Extracorporeal shock wave for the treatment of chronic venous ulcers: A pilot study

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DECLARATION

I, the undersigned, declare that this thesis has been constructed entirely by myself and that no material contained in the thesis has been used in any other submission for an academic award. All sources and referenced material are acknowledged.

Signed:

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ABSTRACT

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This thesis reports a pilot study investigating the use of extracorporeal shock wave therapy (ECSW) in the treatment of chronic venous ulcers. The studies primary aim was to assess the clinical effectiveness of this treatment when combined with current best practice, multilayer compression bandaging.

Venous ulceration of the lower limbs is a well-recognised, chronic condition. It affects a significant proportion of the population, results in reduced quality of life and is associated with substantial financial burden to health care systems.

ECSW was first put to clinical use in the treatment of kidney stones (urolithiasis) and later in the treatment of orthopaedic non-union fractures. More recently, the ability of ECSW to improve the healing of soft tissue wounds has been assessed.

A review of the current literature base revealed a limited number of clinical studies which included venous ulceration in their cohort. Despite this, positive outcomes were reported including complete wound healing in around a third of patients, improved healing rates and reductions in pain and exudate levels. Justification for a study focusing upon the effect of ECSW in the treatment of this specific condition was established, including the need for focus upon quality of life outcomes.

Quantitative methodology was employed in the structuring of a prospective pilot study, utilising a before-after design. 28 participants were recruited, none were lost to follow up. ECSW was administered alongside current best practice treatment, simple primary wound dressings and multilayer compression therapy. Treatment was delivered at two week intervals for a maximum of six treatments, with study follow up at 6 months. Wound healing, effect upon pain, exudate level and impact upon quality of life were measured to establish clinical effectiveness.

Through discussion of study results, this thesis concludes that ECSW appears to be a safe treatment modality, beneficial in the management of longstanding, large ulcers, not responding to multilayer compression therapy.

Building upon the findings of this study, further research is required to validate the use of ECSW in the treatment of chronic venous ulceration.

Key words: *Extracorporeal; shock wave; ECSW; venous ulcer; leg ulcer; acoustic wave; chronic ulcer.*

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CHAPTER 1 - INTRODUCTION AND BACKGROUND

1.1 Introduction

Venous ulceration of the lower limbs is a well-recognised, chronic condition affecting a significant proportion of the population and is associated with substantial financial burden to health care systems (d Baumgartenc 2002, Ellison, Hayes et al. 2002).

Extracorporeal shock wave therapy (ECSW) is proposed as a new modality of treatment in the management of chronic venous ulcers. The primary aim of this study is to assess its clinical effectiveness when combined with current best practice, multilayer compression bandaging.

1.2 Structure of the thesis

The first chapter of this thesis aims to provide an informative background to the research topic, introducing the underlying condition and the treatment being investigated. With this established, chapter two examines the existing knowledge base by way of literature review, seeking a specific context in which to frame the need for this study.

Chapter three's purpose is twofold, introducing study aims and outcome measures in relation to the theory of research methodology, before outlining the study design and methods.

Results are presented and summarised in chapter four before discussion with consideration of the existing and current knowledge base in chapter five. Within this same chapter, limitations, further research needs and implications for practice are discussed before drawing conclusion in chapter six.

1.3 Background - Lower limb venous ulceration

1.3.1 Defining venous ulceration

The terminology used to define venous ulceration varies between studies and between clinical guidelines. NICE guidelines now discuss venous ulceration in terms of uncomplicated venous ulcers and non-healing venous ulcers, the later meeting the criteria of not having healed after 2 to 3 months of standard treatment (National Institute for Health and Care Excellence 2012). SIGN guidelines provide an explicit definition whereby chronic venous leg ulcers are defined as an open lesion between the knee and the ankle joint which has remained unhealed for at least 4 weeks and occurs in the presence of venous disease (SIGN 2010).

Within this thesis the term venous ulcer or ulceration has been used when discussing the overall condition and aims to include both uncomplicated and non-healing venous ulcers. Chronic venous ulcer or ulceration has been used to define non-healing venous ulcers, not responding to standard treatment and in situ for greater than 4 weeks.

1.3.2 Aetiology, epidemiology and natural history

The causes of leg ulceration are varied and often multifactorial (Smith 2006); primary aetiological factors include venous insufficiency, arterial insufficiency and diabetes (Mekkes, Loots et al. 2003). Studies have shown that 70 to 80% of patients with leg ulcers have a venous component and that they are the most common type of leg ulceration treated in the community (Valencia, Falabella et al. 2001, Crane, Cheshire 2008).

Leg ulcers of venous aetiology are the manifestation of severe, chronic venous disease (van Gent, Wilschut et al. 2010); prevalence is estimated at between 0.3% and 0.5% (per 1000 population) in the United Kingdom, which increases in the over 65 age group (d Baumgartenc 2002, Vowden, Vowden 2009). The natural history of the disease is one of a continuous cycle of healing and breakdown over decades (Smith 2006, Raju 2010). The healing of active venous ulcers can be slow and recurrence rates high (Egemen, Ozkaya et al. 2012).

Patients with venous ulcers have a significantly impaired quality of life including experience of reduced mobility, pain, stress and loss of dignity (Persoon, Heinen et al. 2004, Wilson 2004). Social isolation can be common place and is frequently associated with malodorous wounds, swelling and anxiety around exudate levels (Walters, Morrell et al. 1999, Herber, Schnepp et al. 2007).

Treatment of this condition results in a considerable cost to the NHS and accounts for 1 to 3% of the entire healthcare budget, a cost estimated in 2002 as between £300m and £400m (Ellison, Hayes et al. 2002, Ragnarson Tennvall, Hjelmgren 2005, Carradice, Mazari et al. 2011).

1.3.3 Pathophysiology

Ulceration occurs in the presence of venous disease as a result of chronic venous insufficiency and ambulatory venous hypertension (Eberhardt, Raffetto 2005, Smith 2006). Most commonly, chronic venous insufficiency is attributable to a defect or weakness of the vein wall, leading to valve incompetence of the deep, superficial or perforating veins of the leg (Nicolaides, Cardiovascular Disease Educational and Research Trust et al. 2000, Schmid-Schonbein, Takase et al. 2001). The presence of an ineffectual calf muscle pump mechanism, the method

by which venous pressure is raised and blood propelled through the vein toward the heart, is a known factor contributing to venous hypertension (Beebe-Dimmer, Pfeifer et al. 2005, O'Brien, Edwards et al. 2012). In turn, the efficiency of the calf muscle pump relies upon competency of the venous valves and good mobility, especially of the ankle joint (Dixy, Brooke et al. 2003, Meissner, Moneta et al. 2007).

Valve incompetence and venous hypertension leads to microcirculatory skin changes and localised tissue damage (Mekkes, Loots et al. 2003, Etufugh, Phillips 2007). Risk factors for the development of chronic venous insufficiency have been widely thought to include age, gender, genotype, obesity, and pregnancy (Valencia, Falabella et al. 2001, Bergan, Kumins et al. 2002). Complications as a result of deep vein thrombosis have been shown to cause chronic venous insufficiency attributable to either valve damage or vein obstruction (Kahn, Ginsberg 2002, Thomas 2013).

It is considered likely that behavioural factors such as prolonged standing or generally reduced mobility also have an influence upon the development of chronic venous insufficiency (Kahn, Ginsberg 2002, Eberhardt, Raffetto 2005).

An increasingly frequent and under-reported cause of venous insufficiency arises in cases of intravenous drug misuse (Del Giudice 2004). The cause of venous insufficiency amongst intravenous drug users stems from deep vein thrombosis and repeated vein trauma at injection sites, affecting the superficial and deep veins of the lower limb (Pieper, Templin 2001, Senbanjo, Strang 2011).

Two main mechanisms have been proposed to account for the tissue damage and subsequent ulceration that can occur as a result of chronic venous insufficiency. The fibrin cuff hypothesis, postulates that venous hypertension leads to increased exudation of fibrin, a protein involved in the clotting of blood, into the surrounding

tissues and leads to the formation of fibrin cuffs around capillaries which impairs gas exchange, leading to tissue ischemia (Hahn, Unthank et al. 1999, Smith 2006).

The leukocyte trapping hypothesis, postulates that white blood cells (leukocytes) which have become trapped in the microcirculation, migrate into surrounding tissues and lead to an inflammatory response with impairment of normal proliferation and skin healing (Abbade, Lastória 2005, Sevim, Unal et al. 2014).

1.3.4 Quality of life

Chronic venous ulceration is a condition whereby people suffer with an open wound and associated morbidity for many months, in some cases years and decades (Reichenberg, Davis 2005). Living with chronic venous ulceration leads to substantial impairment of quality of life (QOL). Severity of the condition, specifically size and duration of ulceration have been shown to be indicative of the impact upon a person's QOL (Franks, Moffatt 2006). Studies have consistently revealed poorer perceived health in the domains of pain, mobility, physical and social functionality in groups of men and women living with a chronic venous ulcer (González-Consuegra, Verdú 2011).

Studies utilising validated QOL assessment tools, such as the SF-36 questionnaire, have highlighted age as a key factor affecting QOL amongst those suffering from chronic venous ulceration, with the most elderly experiencing poorer QOL (Kaplan, Criqui et al. 2003, Hopman, VanDenKerkhof et al. 2014). Measurement of QOL provides understanding of the impact disease has upon the patient, yet many studies investigating venous disease and the treatment of chronic venous ulceration fail to consider QOL outcomes (Andreozzi, Cordova et al. 2005). Both

generic and disease specific QOL questionnaires have been shown to be useful in assessment; studies suggest their combined use provides a more comprehensive and useful clinical appraisal (de Vries, Ouwendijk et al. 2005, Engelhardt, Spech et al. 2014).

The physical problems associated with chronic venous ulceration result in psychological complications such as anxiety, depression and altered body image, further contributing to greatly reduced QOL (Walters, Morrell et al. 1999, Maddox 2012). These issues are compounded by socially restrictive dressing regimes and large, bulky compression bandages (Smith, Guest et al. 2000).

1.3.5 Pain

Venous ulcers have not always been considered as painful when discussed in literature; some, mainly older studies completely disassociated pain with venous ulceration, whilst others consider venous ulceration to be far less painful than arterial ulceration. The majority of more recent studies recognise and accept that there is an association between venous ulceration and pain (Valencia, Falabella et al. 2001, Abbade, Lastória 2005, Edwards, Finlayson et al. 2014).

Pain is now regularly cited as the primary concern of patients living with a venous ulcer and directly affects several key QOL domains (Herber, Schnepp et al. 2007). Both neuropathic and nociceptive pain types have been linked to venous leg ulcers (Jørgensen, Friis et al. 2006, Woo, Sibbald et al. 2008). The former relates to damaged nerve tissue and the later results from actual tissue damage (Tsuda, Inoue et al. 2005). Clinical assessment to define type of pain appears to remain subjective and mainly involves the patient's description of sensation. Descriptions of neuropathic pain often include terms such as burning or shooting pain

sensations, whereas nociceptive pain has often been portrayed as sharp, aching or throbbing pain sensations (Woolf, Mannion 1999, Price, Fogh et al. 2007).

Chronic venous ulcers are susceptible to recurrent infection; the association between infection and wound pain is well documented. When present, infection almost certainly contributes to the pain burden of chronic venous ulcers (Cutting, White et al. 2013).

The prevalence of pain amongst those suffering venous ulceration is difficult to determine. A Cochrane Collaboration review focusing upon topical agents or dressings for pain in venous ulcers cites the prevalence of pain for this condition as ranging from 17% to 65%; this is certainly collaborated by other venous ulcer studies where pain prevalence is generally concluded to be in excess of 60% (Briggs, Nelson 2001, Nemeth, Harrison et al. 2003, Heinen, Persoon et al. 2007, Edwards, Finlayson et al. 2014).

Yet pain is much neglected as an outcome measure in studies where total healing or rate of healing tends to take precedence (Cooper, Hofman et al. 2003). This may in part be due to the difficulty of measuring pain, a subjective experience shaped by many factors (Younger, McCue et al. 2009). Simple, validated, rating scales have been successfully employed in a number of studies, including the use of visual analogue scales to record patient reported pain levels (Ferreira-Valente, Pais-Ribeiro et al. 2011). The limitation of these assessment tools lies in their inability to describe type or quality of pain, focusing only upon pain intensity (Cooper, Hofman et al. 2003).

Studies exploring the use of visual analogue scores (VAS) to evaluate pain have suggested that a clinically significant change or reduction in score may be dependent upon baseline severity, with those registering a greater baseline score requiring a greater reduction to achieve clinical significance. Despite this, several

studies have concluded that an approximately 30% shift in VAS may constitute a clinically significant change (Bird, Dickson 2001, Farrar, Young et al. 2001, Jensen, Chen et al. 2003).

1.3.6 Exudate

Large volumes of wound exudate are synonymous with chronic venous ulceration, causing further discomfort and pain through excoriation of the skin and psychological distress associated with leakage and odour (Edwards, Finlayson et al. 2014).

In theory wound exudate should be quantifiable utilising a continuous measurement scale. Few techniques have been investigated; the method of weighing dry and wet dressings to assess exudate quantity has been described as ineffectual and impractical (Cutting 2003, Dealey, Cameron et al. 2006). In daily practice volume of exudate is recorded as low, medium or high and remains a subjective measurement which will vary between practitioners (Grey, Harding et al. 2006).

The role of wound exudate in the healing of venous ulcers is poorly understood; several studies have inferred that venous ulcer exudate can significantly inhibit the process of angiogenesis leading to increased healing times (Drinkwater, Smith et al. 2002, Ulrich, Lichtenegger et al. 2005).

1.3.7 Current treatment and best practice

The assessment and diagnosis of venous disease as the underlying ulcer aetiology involves an array of healthcare professionals (Brem, Kirsner et al. 2004). National

guidelines indicate assessment of ankle brachial indices (ABI) should be performed to rule out arterial disease, alongside further diagnostic assessments including duplex ultrasound imaging to identify venous reflux (SIGN 2010, Lurie, Comerota et al. 2012). Treatment is usually carried out and overseen by community and hospital nursing teams, in many cases via specialist ulcer clinics (Maddox 2012, Edwards, Finlayson et al. 2013). The truly chronic nature of the condition can in some cases lead to the need for lifelong treatment (Collins, Seraj 2010, Van Hecke, Verhaeghe et al. 2011).

The current gold standard in the management of venous ulcers revolves around high compression multilayer bandaging (SIGN 2010). Multilayer compression bandaging aims to improve venous return and reduce venous hypertension (Stansal, Lazareth et al. 2013, Nelson, Harrison 2014). A Cochrane review of randomised controlled trials identified seven studies comparing compression with no compression and concluded that compression increases ulcer healing rates when compared to no compression (Cullum, Nelson et al. 2001).

In the United Kingdom, elastic multi-component bandages such as four layer bandaging and comparative two layer systems are used; these consist of an initial layer of orthopaedic wool, an elastic bandage and an elastic cohesive bandage as the outer layer (Todd 2011, Partsch 2013). The high pressure is sustained for a considerable time allowing for a weekly change of dressings. With multilayer compression therapy, healing rates of around 70% at six months have been achieved in specialist clinics. Twelve month recurrence rates vary greatly between 26% and 69% (Iglesias, Nelson et al. 2004, Barwell, Taylor et al. 2000).

Both four layer and two layer compression bandaging systems are utilised in practice; opinion has traditionally been divided regarding which provides the best wound healing outcome (Moffatt, Mccullagh et al. 2003, Mosti, Mattaliano et al.

2008). A Cochrane systematic review concluded that each system yields similar healing rates and that both are appropriate treatment options (O'Meara, Cullum et al. 2012).

Several systematic reviews and current best practice guidelines recommend simple, non-adherent wound dressings be used alongside compression treatment (O'Donnell Jr, Lau 2006, SIGN 2010). Consistently, no one dressing type has prevailed in clinical trials as superior in terms of number of ulcers healed. Given this outcome consideration should be given to the absorption of exudates and the protection of surrounding tissues in selection of a primary wound dressing (Tang, Marston et al. 2012, Thomas 2013, Lazarus, Valle et al. 2014).

1.3.8 Variables affecting response to compression therapy

Poor compliance with medical treatment by those suffering chronic, long term conditions is well reported (Roebuck, Liberman et al. 2011). Several studies have examined the issues surrounding poor compliance with compression bandaging; unequivocally the primary cause is lack of patient education and poor provision of treatment information (Edwards 2003, Annells, O'Neill et al. 2008). Beyond this explanation several modalities of the treatment impede patient compliance. The application of compression bandaging adds significant bulk to the leg which can cause problems with the fit of clothing and footwear (Stansal, Lazareth et al. 2013). Poor application technique can lead to patients experiencing pain, oedema and tissue damage; the later due to excessive pressure upon prominent areas, in much the same way as the development of pressure sores (Todd 2011).

Compression has proven effective in the treatment of venous ulcers, with the highest success found in ulcers of less than six months duration and of less than

5cm^2 wound area (Watson, Kang'ombe et al. 2011, Nelson 2001a). Stubborn, hard to heal venous ulcers, older in duration and unresponsive to compression therapy have led to the investigation and development of many novel treatments, often referred to as advanced wound care techniques (Rippon, Davies et al. 2007).

1.4 Background - Extracorporeal shock wave therapy

1.4.1 Shock waves

Shock waves are most easily described as pulses of acoustic, or sound energy with very specific characteristics (Mittermayr, Hartinger et al. 2012.). Acoustic waves manifest and spread as disruptions in surrounding pressure levels, the most common example are acoustic audio waves which create a small disturbance through a medium such as air and can be audible to the human ear (Rassweiler, Knoll et al. 2011). Acoustic pressure levels are expressed in terms of frequencies; the entire range of frequencies can be divided into three sections: audio, ultrasonic and infrasonic. Clinically useful acoustic shock waves fall into the ultrasonic frequency bracket (Ogden, Tóth-Kischkat et al. 2001).

The waveform of each acoustic shock wave pulse consists of a quickly achieved (<1 nanosecond), sharp spike of high amplitude acoustic pressure which is immediately followed by a slightly more drawn out period (several microseconds) of lower amplitude pressure (Ito, Fukumoto et al. 2009, Goertz, Lauer et al. 2012). There are two effects observed in the creation of a shock wave pulse; the primary impact of energy in the initial spike of high amplitude pressure and the secondary impact of energy released via cavitation bubbles (Ogden, Tóth-Kischkat et al. 2001). Cavitation bubbles are created by the initial shock wave propagation and release large amounts of energy upon their collapse. It has been suggested that

the effect of cavitation may be responsible for some clinical therapeutic effects, possibly more so than the initial high amplitude pressure release itself (Nishida, Shimokawa et al. 2004, Gerdesmeyer, von Eiff et al. 2005).

The characterisation of shock waves often includes a description of energy flux density, the rate at which energy is transferred through the physical medium. A low or high flux density will directly result in the delivery of low or high levels of energy. Lower flux densities appear to be associated with therapeutic effects; adversely, a high flux density results in destructive outcomes as seen in the treatment of urinary calcinosis (Rassweiler, Knoll et al. 2011, Antonic, Mittermayr et al. 2011).

Shock waves are generated through the process of converting electric energy into acoustic energy. This is achieved via a transducer utilising one of the following three methods currently being used in clinical practice: electromagnetic generation utilises a strong magnetic field to create a slow, low pressure acoustical pulse; piezoelectric generation relies upon the rapid contraction and expansion of piezoelectric crystals, achieved through the application of a high voltage pulse and electrohydraulic, whereby a shock wave pulse is released by high voltage electrode water vaporisation (Ogden, Tóth-Kischkat et al. 2001, Mouzopoulos, Stamatakos et al. 2007).

1.4.2 Clinical use

Extracorporeal shock waves were first put to clinical use during the 1970s in the treatment of urolithiasis, whereby kidney stones (urinary calcinosis) are broken up by the shock wave energy (Shrivastava 2005). Since then their application has been extended to the therapeutic treatment of fractured bones with an interrupted

healing process (non-union fractures), tendon injury and osteonecrosis, a condition whereby bone breaks down faster than it can be replenished (Schaden, Thiele et al. 2007).

More recently, its ability to improve the healing of wounds, ulcers and burns has been assessed. The incidental discovery that shock waves may have an effect upon wound healing was made around 2007 (Schaden, Thiele et al. 2007, Arnó, García et al. 2010, Mittermayr, Hartinger et al. 2012.); the treatment in this context has remained novel.

The mechanism of how ECSW may aid wound healing is poorly understood at present, however several animal model studies have shown increased levels of signal proteins (vascular endothelial growth factor (VEGF) and factor HIF-1alpha) following treatment. These proteins are in part responsible for the restoration of tissue oxygen supply when blood circulation is inadequate (Wang, Wang et al. 2004, Chen, Wang et al. 2004, Nishida, Shimokawa et al. 2004). In humans, ECSW has been shown to promote the formation and development of blood vessels (angiogenesis) and to reduce inflammation (Wang, Yang et al. 2011). This angiogenic process appears to be stimulated by the application of shock waves and plays an important role in wound healing (Stojadinovic, Elster et al. 2008, Mittermayr, Hartinger et al. 2012.). In addition ECSW may, through the application of shear stress forces via the cavitation effect, alter the physical properties of endothelial cells (Mariotto, Cavalieri et al. 2005).

The use of ECSW to treat soft tissue wounds is an innovative therapy which has slowly emerged over the last ten years. Its effectiveness in the management of specific wound subgroups is unknown. Review of the existing evidence and knowledge base is required to justify the study of its use in the treatment and management of chronic venous ulceration.

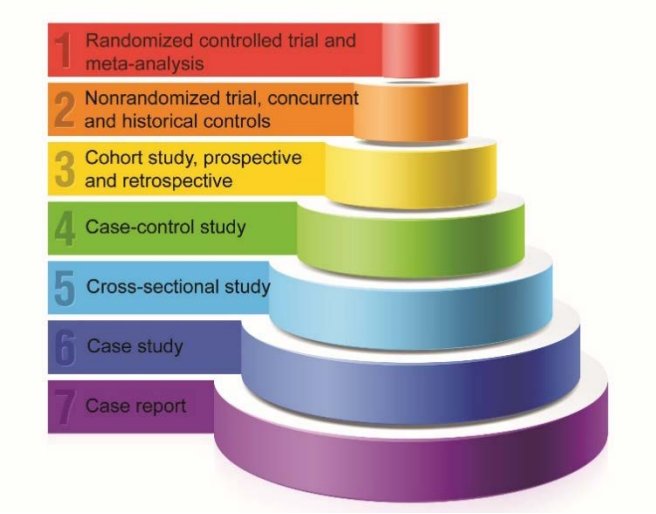
CHAPTER 2 - LITERATURE REVIEW

Extracorporeal shock wave therapy in the management and treatment of lower limb venous ulceration

2.1 Hierarchy of evidence

At the foundation of evidence based practice there exists an accepted hierarchy of evidence. This hierarchy gives most credence to research outcomes which have the highest levels of validity, achieved via specific methodology (Evans 2003, Merlin, Weston et al. 2009). It is broadly accepted that randomised controlled trials (RCTs) are superior to non-randomised, experimental designs and observational studies, with case studies and reports regarded as far poorer sources of evidence (Hadorn, Baker et al. 1996, Sprague, McKay et al. 2008). Systematic reviews incorporating meta-analysis of data from multiple studies often sit at the very peak of the evidence hierarchy (Jones 2010). Systematic reviews published by the highly regarded Cochrane Collaboration aim to provide unbiased overviews of evidence through the use of rigorous methodologies and explicit literature search strategies (Haines, McKnight et al. 2008).

