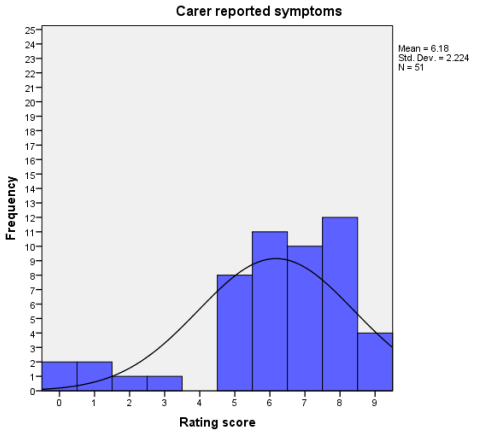
If you have any questions please send them to hc11s4h@leeds.ac.uk

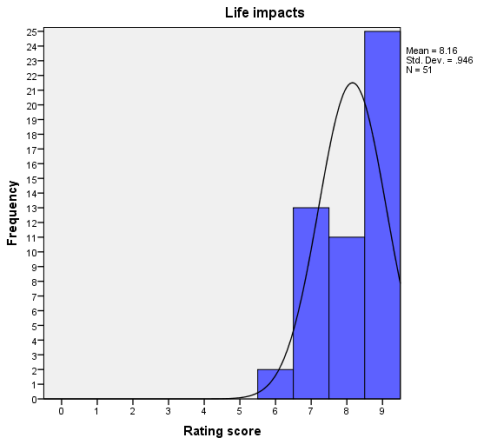
Appendix 8 Histograms for Each Outcome Domain Rated in the eDelphi on the Outcome Domains (stage 2) Round One

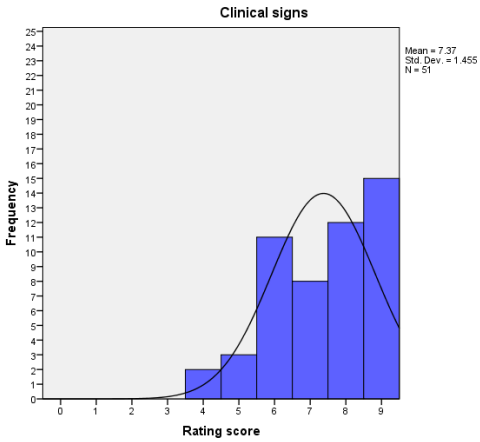




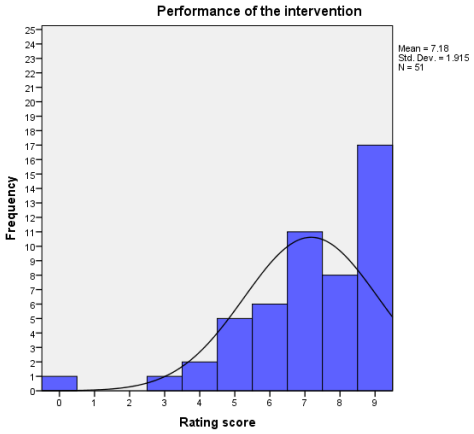


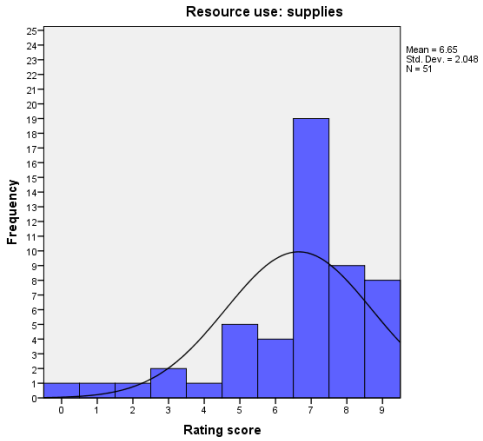


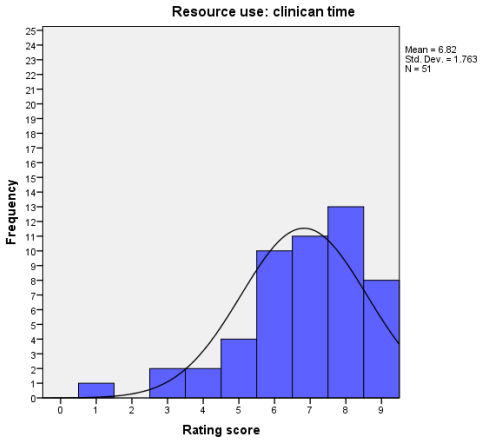


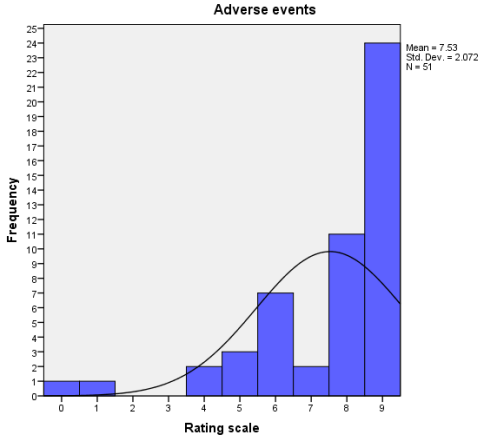



Clinical measurement
Mean = 6.82
Std. Dev. = 2.123
N = 51
Frequency
Rating score

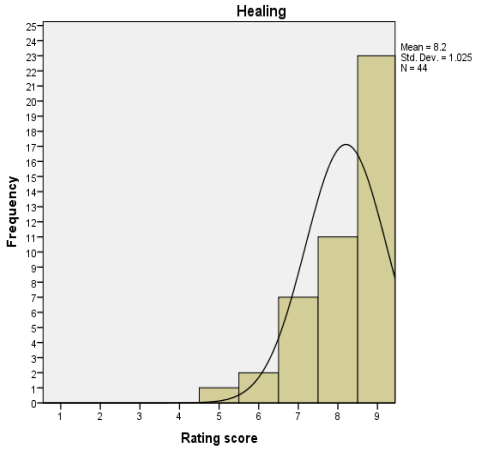

Performance of the intervention
Mean = 7.18
Std. Dev. = 1.915
N = 51
Frequency
Rating score


