The Clinical Efficacy & Feasibility of using Horsechestnut Seed Extract in the Treatment of Venous Leg Ulceration

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The Clinical Efficacy & Feasibility of using Horsechestnut Seed Extract in the Treatment of Venous Leg Ulceration

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A thesis submitted in partial fulfillment of the requirements for the award of

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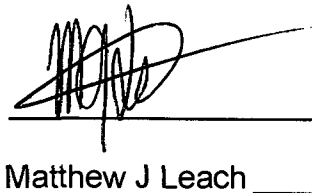
List of Abbreviations

ABPI:	Ankle Brachial Pressure Index
ACTH:	Adrenocorticotropic Hormone
ADR:	Adverse Drug Reactions
ADRAC:	Adverse Drug Reactions Advisory Committee
AMWIS:	Alfred-Medseed Wound Imaging System
ATP:	Adenosine Triphosphate
BD:	Twice Daily
BMI:	Body Mass Index
CBA:	Cost Benefit Analysis
CN:	Clinical Nurse
CNC:	Clinical Nurse Consultant
CTN:	Clinical Trial Notification
CV:	Content Validity Index
CVI:	Chronic Venous Insufficiency
DVT:	Deep Vein Thrombosis
EBP:	Evidence Based Practice
EN:	Enrolled Nurse
GP:	General Practitioner
HCSE:	Horsechestnut Seed Extract.
HR:	0-(β-hydroxyethyl)-rutosides
HREC:	Human Research Ethics Committee
IV:	Intravenous
LD_{50}:	Lethal Dose resulting in fifty percent mortality
MP:	Medical Practitioner
NO:	Nitric Oxide
PCS:	Paired Coding System
PSPL:	Post-Subfascial Perforator Ligation
PSST:	Pressure Sore Status Tool
PUSH:	Pressure Ulcer Scale for Healing
QID:	Four times a day

RCT:	Randomised Controlled Trial
RM-ANOVA:	Repeated Measures – Analysis Of Variance
RN:	Registered Nurse
SD:	Standard Deviation
SPSS:	Statistical Package for the Social Sciences
SVT:	Systemic Venous Therapy
SWHT:	Sussman Wound Healing Tool
TDS:	Three times a day
TGA:	Therapeutic Goods Administration
TNF-α:	Tumour Necrosis Factor - alpha
VLU:	Venous Leg Ulcer.
WAT:	Wound Assessment Tool
WCSAC:	Wound Care Society Assessment Chart
WHS:	Wound Healing Scale
WHST:	Wound Healing Society Tool (WHST)

DECLARATION

" I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the University of South Australia or any other institute of higher learning, except where due acknowledgement has been made in the text "

Signature: 

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ABSTRACT

Venous leg ulceration (VLU) affects roughly 0.6 percent of the western population, with the management of this condition in Australia alone accounting for between AUD$554 and AUD$655 million in health care expenditure every year. Apart from these financial implications, VLU is also associated with a number of adverse psychosocial effects, including depression, anxiety, social isolation, impaired mobility and reduced working capacity. Whilst compression therapy remains the primary treatment of choice for VLU, discomfort, poor compliance and potentially serious complications demand that a more convenient, safer and efficacious treatment of venous ulceration be developed. A herbal extract proposed to advance venous ulcer healing through its venotonic, anti-inflammatory, anti-oedema, anti-enzymatic and anti-exudative properties is Horsechestnut Seed Extract (HCSE).

The clinical feasibility of using HCSE in the treatment of VLU was explored across four investigations. The first study (Stage I) used a triple-blind, randomised, placebo-controlled trial to examine the clinical efficacy of HCSE. This trial was designed to test the primary hypothesis that orally administered HCSE is associated with a significant increase in the number of healed venous leg ulcers when compared to placebo at week twelve. Fifty-four participants with venous leg ulceration were enrolled in the trial and randomly assigned to the HCSE or placebo group for twelve weeks. Ulcers were assessed at baseline and then at weeks four, eight and twelve by using the wound assessment tool (WAT) and the Alfred-Medseed Wound Imaging System (AMWIS). The difference between groups in the

number of healed venous leg ulcers, as well as the change in wound surface area, depth, volume, pain and exudation, was not found to be statistically significant. However, HCSE did have a significant effect on the percentage of wound slough over time ($F=2.76$, $p=0.045$), and in the number of dressing changes at week twelve ($t=-2.71$, $p=0.009$). In terms of tolerance, the number of participants reporting an adverse effect in the HCSE group was significantly greater than that reported in the placebo group ($\chi^2=6.03$, $p=0.014$), although the reactions to HCSE were generally mild and transient in nature.

In the second investigation (stage II), a comparative case study was conducted to identify the types of patients that were most likely to benefit from HCSE therapy. From the two characteristic cases of wound healing, and the two archetypal cases of non-healing that were selected from the HCSE and placebo groups, a number of predictors of VLU healing were identified. Firstly, it was established that treating VLU with placebo may be most effective in female patients with smaller, less chronic wounds, and in those without signs of heavy wound colonisation. For patients treated with HCSE, it is likely that treatment will be most effective in those with mild to moderate chronic venous insufficiency (CVI), smaller, less chronic wounds, a shorter history of ulceration, and in those without signs of wound infection.

The third study (stage III) compared the difference in treatment costs between the HCSE and placebo groups, including the cost of nursing care, dressing materials and HCSE. Horsechestnut Seed Extract was found to be a more cost-effective treatment of venous ulceration than placebo. In fact, incorporating HCSE into the management of VLU saved the health care provider around AUD$101 per patient,

per week, with an average saving of AUD$95 in organisational costs, and AUD$10 in dressing materials.