Figure 1 – Evidence hierarchy



(Donatell 2015)

Though the type of evidence hierarchy illustrated in figure 2 is well established and broadly accepted, its legitimacy has frequently been challenged. It has been suggested that evidence based practice requires the acknowledgement of experiential and reflective research methodologies and that the stature of this type of evidence should be elevated (Petticrew, Roberts 2003). These approaches within the conventional hierarchy of evidence are considered weak, yet many believe they better represent the reality of daily practice where the rigorously controlled conditions of an RCT are unlikely to be replicated or applicable to unique patient characteristics (Mantzoukas 2008, Concato 2004).

In the review of literature pertaining to the use of ECSW in the treatment of lower limb venous ulceration, the intent is to seek out and consider all available evidence ranging from systematic review of RCTs to individual case study. The aim will be to deliver a comprehensive overview of the research outcomes informing the basis of this study.

2.2 Search strategy

The well-defined and validated PICO acronym and concept was used to develop the search strategy for this review. The framework, which focuses upon four essential study components: Population, Intervention, Comparison and Outcome (Birch, Eady et al. 2003), was used to construct search terminology and to define relevant questions (Gerrish, Lacey 2010, Schardt, Adams et al. 2007).

Cochrane Collaboration methodology suggests that extensive, systematic search strategies should not only include the use of text words, potentially found in titles and abstracts, but also indexed keywords often unique to individual databases; one such example would be the use of MeSH descriptors (Jadad, Cook et al. 1998, Higgins, Green 2008).

Table 1 shows the refined search string utilised in the literature search. Table 2 summarises all search results; The Scottish Intercollegiate Guidelines Network (*SIGN*) adapted algorithm (Appendix A) was used to classify study designs (Scottish Intercollegiate Guidelines Network (SIGN) 2014).

Table 1 – Search term string

#1	MeSH descriptor: [Ultrasonic Surgical Procedures] explode all trees
#2	MeSH descriptor: [Ultrasonic Therapy] explode all trees
#3	MeSH descriptor: [Sound] this term only
#4	MeSH descriptor: [High-Energy Shock Waves] explode all trees
#5	(Shockwave* or (shock* near wave*))
#6	Ultraso*
#7	Lithotrip*
#8	ESWT
#9	ECSW
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	MeSH descriptor: [Leg Ulcer] explode all trees
#12	((varicose next ulcer*) or (venous next ulcer*) or (leg next ulcer*) or (stasis next ulcer*) or (crural next ulcer*) or "ulcer cruris" or "ulcer* cruris")
#13	#11 or #12
#14	#10 and #13

Table 2 – Search of electronic databases - results

Database	**Results (n)**
MEDLINE	263
EMBASE	204
CINAHL	28
CENTRAL (Cochrane)	10
Web of science	132
Total	**637**
Duplicate studies removed	307
Irrelevant studies removed	323
Total for appraisal	**7**

Of the 637 results initially returned, 307 were identified as duplicates and removed. The titles and abstracts of the remaining 330 articles were reviewed and evaluated for relevance. A large number, 323 in all, were found to be irrelevant and comprised mainly of studies concerned with the use of ECSW for orthopaedic

application including the treatment of non-union fractures, tendinopathies and osteonecrosis. The treatment of burns, surgical skin flaps and diabetic foot ulcers also featured within the group of studies excluded. A single study was available in German language format only and therefore also excluded; in retrospect further endeavour to obtain translation of this paper should have been sought and may have resulted in its inclusion.

The reference lists of the studies identified for inclusion were screened in an attempt to highlight any additional studies not discovered in the search of electronic databases. On this occasion no additional studies were identified.

A summary table of the remaining seven studies can be found in appendix B.

2.3 Systematic review of Randomised Controlled Trials

In the absence of an existing systematic review of RCTs, a Cochrane review of randomised controlled trials was initiated and the protocol stage completed (Appendix C). This proceeded after completion of appropriate training and with the support of the Cochrane wounds group. None of the 170 RCT's returned in search results met inclusion criteria for the systematic review; a strong indicator of the need for further research in this field.

2.4 Literature reviews

Two published literature reviews were identified; extracorporeal shock wave therapy for wound healing: Technology, mechanisms, and clinical efficacy (Mittermayr, Antonic et al. 2012) and Shock Wave Therapy in Wound Healing (Qureshi, Ross et al. 2011). Between the two reviews ten studies are included of

varied design investigating the efficacy of ECSW in the treatment of soft tissue wounds. Only two of the included studies feature venous ulceration in their sample; both studies are discussed in each literature review.

Both literature reviews fail to distinguish results by wound type other than to state that venous ulceration represented the wound type with lowest healing rates (33% compared to at least 66% in all other wound types). Many defining factors are absent from both reviews; time to complete healing, study duration and concomitant treatment are all missing from discussion. One shared conclusion identifies smaller wounds (≤10cm^2) of shorter duration (≤1 month old) as most likely to achieve complete healing. Neither literature review includes discussion of statistical analysis.

Both literature reviews identify ECSW as a safe treatment modality with potential in the treatment of soft tissue wounds. The lack of study specific information and the non-systematic approach to review, make it impossible to extrapolate conclusions from these literature reviews about the effectiveness of the treatment in the management of venous ulceration, though it appears healing rates in excess of one third may have been achieved. The validity of these findings and any potential bias is difficult to ascertain.

Both reviews recommend further study of the treatment for specific wound types in order to better define subsets of patients who may benefit the most.

2.5 Non-randomised trials and studies

Two prospective studies and a third retrospective study were identified as stand-alone studies within the literature search.

Of the three studies, two directly address the effectiveness of ECSW in the treatment of soft tissue wounds, including wounds of venous aetiology. The third paper is primarily concerned with the influence of wound aetiology and comorbidity upon the success of ECSW in the soft tissue wound context.

Shock Wave Therapy for Acute and Chronic Soft Tissue Wounds: A Feasibility Study (Schaden, Thiele et al. 2007), is considered the seminal work in this area. It is certainly the first report of ECSW's potential to aid the healing of soft tissue wounds. This non-randomised study includes 208 participants with complicated, non-healing wounds of varying origin. Venous ulceration accounts for 12% (25 wounds) of the studied wounds. Within this group, mean baseline wound area was 10.3cm^2, an average of 3.7 sessions were administered with 60 day follow up. Treatment was delivered either weekly or fortnightly; amount of shock wave administered varied dependent upon wound area. Unfocused, electrohydraulic shock waves, with an energy flux density of 0.1mJ/mm^2 were utilised in treatment. Primary outcome measure is complete wound healing with analysis of factors indicating likelihood of success.

36% of the venous ulcers studied are reported to have healed in a mean of 43.5 days. Multivariate logistic regression analysis showed significant difference in success of treatment based upon wound aetiology, with venous and arterial insufficiency indicating least positive outcomes. Wound size and duration emerged as predictors of wound healing; wounds of baseline area ≤10cm^2 and of duration ≤1 month were found to be statistically more likely to respond to treatment. It is further suggested that emphasis be placed upon the impact of wound duration, with wounds ≥10cm2 of duration ≤1 month also showing good response rate; essentially acute wounds showed greater response than chronic wounds.

Improved patient experience of wound pain and a reduction of wound exudate is demonstrated through further statistical analysis of data, though there is no report of the scale or method by which these outcomes were measured and no greater or more detailed measure of QOL is utilised.

Very little detail is presented regarding concomitant treatment and historical treatment; combined with a lack of control group, this may limit the validity of results. By the authors own admission, there is a risk of bias whereby the increased wound care and debridement as a result of the study conditions may have contributed to positive outcomes, potentially perceived as attributable to the new intervention. Without control group or separate study arm for comparison it is difficult to know how this risk could have been reduced.

The second study, Extracorporeal Shock Wave Therapy for the Management of Chronic Ulcers in the Lower Extremities (Saggini, Figus et al. 2008), addresses this issue in the design of a non-randomised controlled study whereby 30 participants were recruited and treated with ECSW and a further 10 participants entered into a control group treated with regular, conservative dressings. Venous ulceration accounts for 40% (11 wounds) of the treatment group and 50% (5 wounds) of the control group.

Baseline wound area data is only presented for the responding wound group and ranges from $1cm^2$ to $9.7cm^2$. A minimum of 4 and a maximum of 10 treatment sessions were given; no follow up period is reported.

Treatment was delivered every two weeks; amount of shock wave administered was calculated as 100 pulses per cm^2 of wound area. Electrohydraulic shock waves, with an energy flux density of $0.037mJ/mm^2$ were utilised in treatment; it is unclear whether shock waves were focused or unfocused. Complete wound

healing is the main outcome measure with consideration given to impact upon participant experience of wound pain and exudate levels.

There appears to be a discrepancy between the number of participants recruited with venous ulceration (12 wounds) and the number reported within the results section (11 wounds). Though no explanation is given, it is possible this participant was lost to follow up or excluded for some other reason. Within the treatment group, 36% of the venous ulcers are reported to have healed by end of study, no time period to primary outcome is presented. In the remaining venous ulcers, reductions of wound surface area are observed at between 32 and 70%. In comparison, none of the venous ulcers in the control group had healed by end of study. Furthermore, statistical analysis showed significant difference in the wound area reductions from baseline to final measurement in the ECSW group and no statistical significance in the control group.

A substantial decrease in wound exudate is reported for all wounds in the treatment group, though little data is actually presented. Pain was evaluated utilising a numeric box scale (NBS); 80% of participants within the treatment group reported a 1 – 3 point decrease in pain score over the study period. Similar data is not presented for the control group, however it is stated that no statistical significance was shown in NBS scores for the control group. Beyond the reporting of exudate and pain data, no further measure of QOL is included.

No information is included regarding concomitant treatment or the nature of conservative dressing utilised within the control group. Though the overall sample size is acceptable for a study of this type, the sub group of interest (venous ulceration) is small at 11 wounds of which only 4 achieved complete wound healing, making generalisation difficult.

The final study identified, The Influence of Comorbidities and Etiologies on the Success of Extracorporeal Shock Wave Therapy for Chronic Soft Tissue Wounds: Midterm Results (Wolff, Wibmer et al. 2011), retrospectively utilises the data set collected in Schaden et al's initial 2007 paper. The focus of this new paper is to determine what influence existing comorbidities and wound aetiologies had upon the success rate of ECSW in the treatment of soft tissue wounds. Follow up appears to have been extended from the original study to a mean of 31.8 months, during which time it is reported that no wound recurrence occurred where complete healing had occurred. Further multivariate logistic regression analysis is undertaken to identify positive or negative factors influencing the success of ECSW. The authors conclude that existing comorbidities and wound aetiology have no statistically significant influence upon the effect of ECSW therapy in the healing of soft tissue wounds. As the data set is taken from the original 2007 study, the same limitations affect the outcomes of this paper.

The lack of detail with regards concomitant treatment (wound dressings) in all three studies and varied, if not absent, follow up periods may limit the ability to compare outcomes with those reported for current best practice treatments. It may not be feasible to make comparisons in this way; as both primary studies point out, the wounds considered for advanced wound care techniques tend to be those which have failed to heal or improve via conventional treatment. These hard to heal wounds may not ever achieve rates of healing equal to those reported for treatments such as multilayer compression therapy. In such case, the reported 36% of venous ulcers healed in both studies discussed here may be more impressive than first appears.

2.6 Case reports

In 2013, (Stieger, Schmid et al. 2013) reported a single case study of ECSW utilised in the treatment of a 56 year old female patient suffering from chronic lower limb venous ulceration of duration at least six years. Aetiology had been confirmed by way of duplex ultrasound and surgical stripping of the incompetent great saphenous vein undertaken some eight years previous. Regular surgical debridement, compression bandaging, vacuum therapy and a variety of wound dressings had failed to aid wound healing. ECSW was undertaken alongside compression bandaging and a simple hydrofibre primary dressing; treatment was given weekly for a total of 30 sessions. Baseline wound area was 200cm^2; 2000 pulses of shock wave energy were administered at each session utilising an energy flux density of 0.25mJ/mm^2. Complete wound healing was achieved at 30 weeks. There is no assessment of pain, exudate or any QOL measure. No follow up period is reported, though one episode of ulcer recurrence is described which was treated successfully at an early stage.

A case of multiple, bilateral venous ulceration treated with ECSW was reported in 2012 by (Fioramonti, Onesti et al. 2012). The 63 year old female patient suffered with two ulcers to the right leg (baseline area 1.5x2cm^2 and 4x2cm^2) and one ulcer to the left leg (baseline area 4x1.5cm^2). Both ulcers on the right were treated weekly with ECSW for a total of six sessions; it is unknown whether shock waves were focused or unfocused. 100 pulses per cm^2 of shock wave energy were administered utilising an energy flux density of 0.037mJ/mm^2. The ulcer situated on the left leg was treated conservatively and without ECSW. Complete wound healing occurred in both ulcers situated on the right leg at six weeks, whilst the conservatively treated ulcer on the left leg remained unhealed.

As with the previous case report, no assessment of pain, exudate or any QOL measure is undertaken. No follow up period or incidence of recurrence is reported.

2.7 Conclusion

Overall, the evidence supporting ECSW in the treatment of venous ulceration appears positive. Though a very limited number of clinical studies were identified which included venous ulceration in their cohort, positive outcomes were reported including complete wound healing in around a third of patients, improved healing rates and reductions in pain and exudates. The validity of results from both clinical studies and case reports could be questioned; detail of methods and measures employed in the collection of data is universally lacking. The percentage of each studies sample focusing upon venous ulceration was small, making generalisation difficult. Furthermore, the majority of studies and cases reviewed have been designed without a control group. In such cases comparison to historic controls, whereby the effect of the intervention is compared to previous treatment outcomes can be utilised; the studies reviewed here pay little reference to historical or indeed concomitant treatments. Validated QOL measurement would have added much value to the outcomes of the reviewed studies and it is unfortunate that they were not included. There are no reports of adverse events in any study; the treatment would appear to be a safe, viable treatment option.

Study authors have identified that their samples represent hard to heal wounds where conventional or accepted best practice techniques have failed to heal or improve a chronic wound. It seems imperative that results be considered in this context and not directly compared to the outcomes of current best practice; for example, multilayer compression therapy. Though healing rates of around 70% at six months have been demonstrated with multilayer compression therapy, what

is effectively being reported within the reviewed ECSW studies are samples taken from the remaining 30% of un-responding, hard to heal wounds. The generalisability of these results to the majority of patients with venous ulceration is unclear.

Currently the role of ECSW as a primary treatment or adjuvant to best practice in routine care is unclear and requires assessment. Generally positive outcomes and the absence of adverse events suggest a study focusing upon venous ulceration alone would be justifiable. Poor reporting of study methodology is detrimental to the validity of the existing knowledge base. Prospective studies focusing upon the treatment of venous ulceration should be of clear technique and design; this would ideally include concomitant use of current best practice treatment, multilayer compression therapy. Patient related outcome measures (PROMs), specifically QOL assessment, are underreported and should not only be included, but prioritised in study design.

CHAPTER 3 - METHODOLOGY AND RESEARCH DESIGN

3.1 Aims and outcome measures

Primary aim: to assess the clinical effectiveness of ECSW in the healing and management of chronic venous ulceration, when combined with multilayer compression bandaging.

Secondary aim: to assess the effect of ECSW on participant reported ulcer pain and exudate levels.

To assess clinical effectiveness, the principal outcome measure was time to complete healing of the reference ulcer and improved QOL; secondary measures focused upon reduced pain scores, exudate levels and time to 50% reduction in ulcer area. In accord with quantitative methodology these outcome measures are reliant upon empirical observations, generating consistent numerical data (Ellis 2013). These aims and core elements shape and inform the design of this prospective, quantitative study.

In addition to the assessment of these clinical outcomes, this study also sought to evaluate the processes of the study itself. The purpose of which was to ascertain the validity of the methodology, methods and tools utilised in its execution. The outcome of such evaluation would be to help inform a further or greater study.

3.2 Methodology

The philosophical basis for the design of this study is firmly rooted in positivism, the belief that knowledge is derived from direct measurement or observation. The positivist approach to research generally dispels such notions as intuition and speculation, instead favouring practical results and empirical measurement,

aiming for a high degree of objectivity (Moule, Goodman 2009, Gerrish, Lacey 2010). It is for these reasons that positivism is most associated with quantitative research methods and design, the basis and direction for the structure of this study (Parahoo 2006).

Within the sphere of quantitative methodology, three main concepts of research design are most often described: experimental, non-experimental and quasi-experimental (Burns, Grove et al. 2011, Boswell, Cannon 2014). Historically, literature describing health care research methodology and design has promoted experimental designs, namely clinical trials and randomised controlled trials (RCT), as the gold standard of healthcare research (Cormack 2000, Crookes, Davies 2004). When considering an appropriate research design for this study several issues render purely experimental designs implausible; the foremost of these issues is the need for substantiative, supporting evidence to justify the requirement for a randomised controlled trial (Bassett 2001). It has been established through literature review that the incidence of venous ulceration examined within ECSW studies is unsatisfactory to fully inform practitioners of its effectiveness in the treatment of this condition. This lack of underpinning knowledge would be detrimental to the external validity of an experimental design; without systematic review of known outcome measures, the sample size required to generalise the results of a randomised controlled trial could not be calculated (Watson 2008, Dekkers, von Elm et al. 2010). It is therefore appropriate in this situation to consider the structuring of a pilot or feasibility study utilising a non-experimental or quasi-experimental design.

The terms pilot and feasibility are often used interchangeably, are reported poorly and have traditionally received little attention within research methodology

textbooks (Gardner, Gardner et al. 2003). Several studies have sought to better define these terms and the expectations of their purpose.

Feasibility studies appear to be best defined as exploratory pieces of work preceding the design of a main study; outcomes focus upon the estimation of parameters key to the main studies design such as standard deviation of outcomes to calculate the main studies required sample size. Crucially, feasibility studies do not evaluate the outcome of interest, which in this case would be the effectiveness of a clinical intervention (Bowen, Kreuter et al. 2009, Arain, Campbell et al. 2010). Pilot studies are also exploratory in nature and focus upon the evaluation of components of research design prior to the event of a main trial or study (Lancaster, Dodd et al. 2004, Leon, Davis et al. 2011). It is most likely for these reasons that the terms pilot and feasibility are often wrongly interchanged. The pilot study is best described as a smaller scale version of the main study, evaluating how study components such as recruitment or data collection tools perform. An interesting feature of the pilot study is that data evaluating the outcome measure of interest can contribute to the outcomes of the main study, this has been referred to as an internal pilot study. Adversely this same data can be analysed and presented of its own accord independently of the main study, often described as an external pilot (Hertzog 2008, Arain, Campbell et al. 2010).

Research of Non-experimental or Quasi-experimental design is often described as a weaker source of evidence, suffering from greater confounding factors which are detrimental to the internal validity of a study (von Elm, Altman et al. 2007). Bias in participant selection, group allocation and study performance appear to be the foremost reported concerns. These risks are greatly reduced in experimental design through the process of randomisation and control (Maltby 2010, Newell, Burnard 2011).

Yet studies of this type have a place in research design and are credible sources of knowledge indicative of real world, daily practice (Papanikolaou, Christidi et al. 2006). Quasi-experimental studies can allow conclusions to be drawn about the effectiveness of an intervention without the requisite randomisation of participants to control groups; the effect of the independent variable can be observed in a more natural setting (Ellis 2013, Jolley 2013). Various methods of statistical analysis can be employed to combat the problems associated with a lack of randomisation (Newell, Burnard 2011).

One applicable model is a before-after design; a quasi-experimental strategy which can produce reliable data by controlling threats to internal validity (Glass 2008, Polit, Beck 2012). A before-after design can employ a control group or function with the intervention group alone. When a separate control group is not utilised, pre intervention followed by multiple post intervention measurements can increase confidence in study results. It is generally understood that not utilising a control group puts at risk the internal validity of a study.

This prospective pilot study utilises a before-after design without a control group; the multiple observations required should reduce the chance of mistaken conclusions and allow detailed analysis of outcome data and trends (Anderson 2011).

3.2.1 Population and sampling

The target population from which this study's sample is chosen are those affected by chronic venous ulceration; specific inclusion and exclusion criteria are used to further refine this group (Boswell, Cannon 2014). From the target population, the goal within quantitative research is to choose a sample which contains participants

whose characteristics can be said to generalise to the wider target population (Gill 2010); various sampling techniques can aid in this process.

Probability sampling, most often divided into random and cluster sampling techniques, appear to be regarded as the preferred strategies in quantitative research (Crookes, Davies 2004, Matthews, Kostelis 2011). This is primarily due to their ability to consistently produce a highly representative sample; they do however tend to require sizable accessible populations, often only attainable over longer periods of time (Polit, Beck 2013).

Non-probability sampling is widely described in literature as being unable to produce samples from which data can be generalised into the target population (Parahoo 2006). Yet this appears to present a dichotomy, as non-probability strategies are utilised frequently in research design, particularly in exploratory studies where underpinning knowledge or previous research is limited. The consideration of practicality is also of great importance; limitations of time and resource, including financial, are cited as valid reasons to pursue non-probability sampling strategies (Newell, Burnard 2011).

A convenience sample, whereby those selected for inclusion are taken from the easiest, most direct source without any form of subjective input, could have been employed (Burns, Grove et al. 2011). However, homogenous sampling allows the selection of a sample in which very specific characteristics are shared amongst the participants. Though this could be perceived as a limitation to the generalisation of results, it creates a sample of particular interest, best placed to answer the research question in this small, prospective study (Polit, Beck 2013, Crookes, Davies 2004).

The size of the prospective sample should be of an appropriate volume to sufficiently achieve the study aims, normally to demonstrate a difference or

similarity between groups of data (Cormack 2000). As a general rule, larger sample sizes have a higher chance of detecting a difference or similarity between groups of data (Newell, Burnard 2011). This is not to say that sample sizes should always be large, or larger than required; an excessive sample size may be inappropriate, wasteful of resources or be unethical. Interestingly, the estimate of sample size has been described as being at worst, a well educated guess and seems to hinge upon the estimation of size of effect, underpinned by clinical judgement (Whitley, Ball 2002).

The concept of effect size examines the extent of the relationship between two variables, quantifying the strength of the trend to be generalised to the wider population. If the size of the effect is large, it should be easier to detect and thus require a smaller sample size (Watson 2008). Though drawing from small samples, reviewed studies showed good effect size in analysis of results; a similar, moderate to small sample size in this prospective study should be equally capable of demonstrating treatment effect.

3.2.2 Data collection and analysis

It is of the utmost importance that the data collected from the sample answers the research question, achieving the specified objective. The use of existing, validated tools such as surveys and established scoring mechanisms can assist robust collection of data in quantitative studies (Moule, Goodman 2009). The core of data required to fulfil the aims of this study requires the collection of biophysiological data; not involving the taking of materials for laboratory analysis, such as blood or tissue samples, but the systematic measurement of a condition's specific symptoms in situ (Boswell, Cannon 2014).

The types of data collected in quantitative research appears to be most simply described as discrete or continuous (Gerrish, Lacey 2010). This study makes use of both discrete data, wherein numerical data is collected but is only measured in terms of whole numbers and continuous data featuring information of any numerical value within a particular range (Fitzpatrick, Wallace 2006).

The numerical data generated in this, and indeed any, quantitative study falls within the conventional measurement scales of nominal, ordinal, interval or ratio scales (Maltby 2010). Data collected utilising an ordinal scale of measurement is generated via externally validated QOL surveys utilising ranked order responses (Martin, Thompson 2000). Reported pain experience is also quantified using another example of ordinal measurement, visual analogue scores (VAS); making use of a low to high numerical score that does not rely upon an equally spaced measure, such as the measure of length or time which are examples often cited in the discussion of interval or ratio measurement scales (Parahoo 2006, Hjermstad, Fayers et al. 2011).