Resource use: supplies
Mean = 6.65
Std. Dev. = 2.048
N = 51
Frequency
Rating score


Resource use: clinican time
Mean = 6.82
Std. Dev. = 1.763
N = 51
Frequency
Rating score


Adverse events
Mean = 7.53
Std. Dev. = 2.072
N = 51
Frequency
Rating scale

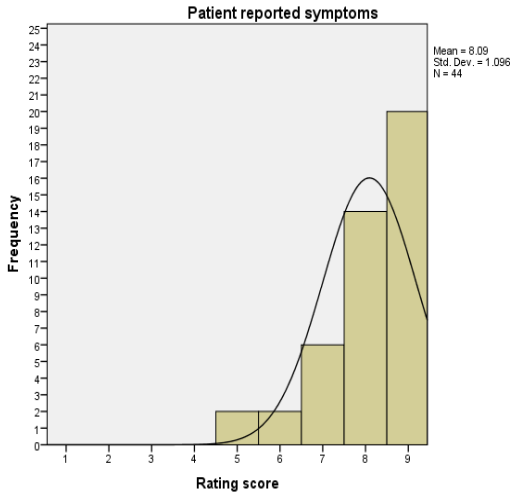
Appendix 9 Histograms for Each Outcome Domain Rated in the eDelphi on the Outcome Domains (stage 2) Round Two



Statistics

Healing

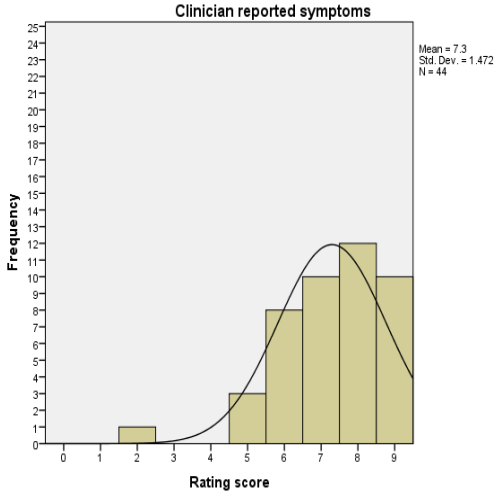
N	Valid	44
	Missing	0
Skewness		-1.247
Std. Error of Skewness		.357



Statistics

Patient reported symptoms

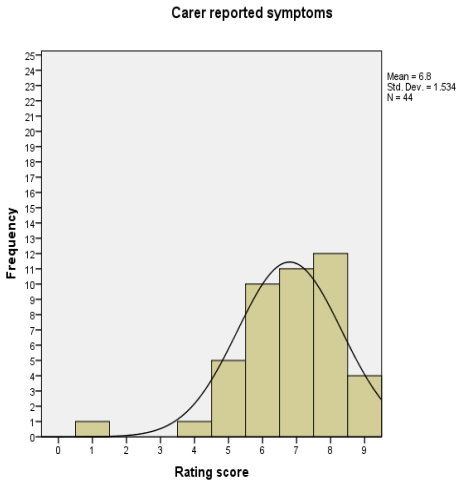
N	Valid	44
	Missing	0
Skewness		-1.298
Std. Error of Skewness		.357



Statistics

Clinician reported symptoms

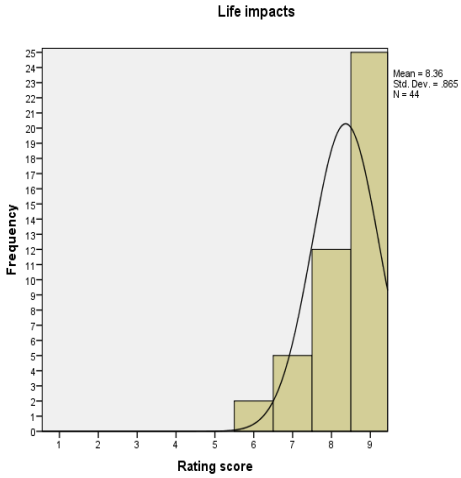
N	Valid	44
	Missing	0
Skewness		-1.136
Std. Error of Skewness		.357



Statistics

Carer reported symptoms

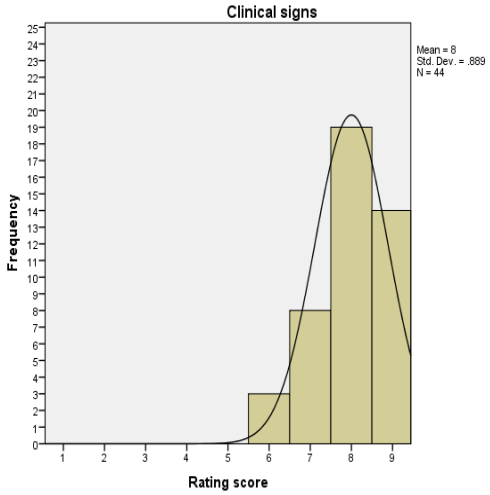
N	Valid	44
	Missing	0
Skewness		-1.260
Std. Error of Skewness		.357



Statistics

Life impacts

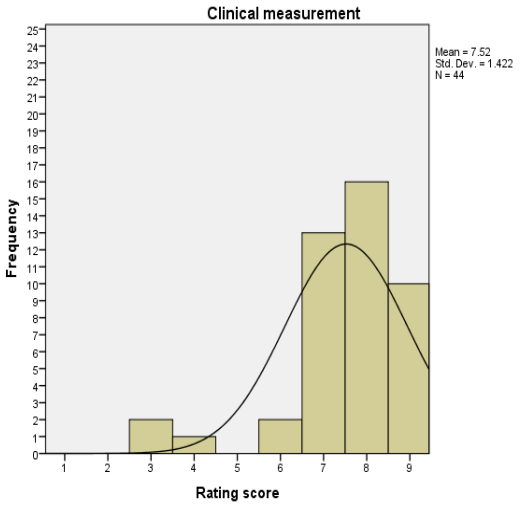
N	Valid	44
	Missing	0
Skewness		-1.250
Std. Error of Skewness		.357