The fourth study (stage IV) used a descriptive survey to investigate the feasibility of integrating HCSE into mainstream care by exploring client and practitioner opinion and use of natural medicine, venotonic therapy and HCSE within the context of VLU management. The self-administered questionnaire was mailed to a convenience sample of 122 district nurses and 63 stage I-exposed clients with VLU, and to a random sample of 85 medical practitioners throughout metropolitan Adelaide, yielding a response rate of 32, 79 and 33 percent, respectively. Of the three groups surveyed, nurses were the most likely to support and use HCSE, venotonic agents, and other natural modalities in the management of VLU, while clients were the most amenable to using these therapies in future. Even so, it is unlikely that many patients and practitioners would use these treatments in the management of VLU given the paucity of clinical evidence and the lack of personal knowledge. Notwithstanding, the modest response rate and the small sample of clinicians in this study suggests that further investigation is needed to corroborate these findings.

Even though HCSE is likely to hamper the pathogenesis of venous insufficiency, and in turn, facilitate venous ulcer healing, the stage I trial did not support such a claim. However, taking into account the small sample and insufficient power of the stage I trial, and the significant improvement in wound slough, visit frequency and organisational costs, it appears that HCSE may be useful in the management of VLU. The clinical efficacy and feasibility of using HCSE in the treatment of venous ulceration therefore warrants further investigation.

Keywords: Comparative case study; Cost-benefit analysis; Descriptive survey; Horsechestnut Seed Extract; Natural medicine; Randomised controlled trial; Venous leg ulceration; Venotonic therapy.

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

The use of natural medicine by the general population, and among health care professionals, is increasing worldwide (Lewith, Hyland & Gray 2001; Stone 1999; Tattam 1995; Zollman & Vickers 1999). This surge in public interest has been attributed to a decrease in client satisfaction with orthodox medicine (Zollman & Vickers 1999), as well as an increase in patient responsibility over personal health and wellbeing (Chadwick 1999; Sirois & Gick 2002). Nurses, however, may be turning to complementary medicine in order to support patient health and healing (McCabe 1996), to augment nursing practice (Leach 2002; Taylor 1996), and to improve professional autonomy (Chadwick 1999). Medical practitioners (MPs), on the other hand, may choose to use natural modalities to complement orthodox treatment when conventional techniques are ineffective (Marshall, Gee, Israel, Neave, Edwards, Dumble, Wong, Chan, Patel, Poon & Tam 1990; Verhoef & Sutherland 1995). This shift toward natural medicine may therefore indicate a need to improve upon the range of existing health care options in order to effectively meet patient needs.

Mounting interest in complementary medicine is particularly evident among individuals with skin disorders (Ernst 2000), with the lifetime prevalence of these patients using natural therapies ranging from thirty-five to sixty-nine percent (Ernst 2000). In fact, the use of these modalities is reported to be most prevalent among clients with chronic and severe skin conditions (Berg & Arnetz 1998; Ernst 2000; Sirois & Gick 2002). One reason why these patients may be turning to complementary medicine is that conventional practice is not yet effective at preventing or treating chronic disorders (Coates & Jobst 1998;

White 2003). Even so, sound clinical evidence is needed to confirm that these therapies are in fact safe and effective in the treatment of chronic wounds.

1.2 Background and Statement of the Problem

The most prevalent type of chronic wound in the western world is venous leg ulceration (VLU) (Lopez & Phillips 1998; Ouahes & Phillips 1995; The Alexander House Group 1992), which affects around 0.6 percent of the western population (Nelzen, Bergqvist & Lindhagen 1996). The prevalence, as well as the chronic and recurrent nature of VLU, may explain why the management of this condition accounts for more than one percent of total health care expenditure in the United Kingdom and France (Baker & Stacey 1994), which does not include the indirect costs associated with social isolation, immobility, pain, depression and unemployment. Despite the fact that venous ulceration is a major health issue, there is still a limited range of treatment options available to patients.

There appears to be consensus that the treatment of VLU should be focussed on addressing the aetiology of the wound (Ouahes & Phillips 1995; Zimmet 1999), that is, the underlying venous insufficiency. Compression therapy partially addresses this insufficiency, and is consequently the cornerstone of treatment in Australia, the United States and the United Kingdom. Notwithstanding, the safety and efficacy of compression therapy as a treatment of VLU remains debatable. The application of topical dressings in the management of VLU is also controversial as most products fail to address the underlying aetiology of the wound. The treatment of chronic venous insufficiency (CVI) with venotonic agents, such as Horsechestnut Seed Extract

(HCSE), may instead provide a more appropriate and effective solution to the management of venous ulceration.

The seeds of the Horsechestnut tree have been used for their venotonic effects since the late sixteenth century (Blumenthal 2003), but in recent years, have demonstrated a number of additional pharmacological effects, including anti-oedema (Mills & Bone 2000; Sirtori 2001); anti-inflammatory (Mills & Bone 2000; Sirtori 2001); anti-exudative (Bruneton 1995; Gruenwald, Brendler & Jaenicke 2000; Rothkopf & Vogel 1976) and astringent activity (Ody 1993). It is argued that these properties are essential for the effective treatment of venous disorders with irreversible dilation (Annoni, Mauri, Marincola & Resele 1979). Therefore, given that HCSE attenuates the pathogenesis of CVI, and venous insufficiency is the precursor of VLU, it is likely that HCSE will hasten wound healing and reduce ulcer recurrence. However, the effectiveness of HCSE as a treatment of venous ulceration has not been explored. Furthermore, if evidence was available, it remains unclear if practitioners and clients would use HCSE or other venotonic agents in the management of VLU. Therefore, the primary purpose of this thesis was to evaluate the clinical efficacy, cost-effectiveness and feasibility of using orally administered HCSE in the treatment of venous ulceration. A flow chart of this four-stage investigation is illustrated in Appendix 1.