Within this pilot study ratio measurement scales, specifically the measurement of wound area, will be utilised in the collection of wound measurement data. These measurements differ from interval measurement scales, as a measurement of zero area will indicate the complete absence of a measurable wound (Pedhazur, Schmelkin 2013).

Quantitative data of the type discussed can be analysed at various statistical levels; most commonly, descriptive statistics and inferential statistics are utilised (Riffenburgh 2012). The function of descriptive statistical analysis is to summarise the data collected from the study sample in terms of averages, or central tendency and the reporting of variance, including standard deviation (Watson 2008). These summaries refer only to the study's sample, unlike the use of inferential statistical

analysis, the goal of which is to draw conclusion from the data collected which may be generalised to the wider population (Peat, Barton 2005, Riffenburgh 2012). Specific statistical models are utilised to demonstrate degrees of confidence in the drawn conclusions and statistical significance. Both descriptive and inferential analysis was employed in the examination of study data.

3.2.3 Ethical considerations

In consideration of ethical implications and the research process, many factors must be taken into account to safeguard both participant and researcher. Fidelity, veracity and justice are three closely related ethical principles concerned with the fair treatment and safeguarding of participants (Cormack 2000). Within this study the fair and ethical treatment of all participants was ensured through honesty and transparency, whereby participant's welfare was paramount, though it may be detrimental to the objectives or completion of the study.

The principal of non-maleficence, whereby no intentional harm should come upon participants was diligently observed; had any sign of potential harm or risk of harm occurred during the study it would have been reported accordingly after cessation of treatment (Burns, Grove et al. 2011).

3.3 Study methods and procedures

For the purposes of this pilot study a chronic venous leg ulcer was defined as an open lesion between the knee and ankle joint that has remained unhealed for at least four weeks and has occurred in the presence of clinical signs of venous disease (SIGN 2010). These include: haemosiderosis, lipodermatosclerosis,

oedema, eczema, malleolar flare, atrophie blanche, stigmata of previous venous ulceration, and/or varicose veins (Smith 2006).

Participants may have had more than one ulcer, situated on one or both legs. A single, reference ulcer was selected for treatment; this was the ulcer thought most likely to be the slowest healing. This judgement was based upon its size, duration or appearance. In participants with multiple ulcers, where the reference ulcer only was treated with ECSW, the secondary ulcers were also measured and rate of healing determined for comparison.

3.3.1 Inclusion and exclusion criteria

Table 3 – Inclusion and exclusion criteria

Inclusion criteria
• The presence of leg ulceration assessed to be due to underlying venous insufficiency • The reference ulcer must be in excess of area 1cm^2 • The reference ulcer must have persisted despite at least 6 weeks of treatment with multilayer compression bandaging
Exclusion criteria
• ABI pressures less than 0.8 • Participants with known rheumatoid arthritis or systemic vasculitis • Participants with diabetes • Suspicion of malignancy or known malignancy within the ulcer • Acute Deep vein thrombosis • Age less than 18 years • Life expectancy of less than 1 year • Allergy to compression bandaging materials • Participants unable to tolerate multilayer compression therapy • The participant is unable to speak/understand English • Inability to give informed consent

3.3.2 Recruitment

In the recruitment of a sample, a homogenous sampling strategy utilising strict inclusion and exclusion criteria (Table 3) was been used to select participants from the available population. This consisted of participants recruited from hospital wards, out-patient and community clinics.

This study sought to compare reported ulcer healing rates in participants who have undergone standard compression therapy, with the healing rate data collected from participants undergoing ECSW combined with standard therapy. Therefore in the consideration of sample size, estimating size of effect should also draw upon the outcomes of systematically reviewed literature pertaining to compression therapy for venous ulceration.

The largest systematic review of this kind was published by The Cochrane Collaboration (Cullum, Nelson et al. 2002) and was most recently updated in 2013. Of the forty-eight RCTs included, 40% had sample sizes of 50 or fewer participants, 67% recruited 100 or less participants. From within the review, eight RCTs specifically question the effectiveness of compression therapy in the healing of venous ulcers; these studies most closely resemble the aim of this before-after study. Sample sizes vary, with a median average of 51 participants (SD=79), relatively small but justified due to the large size of effect reported. It was therefore estimated that a sample size of 40 participants was reasonable for this non randomised study.

Participants were screened for eligibility and potential participants assessed to be eligible were issued with the participant information sheet and the study explained in detail. Following this, participants were given time (a minimum of 24 hours) to reflect and discuss with family and friends before being asked to sign the study consent form. Permission was obtained to inform the participant's GP by letter of

their involvement in the study. Once recruited, participants were free to withdraw should they have wished at any stage. On entry into the study participants were given a unique identification number, used throughout the study. Example participant documentation from this recruitment stage can be found under appendix D.

3.3.3 Collection of study data

Participants were asked to attend an initial, pre-treatment research clinic appointment. A concise medical history was taken, assessing comorbidities, current medication, allergies and mobility. Body Mass Index (BMI) was calculated and recorded in order to categorise participants weight; the most commonly accepted ranges were utilised whereby a BMI of <18.5 is considered underweight, 18.5 to 25 normal weight, 25 to 30 overweight and >30 considered obese (World Health Organization 2006).

A specific history of the current episode of ulceration including duration, number of previous episodes and previous clinical treatments was also taken. Ulcer aetiology was confirmed by ABI and by analysis of duplex ultrasound imaging. Participants were also screened for the presence of varicose veins; if present CEAP classification and the venous clinical severity score was used to assess (Rutherford, Padberg Jr et al. 2000, Eklöf, Rutherford et al. 2004).

Ulcer assessment began by recording the number of ulcers present and their position drawn on a leg diagram. The reference ulcer was clearly identified and all ulcers assigned a number. Concise ratio scale measurements, relating to each ulcer, were collected in several ways including serial measurement of the surface area of each ulcer, used as an index of healing and performed by tracing the

margins at each clinic appointment. Traditionally performed manually, utilising tracing paper and pen this method of wound area measurement can be inaccurate, invasive and difficult to reproduce. Within this study, wound margin tracings were made utilising three dimensional (3D) digital imaging software, a system which has been shown to produce extremely accurate, repeatable wound measurements which include both wound area and volume (Bowling, King et al. 2009, Savage, Jeffery 2013).

Ordinal scale measurement, in the form of visual analogue scores (VAS) were used to collect data pertaining to participants experience of pain in relation to their ulceration. Wound exudates were recorded using a low, medium, high scale. All baseline data was recorded on a customised data collection form (Appendix E).

QOL was assessed by collecting data from each participant through the completion of the disease specific, Charing Cross Venous Ulcer Questionnaire (CXVUQ) and generic QOL of life SF-36 and EQ-5D questionnaires, all of which are recognised, externally validated data collection tools based upon ordinal measurement scales (Ware Jr, Gandek 1998, Smith, Guest et al. 2000). These questionnaires were completed by participants at every research clinic appointment.

The CXVUQ consists of 20 disease specific questions scored on a 1 to 5 point Likert scale; lower scores indicate better QOL of life (Wong, Lee et al. 2006). In 2007 an error in the CXVUQ scoring system was reported whereby questions 3 and 7 of the original publication had been incorrectly scaled (Jull, Parag 2007). In this study all CXVUQ data was corrected for this error. As a disease specific questionnaire, less literature is available describing the CXVUQ than for generic QOL measurement tools. There appears to be scant if any information available regarding Minimally Important Differences (MID) for CXVUQ scores. Most studies seem therefore to focus upon statistical rather than clinical significance in

discussion of changes in score (González-Consuegra, Verdú 2011, Jull, Parag et al. 2010)

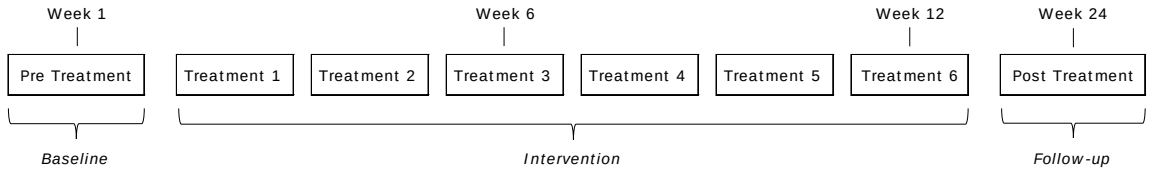
SF-36 QOL questionnaire responses are scored over 8 domains; these domains combine to give additional physical and mental component scores. All scores operate on a scale of 0 to 100, with higher scores indicating greater QOL (Patel, Donegan et al. 2007). Many studies have discussed the MID required to constitute a significant clinical change in SF-36 composite scores, with estimates ranging from a change of 5 to 10 points; much unresolved debate appears to exist regarding variability of SF-36 MID dependent upon the condition being studied (Walters, Brazier 2003, Bjorner, Wallenstein et al. 2007).

The EQ-5D questionnaire is somewhat different; a simple tool consisting of 5 questions plus a visual analogue score defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. An index score ranging from 0.0 to 1.0 is generated from responses, higher index values indicate greater QOL (Rabin, Charro 2001). Based upon the UK data set, the MID required to constitute a clinically significant change in EQ-5D score has been reported as between 0.08 and 0.10; it is important to note that EQ-5D MID outcomes were primarily drawn from studies examining conditions other than venous ulceration (Walters, Brazier 2005, Pickard, Neary et al. 2007).

The data collected at the baseline assessment was treated as the pre-intervention data collection point in the before-after study design. Post baseline assessment, each participant received an initial course of ECSW treatments. These treatments were structured as three sessions delivered at fortnightly intervals. If the ulcer area or volume reduced after the third initial treatment session but had not achieved complete healing, a further course of three treatment sessions were administered over the same time structure. Treatment ceased at three months,

after the maximum of six treatment sessions; participants were then followed up to 6 months and if their ulcer had not healed at that time they continued to receive routine NHS care and treatment. Treatment also ceased if, after three initial treatments the index ulcer was observed to deteriorate in relation to the primary outcome (increase of ulcer size/volume). Data was collected at each treatment session precisely mirroring the methods of measurement utilised at baseline data collection, this created a series of data to be viewed as the intervention stage of the before-after design (Figure 3).

Figure 2 – Before-after design



If the ulcer healed during the treatment or follow up period, a digital photograph of the index ulcer was taken, this image was then analysed by two blinded assessors. If all of the assessors agreed that the ulcer had healed, then the participant was treated as a healed ulcer and followed up as planned. If the ulcer reoccurred, the participant was asked to contact the research team. If any assessor felt that the ulcer was yet to heal, but that healing would probably occur in the next few weeks; weekly photographs were taken until a consensus was reached that the ulcer had healed.

Clinical data was entered into a study database; range and consistency checks were incorporated into the database and an audit of a random 5% of entries performed to assess errors. If a greater than 5% error rate was obtained then all entries were rechecked. Data collected during the course of the research was kept

strictly confidential and accessed only by members of the study team. Participant's personal details were stored on paper format only.

3.3.4 Intervention, wound care and compression

Participants received ECSW routinely every two weeks in an outpatient clinic setting to the reference ulcer only, under no aesthesia. Ultrasound gel was applied directly to the wound bed and the shock wave applicator to aid conduction of shock wave pulses; the ulcerated area was covered with a sterile cellulose barrier. Electrohydraulic shock waves were generated by an MTS Dermagold 100 and applied evenly to the ulcer surface. Each shock wave impulse delivered 0.10mJ/mm^2 energy flux density at a frequency of 5Hz. Quantity of impulses to be delivered were calculated thus: wound area x20 + minimum application of 350 pulses = total shockwave pulses.

A standard wound care regime was maintained throughout treatment and at home between sessions, including wound cleansing with sterile normal saline solution. The wound dressing consisted of a non-adherent mesh dressing, a hydrofibre agent and an absorbent layer; dressings were changed at a minimum period of weekly. Multilayer compression bandaging, already utilised pre study enrolment, continued after assessment of ankle brachial pressures, in accordance with national guidelines (SIGN 2010). The presence of clinical features of infection resulted in clinical review and antibiotic treatment if required. As per current national guidelines all participants received multilayer compression therapy, with the aim of applying 35-40mmHg pressure at the ankle.

3.3.5 Mode of data analysis

All study data was entered into the statistical package software, SPSS version 22 for analysis. Nominal and ordinal data values were given specific labels to help identify variables in the analysis process. The process of cleaning the dataset was performed in order to identify missing data and potential errors. Consistency checks were performed on the completed dataset and an audit of a random 5% of entries performed to assess errors. If a greater than 5% error rate had been found then all entries would have been rechecked.

Missing value analysis was performed to identify number and location of missing values for each variable. The pattern of missing values was also assessed to identify specific areas of incomplete data entry.

The discrete and continuous data generated in this study has been analysed using both descriptive and inferential statistical methods (Maltby 2010). Descriptive statistics were utilised to summarise all of the sample specific data, illustrating trends in terms of central tendency, averages and variance.

The distribution of continuous data was examined using the Shapiro-Wilk test of normality (Petrie, Sabin 2013). The dataset was mainly found to be not normally distributed ($p<0.001$), except for QOL data which fell within normal distribution ($p>0.05$).

Statistical tests of probability were utilised to infer generalisations to the wider population from the sample data. For data not normally distributed these included non-parametric tests such as the Wilcoxon signed ranks test and Friedman test. For normally distributed data, parametric versions of these tests were utilised including repeat measures ANOVA and paired samples t-test. The use of these statistical tests allowed analysis of baseline to follow up and between measures data (Hampton, Havel 2006, Petrie, Sabin 2013).

Other statistical tests utilised included Kaplan-Meir survival curves examining time to healing data and McNemar-Bowkers test, used to examine differences in variance of certain categorical data. Fisher's exact test was used to examine the relationship between baseline characteristics and wound healing outcomes (Anthony 1999, McKillup 2011).

3.3.6 Missing data

44 missing values were identified throughout the dataset, accounting for only 2.7% of data content. Pattern analysis showed a small amount of random missing data. Given the small size of the study sample, much consideration was given to the treatment of missing data. The simplest approach would have been to omit cases containing missing data, often referred to as listwise deletion or complete case analysis (Munro 2005). The impact this would have had upon an already small sample size would have been detrimental to analysis and appears an excessive solution given the overall small quantity of missing values.

Multiple imputation analysis was considered and certainly has some attractive qualities in terms of producing viable missing data substitutions. However, it is a more complicated method which can impact or restrict further statistical analysis of the resultant dataset (Schafer, Olsen 1998, Wayman 2003). Given the small quantity of missing values, this method was rejected in favour of stochastic regression imputation. This form of imputation utilises existing variables to predict the missing value whilst maintaining a degree of random error to each imputed value (Baraldi, Enders 2010). Consistency checks were repeated to ensure the validity of imputed data values.

3.3.7 Ethics and safety

Ethical approval was sought from the local National Research Ethics Service (NRES) and upon first submission, was declined. The NRES committee cited concerns regarding the robustness of the study design and a potential conflict of interest where the researcher was involved in the delivery of treatment. After review and revision, application was resubmitted and a favourable ethical opinion was given by the committee; further ethical approval was then granted from The Robert Gordon University and the local NHS Research and Development department. Documentation relating to ethical approval can be found under appendix F.

With regards consent and confidentiality, the purpose of the research, its format and an explanation of the treatment was discussed with potential participants at an initial research clinic appointment. Written information (Appendix D) was also given and participants received ample time (a minimum of 24 hours) to reflect before signing a written consent form (Appendix D). In gaining written consent the following conditions had to be satisfied. The person giving consent had to be deemed capable of doing so, the participant must have receive appropriate and adequate information, there is freedom of choice, the person giving consent should be aware that consent is an ongoing process and is able to withdraw consent (Bassett 2001).

Data collected during the course of the research was kept strictly confidential and accessed only by members of the study team. Participant's personal details were stored on paper format only and were not entered onto the study database. Participants were allocated an individual specific study number and this alone was used to identify their data. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose

for which it has been acquired. Essential data shall be retained for a period of at least 10 years following close of study.

Annual progress reports, safety reports and a final report at the conclusion of the study have been submitted to the Research Ethics Committee within the timelines defined in the regulations.

3.3.8 Safety

The study was subject to monitoring by the local NHS Research and Development department to ensure that it was being conducted as per protocol, adhering to Research Governance, Good Clinical Practice (GCP) and appropriate legislation. Monitoring feedback and correspondence can be found under appendix G.

It was planned to record all adverse events via research follow-up visits at 6 weeks, 3 months, and 6 months and at all ECSW treatment sessions.

Adverse events were assessed in respect of severity, relationship to study treatment, whether expected or unexpected, duration and whether constituting a Serious Adverse Event (SAE). Non-serious events that are not pre-defined study outcomes were recorded. The following adverse events were expected:

- Discomfort
- Minor bleeding
- Wound infection

CHAPTER 4 - FINDINGS

4.1 Participant characteristics

34 participants were screened for suitability; 28 met inclusion criteria and entered the study, 6 were excluded; this is illustrated in the CONSORT diagram (Figure 4). Demographics and baseline ulcer characteristics are summarised in table 4 and 5. The cohort consisted of 14 men and 14 women with a median age of 69 years (IQR=33). Median baseline ulcer area was 22.89cm^2 (IQR=36.49), with a chronic duration of greater than six months in all but one participant.

Figure 3 – CONSORT diagram

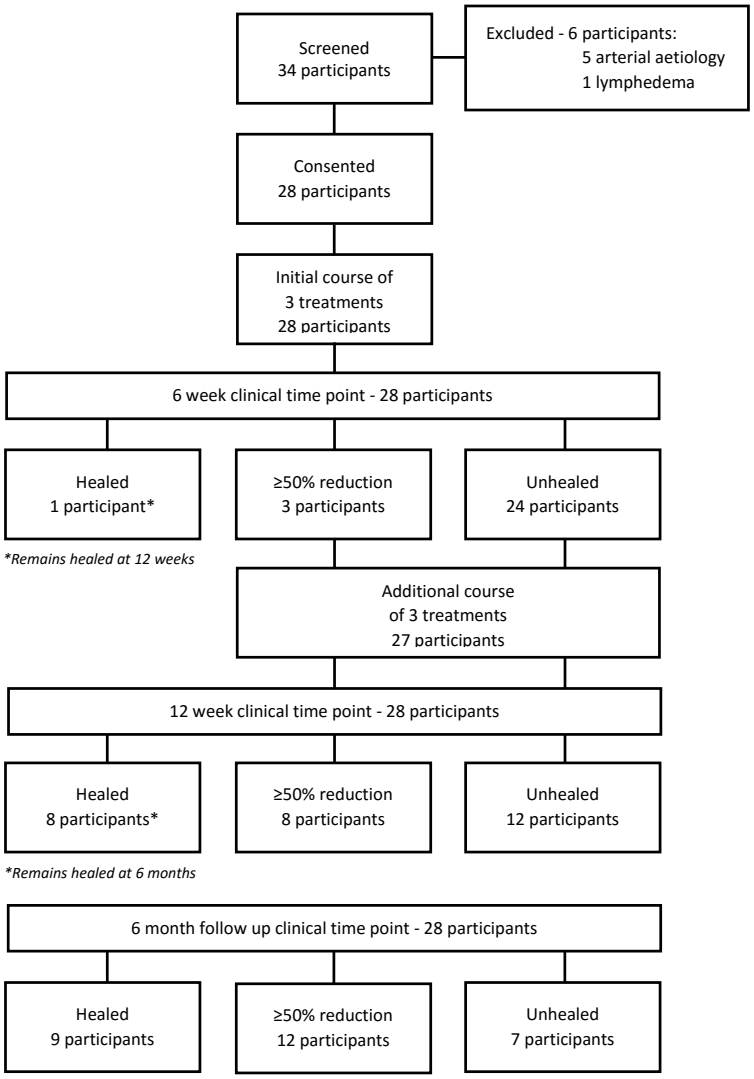


Table 4 - Participant demographics

Characteristic	N	(%)
Sex		
Male	14	(50)
Female	14	(50)
Age		
18-30 years	0	(0)
31-50 years	7	(25)
51-65 years	4	(14)
Over 65 years	17	(61)
Comorbidities		
Ischemic heart disease	6	(21)
Hypertension	7	(25)
COPD	4	(14)
Chronic Kidney Disease	4	(14)
Previous IV drug misuse	6	(21)
Patients with multiple comorbidities	9	(31)
Body Mass Index		
Underweight	2	(7)
Optimal	5	(18)
Overweight	7	(25)
Obese	14	(50)
Mobility		
Fully mobile	15	(54)
Requires assistance to mobilise	8	(28)
Immobile	5	(18)
Venous history		
Previous venous surgery	2	(7)
Previous deep vein thrombosis	9	(31)

Table 5 - Baseline ulcer characteristics

Characteristic	N	(%)
Index ulcer - surface area		
Area < 5cm^2	4	(14)
Area 5-20cm^2	8	(28)
Area 21-50cm^2	12	(44)
Area > 50cm^2	4	(14)
Affected limb		
Bilateral	3	(11)
Left leg only	12	(43)
Right leg only	13	(46)
Current ulcer episode duration		
< 6 months	1	(3)
6-20 months	19	(69)
21-50 months	7	(25)
> 50 months	1	(3)
Ulcer history		
One occurrence (current)	22	(79)
Recurrent episodes	6	(21)

4.2 Wound healing

At 6 month follow up 9 participants index wounds had healed; a further 12 wounds had a reduction in surface area of ≥50%. 5 participant's wounds achieved ≤50% area reduction; the surface area of 2 wounds remained unchanged from baseline. None of the studied wounds deteriorated.

The median wound area for the cohort reduced from 22.89cm^2 (IQR=36.49) at baseline to 6.50cm^2 (IQR=19.26) at 6 month follow up, a statistically significant 72% reduction ($p<0.001$), illustrated in figure 4.

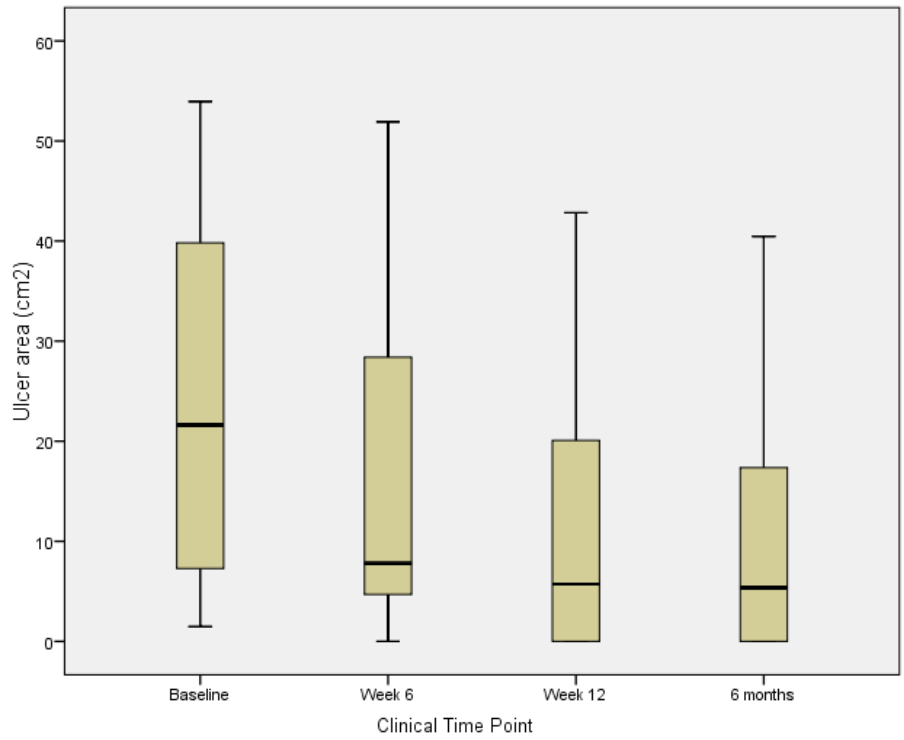
Analysis of the median wound area between each clinical time point and for each wound healing outcome (table 6), shows a statistically significant reduction between measurements for those who healed their wound ($p<0.001$) and for those achieving ≥50% reduction of surface area ($p=0.004$).