Statistics

Clinical signs

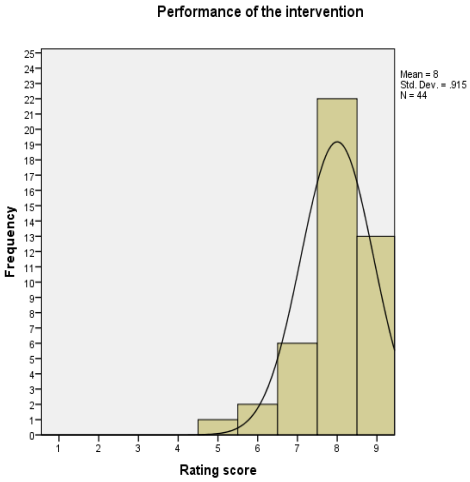
N	Valid	44
	Missing	0
Skewness		-.624
Std. Error of Skewness		.357



Statistics

Clinical measurement

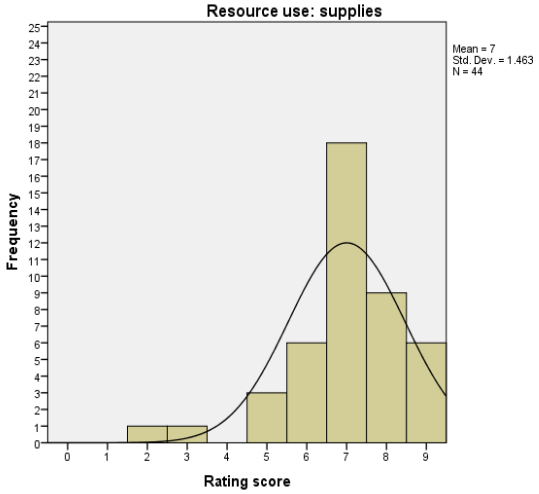
N	Valid	44
	Missing	0
Skewness		-1.725
Std. Error of Skewness		.357



Statistics

Performance of the intervention

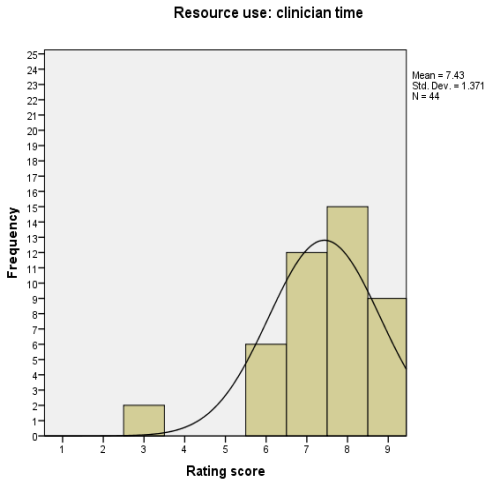
N	Valid	44
	Missing	0
Skewness		-1.145
Std. Error of Skewness		.357



Statistics

Resource use: supplies

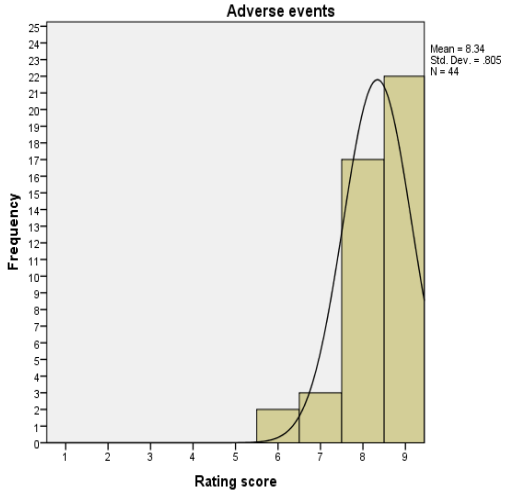
N	Valid	44
	Missing	0
Skewness		-1.261
Std. Error of Skewness		.357



Statistics

Resource use: clinician time

N	Valid	44
	Missing	0
Skewness		-1.468
Std. Error of Skewness		.357



Statistics

Adverse events

N	Valid	44
	Missing	0
Skewness		-1.272
Std. Error of Skewness		.357

Appendix 10 News Item eDelphi on the Outcomes (stage 3) Round One

Would you like to help develop a core set of outcomes for venous leg ulceration?

We would like to invite you to take part in a study entitled "Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration". This study is being led by members of the CoreVen (Core outcome set for Venous leg ulceration) project team who are researchers from the University of Leeds, UK and the National University of Ireland Galway.

The CoreVen project aims to determine what outcomes are really important and should be included as core for any trial evaluating treatment effectiveness in venous leg ulceration. An outcome is a measurement used to assess the effect of a treatment such as the assessment of effectiveness (benefits) or side effects (risk). The current problem is that the types of outcomes reported vary considerably across trials and as a result it is very difficult to determine treatment effectiveness from the overall body of evidence. The application of a core outcome set has the potential to facilitate the comparing, contrasting and synthesising of outcome data across trials. This can make research evidence accessible to those involved in clinical decision making. The advantage of easier decision making will benefit patients' treatments by enabling a clearer judgement on the intervention that is being provided.

It will take approximately 25 minutes to complete the round 1 survey and approximately 20 minutes to complete the round 2 online survey. Details of the round 2 survey will be sent via email once the results from the round 1 survey have been analysed.

The School of Healthcare Research Ethics Committee, University of Leeds, UK, has granted approval (HREC17-028). A copy of the ethics approval documentation can be forwarded to you on request.

If you would like to take part or would like more information please contact Sarah Hallas by sending an email to *********@leeds.ac.uk.