1.3 Aims and Objectives of the Study

Each stage of the thesis was developed around the following conceptual aims and objectives, which are later operationalised in chapters three, five, six and eight.

Stage I: Randomised Controlled Trial

Aim:

- To determine whether orally administered HCSE improves venous ulcer healing.

Objectives:

- To test the primary hypothesis that HCSE treatment is associated with a significant increase in the number of healed venous leg ulcers when compared to placebo.
- To test the secondary hypothesis that HCSE treatment is associated with a significant reduction in wound size.
- To test the secondary hypothesis that HCSE treatment is associated with a significant reduction in the severity of venous insufficiency symptoms.
- To test the secondary hypothesis that HCSE treatment is associated with a significant improvement in wound topography.
- To test the secondary hypothesis that HCSE treatment is associated with a significant reduction in wound size and leg ulcer incidence after the intervention is ceased.

Stage II: Comparative case study

Aim:

- To explore why venous ulcer healing only occurs in some patients receiving HCSE and placebo treatment.

Objectives:

- To identify the factors that predict venous ulcer healing in patients receiving HCSE and placebo treatment.

- To discuss the types of patients that may benefit from HCSE or placebo treatment in the management of venous ulceration.

Stage III: Cost Benefit Analysis

Aim:

- To determine whether the treatment of venous ulceration with HCSE and conventional therapy is more cost effective than conventional treatment.

Objective:

- To establish the relative costs of treating venous ulceration with HCSE in comparison to placebo.

Stage IV: Descriptive Survey

Aim:

- To explore client, district nurse and medical practitioner opinion, and current and future use, of natural medicine, venotonic therapy and HCSE in relation to venous ulceration.

Objectives:

- To answer the question do district nurses, medical practitioners and clients believe that natural medicine, venotonic therapy and HCSE are safe, effective and suitable for the treatment of venous ulceration?
- To answer the question do clients, district nurses and medical practitioners use natural medicine, venotonic therapy or HCSE in the management of venous ulceration?
- To answer the question do clients, district nurses and medical practitioners plan to use natural medicine, venotonic therapy or HCSE for venous ulceration in future?

- To answer the question is there any association between participant characteristics and subject opinion of natural medicine, venotonic therapy and HCSE, or with the clinical application of HCSE?

1.4 Rationale & Theoretical Framework

Evidence-based practice (EBP) is a formal problem-solving framework (Montori & Guyatt 2002) that facilitates '...the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients' (Sackett, Rosenberg, Muir Gray, Haynes & Richardson 1996: 71). Apart from the implications on clinical practice, the capacity of EBP to link study findings to a profession's body of knowledge also indicates that evidence-based practice is a useful theoretical framework for research, and may therefore provide an effective solution to the research-practice divide (Pape 2003; Trinder 2000).

Archibald Cochrane, a Scottish medical epidemiologist, conceived the concept of best practice in the early 1970s (Hill 2000; McKenna, Ashton & Keeney 2004). However, it was not until after Cochrane's death in the late 1980s that medicine began to demonstrate an interest in the evidence-based practice paradigm with the establishment of the Cochrane collaboration (Hill 2000; Reynolds 2000). Since then, professional interest in EBP has grown (Closs & Cheater 1999; Evans 2003; Leung 2001; Straus & McAlister 2000; Tod, Palfreyman & Burke 2004). This shift toward EBP has allowed health professionals to move from a culture of delivering care based on tradition, intuition, authority and pathophysiologic rationale, to a situation where decisions are guided and justified by the best available evidence (Evidence-based medicine working group 1992; McKenna *et al* 2004; Montori & Guyatt 2002;

Pape 2003; Romyn, Allen, Boschma, Duncan, Edgecombe, Jensen, Ross-Kerr, Marck, Salsali, Tourangeau & Warnock 2003; Sackett & Rosenberg 1995; Tod *et al* 2004; Trinder 2000). EBP therefore limits practitioner and consumer dependence on evidence provided by privileged persons and authorities (Trinder 2000) by bestowing clinicians with a framework to critically evaluate claims. Even so, there remains some debate over the definition of evidence in the EBP paradigm (Romyn *et al* 2003).

1.4.1 DEFINING EVIDENCE

Evidence is a fundamental concept of the EBP paradigm. Even so, there is little agreement between practitioners, academics and professional bodies as to the meaning of evidence. Indeed, the insufficient definition of evidence and the different methodological positions of clinicians and academics may all contribute to these discrepant viewpoints. From the broadest sense, evidence is defined as '...any empirical observation about the apparent relation between events' (Montori & Guyatt 2002: 522). Whilst this definition suggests that most forms of knowledge could be considered evidence, Romyn *et al* (2003: 186) assert that the evidence used to guide practice should be '...subjected to historic or scientific evaluation'. Hence, not all evidence is considered the same. These differences in the quality of information are known as the hierarchy of evidence.

The hierarchy of evidence informs practitioners which information is likely to provide the greatest impact on clinical decisions (Montori & Guyatt 2002). According to Table 1.1, decisions based on findings from randomised controlled trials (RCTs) may therefore be more sound than those guided by case series results. It was for this reason that the stage I study utilised an RCT design (see

chapter 3). When findings from controlled trials are unavailable or insufficient, however, decisions should be guided by the next best available evidence (Closs & Cheater 1999; Sackett *et al* 1996). Hence, a comparative case study was incorporated into the thesis to support the stage I results (see chapter 5). The hierarchy of evidence can also be used to identify research findings that supersede and invalidate previously accepted treatments and replace them with interventions that are more safe, efficacious and cost effective (Pape 2003; Sackett *et al* 1996). For these reasons, clinical decision-making may benefit from using EBP and the hierarchy of evidence.