Table 6 - Wound healing measurement results

Outcome	Median area (cm^2) (IQR) at each clinical time point				Friedman test *p* value
	Baseline	6 weeks	12 weeks	6 months	
Healed	22.96 (39.44)	6.00 (4.75)	0	0	<0.001
Reduced by ≥50%	9.99 (24.93)	8.82 (20.31)	10.99 (13.74)	6.50 (10.72)	0.004
Reduced by ≤50%	41.94 (36.33)	35.20 (26.60)	34.36 (24.90)	33.06 (38.74)	0.692
Total cohort	22.89 (36.45)	8.45 (28.78)	8.31 (23.88)	6.50 (19.26)	<0.001

Outcome	Median area (cm^2) (IQR) at each clinical time point		Wilcoxon test *p* value
	Baseline	6 months	
Total cohort	22.89 (36.45)	6.50 (19.26)	<0.001

Figure 4 – Ulcer area at each clinical time point



In participants who healed their ulcer, the median time to complete wound healing was 8 weeks (IQR=5) which involved 4 ECSW treatments. The median rate of healing was 1.91cm^2 (IQR=2.77) per week.

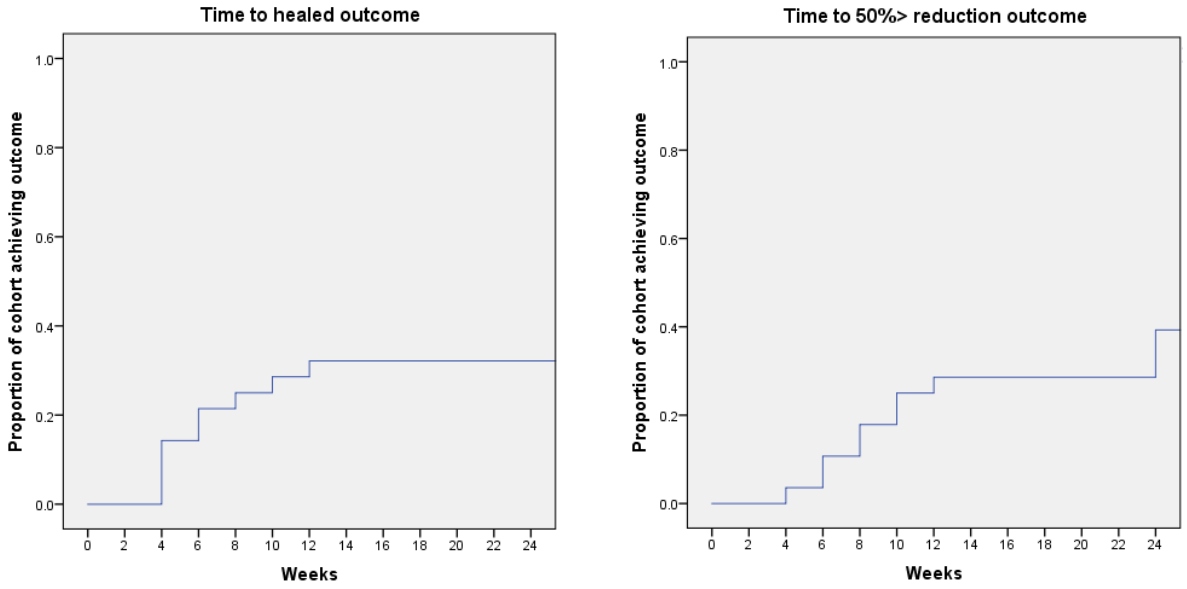
Wounds which achieved a ≥50% reduction of surface area did so in a median of 10 weeks (IQR=17.5) which involved 5 ECSW treatments. The median rate of healing was 0.45cm^2 (IQR=1.10) per week.

Of the three participants with multiple ulcers, the index ulcer was unhealed at 6 months. The rate of healing of the index ulcers treated with ECSW was median 0.43cm^2 (IQR=NA) per week; for secondary ulcers not treated with ECSW the median rate of healing was 0.09cm^2 (IQR=NA) per week.

The proportion of the cohort achieving healed or ≥50% reduction of surface area outcomes at each clinical time point, as well as those remaining at risk, is illustrated by Kaplan Meir Survival Curves in figure 5.

Wound healing outcome examples are illustrated in figures 6 and 7.

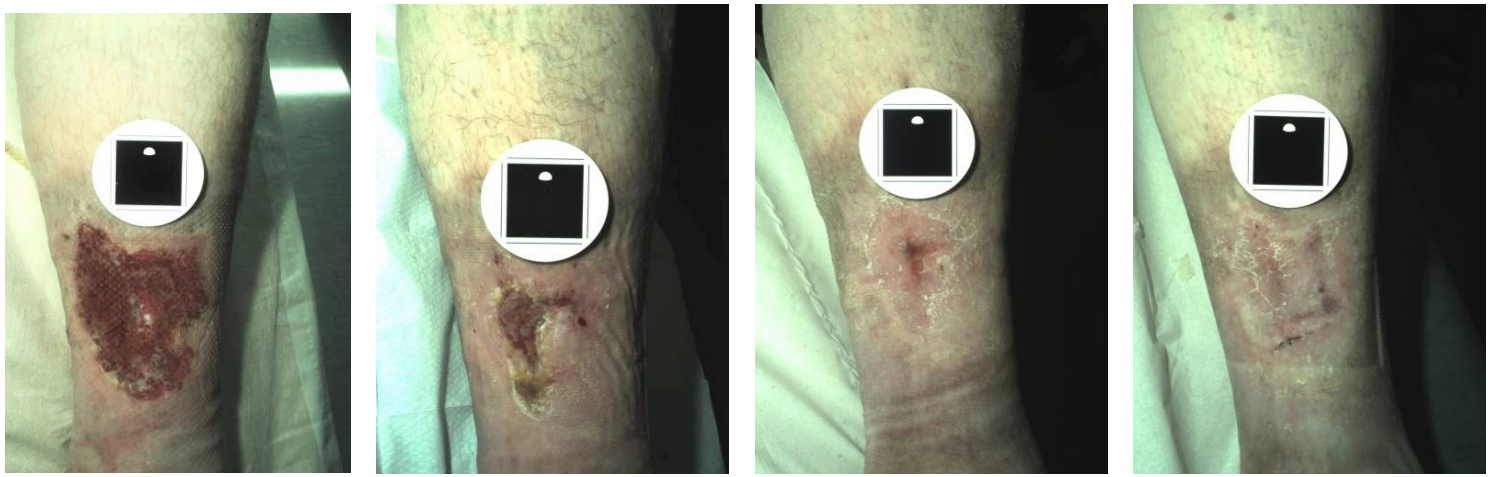
Figure 5 – Kaplan Meir Survival Curve



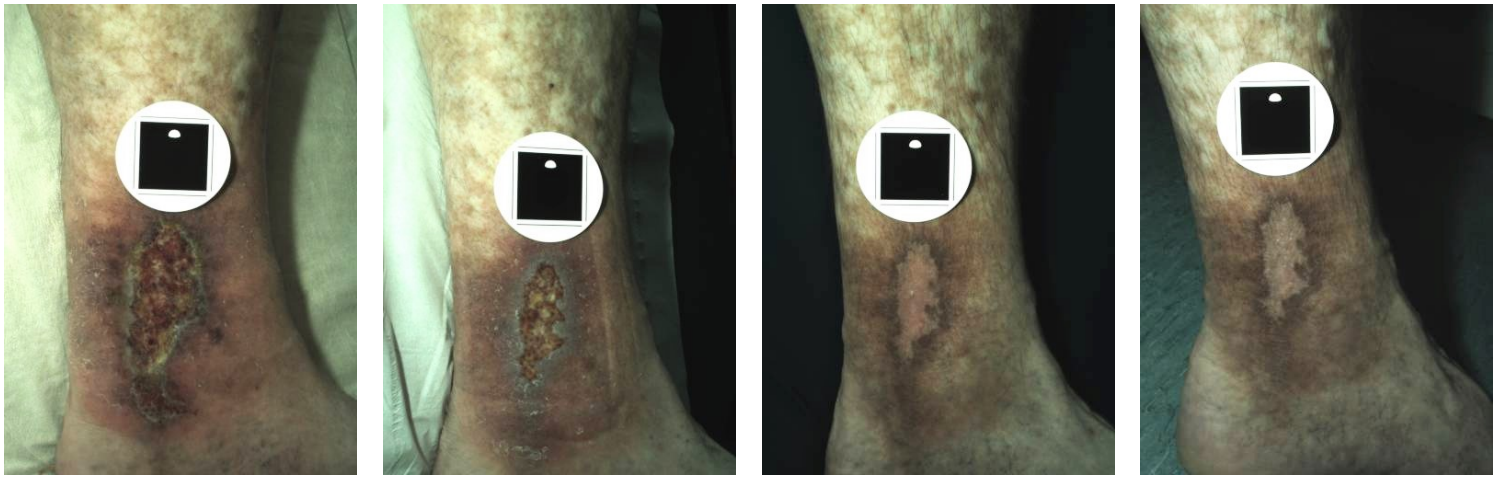
Remainder at risk at each clinical time point

Outcome	Clinical Time Point (weeks						
	2	**4**	**6**	**8**	**10**	**12**	**24**
Healed (n=9)	28	24	22	21	20	19	19
≥50% reduction (n = 12)	28	27	25	23	21	20	16

Figure 6 – Wound healing examples – Participants achieving wound closure

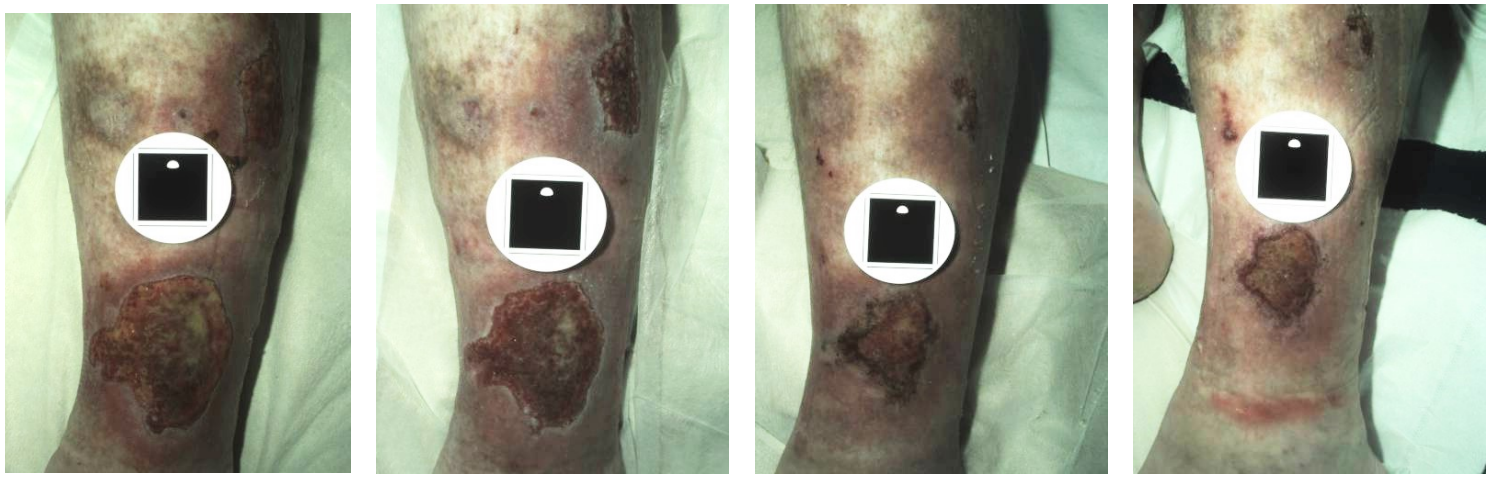


Participant A: Baseline | 6 weeks | 12 weeks | 6 months

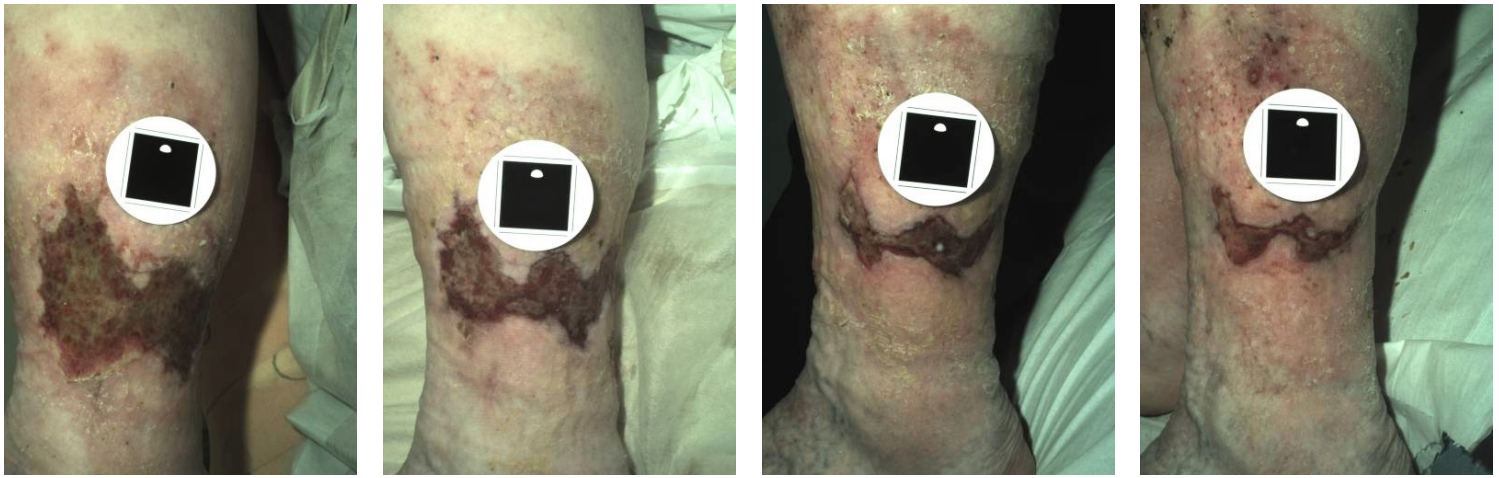


Participant B: Baseline | 6 weeks | 12 weeks | 6 months

Figure 7 – Wound healing examples - ≥50% wound area reduction



Participant C: Baseline | 6 weeks | 12 weeks | 6 months



Participant D: Baseline | 6 weeks | 12 weeks | 6 months

4.2.1 Baseline characteristics and wound healing outcome

Baseline characteristics for each outcome measure are summarised in table 9.

There was a tendency for median baseline ulcer area to be smaller in the healed group than in those achieving ≤50% area reduction ($p>0.05$). This is also true of the group achieving ≥50% reduction when compared to those achieving ≤50% area reduction ($p>0.05$). However, the relationship is unclear; those achieving ≥50% reduction failed to completely heal despite having a smaller baseline ulcer area than the healed group. Similarly, baseline ulcer duration appeared shorter for the healed group than for those achieving ≤50% area reduction ($p>0.05$). This differs in the ≥50% reduction group which had a shorter baseline duration than the healed group, but failed to completely heal.

Comparison of baseline median BMI shows those who healed their wound were closer to a healthy weight (BMI 18.5 to 25), whilst those in the ≥50% and ≤50% reduction group tended to be overweight (BMI 25 to 30) or obese (BMI >30) ($p>0.05$).

Table 7 - Baseline characteristics and wound healing outcome

Characteristic	Healed N=9	≥50% reduction N=12	≤50% reduction N=7
Male (N) (%)	6 (67)	4 (33)	4 (57)
Female (N) (%)	3 (33)	8 (67)	3 (43)
Median Age (years) (IQR)	68 (26)	72 (36)	71 (39)
Body Mass Index (BMI) (IQR)	25.90 (10.6)	30.00 (6.4)	30.00 (4.4)
Baseline Ulcer Area (cm^2) (IQR)	22.96 (39.44)	9.99 (24.93)	41.94 (36.33)
Current Ulcer Duration (months) (IQR)	14 (28)	9 (11)	18 (17)
Duration of Compression Use (months) (IQR)	8 (11)	7 (6)	8 (5)
Previous Deep Vein Thrombosis (N) (%)	2 (22)	4 (33)	3 (43)
Ischaemic Heart Disease (N) (%)	1 (11)	2 (17)	3 (43)
History of Intravenous Drug Misuse (N) (%)	1 (11)	4 (33)	1 (14)
Mobility			
Fully mobile (N) (%)	5 (55)	7 (58)	3 (43)
Requires assistance to mobilise (N) (%)	3 (33)	3 (25)	2 (28)
Immobile (N) (%)	1 (11)	2 (17)	2 (28)

4.2.2 Shock wave energy

All wounds received 0.10mJ per mm^2. The median shock wave energy delivered at each treatment is summarised in table 10. Healed wounds received total median energy of 211.50mJ (IQR=124.40), wounds achieving a ≥50% area reduction received 302.45mJ (IQR=236.90), wounds in the ≤50% area reduction group received 538.10mJ (IQR=733.80).

Though no statistical difference was shown between the total median shock wave energy delivered to participants in any of the three outcome groups (p=0.411), there was a trend for higher energy values to be delivered to the ≤50% area reduction group compared to the healed and ≥50% reduction groups.

Table 8 - Median total energy delivered at each treatment

Treatment	Median Energy (mJ) (IQR)			
	Healed	≥50% reduction	≤50% reduction	Total Cohort
1	80.90 (79.00)	55.00 (50.00)	118.90 (73.00)	80.75 (73.00)
2	52.30 (21.00)	52.50 (55.00)	114.10 (39.00)	60.75 (56.00)
3	47.00 (10.00)	52.65 (41.00)	104.00 (152.00)	49.00 (55.00)
4	37.00 (44.00)	48.00 (12.00)	102.70 (155.00)	44.60 (52.00)
5	0	43.70 (68.00)	101.80 (156.00)	33.62 (68.00)
6	0	45.50 (65.00)	89.03 (148.00)	32.77 (55.00)
Total Energy	221.50 (124.40)	302.45 (236.90)	538.10 (733.80)	275.85 (254.60)

4.3 Pain

Pain scores (VAS) reduced for 27 of the 28 participants. The median pain score for the cohort reduced from 6 (IQR=3) at baseline to 2 (IQR=4) at 6 month follow up, a statistically significant reduction (p<0.001).

Analysis of median pain score between each clinical time point and for each wound healing outcome (table 11), shows a statistically significant reduction between measurements for those who healed their wound ($p<0.001$), for those achieving ≥50% reduction of surface area ($p<0.001$) and for those achieving ≤50% area reduction ($p=0.006$).

Table 9 - Median pain score

Outcome	Median pain score (VAS) (IQR) at each clinical time point				Friedman test *p* value
	Baseline	6 weeks	12 weeks	6 months	
Healed	4 (3)	2 (3)	0	0	<0.001
Reduced by ≥50%	5 (2)	3 (4)	2 (1)	2 (3)	<0.001
Reduced by ≤50%	8 (3)	5 (1)	5 (1)	5 (2)	0.006
Total cohort	6 (3)	3 (3)	2 (4)	2 (4)	<0.001
Outcome	**Median pain score (VAS) (IQR) at each clinical time point**				**Wilcoxon test *p* value**
	Baseline		**6 months**		
Total cohort	6 (3)		2 (4)		<0.001

4.4 Exudate

At 6 month follow up the number of participants with an exudate level recorded as 'high' at baseline reduced from 9 to 1 and those recorded as 'medium' reduced from 18 to 5. Analysis of the equality of frequencies between baseline and 6 month follow up (table 12), shows the reduction of exudate levels to be statistically significant ($p<0.001$). First reduction of exudate occurred at median 6 weeks (IQR=4), after 3 ECSW treatments.

Observation of exudate levels at each clinical time point (table 13) shows a tendency for poorer outcomes to be associated with higher baseline exudate levels ($p>0.05$).

Table 10 - Variance of exudate levels at baseline and 6 months

Baseline exudate	Exudate at 6 month follow up				
	None	Low	Medium	High	Total
None	0	0	0	0	0
Low	1	0	0	0	1
Medium	7	8	3	0	18
High	0	6	2	1	9
Total	8	14	5	1	28

Table 11 - Exudate levels at each clinical time point

Outcome	Exudate levels at each clinical time point											
	Baseline			6 weeks			12 weeks			6 months		
	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
Healed	1	8	0	5	3	0	1	0	0	1	0	0
Reduced by ≥50%	0	9	3	4	8	0	10	2	0	10	2	0
Reduced by ≤50%	0	1	6	1	3	3	3	3	1	3	3	1
Total cohort	1	18	9	10	14	3	14	5	1	14	5	1

4.5 Quality of life

4.5.1 SF-36 physical and mental component scores

SF-36 physical component scores (table 14) improved for 22 of the 28 participants. For the total cohort, improvement with statistical significance was shown from baseline to 6 month follow up ($p<0.001$) and between each clinical time point ($p<0.001$).

There was a tendency for SF-36 physical component scores to be higher, indicating better QOL, at 12 weeks and 6 months in those participants who healed their ulcer. Scores improved with statistical significance between clinical time points for those who healed their wound ($p=0.014$) and for those achieving >50% area reduction ($p=0.044$).

SF-36 mental component scores (table 15) improved for 21 of the 28 participants. For the total cohort, improvement with statistical significance was shown from baseline to 6 month follow up (p=0.003) and between each clinical time point (p=0.004). However, when individual wound healing outcomes were analysed, no statistical significance was shown between clinical time points for those who healed their wound (p=0.127), those achieving >50% area reduction (p=0.069) or for those achieving ≤50% area reduction (p=0.232).

Comparison of mean SF-36 physical and mental component scores at each clinical time point is illustrated in table 16.