Appendix 11 Ethics Approval Letter [HREC17-028]

Faculty of Medicine and Health

Research Office

University of Leeds
Worsley Building
Clarendon Way
Leeds LS2 9NL
United Kingdom

✆ +44 (0) 113 343 31642

UNIVERSITY OF LEEDS

09 February 2018

Sarah Hallas
PhD student
School of Healthcare
Faculty of Medicine and Health
Baines Wing
University of Leeds
LEEDS LS2 9JT

Dear Sarah

Ref no: HREC17-028

Title: Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration

Thank you for submitting your documentation for the above project. Following review by the School of Healthcare Research Ethics Committee (SHREC), I can confirm a favourable ethical opinion based on the documentation received at date of this letter and subject to the following condition:

- **Evidence of permission from Ireland should be submitted once obtained**

Document Received	*Version*	*Date Submitted*
Ethical_Review_Form_V3 version 1.0	1.0	16/01/2018
1a. Gatekeepers email invites version 1.0	1.0	16/01/2018
1b. Steering group email invites covering email version 1.0	1.0	16/01/2018
1c. Twitter tweet- link for surveys version 1.0	1.0	16/01/2018
1d. Wounds UK email invites version 1.0	1.0	16/01/2018
1e. Gatekeepers permission request email for guideline developers version 1.0	1.0	16/01/2018
2a. Email invitation outcomes round 1 version 1.0	1.0	16/01/2018
2b. Email invitation outcomes round 1 for patients version 1.0	1.0	16/01/2018
3a. Gatekeepers email invites round 2 version 1.0	1.0	16/01/2018
3b. Steering group round 2 email invitation covering email version 1.0	1.0	16/01/2018
4a. Email invitation outcomes round 2 version 1.0	1.0	16/01/2018
4b. Email invitation outcomes round 2 for patients version 1.0	1.0	16/01/2018
5a. Gatekeepers email reminders version 1.0	1.0	16/01/2018
5b. Gatekeepers email reminders for round 2 version 1.0	1.0	16/01/2018
5c. Steering group email reminders round 1 version 1.0	1.0	16/01/2018
5d. Steering group email reminders round 2 version 1.0	1.0	16/01/2018
6a. Email reminders version 1.0	1.0	16/01/2018
6b. Email reminders round 2 version 1.0	1.0	16/01/2018
7a. Gatekeepers thank you email and results version 1.0	1.0	16/01/2018
7b. Steering group thank you email and results version 1.0	1.0	16/01/2018
8. Thank you email and results version 1.0	1.0	16/01/2018
300 word summary news item version 1.0	1.0	16/01/2018
500 word summary news item version 1.0	1.0	16/01/2018
Banner version 1.0	1.0	16/01/2018

Bristol Online Survey round 1 introduction page for survey accessed through Twitter version 1.0	1.0	16/01/2018
Bristol Online Survey round 1 introduction page version 1.0	1.0	16/01/2018
Bristol Online Survey round 2 introduction page for survey accessed through Twitter version 1.0	1.0	16/01/2018
Bristol Online Survey round 2 introduction page version 1.0	1.0	16/01/2018
Conference or workshop permission request email version 1.0	1.0	16/01/2018
Document explanation version 1.0	1.0	16/01/2018
Email containing banner version 1.0	1.0	16/01/2018
EWMA Conference permission request email for consensus meeting version 1.0	1.0	16/01/2018
EWMA data collection version 1.0	1.0	16/01/2018
EWMA draft abstract for programme handbook version 1.0	1.0	16/01/2018
EWMA handout version 1.0	1.0	16/01/2018
Fieldwork_Assessment_Form_medium_risk_final_protected_nov_15	1.0	16/01/2018
Participant information sheet version 1.0	1.0	16/01/2018
Participation slide EWMA version 1.0	1.0	16/01/2018
Participation slide version 1.0	1.0	16/01/2018

Please notify the committee if you intend to make any amendments to the original research as submitted at date of this approval. This includes recruitment methodology and all changes must be ethically approved prior to implementation. Please contact the Faculty Research Ethics Administrator for further information FMHUniEthics@leeds.ac.uk

Ethical approval does not infer you have the right of access to any member of staff or student or documents and the premises of the University of Leeds. Nor does it imply any right of access to the premises of any other organisation,

including clinical areas. The SHREC takes no responsibility for you gaining access to staff, students and/or premises prior to, during or following your research activities.

Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, and other documents relating to the study. This should be kept in your study file, and may be subject to an audit inspection. If your project is to be audited, you will be given at least 2 weeks notice.

It is our policy to remind everyone that it is your responsibility to comply with Health and Safety, Data Protection and any other legal and/or professional guidelines there may be.

The committee wishes you every success with your project.

Yours sincerely

H Convey

Helen Convey
Chair, School of Healthcare Research Ethics Committee

Appendix 12 Participant Information Sheet Meeting at the EWMA conference. eDelphi on the Outcomes (stage 3) Round Two

CoreVen (Core outcome set for Venous leg ulceration**)**

Participant Information Sheet

Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration

We would like to invite you to take part in the above-named study but before you decide it is important for you to understand why the research is being carried out and what it will involve. Please ask one of the meeting facilitators (Sarah Hallas or Georgina Gethin) if there is anything that is not clear or if you would like more information before deciding whether to take part. Please read the following information carefully.

Purpose of this study

This study is part of a project called CoreVen (Core outcome set for Venous leg ulceration), which aims to determine what outcomes are really important and should be included as core for trials on venous leg ulcers interventions.

Clinical trials in this field are designed to evaluate the effectiveness of treatment strategies for venous leg ulceration. An outcome is a measurement used as part of a clinical trial to assess the effect of a treatment in terms of benefits and risks. The problem is that the outcomes reported in different trials vary considerably and as a result it can be difficult to judge which interventions are most helpful. Inclusion of a core set of outcomes in all trials evaluating treatments for venous leg ulcers has the potential to facilitate the comparing, contrasting and synthesis of outcomes across trials; this in turn can help make research evidence more accessible for clinical decision makers.

A two-round online survey has explored consensus on which domains are important. We now need to decide which specific outcomes, falling within the domains, are important. Domains are broad, descriptive categories under which several, more specific, outcomes might be grouped.