Table 1.1: The hierarchy of evidence

Level I	Systematic reviews
Level II	Well designed randomised controlled trials
Level III-1	Pseudo-randomised controlled trials
Level III-2	Comparative studies with concurrent controls, such as cohort studies, case-control studies or interrupted time series studies
Level III-3	Comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
Level IV	Case series and pre-test / post-test studies

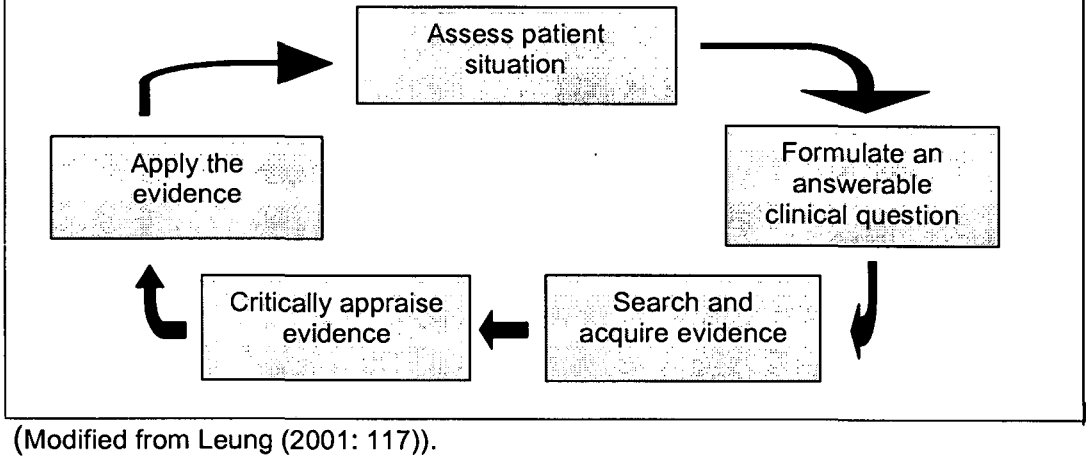
(National Health & Medical Research Council (1999: 56)).

1.4.2 THE EVIDENCE-BASED PRACTICE FRAMEWORK

The EBP paradigm consists of a series of steps that assist the practitioner in finding a solution to a clinical problem (see Figure 1.1). The five-stage process begins with the identification of a clinical problem and the subsequent formation of a structured and answerable question (Closs & Cheater 1999; Leung 2001; McKenna *et al* 2004). Following the problem stage, the literature is searched for the best available evidence to answer the proposed question (Closs & Cheater 1999; Evidence-based medicine working group 1992; McKenna *et al* 2004; Sackett *et al* 1996). The evidence is then critically appraised for its validity,

quality and generalisability (Closs & Cheater 1999; Sackett & Rosenberg 1995; Straus & McAlister 2000). Once evaluated, the best available evidence is integrated into clinical practice in conjunction with clinical expertise and available resources (Straus & McAlister 2000).

Figure 1.1: The evidence based practice paradigm

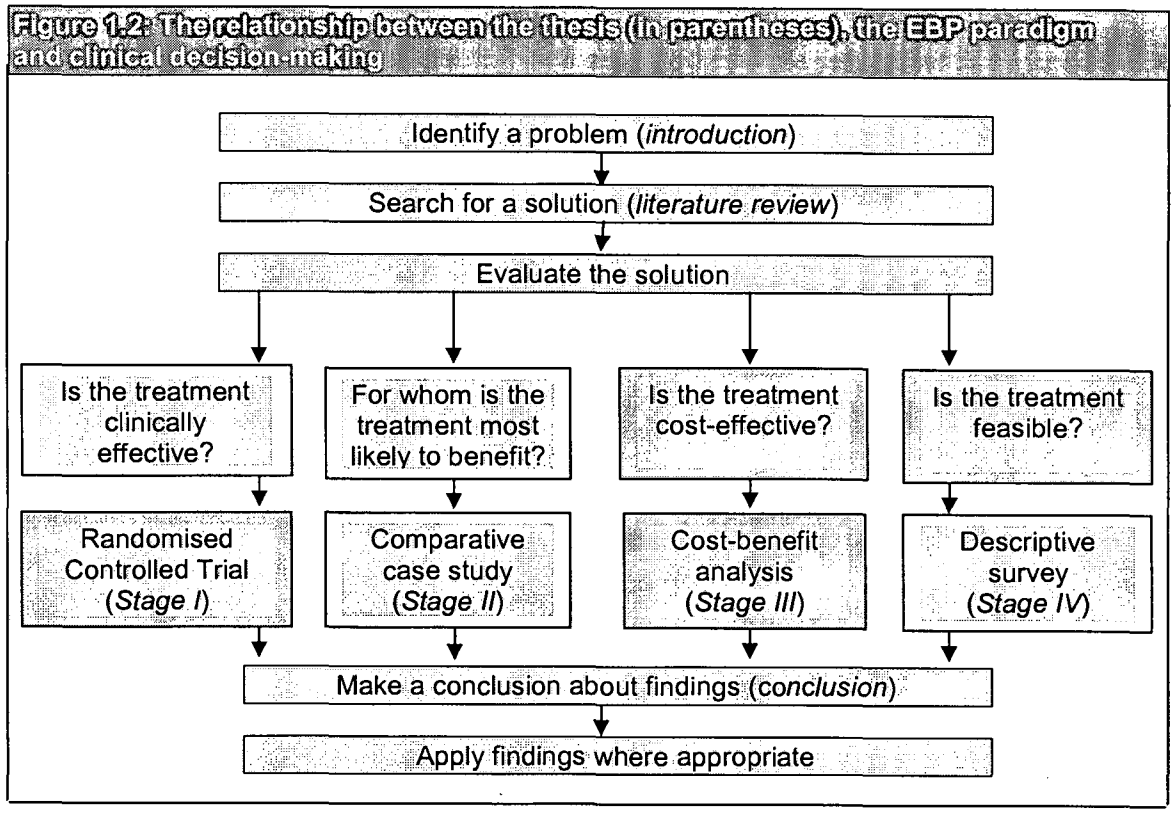


(Modified from Leung (2001: 117)).