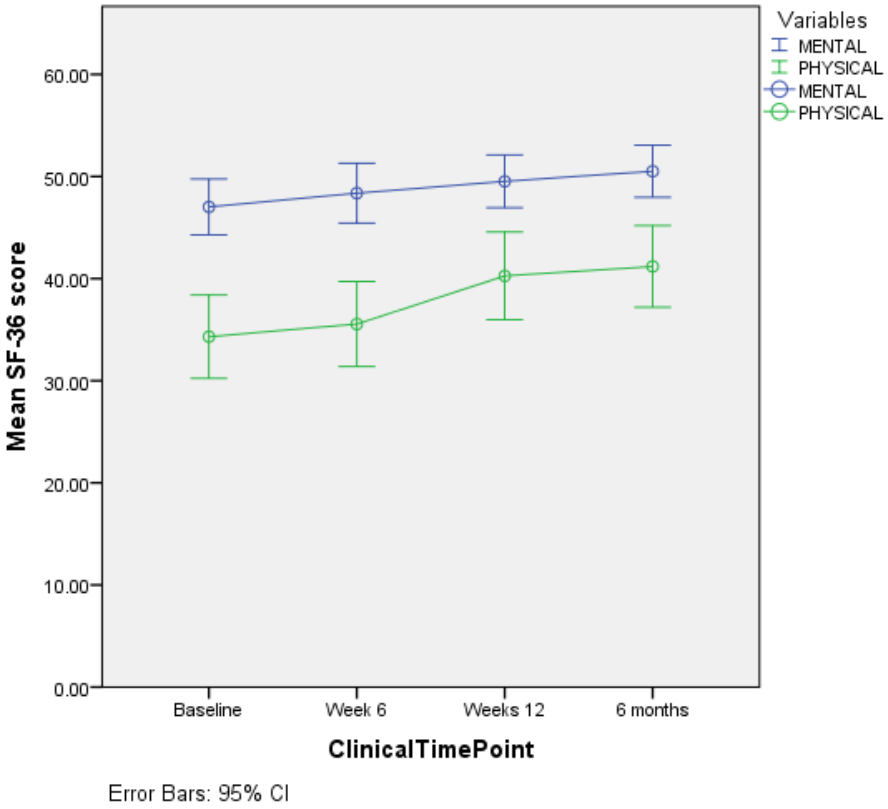
Table 12 - SF-36 physical component scores

Outcome	Clinical time point				Repeat measures ANOVA *p* value
	Baseline (SD)	6 weeks (SD)	12 weeks (SD)	6 months (SD)	
Healed	36.19 (10.79)	39.48 (10.71)	45.68 (11.33)	46.22 (9.70)	0.014
Reduced by ≥50%	35.40 (10.62)	35.33 (11.22)	39.00 (12.13)	39.51 (12.34)	0.044
Reduced by ≤50%	30.02 (10.27)	30.85 (9.21)	35.46 (6.09)	37.60 (4.06)	0.077
Total cohort	34.31 (10.50)	35.55 (10.73)	40.26 (11.07)	41.19 (10.32)	<0.001
Outcome	Clinical time point				Paired t-test *p* value
	Baseline (SD)		6 months (SD)		
Total cohort	34.31 (10.50)		41.19 (10.32)		<0.001

Table 13 - SF-36 mental component scores

Outcome	Clinical time point				Repeat measures ANOVA *p* value
	Baseline (SD)	6 weeks (SD)	12 weeks (SD)	6 months (SD)	
Healed	51.11 (6.91)	51.09 (5.69)	53.53 (4.43)	54.44 (4.50)	0.127
Reduced by ≥50%	44.51 (6.62)	47.82 (8.59)	48.06 (7.32)	48.42 (7.64)	0.069
Reduced by ≤50%	46.03 (6.36)	45.77 (7.60)	46.86 (6.22)	49.03 (5.23)	0.232
Total cohort	47.01 (7.04)	48.36 (7.54)	49.52 (6.66)	50.51 (6.59)	0.004
Outcome	Clinical time point				Paired t-test *p* value
	Baseline (SD)		6 months (SD)		
Total cohort	47.01 (7.04)		50.51 (6.59)		0.003

Figure 8 – Comparison of mean SF-36 component scores



4.5.2 EQ-5D index scores

EQ-5D index scores (table 17) improved for 27 out of 28 participants. For the total cohort, improvement with statistical significance was shown from baseline to 6 month follow up ($p<0.001$) and between each clinical time point ($p<0.001$).

The EQ-5D score was higher, indicating greater QOL, at 12 weeks and 6 months in participants who healed their wound. EQ-5D scores improved with statistical significance between clinical time points for those who healed their wound ($p=0.002$) and for those achieving >50% area reduction ($p=0.025$).

Table 14 - EQ-5D index scores

Outcome	Clinical time point				Repeat measures ANOVA *p* value
	Baseline (SD)	6 weeks (SD)	12 weeks (SD)	6 months (SD)	
Healed	0.77 (0.10)	0.78 (0.98)	0.91 (0.11)	0.91 (0.11)	0.002
Reduced by ≥50%	0.70 (0.56)	0.70 (0.56)	0.77 (0.10)	0.77 (0.12)	0.025
Reduced by ≤50%	0.68 (0.62)	0.68 (0.77)	0.72 (0.65)	0.76 (0.79)	0.058
Total cohort	0.71 (0.81)	0.72 (0.86)	0.80 (0.12)	0.81 (0.12)	<0.001
Outcome	**Clinical time point**				**Paired t-test *p* value**
	Baseline (SD)		**6 months (SD)**		
Total cohort	0.71 (0.81)		0.81 (0.12)		<0.001

4.5.3 CXVUQ scores

Disease specific, CXVUQ scores (table 18) improved for 21 of the 28 participants. For the total cohort, improvement with statistical significance was shown from baseline to 6 month follow up ($p<0.001$) and between each clinical time point ($p<0.001$).

The greatest improvement at 12 weeks and 6 months is seen in participants who healed their wound. CXVUQ scores improved with statistical significance between clinical time points for those who healed their wound ($p<0.001$), those achieving ≥50% area reduction ($p=0.035$) and for those achieving ≤50% area reduction ($p=0.024$).

Table 15 - CXVUQ scores

Outcome	Clinical time point				Repeat measures ANOVA *p* value
	Baseline (SD)	6 weeks (SD)	12 weeks (SD)	6 months (SD)	
Healed	62.67 (12.13)	58.33 (14.53)	29.56 (17.26)	29.00 (15.10)	<0.001
Reduced by ≥50%	65.42 (6.86)	67.67 (7.56)	61.93 (8.25)	62.08 (10.44)	0.035
Reduced by ≤50%	76.71 (13.72)	76.57 (12.20)	69.56 (6.87)	59.68 (6.03)	0.024
Total cohort	67.36 (11.67)	66.89 (12.96)	53.43 (10.39)	50.85 (18.85)	<0.001
Outcome	**Clinical time point**				**Paired t-test *p* value**
	Baseline (SD)		**6 months (SD)**		
Total cohort	67.36 (11.67)		50.85 (18.85)		<0.001

4.6 Summary of key results

At 6 months: 9 wounds had healed, 12 had a ≥50% reduction in surface area and 7 had a less than <50% reduction. For the cohort, the rate of healing = 1.91cm^2 (IQR=2.77) per week. Median time to complete wound healing outcome was 8 weeks. Median time to ≥50% reduction outcome was 10 weeks.

Baseline ulcer area tended to be smaller and the ulcers were of shorter duration in the healed group compared to those achieving ≤50% area reduction. Higher baseline BMI appears to be associated with poorer outcomes. Higher levels of exudate at baseline also appears to correlate with poorer outcomes.

Pain scores significantly reduced for 27 participants (96%); significant reduction was apparent at a median 4 weeks. Exudate levels also significantly reduced for 27 participants; significant reduction was apparent at median 6 weeks.

SF-36 physical and mental component scores as well as EQ-5D index scores showed significantly improved QOL for total cohort. Greatest improvement occurred in those that healed. Disease specific CXVUQ scores showed significantly improved QOL for the total cohort and between clinical time points regardless of clinical outcome.

CHAPTER 5 - DISCUSSION

5.1 Introduction

The primary aim of this study was to assess the clinical effectiveness of ECSW in terms of ulcer healing when used in combination with multilayer compression therapy. The secondary aim was to determine the effect of ECSW on participant reported ulcer pain, exudate levels and QOL.

In the following chapter the various outcomes of this study will be discussed in the context of the existing knowledge base. As a pilot study, consideration will also be given to the limitations of the study, its design and its implications for future research and practice.

5.2 Interpretation of results

5.2.1 Wound healing

In terms of the primary outcome measure, 9 participants (32%) achieved complete wound closure and remained healed at 6 months. The median time to complete wound closure for the group of 9 participants achieving this outcome was 8 weeks.

The secondary outcome measure of a ≥50% wound area reduction, occurred in a further 12 participants (43%); for these 12 participants the median time to achieve this outcome was 10 weeks.

5 participants (18%) achieved a ≤50% wound area reduction; 2 (7%) participant's wounds remained unchanged. No wounds deteriorated.

The rate of complete wound healing obtained in this study is considerably less than the 70% achieved utilising multilayer compression bandaging alone in a number of RCTs where ulcer duration average was 7.5 months and baseline wound area 9cm^2. (Kikta, Schuler et al. 1988, Charles 1991, Colgan, Teevan et al. 1996, Cordts, Hanrahan et al. 1992). There are a number of potential reasons why similar healing rates were not achieved in this study.

Firstly, this study's sample was mainly composed of patients who had failed to heal their ulcers with multilayer compression therapy in primary care and had therefore been referred to a specialist clinic in a secondary care environment. This is reflected in the long median duration of ulcers in this study (13.5 months, IQR=14).

The participants in this study all had large ulcers (median area 22.89cm^2, IQR=36.49). Studies have repeatedly suggested that venous ulcers ≥5cm^2 in area and of duration ≥6months are least likely to heal utilising multilayer compression therapy alone (Nelson 2001b, Phillips, Machado et al. 2000, Parker, Finlayson et al. 2015). It is known that patients age is a key prognostic factor in the healing of venous ulcers, with many studies suggesting delayed wound healing associated with the over 65 age group (Thomas 2001, Labropoulos, Wang et al. 2012). Within this study the median age was 69 years; 17 participants (61%) were over the age of 65 years. It can therefore be surmised that the sample consisted of chronic, hard to heal wounds which had not responded to multilayer compression therapy alone and were unlikely to.

Previous case series have shown wound healing rates of around 30% with ECSW therapy in the treatment of a diverse range of wound types. Thus the 32% wound

healing rate in this study is comparable (Schaden, Thiele et al. 2007, Saggini, Figus et al. 2008).

The study contains insufficient numbers of participants with multiple ulcers to make significant comparisons. However, of the three participants with multiple ulcers, the primary wound treated with ECSW reduced in size at a faster average rate (0.43cm^2 per week) when compared to the secondary wound which did not receive ECSW (0.09cm^2 per week). In all three cases neither primary nor secondary wound achieved complete wound closure.

The secondary wound healing outcome of a ≥50% reduction in wound area occurred in a larger proportion of the cohort. It is of interest that this group had ulcers which tended to be of a smaller ulcer area and of shorter duration than those who healed. It is noted that pre-treatment levels of exudate were higher in those wounds which did not heal but achieved a ≥50% wound area reduction and are yet higher still in the group achieving ≤50% wound area reduction. This suggests that higher baseline exudate levels may reduce the ability of ECSW to achieve healing. Studies have suggested that in some cases venous ulcer exudate may inhibit the process of angiogenesis, the very process that ECSW may seek to encourage (Drinkwater, Smith et al. 2002, Ulrich, Lichtenegger et al. 2005, Wang, Yang et al. 2011).

Body habitus may also have influenced wound healing outcome. There was a trend for participants who healed their wound to be around healthy BMI compared to those who achieved ≥50% and ≤50% wound area reduction who were mainly overweight or obese. Several studies have suggested that being overweight may contribute to the mechanism of venous insufficiency development (Van Rij, De Alwis et al. 2008, Willenberg, Schumacher et al. 2010). In addition, studies

examining wound healing in general have proposed that being overweight or clinically obese, may be an intrinsic factor affecting healing, not least attributable to impaired tissue perfusion (Guo, Dipietro 2010, Pierpont, Dinh et al. 2014). Obesity and poor nutrition are unarguably linked; the implication of poor nutrition in wound healing being that the body does not receive enough of the proteins and vitamins essential for wound healing (Collins 2003, Wilson, Clark 2003).

The relationship between amount of shock wave energy administered and wound healing outcome remains unclear. Though the same amount of energy per cm^2 was delivered to all wounds, there was a trend for larger amounts of energy to be delivered to those achieving ≤50% wound area reduction. This is simply attributable to larger baseline ulcer areas for this group equating to the calculation of larger shock wave energy doses for application, perhaps reinforcing the relevance of baseline ulcer size as prognostic factor for healing.

5.2.2 Pain and exudate

It has been established through review of studies which include QOL data and patient experience that pain is the foremost concern and complaint of those who suffer with chronic venous ulceration (Cooper, Hofman et al. 2003, González-Consuegra, Verdú 2011). There are several key points to note when considering the effect that ECSW had upon patient reported pain scores within this study. From baseline to 6 month follow up pain scores reduced for 27 of the 28 participants, 96% of the cohort. Statistical significance was shown for the improvement regardless of wound healing outcome, suggesting that the treatment had an effect upon pain independent of wound healing itself. Pain scores began to

reduce on average after 2 ECSW treatments. Furthermore, the reduction of median pain score for the cohort from 6 at baseline to 2 at 6 month follow up equates to a 36% shift on an 11 point VAS, constituting a clinically significant reduction.

Multilayer compression therapy alone has not been shown to impact upon patient reported pain levels, indeed it is known that a leading reason for noncompliance with compression bandaging is often cited as high levels of ongoing pain and discomfort (Edwards 2003, Briggs, Closs 2006). The findings in this study are supported by the widely reported analgesic effect of low energy ECSW particularly in the treatment of orthopaedic conditions (Rompe, Hopf et al. 1996, Han, Lee et al. 2015). Two analgesic mechanisms are suggested; the first postulates that the application of shock waves initiates degeneration of epidermal nerve fibres leading to pain relief (Ohtori, Inoue et al. 2001). The second mechanism focuses upon the ability of shock waves to alter the tissue concentration of substance P, an important element involved in pain perception (Maier, Averbeck et al. 2003).

Within this study it appears that ECSW had a statistically significant impact upon exudate levels over the course of the study with the number of participants whose exudate level was recorded as ‘high’ at baseline reducing from 9 to 1 and those recorded as ‘medium’ reducing from 18 to 5 at 6 month follow up.

5.2.3 Quality of life

Studies have repeatedly shown that the greatest impact chronic venous ulceration has upon people’s lives is through physical pain, impaired mobility and a reduced

ability to carry out the daily activities of living (Hopman, VanDenKerkhof et al. 2014, Faria, Blanes et al. 2011).

This is demonstrated in the direct comparison of baseline SF-36 physical and mental component scores in this study. At baseline, participants mean physical component score (34.31, SD=10.50) began at a much lower point than their mental component score (47.01, SD=7.04); similarly, SF-36 data reported in previous studies showed a tendency for physical component scores to be lower at baseline than mental component scores (Charles 2004, Clarke-Moloney, O'Brien et al. 2005).

QOL improved for the cohort throughout treatment with ECSW, regardless of wound healing outcome. For SF-36 questionnaires, the physical component score showed the most improvement with mental component scores also improving, albeit less dramatically. Physical and mental component scores improved with statistical significance for the whole cohort, with greatest improvement noted in those who healed their wound. Clinical significance was shown for change in mean physical component score which improved by 6.88 points, within the Minimally Important Difference (MID) range of a 5 to 10 point shift. Improvement in mean mental component score was not shown to be clinically significant, represented by a 3.5 point shift in score.

Similarly, previous studies of multilayer compression therapy have shown physical component scores tend to show greater improvement than mental component scores, particularly amongst those whose wound healed. (Charles 2004, Clarke-Moloney, O'Brien et al. 2005).

In the context of a cohort which had not responded to multilayer compression therapy, this would suggest the addition of ECSW produced QOL improvements

comparable to studies reporting the benefits of multilayer compression therapy, current best practice. Furthermore, EQ-5D questionnaire scores in this study followed the trend of SF-36 physical component scores with an improvement in QOL for the cohort as a whole and greatest improvement shown in those who healed their wound. Clinical significance was also established with mean EQ-5D index score improving by 0.1 points on the index scale; MID range of score shift required for EQ-5D having been established as 0.08 to 0.1.

Perhaps the most unexpected result comes by way of disease specific CXVUQ scores. Disease specific QOL questionnaires are an important measurement tool; they focus upon specific clinical changes in unique conditions and are considered more sensitive than their generic counterparts (Morgan, Crayford et al. 2001, de Vries, Ouwendijk et al. 2005, Engelhardt, Spech et al. 2014).

CXVUQ scores showed statistically significant QOL improvements for the cohort as a whole, for those who healed their wound, those who achieved ≥50% wound area reduction, but most impressively for those who achieved ≤50% wound area reduction. This indicates that QOL improved without the occurrence of significant wound healing. Pain and high levels of wound exudate dramatically impact upon the QOL of those who suffer chronic venous ulceration; our results indicate that the addition of ECSW reduces these factors, contributing to improved QOL.

Many of the studies investigating compression therapy predate the inception of the CXVUQ, making direct comparisons difficult. One recent RCT reporting compression therapy outcomes showed improvement of CXVUQ score from mean baseline (28.6, SD=17.9) to 6 month follow up (22.4, SD=16.5), a 6.2 point reduction (Wong, Andriessen et al. 2012).

In this study, mean CXVUQ score improved from baseline (67.36, SD=11.67) to 6 month follow up (50.85, SD=18.85), a 16.51 point reduction. Mean baseline ulcer area varies greatly: 7.8cm^2 in the compression study versus 22.89cm^2 in this study. Despite a greater reduction between scores, QOL at 6 months appears poorer in this study than for the compression study. However, baseline CXVUQ score in this study was far higher and ulcer sizes far greater. It is difficult to discuss clinical significance in the absence of reported and validated Minimally Important Differences (MID) for CXVUQ scores.

5.2.4 Safety

No unexpected adverse events or serious adverse events were recorded throughout the duration of this study. Of the expected non-serious adverse events only very minor wound bleeding was encountered. None of the studied ulcers required treatment for wound infection and there were no reports of discomfort derived directly from the study treatment.

5.3 Limitations of the study

As a pilot, reporting of the limitations of this study, its design and components is of great import. The elements which worked well led to the successful reporting of results and prompted discussion of findings. What follows should not only help critique this study but help to improve and inform future studies.

5.3.1 Sample size and population

The number of participants in this study is small when compared to many of the prior RCTs investigating multilayer compression bandaging. The limitation of a small sample size occurs primarily in the use of statistical analysis and the generalisability of results (Campbell, Machin 1990, Button, Ioannidis et al. 2013). Several trends emerged in analysis of study results without statistical significance being shown, potentially due to the small number of participants being studied. This identifies the risk of potential type II statistical errors, the failure within statistical analysis to detect an effect that is present (Anthony 1999). Yet this was a pilot study, examining a specific and new hypothesis; there is merit in utilising a smaller sample size in this type of study where the new hypothesis can be tested or research question answered without the resources of a larger study (Parahoo 2006).

The population from which the sample was chosen may also be viewed as a limitation of the study. Analysis of participant demographics established that the sample represents a group who fall into the category of ‘hard to heal wounds’, mainly elderly patients referred to a specialist clinic in the secondary care environment. The wounds themselves were large and of long duration thus truly chronic in nature. The sample recruited met the requirement of those suffering chronic venous ulceration, what was perhaps undervalued was the severity of the particular cases included.

A different recruitment strategy could have been considered in order to capture a more representative sample. This would consist of less chronic presentations of the condition, personifying a wider range of ages, wound sizes and ulcer durations, most likely found in the primary care setting. Alternatively, the potential role of

ECWS could be regarded as an adjuvant to multilayer compression therapy in the hard to heal wound group.

5.3.2 Study design

The study is of a simple, quasi-experimental, time series design without a separate control group. The lack of control group may limit the potential of this study, some would even class this as a critical limitation (Ho, Peterson et al. 2008). Without a control group it can be difficult to eliminate alternate explanations for study results (Burns, Grove et al. 2011). Within this study there is an element of historic control whereby specific but historic criteria, some of which matches the type of data collected within the study, is known about each participant. Of this historic control data, perhaps most importantly, the duration for which the wound has remained unhealed and the duration of compliance with multilayer compression therapy alone prior to entry into the study is known. Although this does not replace the benefit of a separate control group, in this exploratory study it allows us to begin to see the relationship between study treatment and improved outcomes for individual participants and for the cohort as a whole. Historic controls are however susceptible to confounding factors and for the purposes of comparison, are not as reliable as randomising participants to a treatment or control group (Parahoo 2006, Burns, Grove et al. 2011). Therefore in this pilot study data from historic controls has not been employed in statistical analysis, it is instead utilised as a context against which to consider results.

Undoubtedly herein lies the potential for further research and the progression to an RCT, the primary benefit of which would be increased internal validity of the study through the addition of randomly designated treatment and control groups.

5.3.3 Risk of bias

Selection bias is often cited as the greatest threat to the internal validity of a study; it occurs when participants are selected on the basis of a variable that is associated with the outcome and is often affiliated with non-randomised studies (Parahoo 2006, Boswell, Cannon 2014). An appropriate example would be the selection of participants with small wounds of short duration as they are most likely to heal during the course of the study. Randomisation helps to remove selection bias (Newell, Burnard 2011); however it has shown that the sample in this study consists mainly of participants least likely to respond to treatment. There remains a risk of this being perceived as selection bias in the opposite direction; the likelihood however is that risk of selection bias is low.

Within the study there does exist a risk of performance bias, whereby the cohort may have been exposed to influencing factors other than the treatment being studied (Parahoo 2006, Boswell, Cannon 2014). By attending study appointments participants received the time, care and attention of specialist nursing staff in an environment which differs from their usual, routine care. The argument could be made that outcomes were potentially influenced by the addition of specialist care and attention. This could have been avoided through the use of blinding methodology to reduce performance bias, masking personnel and participants to differences in treatment (Polit, Beck 2013).

5.3.4 Economic analysis

This study focused upon clinical outcomes and did not consider the financial implication of the treatment or its delivery. Factors considered in other studies analysing the cost of compression therapy have included the value of dressings and bandaging systems, nurse's time, administration, travel and overhead costs for the facility delivering care (Olin, Beusterien et al. 1999, O'Brien, Grace et al. 2003). The use of ECSW as an adjuvant to compression therapy clearly adds financial cost in the purchase or hire and maintenance of a shock wave lithotripter. However, when utilised in a group unresponsive to compression therapy there may be an offset between increased treatment cost and reduced time to healing.

5.4 Implications for practice

ECSW appears to show potential as an adjuvant treatment in the healing and management of chronic venous ulceration alongside multilayer compression bandaging. It represents a treatment modality which led to improved wound healing outcomes in 75% of the ulcers studied (32% complete wound closure), all of which had remained static and unhealed for 13.5 months on average. Though further research is required, ECSW should be regarded as a safe treatment worthy of consideration in the treatment and management of this chronic condition.

Primary and secondary wound healing outcomes, along with pain and exudate reductions were achieved within a time frame of 12 weeks. Similarly, the greatest improvements in QOL were observed within the same time frame.

There are many variables in the delivery of this treatment which may affect its effectiveness and the time period in which outcomes may be achieved. Exploration

of contrasting treatment durations and frequency intervals, as well as variations of delivered energy levels and pulse frequencies should be considered in future studies.

The results of this study have direct implications for nursing practice and the delivery of patient centred care. Outcomes indicate that ECSW potentially offers a beneficial, therapeutic option in the care of patients not responding to multilayer compression therapy. The benefit to patients QOL alone justifies consideration of this treatment and certainly merits the attention of future nurse led study.

5.5 Future research needs

The results of this pilot study have shown that there is a clear requirement for further research into the use of ECSW to treat chronic venous ulceration. An RCT of greater sample size based upon a power calculation, potentially recruiting from primary care, is justified and would provide the methodology required to better define and demonstrate treatment effect. There is potential for the application of this treatment beyond the group of patients who fail to respond to compression therapy alone; the selection of any future sample should attempt to address this in its recruitment strategy improving the generalisability of results.

The relationship between amount of shock wave energy delivered and outcome requires further exploration, as does the role of baseline wound exudate as an influence upon treatment efficacy.

Unusually, no wound infections were encountered throughout the study; a further research pathway would be to investigate any potential antimicrobial effect that ECSW may impart.