The domains that were rated as important are as follows:

- Healing
- Patient reported symptoms
- Clinician reported symptoms
- Life impacts
- Clinical signs
- Clinical measurement
- Performance of the intervention
- Resource use: supplies
- Resource use: clinician time
- Adverse events

We would like to invite you to contribute to part 2 of a two-round survey on the importance of different outcomes in evaluations of treatments for venous leg ulcers.

Who is doing the study?

This study is being undertaken by Miss Sarah Hallas as part of a PhD in the School of Healthcare at the University of Leeds, UK. Professor Andrea Nelson and Dr Susan O'Meara (School of Healthcare, University of Leeds, UK) and Dr Georgina Gethin (School of Nursing and Midwifery, National University of Ireland Galway) are supervising this research. Further details on the CoreVen project can be found on:

http://www.comet-initiative.org/studies/details/680?result=true

Why have I been asked to participate?

As part of this project we are seeking to include views from all people who are affected by venous leg ulcers whether as a patient, carer, nurse, doctor, researcher or other professional related to healthcare. You have been invited to participate in this study because you have been identified as belonging to one of these groups.

What will be involved if I take part in this study?

Your participation in this study is entirely voluntary. If you choose to take part, we will ask you to complete a survey which can either be accessed via a link

displayed on the screen or you can complete the same survey on paper. At the start of either format of the survey you will be asked to confirm whether you are willing to participate

You will be presented with a list of outcomes that fall within the domains that were rated as important in a previous study. There will be a rating scale below each outcome. You will be asked to rate each outcome in terms of importance on a scale of 1 to 9 (1 being not important and 9 being extremely important). The questions on the survey that require a response will be highlighted with *'*Required'* next to them. There are some responses that are optional, you will be informed that they are optional at the beginning of the question.

Please note that by completing the Survey you are consenting to take part in the study.

What are the advantages and disadvantages of taking part?

The findings from this study have the potential to inform the design of future research addressing the effectiveness of treatments for venous leg ulcers. In turn, this research will provide useful information to assist clinical decision making in terms of identifying the best treatment options for patients. It is foreseen that by having a core set of outcomes in trials it will make it easier and more efficient for the reader to compare and contrast the evaluations of interventions.

The survey should take approximately 25 minutes to complete.

Can I withdraw from the study at any time?

You are under no obligation to take part in the study. Once you start the online survey you may withdraw at any point providing you do not click on the 'Finish' button at the end. This will mean that your responses will not be used for analysis or any other purpose. You do not need to give a reason for discontinuing the survey.

If you complete the survey and click on 'Finish' at the end your responses will be merged with those from other participants and used as part of our analysis of the data. Once you click on 'Finish' it will not be possible to withdraw your responses because they will be anonymised.

If you decide to complete the paper-based survey, please note that you will not be able to withdraw your responses once the survey has been collected as the survey will be anonymised.

Will the information I give be kept confidential?

The online survey will be conducted using the Bristol Online Survey which is fully compliant with all current UK data protection laws. All information obtained from you will be kept confidential at all times.

All data will be password protected on the Bristol Online Survey and on the password protected secure network of the University of Leeds.

The paper-based surveys will be stored securely and scanned at the earliest opportunity. Scanned documents will be stored securely on the University of Leeds secure drive. The paper copies will then be destroyed.

Other members that will have access to the data, from both the online and paper-based surveys, will be Professor Andrea Nelson (University of Leeds), Dr Susan O'Meara (University of Leeds) and Dr Georgina Gethin (National University of Ireland Galway).

What will happen to the results of the study?

Your responses from the Bristol Online Surveys will be analysed, along with other participant's responses.

If you would like to be sent the results of the consensus process please write you email address on the separate piece of paper we have provided at the front of the room. Please do not write your email address on the survey.

Who has reviewed this study?

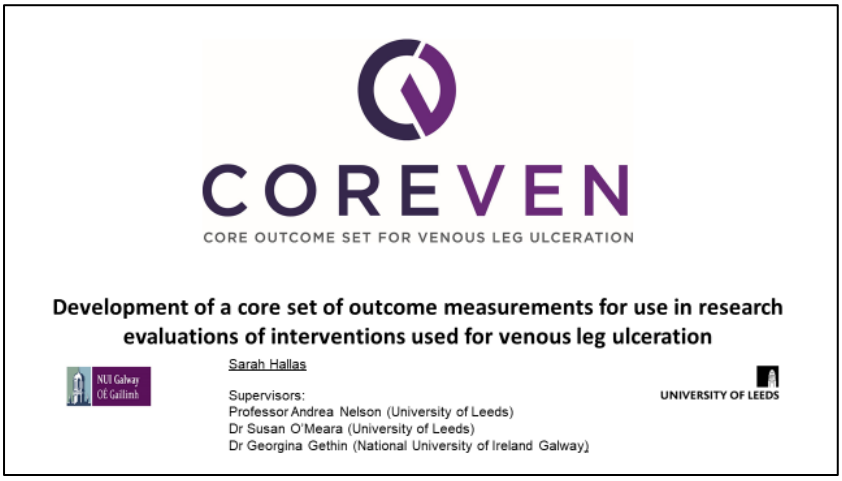
Ethical approval has been granted by the University of Leeds School of Healthcare Research Ethics Committee, UK, reference: HREC17-028.