As well as considering the availability of resources, the EBP paradigm also '...requires the judicious application of research findings in the patient context...and an understanding of the values of persons involved in...clinical decisions' (Montori & Guyatt 2002: 522). Hence, studies only investigating the clinical efficacy of an intervention may not meet all the requirements of the EBP framework. This is because clinical evidence provides only one element of the decision-making process (Montori & Guyatt 2002; Williams & Garner 2002). Clinical decisions should therefore take into account client preferences, values and expectations (Montori & Guyatt 2002; Straus & McAlister 2000). In other words, effective decision-making depends on the provision of professional expertise, clinical evidence (stage I and II), economic justification (stage III) and consumer perspective (stage IV). The four stages previously highlighted in parentheses identify the structure of the thesis, but also provide a framework to

determine whether HCSE is clinically effective; cost-effective; appropriate, and well supported. Providing evidence on the effectiveness, appropriateness and feasibility of HCSE will provide a sounder base for evaluating HCSE in that the evidence will acknowledge '...the many factors that can have an impact on (treatment) success' (Evans 2003: 79). Figure 1.2 illustrates the relationship between the thesis, the EBP paradigm and clinical decision-making.

Figure 1.2: The relationship between the thesis (in parentheses), the EBP paradigm and clinical decision-making



1.4.3 Rationale for EBP

There are many benefits to practitioners, consumers and the health care system in adopting the evidence-based practice paradigm. For instance, EBP gives rise to a more transparent clinical decision-making process (Reynolds 2000; Trinder 2000). Whilst practitioners may not welcome this increased level of scrutiny, greater accountability over decision-making is likely to benefit consumers. So, as patient expectations increase and practitioners become more accountable for their actions (Closs & Cheater 1999; Klardie, Johnson, McNaughton &

Meyers 2004; McKenna *et al* 2004), the traditional sourcing of inconsistent and incomplete information from peers and procedure manuals may become outdated (Baxter & Baxter 2002; Montori & Guyatt 2002). Evidence-based practice therefore challenges existing procedures and facilitates the integration of new and effective interventions into clinical practice. Yet, unless practitioners are adequately informed and motivated about EBP, and resources are made available for staff to access evidence-based material, clinicians may have difficulty in adopting an EBP approach (Grol & Wensing 2004; Seers & Milne 1997).

Evidence based practice may also improve client outcomes and the quality of care, and reduce the costs of treatment, the risk of medical error and patient mortality through improved decision making (Leung 2001; McKenna *et al* 2004; Romyn *et al* 2003; Sackett *et al* 1996; Tod *et al* 2004; Williams & Garner 2002). Although these cost savings may be attributed to the elimination of unnecessary and ineffective interventions (Leung 2001), the provision of high quality evidence does not necessarily equate to cost reductions (Sackett *et al* 1996). Instead, the cost effectiveness of alternative interventions should be evaluated using cost-benefit analysis (CBA). For this reason, a CBA was conducted to complement the stage I trial (see chapter 6).

The disparate practices across institutions are another concern in health care and in particular, in wound management. According to Montori and Guyatt (2002), the need for more consistent approaches to patient problems is long overdue. To address the inconsistencies in wound care, practitioners should be

encouraged to adopt an EBP approach (Baxter & Baxter 2002; Leung 2001; Montori & Guyatt 2002; Sackett & Rosenberg 1995). Failure to utilise evidence-based practice may delay the integration of innovative treatments into clinical care (Closs & Cheater 1999; Pape 2003), which could contribute to adverse client outcomes (Tod *et al* 2004). As well as EBP, new interventions may be more readily incorporated into practice by identifying and addressing barriers to implementation through the use of feasibility studies. Hence, a feasibility survey (stage IV) was developed to support the stage I trial.

Failing to deliver evidence-based practice may also reduce the credibility of a profession (Romyn *et al* 2003) and in turn, isolate members of the profession from the multidisciplinary team. In other words, practitioners choosing to ignore EBP may not confidently justify the continuation or changing of clinical practices (Pape 2003; Romyn *et al* 2003; Zeitz & McCutcheon 2003). EBP may therefore improve multidisciplinarity (Trinder 2000) and consistency of clinical care, and more effectively meet the health care needs of individuals (Romyn *et al* 2003). Despite the benefits to both practitioners and consumers, however, EBP is not without limitations.

1.4.4 Limitations of EBP

There are many critics of EBP, but as yet, these arguments hold little coherence or strength (Trinder 2000). Some of the resistance in accepting evidence-based practice has been attributed to the underlying positivist philosophy of EBP with concerns that a reductionist approach oversimplifies or inadequately addresses complex patient situations (Trinder 2000; Williams & Garner 2002). There is also an assumption that hard science is the only evidence accepted in the

model (Closs & Cheater 1999; Walker 2003; Williams & Garner 2002). The belief that EBP relies only on evidence from RCTs, however, is a common misconception. Whilst the RCT is particularly useful for evaluating the effects of an intervention, such as HCSE, it can be less effective in answering questions about patient attitudes, experience, prognosis and diagnosis (McKenna *et al* 2004; Straus & McAlister 2000). Therefore, the criticism toward EBP may not necessarily be directed at the model, but with the type of evidence accepted. A major challenge for EBP is to then recognise that other types of data, such as qualitative findings, are also valid forms of evidence (Trinder 2000). To address these concerns, the type of evidence adopted should therefore be dictated by the type of question asked (Reynolds 2000).