CHAPTER 6 - CONCLUSION

In this study, ECSW achieved wound closure in 32% of participants with a further 43% achieving a ≥50% wound area reduction. Participant reported pain scores and exudate levels reduced for 96% of participants treated with ECSW.

QOL, measured with generic and disease specific tools, improved for the whole cohort over the studied six month period regardless of wound healing outcome.

ECSW should be regarded as a safe therapy worthy of consideration in the treatment and management of this chronic condition. Its role in the treatment of small ulcers of short duration is unclear; however for large ulcers, of long duration, not responding to multilayer compression therapy, there appears to be substantial benefit.

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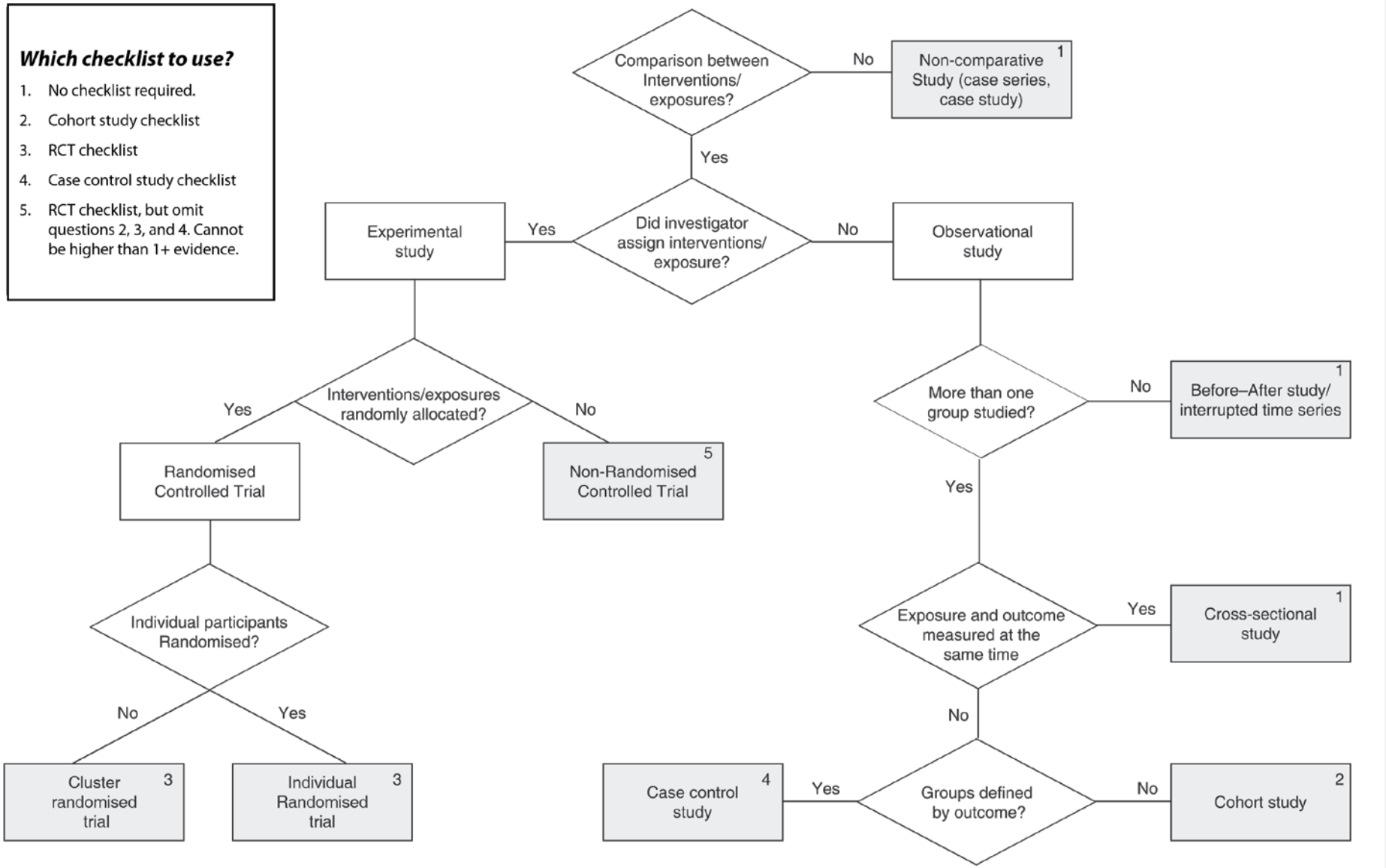
Appendix A

The Scottish Intercollegiate Guidelines Network (*SIGN*)

Adapted algorithm

Algorithm for classifying study design for questions of effectiveness



Adapted from NICE (www.nice.org.uk)

Appendix B

Summary of studies included in literature review

Summary of studies included in literature review

Reference	Study design	Population and characteristics	Intervention and control	Outcome category	Results primary outcome and statistics	Level of evidence SIGN	Weakness/limitations
Mittermayer 2012	Literature review	Wounds of varying aetiology. 7 studies included of which 2 include venous stasis ulcers.	Focused and unfocused electrohydraulic shockwave. 0.037 to 0.15mJ/mm2 energy. Pulses per cm2 vary from 100 to 500.	Complete wound healing. Time to complete healing (rate).	One study shows poorest shockwave response in venous stasis ulcer group. No statistical analysis.	1++	No meta-analysis of data.
Qureshi 2011	Literature review	Preclinical studies in animals, in vitro studies, prospective and retrospective. 8 studies included, only 2 included venous stasis ulcers.	Focused and unfocused shockwave. 0.037 to 0.1mJ/cm2.	Reduction of wound size. Complete wound healing. 50% wound healing. Pain reduction.	36% of venous ulcers complete healing and significant pain reduction in one study. Venous stasis ulcers worst responders in study comparing various wound aetiologies.	1++	No QOL measure. No exudate measure
Saggini 2008	Clinical trial	Intervention group 30, control group 10. Chronic lower limb ulceration. Posttraumatic, venous stasis and diabetic ulcers.	Focused shockwave. 0.037 mJ/mm2 energy at 4Hz. Treatment repeated every two weeks – minimum 4, maximum 10 sessions. Two groups, standard treatment and standard plus shockwave.	Wound row surface area. NBS self-assessment. Pain scale. Exudate amount.	Intervention group 16 ulcers healed (4 venous). Significant difference row surface area and exudate ($p<0.01$). Analysis of NBS scores showed significant decrease of pain ($p<0.001$).	2+	No randomisation. No QOL measure. No follow up period.

Stieger 2013	Case study	Single patient case study. Chronic venous leg ulcer.	2000 pulses per session – 0.25 mJ/mm2 energy at 4Hz. Weekly treatments – 30 sessions.	Complete wound healing. Time to complete wound healing.	Complete re-epithelialisation achieved at 30 weeks/sessions. Recurrence of ulcer at two weeks post healing.	3/4	Single case study. Short follow up period. No QOL measure. No pain or exudate measure. Focused or unfocused?
Fioramonti 2012	Case study	Single patient case study. Chronic, bilateral venous leg ulcer.	100 pulses per cm2 at 0.037mJ/mm2 energy – 4Hz. Weekly treatment, 6 sessions. Right leg treated shockwave – left leg conventional dressings only.	Complete healing.	Right leg ulcers (shockwave) healed at 6 weeks. Left leg (dressings only) unhealed at 6 weeks.	3/4	Single case study. No follow up period. No QOL measure. No pain measure. No exudate measure.
Schaden 2006	Feasibility study	208 patients – nonhealing acute and chronic soft-tissue wounds. 25 (12%) wounds venous stasis ulcer. Follow up at 44 days	100 to 1000 pulses per cm2 at 0.1mJ/mm2. 1 – 2 weekly, 3 treatment maximum.	Complete healing.	15.4% drop out. 156 (75%) complete wound healing. 16 venous stasis ulcers reduced in size but did not heal, 9 achieved complete wound healing. Overall, venous stasis ulcers achieved worst healing rates (36%)	2+	No QOL measure. No pain measure. No exudate measure.

Wolff 2011	Observational study	282 patients – chronic soft tissue wounds of which 38 were venous ulcers. Single group assignment (one armed, open, prospective.). Median follow up 38 months.	Unfocussed shockwave - 0.1mJ/mm2 energy – median pulses 167 per cm2. Weekly then two weekly treatment – 10 weeks.	Successful wound closure.	The influence of comorbidities failed to meet significance level ($p < 0.01$). Logistic regression analysis - wound duration, initial surface area and initial wound bed score shown to influence shockwave success.	2+	Non-randomised. Undefined follow up period.

Appendix C

Cochrane protocol

Extracorporeal shock wave therapy

for the healing and management of chronic venous leg ulcers

Extracorporeal shock wave therapy for the healing and management of venous leg ulcers

Protocol information

Review number: 217

Authors

Contact person

Ben Cooper

E-mail:

Dates

Assessed as Up-to-date:	
Date of Search:	
Next Stage Expected:	
Protocol First Published	Not specified
Review First Published:	Not specified
Last Citation Issue:	Not specified

What's new

Date / Event	Description

History

Date / Event	Description

Background

Description of the condition

Leg ulcers are chronic wounds most commonly described as open lesions of the skin occurring below the knee on the leg or foot, further characterised by healing times of greater than six weeks (SIGN 2010; Van Gent 2010). The causes of leg ulceration are varied and often multifactorial; primary aetiological factors include venous insufficiency, arterial insufficiency and diabetes (Mekkes 2003).

Venous ulceration is the most common type of leg ulceration seen in the community. Studies have shown that for people with chronic leg ulcers, 70% to 80% of those ulcers have a venous component (Valencia 2001; Crane 2008). Chronic venous leg ulceration has an estimated prevalence of 1% to 2% of the population in developed countries. Point prevalence for the United Kingdom (UK) is estimated to be between 0.3% and 0.5% (per 1000 population), which increases with age (Reichenberg 2005; Vowden 2009; González Consuegra 2011). The natural history of the disease is one of a continuous cycle of healing and breakdown over decades (Smith 2006; Raju 2010).

Venous ulceration is associated with impaired quality of life, reduced mobility, pain, stress and loss of dignity (Persoon 2004; Wilson 2004). Social isolation can be commonplace and is frequently associated with malodorous wounds, swelling and anxiety around exudate levels (Walters 1999; Herber 2007).

Venous ulcers arise as a result of venous valve incompetence and calf muscle pump insufficiency (Palfreyman 1998; Mekkes 2003), which leads to retrograde venous flow, venous hypertension, microcirculatory skin changes and localised tissue damage. Two main mechanisms have been proposed to account for the tissue damage and subsequent ulceration that occurs. The fibrin cuff hypothesis postulates that venous hypertension leads to exudation of fibrin, a protein involved in the clotting of blood, into the surrounding tissues, and leads to the formation of fibrin cuffs around capillaries which impairs gas exchange, leading to tissue damage (Smith 2006). The leucocyte- (white blood cell) trapping hypothesis postulates that leucocytes which have become trapped in the microcirculation migrate into surrounding tissues and lead to an inflammatory response with impairment of normal proliferation and skin healing (Saharay 1998; Hahn 1999).

The current gold standard in the management of chronic venous leg ulcers revolves around high compression multilayer bandaging (SIGN 2010). Multilayer compression bandaging aims to improve venous return and reduce venous hypertension (Valencia 2001; Etufugh 2007). Elastic multi-component bandages such as four layer bandaging and comparative two layer systems are used; these consist of an initial layer of orthopaedic wool, a crepe bandage, an elastic bandage and an elastic cohesive bandage as the outer layer (Marston 1999). The high pressure is sustained for a considerable time allowing for a weekly change of dressings. With multilayer compression therapy, healing rates of around 70% at six months have been achieved in specialist clinics. Simple, nonadherent primary wound dressings are currently recommended in conjunction with compression bandaging (SIGN 2010). Other known treatments for this condition include the use of various impregnated primary dressings, hyperbaric oxygen therapy and treatment of underlying venous insufficiency via surgery, endovenous laser (EVLT), radiofrequency (RFA) and sclerotherapy treatments.

Description of the intervention

Extracorporeal shock waves (ECSWs) are low energy pulse waves that were first put to clinical use in the treatment of urolithiasis, whereby kidney stones (urinary calcinosis) are broken up by the shock wave energy (Shrivistava 2005). Since then their application has been extended to the treatment of fractured bones with an interrupted healing process (non-union fractures), tendon injury and osteonecrosis, a condition whereby bone breaks down faster than it can be replenished (Schaden 2007). More recently, the ability of ECSWs to improve the healing of wounds, ulcers and burns has been assessed. The incidental discovery that shock waves may have an effect upon wound healing was made in 2006 (Schaden 2007; Arno 2010; Mittermayr 2011); the treatment in this context has remained novel.

Shock waves carry energy, have a short life cycle and are able to travel through a physical medium such as liquid or gas. Shock waves are generated through the transformation of electric energy into mechanical energy. This transformation can occur in one of three ways: electromagnetic generation utilises a strong magnetic field to create a slow, low pressure acoustical pulse; piezoelectric generation relies upon the rapid contraction and expansion of piezoelectric crystals, achieved through the application of a high voltage pulse; and electrohydraulic generation utilises a shock wave pulse released by high voltage electrode water vaporisation (Ogden 2001; Mouzopoulos 2007).

Shock waves are defined by their waveform, number and frequency of impulses, and energy flux density (the rate at which energy is transferred through the physical medium). Standardised, disease-specific protocols pertaining to the use of shock wave therapy in wound care are lacking (Schaden 2007). In the treatment of wounds, lower flux densities are typically used, providing lower energy levels. Regardless of their characteristics or mode of generation, shock waves can be delivered to a target area either in a focused or dispersed manner through the use of specific applicator units (Mittermayr 2011).

All three modes of shock wave generation, electromagnetic, piezoelectric and electrohydraulic, are found in current clinical practice. Both focused and un-focused (dispersed) applicator units have been utilised in the delivery of treatment for soft tissue wounds, with typical energy levels of 0.037mJ/mm to 0.1mJ/mm (Schaden 2007; Saggini 2008).

How the intervention might work

In humans, ECSWs have been shown to promote the formation and development of blood vessels (angiogenesis) and to reduce inflammation (Wang 2011).The mechanism of how ECSW therapy may aid wound healing is poorly understood at present, however several animal model studies have shown increased levels of signal proteins (vascular endothelial growth factor (VEGF) and factor HIF-1alpha) following treatment. These proteins are in part responsible for the restoration of tissue oxygen supply when blood circulation is inadequate (Chen 2004; Nishida 2004; Wang 2004; Ma 2007). This angiogenic process is stimulated by the application of ESCWs and plays an important role in wound healing (Stojadinovic 2008; Mittermayr 2011). In addition ECSW application may, through the application of shear stress forces, alter the physical properties of endothelial cells.

Why it is important to do this review

Venous ulceration is a common, chronic condition resulting in significantly impaired quality of life and substantial burden to all healthcare systems. The use of shock waves in the treatment of venous leg ulcers is an as yet novel

therapy; a comprehensive review of all relevant and available randomised controlled trials is required to inform practice.

Objectives

To assess the effects of extracorporeal shock wave therapy in the healing and management of venous leg ulceration.

Methods

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) reporting an objective measure of wound healing (see 'Types of outcome measures'). There will be no restriction on the basis of language, publication status or age of study.

Types of participants

People over the age of 18 years, from any care setting and socio-economic background, with active lower limb ulceration of venous aetiology. Guidelines in the UK indicate assessment of ankle brachial indices should be performed to rule out arterial disease, and many diagnostic assessments will also include duplex ultrasound imaging to identify venous reflux (SIGN 2010); we will accept studies in which a diagnosis of venous ulceration has been made irrespective of whether the ankle brachial indices were reported.

Studies will be included where lower limb venous ulceration is either the focus of the study or is included within a study evaluating a broader range of soft tissue wounds. In the case of the latter, results will be stratified according to wound aetiology.

Types of interventions

Studies evaluating the use of low energy, focused or non-focused extracorporeal shock waves (ECSWs) in the context of soft tissue wound treatment.

Eligible comparators will include:

- ECSW compared with no treatment or sham treatment
- ECSW compared with dressings (with or without compression treatment)
- ECSW compared with alternative treatment - for example truncal venous surgery (including endovenous laser treatment, radiofrequency and sclerotherapy), hyperbaric oxygen therapy Head to head comparisons of varying types, modes and strengths of ECSW treatment.

Shock waves produced by any of the three accepted methods will be included; these comprise electrohydraulic, electromagnetic and piezoelectric principles of shock wave generation. We will exclude studies examining ECSW

use for the treatment of chronic tendinopathies, impaired bone healing function, urinary and biliary calcinosis and myocardial ischaemia.

Types of outcome measures

Primary outcomes

Complete wound healing measured by:

- Time to complete wound healing
- Proportion of index ulcers completely healed over a six month period
- Adverse effects, including participant-reported pain from intervention (measured using a visual analogue scale, such as a numeric box scale. (NBS)

Secondary outcomes

- Change in ulcer size (percentage change from baseline)
- Quality of life (measured using a standardised generic questionnaire such as: EQ-5D, SF-36, SF-12 or SF-6)
- Effect upon volume of exudates (utilising subjective measurement, such as low, medium, high)
- Effect upon daily ulcer pain (measured using a visual analogue scale, such as an NBS Ulcer recurrence (defined as a new lesion in the skin where complete healing had occurred) Treatment cost.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases:

- The Cochrane Wounds Group Specialised Register
- The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, latest issue)
- Ovid MEDLINE (1946 to present)
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations)
- Ovid EMBASE (1974 to present)
- EBSCO CINAHL (1982 to present).

We will use the following provisional search strategy in CENTRAL and will adapt it as appropriate for the other databases:

#1 MeSH descriptor: [Ultrasonic Surgical Procedures] explode all trees

#2 MeSH descriptor: [Ultrasonic Therapy] explode all trees

#3 MeSH descriptor: [Sound] this term only

#4 MeSH descriptor: [High-Energy Shock Waves] explode all trees

#5 (Shockwave* or (shock* near wave*)) (Word variations have been searched)

#6 Ultraso*:ti,ab,kw

#7 Lithotrip*:ti,ab,kw

#8 ESWT:ti,ab,kw

#9 ECSW:ti,ab,kw

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 MeSH descriptor: [Leg Ulcer] explode all trees

#12 ((varicose next ulcer*) or (venous next ulcer*) or (leg next ulcer*) or (stasis next ulcer*) or (crural next ulcer*) or "ulcus cruris" or "ulcer* cruris"):ti,ab,kw

#13 #11 or #12

#14 #10 and #13

We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity and precision maximising version (2008 revision) (Lefebvre 2011). We will combine the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2014). There will be no restrictions with respect to language, date of publication or study setting. We will also search the following clinical trials registries:

- ClinicalTrials, gov (http://www.clinicaltrials.gov/)

- WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx) EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Searching other resources

We will examine the reference lists of all identified, relevant studies in order to locate further studies not highlighted by the electronic search. We will identify and contact experts and industry representatives to enquire about unpublished or ongoing studies.

Data collection and analysis

Selection of studies

The assessment of studies for potential inclusion will be undertaken by two independent review authors (PB, BC). References drawn from initial searches will be examined for relevance; studies considered for inclusion will be retrieved in full and selected according to the criteria for considering studies for this review described above. Any disagreement regarding the selection of studies for inclusion will be resolved by discussion with a third review author (JB).

We will include a study flow diagram as recommended by the PRISMA statement (Liberati 2009) to illustrate the results of all searching activity and the process of screening and selecting studies for inclusion in the review.

Data extraction and management

A data extraction sheet will be utilised by two review authors (PB, BC) to summarise eligible studies. In cases where multiple publications have arisen from a study, one publication will be identified as the primary reference but all studies will be maximally data extracted.

We will extract the following data:

- Trial authors.
- Year of publication.
- Country where RCT performed.
- Care setting.
- Unit of investigation (participant, leg or ulcer).
- Overall sample size and methods used to estimate statistical power.
- Participant selection criteria.
- Number of participants randomised to each treatment arm.
- Baseline characteristics of participants per treatment arm (gender, age, baseline ulcer area and volume, ulcer duration, prevalence of co-morbidities such as diabetes, prevalence of clinically infected wounds or colonised wounds, previous history of ulceration, baseline levels of wound exudate, and participant mobility).
- Details of the dressing/treatment regimen prescribed for each treatment arm including details of concomitant therapy (for example: compression).
- Duration of treatment.

- Duration of follow-up.
- Statistical methods utilised in data analysis.
- Primary and secondary outcomes measured.
- Primary and secondary outcome data by treatment arm.
- Adverse effects of treatment (per arm with quantity and type).
- Withdrawals (per treatment arm with quantity and reason). Source of trial funding.

Assessment of risk of bias in included studies

Two review authors (PB, BC) will independently assess each included study using the Cochrane tool for assessing risk of bias (Higgins 2011).This tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias (for this review, baseline comparability of groups for factors such as surface area and duration of ulcer). RCTs will be classified as being at an overall high risk of bias if they are rated as 'high risk' for any one of three key domains: allocation concealment, blinded outcome assessment of healing, and completeness of outcome data. RCTs will be classified as being at an overall low risk of bias if rated as 'low risk' in the three key domains of allocation concealment, blinded outcome assessment of healing, and completeness of outcome data.

Individual assessments will be made of participant blinding and blinding of outcome assessors. We will present our assessment of risk of bias using two 'Risk of bias' summary figures; one which is a summary of bias for each item across all studies, and a second which shows a cross-tabulation of each trial by all of the 'Risk of bias' items. Disagreements between review authors will be resolved through discussion with a third review author (JB).

Measures of treatment effect

Data analysis will be performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). One review author will enter quantitative data into Review Manager 5.3, another will check it, and the data will be analysed using RevMan 5.3. We will present the outcome results for each trial with 95% confidence intervals (CI).

We will report estimates for dichotomous outcomes (e.g. ulcers healed during time period, number of infected ulcers) as risk ratios (RR).

Continuous outcomes (such as changes in ulcer area) will be expressed as mean differences (MD) and overall effect size (with 95% CI calculated) or as standardised mean differences (SMDs) if different methods of measurement are used in the studies.

Time-to-event data will be analysed utilising survival, time-to-event approaches, with adjustment for baseline size if data are available. We plan to plot, and, if feasible, pool, estimates of hazard ratio and 95% CI as presented in the trial reports using the generic inverse variance method in RevMan 5.3.

Unit of analysis issues

We will record whether included studies present outcomes in relation to a wound, a participant or as multiple wounds on the same participant. We will analyse the level at which study randomisation has occurred.

Dealing with missing data

Review authors will attempt to contact the trial investigators in cases of missing data. Where trials report complete healing outcomes for only those participants who complete the trial (i.e. participants withdrawing and lost to follow-up were excluded from the analysis), we will treat the participants who were not included in the analysis as if their wound did not heal. Where trials report results for participants who complete the trial without specifying the numbers initially randomised per group, we will present only complete case data. For other outcomes the same analysis will be applied.

Assessment of heterogeneity

We will consider clinical heterogeneity (where trials appear different in terms of participant characteristics, intervention type and duration and outcome type) and statistical heterogeneity. We will assess statistical heterogeneity using the Chi test (P values less than 0.10 will be considered to indicate significant heterogeneity) in conjunction with the I statistic (Higgins 2003). The I statistic estimates the percentage of total variation across trials due to heterogeneity rather than variation due to chance. Heterogeneity will be categorised as follows: I values of 40% or less will indicate a low level of heterogeneity, and values of 75% or above will represent very high heterogeneity.

Assessment of reporting biases

If possible, funnel plots will be used to assess reporting bias if a minimum of 10 studies are available for the meta-analysis of a primary outcome (Sterne 2011).