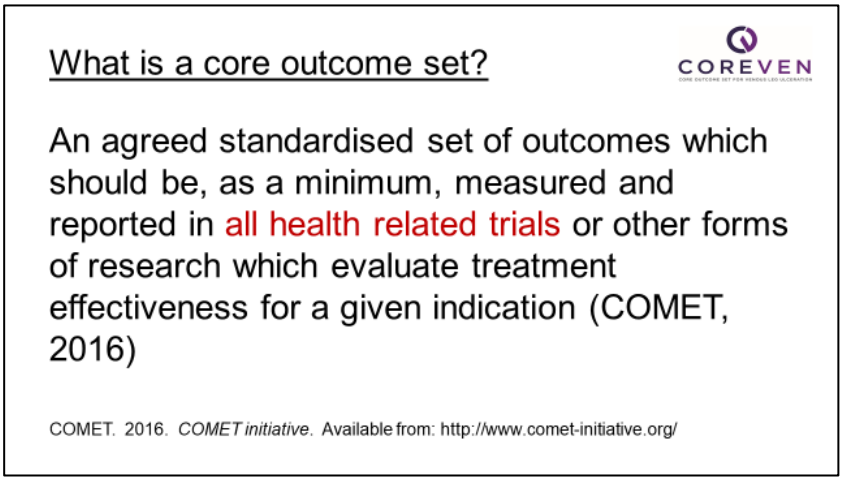
If you would like more information or have any questions or concerns about the study please contact:

Sarah Hallas, [University contact details were provided]
Dr Susan O'Meara (PhD supervisor), [University contact details were provided]

Thank you for taking the time to read this information sheet

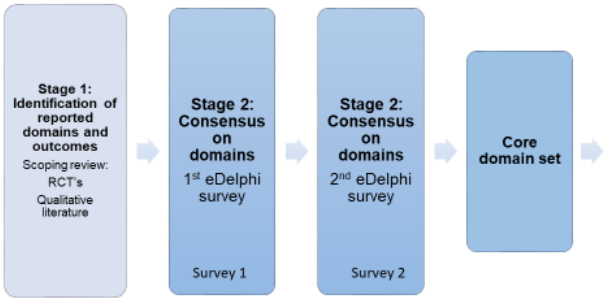
Appendix 13 PowerPoint Presentation Meeting at the EWMA conference. eDelphi on the Outcomes (stage 3) Round Two





What is a domain?

Progress



Related outcomes are 'domains'

What we have found so far....

Domains rated as core:

Healing
Patient reported symptoms
Clinician reported symptoms
Life impacts
Clinical signs
Clinical measurement
Performance of the intervention
Resource use: supplies
Resource use: clinician time
Adverse events

Progress

COREVEN

Stage 1: Identification of reported domains and outcomes
Scoping review:
RCT's
Qualitative literature

Stage 2: Consensus on domains
1st eDelphi survey
Survey 1

Stage 2: Consensus on domains
2nd eDelphi survey
Survey 2

Core domain set

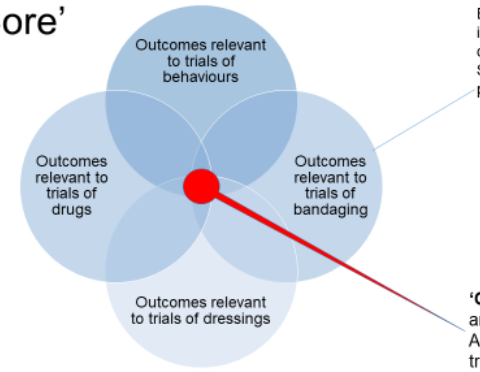
Stage 3: Consensus on outcomes
1st eDelphi survey
Survey 3

Stage 3: Consensus on outcomes
2nd eDelphi survey
Survey 4

Related outcomes are 'domains'

We are here

Defining 'Core'



Example of an important but not core outcome: Sub bandage pressure

'Core' outcomes are relevant to ALL randomised trials, regardless of intervention type

What you can do to help

COREVEN

Survey

Number of patients/ulcers/limbs that completely healed in a trial period. *Required*

Not important	1	2	3	4	5	6	7	8	9	Extremely important
PLACE X										

Patients and Carers	Researchers	Healthcare professionals	Other	Overall score
8	8	8	8	8

Online survey accessible via: https://leeds.onlinesurveys.ac.uk/coreven-ewma

If you would like to take part in the consensus….

By participating in the following consensus meeting you are consenting to take part

Once you have submitted data it cannot be withdrawn because it will be anonymised

CoreVen steering group

Dr Una Adderley (School of Healthcare, University of Leeds, UK)
Professor Jane Nixon (Clinical Trials Research Unit, School of Medicine, University of Leeds, UK)
Dr Jan Kottner (Charité-Universitätsmedizin Berlin, Germany)
Dr Pauline Meskell (Department of Nursing and Midwifery, University of Limerick, Ireland)
Dr Aonghus O'Loughlin (Bons Secours Hospital, Galway, Ireland and Alliance for Research and Innovation in Wounds)
Professor Sebastian Probst (University of Applied Sciences Western Switzerland, Geneva, European Wound Management Association council member)
Mr Wael Tawfick (Saolta University Health Care Group, University of Galway, Ireland; School of Medicine, National University of Ireland Galway and Alliance for Research and Innovation in Wounds)
Dr Thomas Wild (Editor-in-Chief Wound Medicine, University Medical Center Hamburg-Eppendorf, Germany; University of Applied Science Anhalt, Institute of Applied Bioscience and Process Management; Clinic of Plastic, Hand and Aesthetic Surgery and Clinic of Dermatology, Immunology and Allergology, Medical Center Dessau, Academic Teaching Hospital of Martin Luther University of Halle-Wittenburg, Germany)

Thank you….

Do you have any questions?

hc11s4h@leeds.ac.uk

@VLUcoreven

Appendix 14 eDelphi on the Outcomes Round One Survey

The next pages display a facsimile in MS Word format of the survey section that asked participants to rate outcomes relating to healing. It also displays the introduction pages, comment boxes to suggest additional outcomes and qualitative comments, and thank you page.

CoreVen core outcome set Bristol Online Survey 1

Page 1: Introduction

Dear Sir/Madam,

You are being invited to participate in a research study titled 'Development of a core set of outcome measurements for use in research evaluations of interventions used for venous leg ulceration'. The purpose of this study is to determine what outcomes are really important and should be included as core for any future research trial on venous leg ulceration. Your participation in this study is entirely voluntary.

On the following pages, you will see a series of outcomes. We will ask you to rate how important you consider each outcome to be on a numerical rating scale of 1 to 9 ('1' means 'not important' and '9' means 'extremely important').
Once the survey is started you will be able to leave it and return to it at a later time by selecting the 'finish later' option at the end of the page. If you decide to use this option, you will be asked to enter your email address so that a link can be sent to you for returning to the survey. Your responses will be anonymous throughout the study, regardless of whether you use the 'finish later' option.