There is related concern that EBP may also produce dehumanised, routine and decontextualised care (Romyn *et al* 2003) by ignoring clinical expertise and client preference (Closs & Cheater 1999; Evidence-based medicine working group 1992; Williams & Garner 2002). Yet, as well as respecting patient choice (Klardie *et al* 2004), evidence-based practice also requires research findings to be considered alongside clinical expertise (Closs & Cheater 1999; Sackett *et al* 1996; Zeitz & McCutcheon 2003). EBP is therefore patient-centred (Baxter & Baxter 2002), individualised (Pape 2003) and accommodating of practitioner and client needs.

The paucity of high quality, coherent and consistent scientific evidence in nursing and wound care may explain why some clinicians have difficulty engaging in EBP (Closs & Cheater 1999; McKenna *et al* 2004; Pape 2003;

Straus & McAlister 2000). Although systematic reviews have attempted to resolve this problem, clinical experience and traditional evidence are still relied upon in areas where data is absent or ambiguous (Leung 2001; Straus & McAlister 2000). EBP therefore uses the best available evidence to guide decisions, and does not just rely on the use of data from clinical trials (Evans 2003; McKenna *et al* 2004; Straus & McAlister 2000). In fact, if nurses only utilised techniques that were based on sound clinical evidence, nursing practice would be considerably limited (McKenna *et al* 2004).

Other barriers to adopting evidence-based practice are a lack of motivation; disagreement with findings; lack of autonomy, and inadequate research and critical appraisal skills (Grol & Wensing 2004; Pape 2003; Straus & McAlister 2000; Tod *et al* 2004; Trinder 2000). The lack of time, resources and authority to make changes are also major obstacles to the introduction of EBP (Grol & Wensing 2004; McKenna *et al* 2004; Pape 2003; Straus & McAlister 2000; Tod *et al* 2004; Trinder 2000). Yet, the delivery of evidence-based practice may eliminate the time, costs and resources allocated to harmful or ineffective treatments (Baxter & Baxter 2002; Reynolds 2000; Straus & McAlister 2000; Trinder 2000) and in effect, improve patient outcomes and the future demand on clinician time.

1.4.5 Evidence based practice and HCSE

Even though some health professionals remain cautious about embracing EBP (Walker 2003), evidence-based practice provides a useful and '...scientific framework within which to identify and answer priority questions about the effectiveness of...health care' (Sackett & Rosenberg 1995: 624). EBP therefore

provides a suitable theoretical framework for evaluating the efficacy, cost effectiveness and feasibility of HCSE treatment in venous ulceration. As well as guiding research design, the EBP paradigm also delivers a means for linking research findings to clinical practice. Thus, conclusive evidence from the four studies within the thesis may help to improve client outcomes, as well as reduce wound management costs.

1.5 Outline of Thesis

Venous ulceration is a chronic and recurrent condition, adversely affecting patient quality of life, and straining an already burdened health and welfare system. The current chapter has highlighted concerns regarding the present approach to VLU treatment, and as viewed through the EBP paradigm, explains how HCSE may improve the outcomes of venous ulcer care. In the first section of this thesis, the stage I clinical trial is presented. This section consists of three chapters, incorporating a review of the literature on VLU and HCSE; details of the stage one methodology; results from the trial, and a discussion of the main findings. Following on from the trial, is the stage II comparative case study and the stage III cost-benefit analysis. Section two utilises a similar format to section one and provides details of the stage IV descriptive survey. The final chapter highlights the major findings of the four studies, and provides a list of recommendations for future research on HCSE and VLU. In the following chapter, the implications of venous ulceration are discussed, and a case for using HCSE as an innovative treatment of VLU is presented.

Section 1

Stages I, II and III

CHAPTER 2

STAGE I LITERATURE REVIEW

2.1 Introduction

Venous leg ulceration is associated with a myriad of psychosocial and economic implications. A therapy that may both hasten VLU healing and prevent ulcer recurrence, and subsequently limit these implications, is Horsechestnut Seed Extract (HCSE). Through a detailed discussion of VLU and HCSE, this chapter will highlight the unique approach that the extract brings to the management of venous ulceration.

2.2 Leg Ulceration: Epidemiology

The prevalence of leg ulceration in the western world ranges between 0.18 and 0.3 percent of the population (Baker & Stacey 1994; Callam, Ruckley, Harper & Dale 1985; Cornwall, Dore & Lewis 1986; Fowkes 1996). However, given that these figures do not include individuals being treated by persons other than orthodox practitioners (Cornwall, Dore & Lewis 1986; Nelzen, Bergqvist & Lindhagen 1996), the prevalence of leg ulceration is likely to be closer to 0.63 percent (Nelzen, Bergqvist & Lindhagen 1996), which equates to approximately 126,000 Australians at any given time.

Chronic leg ulceration is frequently associated with cyclic episodes of remission and recurrence (Callam *et al* 1985; Goldstone 1994; Ouahes & Phillips 1995; The Alexander House Group 1992), with sixty-seven to ninety percent of affected individuals experiencing more than two recurrent episodes in a lifetime (Baker *et al* 1991; Callam, Harper, Dale & Ruckley 1987a; Dale, Callam, Ruckley, Harper & Berry 1983). The chronicity of leg ulceration is also noteworthy, with fifty to seventy-five percent of patients enduring a period of ulceration of up to nine months (Baker & Stacey 1994; Callam *et al* 1987a); fifty

to seventy-two percent up to one year (Cornwall, Dore & Lewis 1986; Nelzen, Bergqvist & Lindhagen 1991; Salaman 1995), and thirteen to twenty percent exceeding two years (Baker & Stacey 1994; Callam *et al* 1987a). With chronicity and recurrence in mind, at least one in two patients can anticipate a ten-year history of leg ulceration (Callam *et al* 1987a).