Data synthesis

We will present a narrative overview of the studies reviewed, and will utilise RevMan 5.3 to combine outcomes where possible. Included trials will be grouped according to the comparator intervention, which may include no treatment, standard dressings, biological dressings, compression, venous surgery, other novel therapy, varying types, modes and strengths of shock wave therapy and sham treatment. The decision to include studies in a meta-analysis will depend on the availability of treatment effect data and assessment of heterogeneity.

For comparisons for which there is no apparent clinical heterogeneity and the I value is 40% or less, we will apply a fixed-effect model. Where there is no apparent clinical heterogeneity and the I value is greater than 40%, we will apply a random-effects model. However, we will not pool data where heterogeneity is very high (I values of 75% and above). We will grade the quality of the evidence for each primary outcome (complete wound healing measured by the number of ulcers completely healed within the duration of the trial and adverse events) using four levels of quality: high, moderate, low and very low (Schunemann 2011a).

The following factors will be graded:

- Limitations in the design and implementation of available studies, suggesting high likelihood of bias
- Indirectness of evidence (indirect population, intervention, control, outcomes)
- Unexplained heterogeneity or inconsistency of results (including issues with subgroup analyses) Imprecision of results (wide confidence intervals) High probability of publication bias.

'Summary of findings tables'

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables:

- Time to complete wound healing
- Proportion of index ulcers completely healed over a six month period
- Adverse effects, including participant-reported pain from intervention (measured using a visual analogue scale, such as a numeric box scale. (NBS).

Subgroup analysis and investigation of heterogeneity

Potential sources of heterogeneity will be considered and every effort will be made to extract sufficient, compatible data to undertake subgroup analysis of individuals. Subgroups will include demographic divisions, variations in type of shock wave treatment and differing durations of follow-up.

Sensitivity analysis

We plan to undertake sensitivity analyses to explore the influence of risk of bias on effect size. We will also assess the influence of removing from meta-analyses, studies classed as having an overall high risk of bias. These analyses will include only studies that are assessed as having a low risk of bias in all key domains, namely allocation concealment, blinded outcome assessment of healing, and completeness of outcome data for the estimates of treatment effect.

Acknowledgements

We acknowledge the contribution of the peer referees: Susan OMeara, Amanda Briant, Giovanni Casazza, Madhu Periasamy and Jane Nadel.

Contributions of authors

BC: Conceived the review question, developed the protocol and coordinated the protocol development. Wrote and edited the protocol.

PB: Conceived the review question and coordinated the protocol development. Edited and advised on the protocol, and made an intellectual contribution to the protocol. Approved the final version of the protocol prior to submission. Is the guarantor of the protocol.

JB: Coordinated the protocol development. Edited and advised on the protocol, and made an intellectual contribution to the protocol. Approved the final version of the protocol prior to submission.

Contributions of editorial base:

EDITOR: edited the protocol; advised on methodology, interpretation and protocol content and approved the final protocol prior to submission.

Megan Prictor: copy edited the protocol.

Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content and edited the protocol.

Rocio Rodriguez-Lopez: designed the search strategy.

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Arno 2010

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Other published versions of this review

Figures

Sources of support

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK
  This project was supported by the National Institute for Health Research (NIHR) via Cochrane Infrastructure to the Cochrane Wounds Review Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.

Appendix D

Patient information sheet (PIS)

Participant consent form

Letter to GP

PARTICIPANT INFORMATION SHEET

Extracorporeal shockwave for the treatment of chronic venous ulcers:

A Pilot study

Introduction

You are being invited to take part in a local study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information and feel free to ask any questions if you would like more information. Take time to decide whether or not you wish to take part. Thank you for taking the time to read this information sheet.

Venous ulcers are breaks in the skin of the legs which occur in people who have increased pressure in their leg veins (venous disease). The ulcers are treated with dressings and compression bandages which are applied by a specialist nurse. The success of this treatment varies and it may take up to 6 months or longer for the ulcer to heal.

This study aims to see if an additional treatment known as extracorporeal shock wave therapy can improve the healing rates of patients with venous ulcers. Extracorporeal shockwave are low energy shock waves which have been shown in studies involving patients to improve the healing of some wounds. They may act by helping tiny new blood vessels to grow and reducing the number of cells which cause inflammation. Shock waves may also improve the healing of venous ulcers but further studies are required to determine if this is the case.

We have used shock wave therapy in our ward for the past year. Further information is required to help us determine if shock wave therapy when used with routine care can improve healing rates and hence the need for this study.

What is the purpose of the study?

We wish to find out if shockwave therapy can improve the healing of venous leg ulcers when used alongside routine care (dressings and bandages).

Why I have been chosen?

You have been invited because you have been diagnosed as having a leg ulcer (break in your skin) which has occurred due venous disease.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form (you will be given a copy). If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. Even if you decide not to take part, your future treatment will not be affected.

What will happen to me if take part?

If you do decide to take part we will contact you and then arrange a convenient time for you to come up to ward 36 at Aberdeen Royal Infirmary to answer any further questions you might have. If you are still happy to proceed we will ask you to sign a consent form. You will then undergo shock wave therapy in addition to the standard routine care of your leg ulcer(s). If you have more than 1 leg ulcer then only one, which will usually be the worst one in terms of appearance and size will be treated with the shock waves.

You will receive shock wave therapy every two weeks in the outpatient clinic setting. This involves putting some cling film over the ulcer and then applying some gel to aide conduction of shock wave pulses. These will be applied in short bursts for approximately 10 - 15 minutes.

Number of shock wave treatments: Initially you will receive 3 shock wave treatments. If there is found to be an *improvement* in the ulcer the treatments will be continued at 2 weekly intervals to a maximum of 6 treatment sessions in total. You will then continue the standard routine care (dressings and bandages) in the community until the ulcer is healed. You will be asked to attend for review back at the clinic at 6 months from entering the study.

If after 3 treatments there is *no improvement* in your ulcer, we will discontinue the shock wave therapy but will continue with the normal standard ulcer care (dressings and bandages)

in the community. We would still wish to follow you up in the study and see you back at the ward at 2 further visits at 3 and 6 months.

If your ulcer is not healed by 6 months you will continue to be treated and followed in the NHS.

What else will I be asked to do as part of the study?

When you attend you will be asked some questions about how painful your ulcers are and if you have experienced any symptoms during the study. You will also be asked to complete a short questionnaire at every clinic visit, including follow up visits at 6 weeks, 3 months and 6 months.

What are the possible disadvantages of taking part?

You may experience some mild discomfort and minor bleeding of your ulcer during the shock wave treatment. Rarely patients may experience a reaction to the shock wave leading to redness of the ulcer.

Will my taking part in this study be kept confidential?

The information obtained from your medical records and records created, as a part of the study will be checked to make sure the information is accurate. It will then be transferred to a database and processed to analyse the results of the study. The final results may be published for scientific purposes. All information collected about you during the course of study will be kept strictly confidential. Any information which leaves the hospital will have your name and address removed so that you cannot be recognised from it. If you are agreeable we would wish to let your General Practitioner know you are taking part in this study.

What will happen to the results of the research study?

The results of the study may be used in presentations at scientific meetings and/or published in scientific journals but no one will be able identify you. We will let you know the results of the study when it finishes.

Who is organising and funding the research?

The study group is headed by Professor Julie Brittenden and is organised by the Division of Applied Medicine at the University of Aberdeen and the Department of Vascular Surgery at Aberdeen Royal Infirmary. The funding for this study is from a local endowment grant.

Has this study been approved?

The study has been reviewed and approved by the North of Scotland Research Ethics Committee.

Contact for further information

If you have any questions about participation please feel free to ask Professor Julie Brittenden or Mr Paul Bachoo who can provide further information.

Dr Brittenden can be contacted on 01224 559446, or 0845456 6000, bleep 3363

If you would like independent advice or have any questions about the research, you can contact: Mr Euan Munro, Consultant Vascular Surgeon, Aberdeen Royal Infirmary - or - NHS Grampian Research and Development Office, Foresterhill House Annexe, Foresterhill, Telephone 01224 551121.

If you take part in this study you will be given a copy of the information sheet and a signed consent form to keep.

Consent Form

Extracorporeal shockwave for the treatment of chronic venous ulcers - Pilot Study

Please initial box

1	I confirm that I have read and understand the information sheet dated 22/06/13 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Aberdeen, from regulatory authorities or from the NHS Trust/Health Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4	I give permission for photographs to be taken during treatment for assessment.	☐
5	I agree to my GP being informed of my participation in the study.	☐
6	I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Letter to GP

Dear Doctor,

Extracorporeal shockwave for the treatment of chronic venous ulcers:

A pilot study

Your patient has agreed to take part in the above study and has given us permission to inform you. This study aims to see if extracorporeal shock wave therapy in addition to standard dressings and multilayer compression therapy can improve the healing rates of patients with venous ulcers.

Extracorporeal shockwave are low energy shock waves which have been shown in studies involving patients to improve the healing of some wounds. They may act by promoting angiogenesis and reducing local inflammation, Shock waves may also improve the healing of venous ulcers but further studies are required to determine if this is the case. We have used shock wave therapy in our ward for the past year. This observational study is required to help us determine if shock wave therapy when used with routine care can improve healing rates of venous ulcers.

Your patient will receive shock wave therapy every two weeks in the outpatient clinic setting. If after 3 treatment sessions there is found to be an *improvement* in the ulcer the treatments will be continued at 2 weekly intervals to a maximum of 6 treatment sessions in total. Your patient will then continue the standard routine care (dressings and bandages) in the community until the ulcer is healed. If there has been no improvement after 3 sessions they will continue with standard care. Patients will be followed up for 6 months in the study.

Please feel free to contact me if you wish any further information of have any queries or concerns.

Yours sincerely

Appendix E

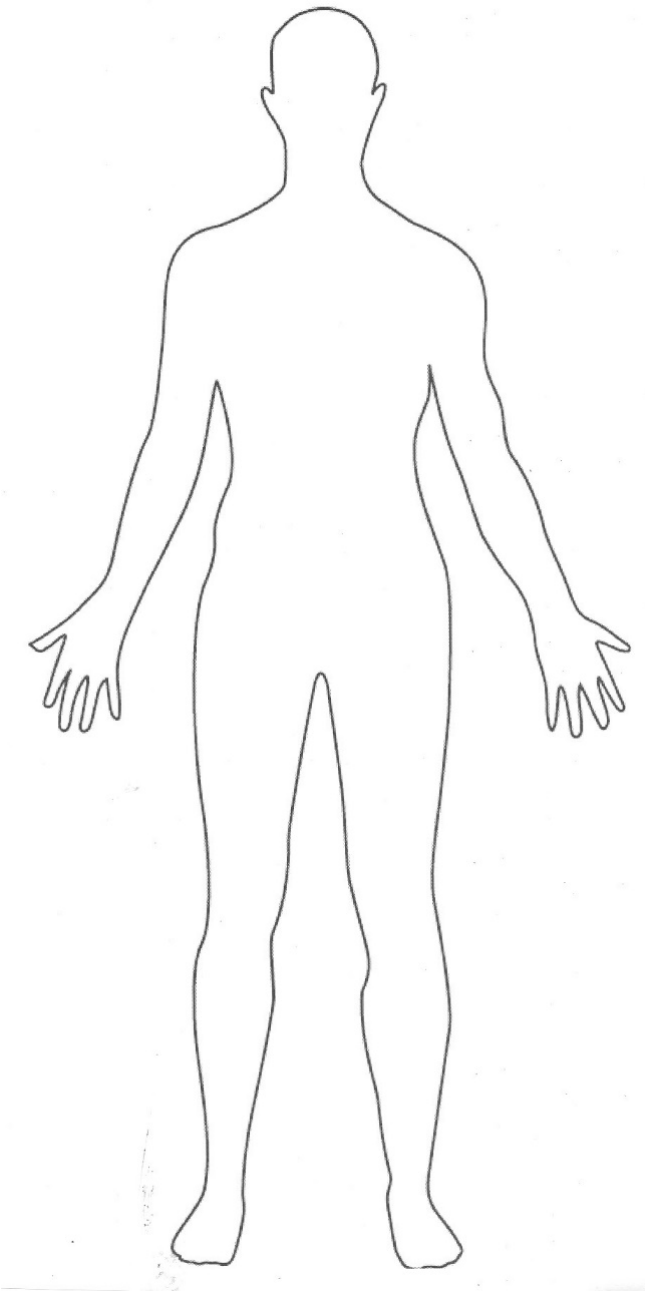
Baseline data collection form

Baseline/Demographic Data collection

Participant name	
NHS CHI	
Body Mass Index	
Age	
Employment status and type	
Socioeconomic status	
Residence	
Level of mobility	
Comorbidities	
Current medications	
Allergies	
Duration of current episode of ulceration	
Number of previous episodes of ulceration	
Length of time since first venous ulcer	
Previous intervention for venous insufficiency	
Varicose vein assessment - CEAP	
ABI – Left leg	
ABI – Right leg	
Duration of current compression therapy	
Ultrasound assessment – venous anatomy	
SFJ	
CFV	
SPJ	
POP	
GSV	
SSV	

Baseline Ulcer assessment

Number of active ulcers	
Reference ulcer number	
Ulcer appearance	
Edge	
Base	
Area ulcer 1	
Area ulcer 2	
Area ulcer 3	
Area ulcer 4	
Volume ulcer 1	
Volume ulcer 2	
Volume ulcer 3	
Volume ulcer 4	
Venous skin changes	



Appendix F

Documentation pertaining to ethical approval

NRES Committees - North of Scotland
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

NHS
Grampian

17 June 2013

Mr Ben Cooper
Department of Vascular Surgery
Ward 36
Aberdeen Royal Infirmary
Foresterhill Road
ABERDEEN
AB25 2ZN

Dear Mr Cooper

Study title:	**Extracorporeal shockwave for the treatment of chronic venous ulcers: An observational study**
REC reference:	**13/NS/0053**
Protocol number:	**3/019/13**
IRAS project ID:	**127290**

The Research Ethics Committee reviewed the above application at the meeting held on 13 June 2013.

Thank you for attending the meeting and clarifying the following points:

- The Committee queried the design of the study, in particular, whether the study was a trial, an observational study or feasibility study. You replied that the study was a feasibility study in relation to the previous study, which would provide more evidence to inform a Randomised Controlled Trial. The Committee wondered what more information you required for a Randomised Controlled Trial. You replied that all the evidence available on this procedure was very vague and it was hoped that this study would provide evidence to support it as a treatment in this field. The Committee added that in the Information Sheet it stated that the study was looking at healing rates, but did not feel that the design of the study would help achieve that. The Committee asked what the healing rate was being compared with. You replied that the healing rate would be compared by the two standard therapies. The Committee wondered whether the patients had been seen in the department before. You replied that the patients will have undergone compression treatment in the community either by the GP or the Practice Nurse. The Committee felt that it was not ethical to repeat the same study. You replied that this study differed from the original study as a broader range would be treated and the procedure being used was much more appropriate for venous ulcers.

- The Committee noted that the study covered a short intervention period but noted reference in the application that patients could have this condition for decades. You replied that patients receiving conventional treatment could live with this for years, but with this treatment, complete healing could be achieved in six sessions.

- The Committee wondered whether you would be comparing the venous ulcer with bi-lateral ulcers on the other leg. You replied that a single ulcer would be treated and the healing speed would monitored compared to the non-treated ulcers.

- The Committee noted in A31 that patients could have as long as they wished to consider taking part, but felt that this should be at least 24 hours. You replied that they would be given a minimum of 24 hours but in reality it would be longer.

- The Committee asked about the recruitment strategy for patients. You replied that the majority of patients would be from GP referral for ulcer treatment. They would be approached at their out-patient appointment. The Committee asked if the patients would be sent a letter. You replied that they would be sent information to see if they wanted to take part. The Committee noted that there was no Letter of Invitation included in the paperwork. You replied that a copy was included in the paperwork. The Committee asked how patients would indicate that they were interested in taking part in the study. You replied that they could telephone. You then added that the recruitment strategy had not been considered. The Committee suggested that this be discussed with the supervisor.

- The Committee noted that the Peer Review had been carried out by someone within the department rather than the Educational Supervisor. You replied that this had been done on the advice of the co-sponsor, the University of Aberdeen.

- The Committee noted that only the University of Aberdeen crest was used on the documentation and felt that this should be changed to the University of Aberdeen logo.

- The Committee wondered why a 'best contact' was being used for such a short study. You replied that it was handy to have this as good practice.

- The Committee noted that data from the study would be archived for 30 years and felt this was excessive. The Committee suggested that the MRC Guidelines, which stated 10 years, be followed. You replied that again, this was on the advice of the co-sponsor.

- The Committee noted that in the Information Sheet, payment was classed as a benefit to taking part in the study. The Committee did not think that payment should be listed as a benefit. The Committee felt that there were potential benefits associated with taking part in the study in terms of healing and quality of life and that these should have been listed. You replied that this had been debated with research colleagues and their advice had been that remuneration should be listed.

- The Committee asked why patients would be signing three copies of the Consent Form as this again was excessive. You replied that this was done on the advice of the co-sponsor.

- The Committee noted that completion of a Questionnaire at 6 weeks had not been included in the Information Sheet.

- The Committee asked whether this was your first project and whether GCP training had been undertaken. You replied yes to both.

- The Committee asked whether you would be treating the patients and collecting their data, and whether there would be an element of conflict of interest. You replied that there was no conflict of interest.

- The Committee wondered what proportion of patients would be bi-lateral. You replied that they would be in the minority, 10-15%. The Committee asked how just treating one ulcer would be justified to patients. You replied that the reason for not treating bi-laterally was more to do with the method of comparing the data. The focus would be on the index ulcer over a period of time. The largest and most chronic wound would be selected and treated.

- The Committee wondered how much pain the treatment would cause. You replied that this was in relation to adverse reactions and from the experience so far, none had been reported locally. You added that adverse reactions had been reported elsewhere and if this did occur, the patient would be assessed and the treatment stopped.

- The Committee wondered whether all ulcers were equal. You replied that it was not so much about size and shape of the ulcer but what had made it occur.

Ethical opinion

The members of the Committee present decided that it was unable to give a favourable ethical opinion of the research, for the following reasons:

- The Committee feel that the study design is not robust, does not include any scientific detail, lacks a power calculation and has no measurable outcomes.

- The Committee feel that there is a conflict of interest as you are not impartial.

- The Committee feel that more thought should be given to how the patients will be recruited.

I regret to inform you therefore that the application is not approved.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Dr Alex Johnstone.

Options for further ethical review

You may submit a new application for ethical review, taking into account the Committee's concerns. You should enter details of this application on the application form and include a copy of this letter, together with a covering letter explaining what changes have been made from the previous application. We strongly recommend that you submit the new application to this REC. However, you may submit the application to a different REC if you prefer.

Alternatively, you may appeal against the decision of the Committee by seeking a second opinion on this application from another Research Ethics Committee. The appeal would be based on the application form and supporting documentation reviewed by this Committee, without amendment. If you wish to appeal, you should notify the relevant Research Ethics Service manager (see below) in writing within 90 days of the date of this letter. If the appeal is allowed, another REC will be appointed to give a second opinion within 60 days and the second REC will be provided with a copy of the application, together with this letter and other relevant correspondence on the application. You will be notified of the arrangements for the meeting of the second REC and will be able to attend and/or make written representations if you wish to do so.

The contact point for appeals is:

Joan Kirkbride
Director of Operations
National Research Ethics Service

Email: joan.kirkbride@nhs.net

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
GP/Consultant Information Sheets	1	April 2013
Investigator CV: Julie Brittenden		May 2013
Student CV: Ben Cooper		18 April 2013
Supervisor's CV: Sheelagh Martindale		7 May 2013
Recruitment Log	1	May 2013
Participant Consent Form	1	13 April 2013
Participant Information Sheet	1	13 April 2013
Protocol	1	13 April 2013
Questionnaire: The Charing Cross Venous Ulcer Questionnaire		27 May 2013*
Questionnaire: EQ-5D-3L Health Questionnaire		27 May 2013*
Questionnaire: The SF-36v2 Health Survey		27 May 2013*
REC application	127290/455645/1/219	23 May 2013
Referees or other scientific critique report		23 May 2013

* date received

Membership of the Committee

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

Declarations of Interest

Declarations of interest were made by Dr Rhoda Mackenzie and Mrs Sian Roughton.

Statement of compliance

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

After ethical review

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

Here you will find links to the following:

a) Providing feedback. You are invited to give your view of the service you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website
b) Re-submission/Appeal.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

13/NS/0053	**Please quote this number on all correspondence**

Yours sincerely

Carol Irvine

pp **Dr Alex Johnstone**
Chair

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

Copy to: University of Aberdeen
Professor Julie Brittenden, NHS Grampian & Aberdeen University
NHSG R&D Department

NRES Committees - North of Scotland (2)

Attendance at Committee meeting on 13 June 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Dolapo Ayansina	Statistician	No	
Mr Stuart Bale	Lay Member - Retired HSE Manager - Shell	Yes	
Dr Hanne Bruhn	Research Fellow - Psychology	Yes	
Dr Jennifer Caldwell	Senior Lecturer in Occupational Therapy	Yes	
Dr Sarah Christie	Lay Member - Reader in Law	Yes	
Mr Gary Cooper	Quality Assurance Manager	Yes	
Dr Stuart Hannabuss	Lay Member - Independent Researcher	Yes	
Dr Georgina Hold	Alternate Vice-Chair & Senior Lecturer - Gastroenterology	Yes	
Mrs Baljit Jagpal	MRI Lead Superintendent	Yes	
Dr Alex Johnstone	Chair & Senior Scientist in Human Nutrition	Yes	
Dr Petr Kalous	Consultant Neonatologist	Yes	
Dr Kirsty Kiezebrink	RCUK Research Fellow in Obesity	Yes	
Miss Rhoda MacKenzie	Senior Lecturer in Medical Education. Vascular Surgeon	Yes	
Professor Iain McEwan	Professor - Personal chair in Molecular & Cellular Endocrinology	No	
Dr Jeremy Morse	Manager of Clinical Skills	No	
Mrs Sian Roughton	Practice Educator Intensive Care Unit/Honorary Lecturer Aberdeen University	Yes	
Dr Ruth Stephenson	Vice Chair and Consultant in Anaesthesia	Yes	
Mrs Fiona Watson	Lay Member - Ex Company Director	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Karen Gauld	Ethics Administrator
Mrs Carol Irvine	Ethics Co-ordinator

NHS Grampian

Prof Julie Brittenden

Consultant Vascular Surgeon &

Chair in Surgery, Aberdeen University

j.brittenden@abdn.ac.uk

Ben Cooper

Vascular Specialist Nurse

bencooper@nhs.net

JB/BC

Date 21/06/2013

Dear Dr Johnstone,

Reference: 13/NS/0053

Thank you for your letter regarding the above study. We are most disappointed with the opinion of the committee and feel that many of the issues raised can easily be addressed. In response to the points raised by the committee we have revised the ethical form, protocol and patient information leaflet.

We would be most grateful if the committee would consider this revised application in light of our responses. We believe that we have addressed all the issues raised. The principal investigator, Julie Brittenden apologises that she was unable to attend in person to the meeting on the 13th June will endeavour to attend in person for the next meeting.

Design of proposed study:

Response: This is an observational study. This is clearly stated in the protocol (protocol, section 6) and the ethical application (IRAS, A1, A7, A13).

Previous study:

Response: This was a retrospective safety/feasibility study only (protocol, section 5). We have no information regarding efficacy – we are unclear what effect if any, ECSW will have on healing rates of patients with venous ulcers who are undergoing standard compression therapy.