By continuing the survey you are consenting to take part in the study. You are under no obligation to take part and you can withdraw from the study at any point providing you do not click on 'Finish' at the end. You do not need to provide a reason for withdrawal. You can stop at any point in the survey. In order for your responses to be used in the analysis you must answer all the 'required' questions and click on 'Finish' at the end. Once you do this, your responses cannot be withdrawn and will be included in the analysis. The questions on the survey that require a response will be highlighted with '*Required' next to it.
There are some responses that are optional, you will be informed that it is optional at the beginning of the question.

Please do not provide any personal details on the survey, other than stating your role (for example patient, researcher, nurse) and country of residence on the first page of the survey.

We anticipate that the survey will take approximately 25 minutes to complete. You will have the opportunity to download the responses you have submitted at the end, we recommend that you do this to allow you to see your previous responses when completing the round 2 survey.

Once the results of this survey have been analysed a summary of the group responses for round 1 will be shown to you on the next, round 2, survey.

We very much appreciate you taking time to complete the survey.

Are you happy to continue to take part in this survey? *Required*

- Yes

Which term best describes your background? (please select only one response that best describes your role) *Required*

Please select exactly 1 answer(s).

- Patient Carer
- Researcher
- Researcher from the industry sector
- Healthcare professional
- Other

If you are a healthcare professional, please state your job role:

If you selected Other, please specify:

Please write your country of residence below: *Required*

Page 2: Healing

We need to decide which outcomes are **core** and should be included in future trials on venous leg ulcer interventions. An outcome is a measurement to assess the effect of a treatment, for example, its effectiveness (benefit) or the assessment of adverse side effects (risks).

You will see below a list of outcomes which can broadly be called 'healing'. Please rate each outcome in terms of how important, on a scale of 1 to 9 (1 being not important and 9 being extremely important). Remember to rate the outcome as extremely important if you think the outcome is core and should therefore be in the core outcome set.

Number of patients/ulcers/limbs that completely healed in a trial period. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Time to complete healing - may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Change in size of ulcer, e.g. length, circumference, area, volume. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Number of reference ulcers achieving a pre-defined ulcer area change (e.g. any reduction, at least 50% reduction, at least 75% reduction). *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Time to achieving a pre-defined ulcer area change in a reference ulcer (e.g. any reduction, at least 50% reduction, at least 75% reduction). *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Change in ulcer severity score. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Healing

Granulation Outcomes. These outcomes are about the type of tissue in the ulcer.

Number of ulcers with granulating tissue. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Number of ulcers with: a. healthy granulation b. at least 75% clean granulation c. unhealthy granulation *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Quantity of granulation tissue measured at a given time point. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Time to a pre-specified level of granulation tissue (e.g. 50%, 75%, 100%). *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Fibrin outcomes. These outcomes are about the type of tissue in the ulcer.

Quantity of fibrin on the ulcer measured at a given time point. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Percentage change in fibrin during the trial period. *Required*

	1	2	3	4	5	6	7	8	9	
Not important	☐	☐	☐	☐	☐	☐	☐	☐	☐	Extremely important

Optional: Is there an outcome relating to healing that you think should be considered, other than what has been listed in this survey?. Please write the outcome in the box below.

Optional: Is there an outcome relating to healing that you think should be considered, other than what has been listed in this survey?. Please write the outcome in the box below.

Optional: Please write any comments relating to the outcomes for the healing domain.

Page 13: Thank you

Thank you for the time you have taken to complete this survey. Your opinion is important to us and your assistance in producing a core outcome set for trials on venous leg ulcer interventions is invaluable.

If you have any questions please send them to hc11s4h@leeds.ac.uk

Appendix 15 Degree of Skewness for Each Outcome Rated in the eDelphi on the Outcomes (stage 2) Round Two

Outcome	Skewness
Number of patients/ulcers/limbs that completely healed in a trial period	-1.703
Time to complete healing - may be of a reference ulcer, of all ulcers on a reference limb, or of all ulcers on both limbs	-2.128
Change in size of ulcer, e.g. length, circumference, area, volume	-1.854
Number of reference ulcers achieving a pre-defined ulcer area change (e.g. any reduction, at least 50% reduction, at least 75% reduction)	-1.189
Time to achieving a pre-defined ulcer area change in a reference ulcer (e.g. any reduction, at least 50% reduction, at least 75% reduction)	-1.271
Change in ulcer severity score	-.926
Number of ulcers with granulating tissue	-.383
Number of ulcers with: a. healthy granulation b. at least 75% clean granulation c. unhealthy granulation	-.437
Quantity of granulation tissue measured at a given time point	-.075
Time to a pre-specified level of granulation tissue (e.g. 50%, 75%, 100%)	-.283
Percentage change in granulating tissue during the trial period	-.659
Quantity of fibrin on the ulcer measured at a given time point	-.346
Percentage change in fibrin during the trial period	-.532
Number of adverse events (type of adverse event/s to be detailed in the paper)	-3.530
Number of patients that experience an adverse event (type of adverse event/s to be detailed in the paper)	-2.290
Number of patients that withdrew due to an adverse event (type of adverse event to be detailed in the paper)	-2.021
Number of serious adverse events (type of adverse event/s to be detailed in the paper)	-2.357

Number of patients/ulcers/limbs with pain	-2.806
Number of patients reporting a pre-specified level of change in pain score during the trial period (e.g. any reduction, at least 50% relief)	-2.198
Investigator reported level of pain	-.035
Change in patient reported pain score/rating during the trial period	-2.104
Pain level during mobilisation	-1.032
Change in ‘comfort’ score/rating during the trial period	-1.112
Comfort rating during dressing change (e.g. dressing removal)	-.838
Change in ‘ache’ scores/rating during the trial period	-.565
Change in heavy legs sensation score/rating during the trial period	-1.157
Change in the scoring/rating of tiredness of the lower limbs during the trial period	-.872
Number of patients reporting heavy leg sensation	-1.079
Change in the scoring/rating of cramps during the trial period	-.742
Number of patients with cramps	-.475
Change in venous claudication severity score during the trial period	-.806
Change in the scoring/rating of skin tenseness around the ulcer during the trial period	-.638
Change in the scoring/rating of restless lower limbs during the trial period	-.810
Change in the scoring/rating of heat/burning during the trial period	-.888
Change in the scoring/rating of itching during the trial period	-1.305
Number of patients reporting itching during the trial period	-1.271
Change in the scoring/rating of tingling or pins and needles during the trial period	-.633
Change in the scoring/rating of tenderness (area i.e. limb or ulcer) during the trial period	-.630
Change in fatigue scores/rating during the trial period	-.437
Change in the Quality of Life score during the evaluation period	-2.721
Change in activities of daily living score	-2.576
Patients perception of their body image	-1.093