As the elderly population continues to rise, it is expected that the incidence of leg ulceration is also likely to increase (Baker & Stacey 1994; Falanga 2000). For example, the incidence of ulceration under the age of sixty years is less than one percent, but at 61 to 70 years of age the incidence escalates to 2.6 percent, climbing again to fifteen percent in those aged over eighty (Baker & Stacey 1994). Women are also at higher risk of developing VLU, with the male to female ratio of leg ulceration shifting from 1:1 before age thirty to 1:2 after thirty years, and to 1:7 after the age of eighty (Callam *et al* 1987a). In view of the projected increase in leg ulcer incidence, the chronicity and recurrent nature of the condition, and the spiralling costs of health care, leg ulceration is likely to demand a greater share of an already burdened health care system over time.

2.3 Leg Ulceration: Financial Implications

The economic implications associated with the management of leg ulceration are considerable (Falanga 1993; Stacey, Jopp-McKay, Rashid, Hoskin & Thompson 1997). In France for instance, the treatment of VLU accounts for 1.1 percent of total health care expenditure, and in the United Kingdom (UK), for around 1.3 percent (Baker & Stacey 1994). Given these figures, and the AUD$50.3 billion spent on health care in Australia during 1998-99 (Trewin 2002), the annual cost of managing VLU in Australia is likely to range between

AUD$554 and AUD$655 million. This compares to the AUD$628 million to AUD$1.3 billion spent in the UK every year (Collier 1996), and the AUD$1 to AUD$1.3 billion spent in the United States (US) (Ouahes & Phillips 1995).

A large part of the cost of treating venous ulceration is incurred during the inpatient and outpatient management of the condition (Yeoh 2000). On an outpatient basis, four months of conventional leg ulcer treatment costs an estimated AUD$3245 per individual (Hakiss, in Falanga 1993). A twenty-four day stay in a private Australian hospital for leg ulcer treatment on the other hand, averages AUD$8734 per admission (Grindlay & MacLellan 1997). Adding to these expenses is the need for community nursing care (Grindlay & MacLellan 1997), although the cost of this service is still unclear.

The financial implications of leg ulceration also include personal costs, such as transport and time lost from work. Patient dependence on social security payments and the possible need for ongoing care in a nursing or residential facility add to this economic burden (Bosanquet & Franks 1996). Phillips, Stanton, Provan and Lew (1994) highlight the significance of these personal costs in a study of sixty-two US patients with leg ulceration, in which more than thirty percent of subjects reported an annual out-of-pocket expense of between one hundred and one thousand US dollars for the treatment of this condition, with the remaining patients spending amounts either above or below this range. The management of VLU is therefore likely to strain both individual and community resources.

2.4 Leg Ulceration: Psychosocial Implications

Leg ulceration is also associated with a number of physiological and psychosocial implications. Phillips *et al* (1994) examined these repercussions in a US study of 62 patients, in which all participants, despite having severe medical problems such as cardiovascular disease, viewed leg ulceration as the most significant condition. Fifty-seven percent (35/62) of subjects also believed that leg ulceration had a profound impact on mobility. Whilst this level of impaired mobility is consistent with results from a large Australian study (n=259) (Baker & Stacey 1994), it is more than five times that reported in the Lothian and Forth Valley survey (n=600) (Callam, Harper, Dale & Ruckley 1988). Disparate findings on working capacity were also evident, with all individuals in the Phillips *et al* (1994) study attributing some amount of job loss, time lost from work or financial constraint to leg ulceration, compared to a quarter of patients in the Lothian and Forth Valley study (Callam *et al* 1988). Thus, considering the estimated two million working days lost to leg ulceration in the US every year (Ouahes & Phillips 1995), and the accordance between this estimate and Phillips *et al* (1994) results, it is likely that there are geographical differences in patient experiences with leg ulceration (Baker & Stacey 1994).

Leg ulceration also has a negative impact on emotional wellbeing, with 68 percent (42/62) of individuals in the Phillips *et al* (1994) study reporting feelings of anger, depression, fear, anxiety or poor self-image specifically associated with VLU. These emotions were significantly associated with a decline in working capacity ($p<0.01$) and mobility ($p<0.05$). Since the degree of limb swelling predicted decreases in working capacity ($p<0.01$) and mobility ($p<0.001$), a reduction in leg oedema, or venous insufficiency, may therefore

improve the quality of life and labour force participation of patients experiencing leg ulceration (Phillips *et al* 1994).

A small study of four English women revealed that leg ulceration may also be coupled with feelings of hopelessness, helplessness and lack of control, as well as loneliness, social isolation, sleeplessness and pain (Charles 1995). Much larger studies have since corroborated these findings (Franks, Bosanquet, Brown, Straub, Harper & Ruckley 1999; Hofman, Ryan, Arnold, Cherry, Lindholm, Bjellerup & Glynn 1997). Interventions that facilitate wound healing are therefore likely to improve these affective measures and quality of life parameters, including pain, sleep, mobility, affect and energy levels (Franks, Moffatt, Connolly, Bosanquet, Oldroyd, Greenhalgh & McCollum 1994; Franks *et al* 1999).

2.5 Leg Ulceration: Aetiology & Pathophysiology

Leg ulcers are generally classified according the prevailing aetiology of the wound, as illustrated in Table 2.1. Of the classifications listed, venous ulceration is the most prevalent in the western world (Lopez & Phillips 1998; Ouahes & Phillips 1995; The Alexander House Group 1992), ranging from between forty-six and seventy-nine percent of all ulcerated limbs in studies to date (Baker *et al* 1991; Cornwall, Dore & Lewis 1986; Nelzen, Bergqvist & Lindhagen 1991; Nelzen, Bergqvist & Lindhagen 1996; Salaman & Harding 1995; Scriven, Hartshorne, Bell, Naylor & London 1997). Based on the possible number of Australian cases of leg ulceration in 2005, it is estimated that somewhere between 58,222 and 99,990 Australians suffer from VLU.