We apologise if it was not clear to the committee that this study is not repetitive. There is no available literature to inform us on the efficacy of ECSW therapy in patients with venous ulcers undergoing standard recommended compression therapy. We would like to reassure the committee that we are not repeating the same study.

The table below clearly summarises the differences. These differences have now been highlighted in the revised protocol.

	Previous study	**Current study**
Inclusion criteria		
Non-compliant to conventional treatment	Included	Excluded
Design	Retrospective Feasibility study	Prospective Observational study
Follow-up period	None	6 months
Number of treatment sessions	Not defined (mean 6 sessions)	3 initial sessions 3 further if responding
Primary End-points		
Ulcer healing rates at 6 months	Not assessed	To be assessed
Quality of life at six months	Not assessed	To be assessed
Secondary End-points		
Ulcer pain	Assessed	To be assessed
Exudate levels	Assessed	To be assessed
Ulcer recurrence	Not assessed	To be assessed
50% reduction in ulcer area	Assessed at 8 weeks only	To assess at 6 months

What is the Comparator?

Response: The SIGN guidelines on the management of venous ulcers and the Cochrane review clearly state expected healing rates of venous ulcers with standard compression therapy. These are specified at 12 and 24 weeks. We will assess the "gold-standard" outcome of complete ulcer healing at these time points. We have clarified this in the protocol (protocol, section 10).

Intervention period:

Response: We agree that this a chronic condition, but the reason for the intervention and follow-up period is addressed in point 3 above. Six months is the standard assessment period for studies in this area.

5) Comparison of venous ulcer with contralateral ulcer if present

Response: we have clearly stated in the protocol that "*The patient may have more than one ulcer, situated on one or both legs. A single, reference ulcer will be selected for treatment; this will be the ulcer thought most likely to be the slowest healing in the view of the clinical team. This judgement may be based upon its size, duration or appearance (slough, exudate, presence of infection etc.)*

In patients with multiple ulcers, where the reference ulcer only will be treated with ECWS, the secondary ulcers will also be measured and rate of healing determined for comparison. In cases where a single ulcer is studied, rate of healing will be compared to rates reported in literature".

6) Time for patient to consider taking part

Response: We have already stated in the protocol and ethical application that potential participants will have a minimum of 24 hours to consider whether they wish to take part in this study (protocol, section 7) (IRAS, A6-2, A27-1, A30-1, A31).

7) Recruitment

Response: We apologise for any confusion here. We will only recruit patients at clinics and patients will not be a sent a letter. They will be informed of the trial and potentially interested patients will be given a copy of the patient information leaflet. A clinic log will be taken and potentially interested patients will be contacted by phone after the clinic. This has been corrected on the IRAS form (IRAS, A27-1).

8) Peer review

This was done through the standard format as specified by the joint NHS Grampian/University of Aberdeen Sponsor. The educational supervisor has been heavily involved in the project and was a co-signature on the IRAS.

9) University Logo

Response: We apologise for this error. This has now been corrected.
(See revised patient information sheet).

10) Best contact

Response: We would be happy to exclude the best contact.
(See revised protocol, section 15) (IRAS A37, A38).

11) Archiving

Response: Thank you for clarification. We will amend this to 10 years.
(See revised protocol, section 15) (IRAS A43, A44).

12) Payment listed as benefit & potential benefits on patient information leaflet

Response: We stated that there is no payment for participation but have now removed this following the committee's comments. (See revised patient information sheet).

Potential benefits - we do not know if this treatment will improve quality of life or healing rates and therefore cannot mention it as a potential benefit. (See revised patient information sheet) (IRAS A24).

13) 3 copies of participant consent

Response: We will photocopy the one signed consent form and file one copy in the medical notes, one copy in our study master file and one copy will be given to the patient as per good clinical practice.

14) Completion of Questionnaire at 6 weeks

Response: Apologies, we have now included the 6 week time point in the patient information leaflet and revised protocol.

(Please see revised patient information sheet) (protocol, section 6).

15) Committee noted that this was the nurse specialist's first project

Response: This project is being done as part of an Msc. The nurse specialist will be supervised by both an experienced PI and educational supervisor. The PI and educational supervisor were unable to attend the meeting due to clinical/educational commitments and are of the opinion that many of the issues raised could have been addressed if they had the opportunity to attend.

16) Conflict of interest regarding treating and collecting the data

Response: Thank you for raising this issue. We would like to reassure the committee that this is not an issue for the primary outcome measures.

The primary outcome measures are: **1)** Time to complete healing - we have stated in the protocol that if the ulcer heals, a digital photograph will be taken and analysed by 2 independent assessors. **2)** QOL- which is patient reported. The patients will either complete this form before they see the research nurse or return it by post.

17) Reasons for only treating one leg in bilateral cases

Response: We have no evidence that this treatment will improve ulcer healing rates.

18) Pain induced by treatment

Response: We have stated that patients may experience some minor discomfort and bleeding (protocol, section 11) (IRAS A18).

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NHS
Grampian

15 July 2013

Mr Ben Cooper
Department of Vascular Surgery
Ward 36 Aberdeen Royal Infirmary
Foresterhill Road
ABERDEEN
AB25 2ZN

Dear Mr Cooper

Study title:	**Extracorporeal shockwave for the treatment of chronic venous ulcers: An observational study**
REC reference:	**13/NS/0084**
Protocol number:	**3/019/13**
IRAS project ID:	**127290**

The Research Ethics Committee reviewed the above application at the meeting held on 11 July 2013.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Dr Rachel Venables, rachel.venables@nhs.net.

Ethical opinion

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

Ethical review of research sites

NHS Sites

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

"Conditions of the favourable opinion" below).

Conditions of the favourable opinion

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

Thank you for attending the meeting with Professor Brittenden and clarifying the following points:

- The Committee asked when the photographs of the ulcers would be taken. Professor Brittenden replied that the photographs were taken as part of routine care and would allow them to be assessed by an Independent Assessor who would be a Clinician within the department. The Committee had noted that this was not mentioned on the Consent Form and asked if this could be included. You agreed to this.

- The Committee wondered if there would be the potential for bias with you being both the treatment provider and the assessor. You confirmed again that there would be independent assessment of the results.

- The Committee noted that on the IRAS application and the Participant Information Sheet there was no mention of the Questionnaires. You agreed to add these.

- The Committee asked about Recruitment Strategy and noted that you would be keeping a Clinic log of who had been given the Participant Information Sheet, which is not normally approved by the Committee. Professor Brittenden replied that only those who agree to be contacted will be placed on this log and contacted at a suitable time to discuss study participation.

- The Committee asked what records of personal information would be stored and how. You replied that only anonymised data would be stored on an NHS Computer, all personal details would be on paper and stored in a locked cupboard, which only you and Professor Brittenden would have access to.

- The Committee noted that a specific person had not been named as a Statistician. Professor Brittenden replied that this was the policy of the Statistics department and a name was not given until a specific advice had been received.

- The Committee wondered if it had been possible to translate the Italian paper and obtain any data from it. Professor Brittenden replied that there was an abstract available but they couldn't access the paper. This study that was being undertaken was a Comparison Study and as yet there is no evidence that this treatment works hence this study.

- The Committee asked if you would expect to see more than a 70% increase in the rate of healing of the ulcers. Professor Brittenden replied that this figure was what was expected with in 6 months of the standard treatment. This new treatment would quantify the effectiveness of it and compare it to standard therapy. Once this part of the study has been completed it may be possible to carry out a Randomised Controlled Trial but as yet there is no evidence for this.

- The Committee noted that in the Participant Information Sheet you had said there were no potential benefits to the participants. Professor Brittenden informed the Committee that they did not know if they would be any benefits and would not give participants a false hope that this might be better than standard treatment.

- The Committee asked what the definition of a non-healing ulcer was. Professor Brittenden replied that it was an ulcer that had not healed after 6 weeks of standard treatment.

- The Committee asked if funding had been received from the NHS Endowments fund. Professor Brittenden replied that no funding had been obtained from this source.

- The Committee wondered if participants who had taken part in the Feasibility Study would be able to participate in this study. Professor Brittenden replied that the participants who had previously taken part had not been able to tolerate standard treatment which is compression and as this was a part of this study they would not be included.

Additional Conditions

- A36 - please confirm where personal details will be stored.

Participant Information Sheet

- Please include the number of questionnaires and the frequency with which the participant would be asked to complete them.

Consent Form

- Please include a point for permission to access photographs of ulcers for analysis.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

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

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter		21 June 2013
Investigator CV – Professor Julie Brittenden		31 May 2013
Unfavourable Opinion Letter		17 June 2013
Student CV: Ben Cooper		18 April 2013
Supervisor's CV: Sheelagh Martindale		07 May 2013
Letter to GP	2	22 June 2013
Participant Consent Form	2	22 June 2013
Participant Information Sheet	2	22 June 2013
Protocol	2	22 June 2013
Questionnaire: The Charing Cross Venous Ulcer		*28 June 2013
Questionnaire: EQ-5D-3L Health Questionnaire		*28 June 2013
Questionnaire: The SF-36v2 Health Survey		*28 June 2013
REC application	127290/470 123/1/2	26 June 2013
Referees or other scientific critique report		25 June 2013

*date received

Membership of the Committee

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

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

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

Further information is available at National Research Ethics Service website > After Review

13/NS/0084	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

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

Yours sincerely

pp

Dr Alex Johnstone
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments
After ethical review – guidance for researchers

Copy to: Professor Julie Brittenden, NHS Grampian & Aberdeen University
NHS Grampian R&D Department
University of Aberdeen

North of Scotland Research Ethics Committee (2)

Attendance at Committee meeting on 11 July 2013

Committee Members:

Name	Profession	Present
Dr Dolapo Ayansina	Statistician	No
Mr Stuart Bale	Lay Member - Retired HSE Manager - Shell	Yes
Mr Russell Brinklow	Community Psychiatric Nurse	No
Dr Hanne Bruhn	Research Fellow - Psychology	Yes
Dr Jennifer Caldwell	Senior Lecturer in Occupational Therapy	Yes
Dr Sarah Christie	Lay Member - Reader in Law	Yes
Mr Gary Cooper	Quality Assurance Manager	Yes
Dr Karen Forrest Keenan	Post Doctoral Research Fellow	No
Dr Stuart Hannabuss	Lay Member - Independent Researcher	Yes
Dr Georgina Hold	Alternate Vice-Chair & Senior Lecturer - Gastroenterology	Yes
Mrs Baljit Jagpal	MRI Lead Superintendent	Yes
Dr Alex Johnstone	Chair & Senior Scientist in Human Nutrition	Yes
Dr Petr Kalous	Consultant Neonatologist	No
Dr Kirsty Kiezebrink	RCUK Research Fellow in Obesity	Yes
Miss Rhoda MacKenzie	Senior Lecturer in Medical Education. Vascular Surgeon	No
Professor Iain McEwan	Professor - Personal chair in Molecular & Cellular Endocrinology	Yes
Dr Jeremy Morse	Manager of Clinical Skills	Yes
Mrs Sian Roughton	Practice Educator Intensive Care Unit/Honorary Lecturer Aberdeen University	Yes
Dr Ruth Stephenson	Vice Chair and Consultant in Anaesthesia	Yes
Mrs Fiona Watson	Lay Member - Ex Company Director	Yes

Also in attendance:

Name	Position (or reason for attending)
Miss Karen Gauld	Ethics Administrator
Dr Rachel Venables	Scientific Officer

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NHS
Grampian

12 August 2013

Mr Ben Cooper
Department of Vascular Surgery
Ward 36
Aberdeen Royal Infirmary
Foresterhill Road
ABERDEEN
AB25 2ZN

Dear Mr Cooper

Study title:	**Extracorporeal shockwave for the treatment of chronic venous ulcers: An observational study**
REC reference:	**13/NS/0084**
Protocol number:	**3/019/13**
IRAS project ID:	**127290**

Thank you for your letter of 12 August 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 15 July 2013.

Documents received

The documents received were as follows:

Document	Version	Date
Covering Letter		12 August 2013

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date
Covering Letter		21 June 2013
Covering Letter		12 August 2013

Investigator CV – Julie Brittenden		May 2013
Unfavourable Opinion Letter		17 June 2013
Student CV: Ben Cooper		18 April 2013
Supervisor's CV: Sheelagh Martindale		07 May 2013
Letter to GP	2	22 June 2013
Participant Consent Form	2	22 June 2013
Participant Information Sheet	2	22 June 2013
Protocol	2	22 June 2013
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Questionnaire: The SF-36v2 Health Survey		*28 June 2013
REC application	127290/470 123/1/2	26 June 2013
Referees or other scientific critique report		25 June 2013

* date received

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

13/NS/0084 **Please quote this number on all correspondence**

Yours sincerely

RS Venables

Rachel Venables PhD
Scientific Officer

Copy to: Professor Julie Brittenden
University of Aberdeen
NHS Grampian R&D Department

Research and Development

Mr Ben Cooper NHS Grampian

Ward 36 - Aberdeen Royal Infirmary

Department Of Vascular Surgery

Foresterhill Road

Aberdeen

AB25 2ZN

Foresterhill House Annexe
Foresterhill
ABERDEEN
AB25 2ZB

Date 08/10/2013
Project No 2013VA002

Enquiries to Lynn Massie
Extension 53846
Direct Line 01224 553846
Email grampian.randdpermissions@nhs.net

Dear Mr Cooper

Management Permission for Non-Commercial Research

STUDY TITLE: Extracorporeal shockwave for the treatment of chronic venous ulcers: An observational study

PROTOCOL NO: v2.0; 22 June 2013

REC REF: 13/NS/0084

Thank you very much for sending all relevant documentation. I am pleased to confirm that the project is now registered with the NHS Grampian Research & Development Office. The project now has R & D Management Permission to proceed locally. This is based on the documents received from yourself and the relevant Approvals being in place.

All research with an NHS element is subject to the Research Governance Framework for Health and Community Care (2006, 2nd edition), and as Chief or Principal Investigator you should be fully committed to your responsibilities associated with this.

It is particularly important that you inform us when the study terminates.

The R&D Office must be notified immediately and any relevant documents forwarded to us if any of the following occur:

- A change of Principal Investigator, Chief Investigator or any additional research personnel
- Premature project termination
- Any amendments – substantial or non-substantial (particularly a study extension) ▪ Any change to funding or any additional funding

We hope the project goes well, and if you need any help or advice relating to your R&D Management Permission, please do not hesitate to contact the office.

Yours sincerely

Susan Ridge
Non-Commercial Manager

c.c. Professor Julie Brittenden
c.c. Dr Gail Holland NHSG-RD-DOC-019 – V3.1 – R&D Management Permission Letter

(Non CTIMP)

Ben Cooper

Ward 36

Aberdeen Royal Infirmary

Date: 10th September 2013

Research proposal number: **13-20**

Research proposal title: Extracorporeal shockwave for the treatment of chronic venous ulcers: an observational study

Dear Ben

The School of Nursing and Midwifery Ethics Review Panel has now reviewed the above research proposal. Please find details of the outcome and recommended actions below.

☐	Proposal approved ✓	You may go ahead with your research, providing approval from any relevant external committee/s has been obtained.*
☐	Proposal approved subject to amendments.	Please review and amend all relevant documents in the light of the comments given, then forward them to the Convenor who will give final approval.
☐	Proposal not approved: significant ethical issues as yet inadequately addressed.	Please review your proposal in light of the issues identified. If you require further clarification or discussion please contact the Convenor. You are welcome to re-submit your proposal when the issues of
☐	Proposal referred to RES and/or the University Ethics sub committee.	Some proposals require consideration and input from colleagues outwith the School of Nursing and Midwifery. We will keep you informed of progress in this regard, and involved in the process as appropriate.

* Where research involves NHS staff or patients, approval through the NRES system must be obtained. Members of the School Panel can advise on this process if necessary.

Comments

Dear Ben

Thank you for your clarification and minor amendments in response to the points raised in review. These are satisfactory and this letter confirms approval from the School's Ethics Review Panel.

Kind regards

Dr Colin Macduff

Acting Convenor

School of Nursing and Midwifery Ethics Review Panel

If you require further information please contact the Acting Panel Convenor, Colin Macduff on 01224 262935

Appendix G

Documentation pertaining to NHSG R&D monitoring

Research & Development

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NHS Grampian

Mr Ben Cooper
Vascular Specialist Nurse
Ward 507
ARI
Foresterhill
AB25 2ZD

Tel NHS internal: 59152
Tel external: 01224 559152
d.stuchbury@nhs.net

Date: 06/05/14

Dear Ben

Project ID - 2013VA002
Project Title – Extracorporeal shockwave for the treatment of chronic venous ulcers: An observational study

Thank you for your participation in the monitoring process. Please find enclosed a copy of the Monitoring Report. Comments and findings are colour coded using a traffic light system. This system highlights significance in either red (requires immediate attention), amber (discuss and review) or green (no further action required). There were no red findings at this visit. I would be grateful if you could review the action points on page 3. I will contact you again shortly to confirm these have been resolved.

I will also send a copy to Dr Gail Holland, Research Governance manager, as sponsor representative.

Should you have any queries please do not hesitate to contact me.

Yours Sincerely,

Diane Stuchbury

Diane Stuchbury
Research Monitor

CC;
Dr Gail Holland, Research Governance Manager, University of Aberdeen & NHS Grampian

Monitoring Visit Report

NHS Grampian

R&D ID: 2013VA002	Sponsor: University of Aberdeen
Principal Investigator: Mr Ben Cooper	
Project Title:- Extracorporeal shockwave for the treatment of chronic venous ulcers: An observational study	
Study Initiation Date:- N/A	Predicted Study End Date:- 09/10/15
Monitor Names:- Diane Stuchbury	

Site Monitoring Visit.
Visit Location: Ward 507
Date : 29/04/14

Staff present during visit:- Ben Cooper and Professor Julie Brittenden

Brief summary of visit

The visit went very well. Ben and Professor Brittenden were very helpful.

Current recruitment status

Participants Recruited: 13	Participants Withdrawn: 0
Expected recruitment from protocol: 30	Overall recruitment status: ongoing

Training and resources

Confirm study has delegation log	Yes ✓ No ☐	
Confirm PI signature is present for all staff	Yes ☐ No ✓	Missing for Paul Bachoo
Confirm CVs for all staff on delegation log	Yes ☐ No ✓	Missing for Paul Bachoo
Confirm all staff have GCP training	Yes ✓ No ☐	Paul Bachoo completed GCP in 2011.
Confirm any changes to site facilities since site initiation/ previous monitoring visit	N/A	
Confirm site facilities remain/are suitable for conducting the study	Yes ✓ No ☐	
Any further comments:		

Monitoring Visit Report

TMF and ISF		
Confirm all trial documentation are correctly and securely stored	Yes ☐ No ✓	Missing documents
Confirm study team has access to documents required to conduct the trial.	Yes✓ No ☐	
Confirm there is an adequate TMF Index	Yes ✓ No ☐	
Complete TMF/ISF essential documents checklist – Appendix 1	Yes ✓ No ☐	
Any further comments: Ethics submission, response and approval missing		
Informed Consent		
Number of consent forms reviewed: 11		
Confirm correct storage of completed consent forms.	Yes☐ No ✓	Stored with patient wound/ulcer photographs and hand written notes in a separate file. **Ben had created a note to file to explain where held.**
Confirm number of consent forms match total number of participant s included in study	Yes☐ No ✓	2 consent forms missing
Confirm participant numbers match the enrolment log	Yes ✓ No ☐	
Complete Monitoring Consent Review Log – Appendix 2	Yes ✓No ☐	
Any further comments: 6 consent forms had wrong version of information sheet documented. 3 had boxes ticked and not initialled. Ben has documented patient name and date on 9 consent forms. 1 error not corrected appropriately. Study number added randomly to consent forms		
Protocol deviations		
Have any protocol deviations been found during visit	Yes ☐ No ✓	
Any other comments:		
General comments		
Study staff were helpful and responded to queries	Yes ✓ No ☐	
Any further comments: **Reminder that annual progress report due in August 2014**		

Action points	Date Resolved	Resolution comments
Training and resources: Paul Bachoo to provide CV and add his signature and initials to delegation log **Paul Bachoo to update GCP training**		

Monitoring Visit Report

TMF and ISF: Ben to file copies of ethics submission, response and approval		
Informed consent: Ben to separate consent forms from photographs and hand written notes and file consent forms in TMF. Remove file note.		
Ben to file 2 missing original consents in TMF and place copies in the medical notes		Ben discussed these were to be found in patient's medical notes
Ben to provide Note to file to explain reason's for completing patient's name and date. Diane to provide note to file template	06/05/14	Diane discussed with Ben Participants should document their own name and date. Discussed SOP 10 and Ben aware this and further SOP information is available on Research Governance website. www.abdn.ac.uk/medical/researchgovernanceDiane
Error correction	29/04/14	discussed with Ben the appropriate way for error correction
In the future, Ben to remove V1.1 information sheet' from consent form V2 (pre populated). Ben to confirm correct information sheet V2 given to participants		
Boxes ticked not initialled	29/04/14	Discussed. Ben to check boxes initialled when taking consent
Ben to document study number in space provided on consent form	29/04/14	Discussed at visit

Monitoring report completed by		
Name (Print)	**Signature**	**Date**
Diane Stuchbury Non Commercial Research Monitor	Diane Stuchbury	5-5-14

Monitoring Visit Report

R&D Review		
Name (Print)	**Signature**	**Date**
Dr Joanne Rodger R&D manager University of Aberdeen & NHS Grampian		05/05/14
Dr Gail Holland Research Governance Manager University of Aberdeen & NHS Grampian	G. Holland	06 May 2014

NHS Grampian

Ben Cooper
Vascular Specialist Nurse Vascular Unit - Ward 507
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZN

Direct Line (01224) 552571
Fax (01224) 552553
Email to bencooper@nhs.net

Dear Diane,

Thank you for the feedback following your recent study monitoring visit. Please see below list of action points highlighted and the actions now taken in response. Should any further information be required please do not hesitate to get back in touch. Many thanks

Ben Cooper

Action points to be addressed	Action taken
Signature missing on delegate log for Paul Bachoo	Now completed by Paul Bachoo
CV missing for Paul Bachoo	Now filed in TMF
Ethics submission, response and approval missing from TMF	Files located and now stored within TMF
Signed consent forms stored with participant source docs and not TMF	Rectified – signed consent forms now stored within TMF
2 missing consent docs	Medical notes ordered to locate missing files
Some details on consent forms filled in by researcher (date, printed name) – provide note to file	Note to file added to TMF to explain reason for assisting several participants. In future this will not occur and participants will entirely complete
Error correction incorrectly documented	Correct method discussed during site vist/monitoring. This will be utilised in future
V1.1 info sheet described in consent V2	Correction made to corresponding docs
Some consent form boxes ticked not initialled	Discussed during site visit – all future consent forms to be completed with initials
Study number to be documented within space provided on consent form	Rectified – existing forms completed and counter signed. Future consent forms will be correctly completed

Research & Development

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NHS Grampian

Mr Ben Cooper
Vascular Specialist Nurse
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Foresterhill
AB25 2ZD

Tel NHS internal: 59152
Tel external: 01224 559152
d.stuchbury@nhs.net

Date: 17/06/14

Dear Ben

Project ID - 2013VA002

Many thanks for your response to our monitoring visit action points. This letter is to confirm that we are happy with your resolutions and the monitoring visit is now closed.

The team's commitment to the monitoring process and to the trial as a whole is commendable.

If you have any comments or have questions regarding other studies, please do not hesitate to contact us.

Yours sincerely,

Diane Stuchbury

Diane Stuchbury
Research Monitor