Ability to wear/find suitable clothes and shoes	1.622
Change in oedema during the trial period – on a trial leg / both legs	-3.170
Number of patients with oedema	-1.834
Number of ulcers with suppuration (pus)	-1.235
Absolute or relative change in pus during the trial period	-1.048
Number of patients with the presence of malodour of the ulcer	-1.580
Severity of odour (from the ulcer)	-1.033
Change in the scoring/rating of erythema during the trial period	-.963
Number of ulcers that had a change in erythema (e.g. decreased, increased)	-1.011
Number of patients with cellulitis	-1.672
Change in the severity of cellulitis during the trial period	-1.526
Number of patients/ulcers/limbs with a change in slough during the trial period	-1.559
Number of ulcers with new areas of slough	-1.374
Percentage of ulcer surface covered in slough	-1.438
Change in the scoring/rating of necrotic tissue during the trial period	-1.249
Percentage of the ulcer surface area covered with necrotic tissue	-1.189
Change in necrotic tissue during the trial period	-1.143
Number of patients with necrotic tissue	-1.091
Change in the scoring/rating of exudate during the trial period	-1.771
Time to cessation of exudate (e.g. number of days, weeks)	-1.310
Rate of change in exudate	-.631
Number of ulcers with exudate	-1.337
Change in the severity of malodourous exudate during the trial period	-1.046
Number ulcers with lymphangitis (inflammation or infection of the lymphatic channels-part of the circulatory system).	-1.041
Number of patients with abnormal skin changes	-1.261
Number of patients with hyperpigmentation (darkening of an area of the skin) during the trial period.	-.382

Time to re-pigmentation (skin regains normal colour).	-.259
Change in the surface area of lipodermatosclerosis (inflammation of the layer of fat under the epidermis) during the trial period.	-.545
Number of patients with denuded peri-wound skin (loss of the top layer of skin on the surrounding skin).	-.923
Change in venous blood flow	-1.756
Changes in valvular competence	-1.314
Number of limbs with superficial femoral incompetence.	-1.022
Diameter of the superficial femoral vein (mm).	-.412
Number of limbs with a pre-specified change in venous insufficiency (e.g. any improvement).	-1.731
Change in venous pressure	-1.391
Change in venous distensibility (swelling).	-.732
Change in ankle/arm pressure ratio during the evaluation period	-.910
Change in transcutaneous partial pressure of oxygen (mmHg).	-1.153
Change in pCO2 (partial pressure of carbon dioxide).	-.421
Change in blood biochemistry (e.g. Urea and electrolytes)	-.272
Change in a pre-specified haematological parameter (for example; Red blood cells, White blood cells, Erythrocyte sedimentation rate).	-.350
Change in glycaemia (blood glucose).	-.444
Change in cholesterol (blood test).	-.172
Change in systolic blood pressure	-.529
Change in diastolic pressure	-.482
Change in heart rate	-.168
Number of patients that had microbiologically determined presence of a particular pathogen/s on the ulcer bed (type of micro-organism to be specified by the trialist)	-.952
Number of patients that had episodes of clinically diagnosed infection	-2.242
Number of patients with sepsis (also known as blood poisoning).	-1.739
Change in mASEPSIS score (wound infection score).	-1.105

Number of dressing changes (e.g. per week, to healing).	-2.158
Time between dressing changes, in days.	-1.814
Number of patients that achieved 7 day wear time	-1.001
Time required for ulcer dressing changes	-1.538
Ease of application- Reported by the researcher	-1.240
Ease of application- Reported by the patient	-2.605
Ease of removal - Reported by the researcher	-.987
Ease of removal - Reported by the patient	-2.014
Patients scoring of satisfaction with the performance of the intervention	-1.723
Healthcare professionals scoring of satisfaction with the performance of the intervention	-1.671
Number with traumatic dressing removal (trauma to the ulcer bed or the surrounding skin).	-1.342
Rating of exudate handling by dressing	-1.271
Number of dressing changes with exudate leakage	-1.584
Number of debridements required to obtain a clean ulcer	-1.311
Time required to debride the ulcer	-.938
Number of patients that required surgical debridement	-1.254
Number of visits where debridement was needed	-1.204
Cost to heal patient/ulcer/limb completely	-2.712
Cost per pre-specified reduction in ulcer area	-1.005
Cost per given time frame (e.g. week, month, year).	-2.061
Total costs to the end of the study	-2.066
Cost of dressings.	-1.214
Nursing or clinician time required per patient/ulcer/limb (cost and/or time).	-1.801
Number of dressing treatments per group	-1.047
Costs required to achieve debridement	-.661
Number of work days lost	-1.763
Patient expenses	-1.225

Number of patients that adhered to treatment advice	-2.568

Appendix 16 Search Strategy

Ovid MEDLINE

1. health technology assessment.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. HTA.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. cullum n.au.
4. 1 or 2
5. 3 and 4

Scopus

(SRCTITLE (health AND technology AND assessment) OR SRCTITLE (hta) AND AUTHOR-NAME (cullum))

Ovid Embase

1. health technology assessment.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2. HTA.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. cullum n.au.
4. 1 or 2
5. 3 and 4

CINAHL

SO health technology assessment OR SO hta AND AU Cullum

Limiters - English Language; Exclude MEDLINE records

Narrow by Journal: - health technology assessment

Search modes - Find all my search terms