Table 2.1: Major classifications of leg ulceration

• Venous	• Pressure	• Haematological
• Arterial	• Diabetic	• Rheumatoid
• Mixed arterial & venous	• Neoplastic	• Infective
• Traumatic	• Metabolic	• Immunological
• Lymphatic	• Neuropathic	• Cryopathic

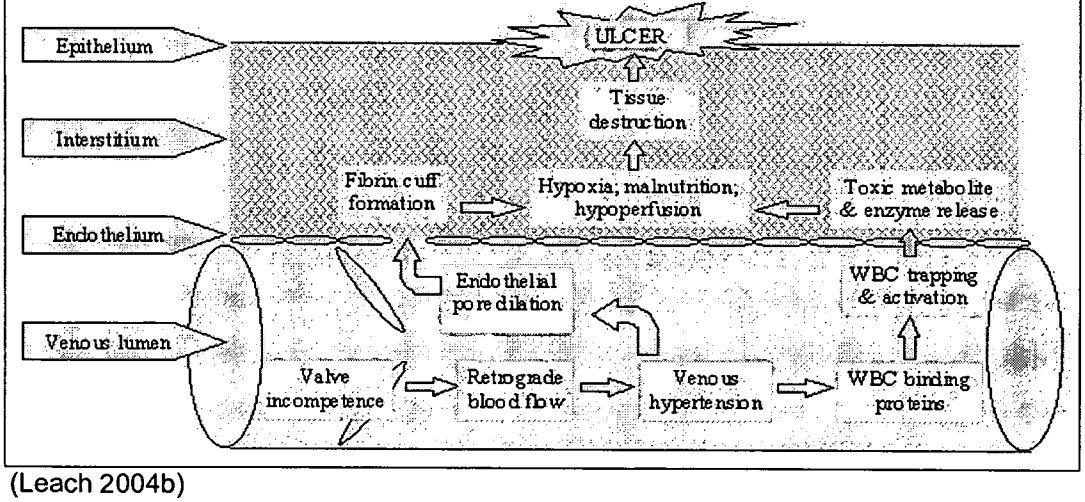
(Collier 1996; Goldstone 1994; Hunter 1996; Johnson 1995; Ouahes & Phillips 1995; Salaman & Harding 1995; Wolfe & Stansby 1998).

Chronic venous insufficiency (CVI), the precursor of VLU (Callam, Harper, Dale & Ruckley 1987b; Goldstein *et al* 1998; Koch 2002; The Alexander House Group 1992; Thomas, Nash & Dormandy 1988), is defined as an insufficient return of lower limb venous blood (Anderson 2002) manifested by pathological changes in the skin and subcutaneous tissue (Chalmers, Buckenham & Bradbury 2002; Fowkes 1996). Originating from an episode of macrovascular injury (Baker *et al* 1991; Bauersachs, Fleming & Busse 1996; Falanga *et al* 1999; Goldstein *et al* 1998; Ouahes & Phillips 1995; Scott *et al* 1995), CVI follows a path of valvular incompetence, venous reflux (Bauersachs, Fleming & Busse 1996; Burkitt & Quick 2002) and ambulatory venous hypertension (Brunner, Hoffmann & Schuller-Petrovic 2001; Collier 1996; Lopez & Phillips 1998; The Alexander House Group 1992; Zimmet 1999). The increased venous pressure causes capillary filtration to rise, leading to interstitial oedema (Bauersachs, Fleming & Busse 1996), integumentary changes and ulceration (Falanga *et al* 1999). Whilst the progression from venous hypertension to the development of leg ulceration is unclear (Falanga 1993; Pappas, Teehan, Fallek, Garcia, Araki, Back, Duran & Hobson 1995; Thomas, Nash & Dormandy 1988), several theories have attempted to enlighten this process.

The fibrin cuff theory suggests that venous hypertension causes capillary distension, resulting in endothelial pore dilation and fibrinogen leakage (Browse

& Burnand 1982). In the presence of Tumour Necrosis Factor (TNF-α), the fibrinogen polymerises into fibrin and develops peri-capillary fibrin cuffs (Browse & Burnand 1982; Claudy, Mirshahi, Soria & Soria 1991). These fibrin cuffs, as demonstrated in Figure 2.1, inhibit oxygen and nutrient transport (Thomas, Nash & Dormandy 1988), resulting in tissue hypoxia, malnutrition and ulceration (Bauersachs, Fleming & Busse 1996). Extracellular matrix proteins within these fibrin cuffs also act as potent chemoattractants for leucocytes and platelets, which in turn, promote inflammation (Pappas *et al* 1995). The presence of pericapillary fibrin in the wounds of patients with venous ulceration partly supports this theory (Claudy *et al* 1991).

Figure 2.1: The pathophysiology of venous leg ulceration



(Leach 2004b)

The nitric oxide theory posits that CVI causes a reduction in endothelial fluid shear stress, leading to a diminution in nitric oxide release and a subsequent elevation in the expression of leukocyte-endothelial binding proteins (Bauersachs, Fleming & Busse 1996). These proteins allow leucocytes to become 'trapped' within the venous endothelium, which obstruct the capillary lumen and reduce tissue perfusion (Bauersachs, Fleming & Busse 1996; Thomas, Nash & Dormandy 1988). The increased tissue resistance (Diehm

1996) and simultaneous reduction in local oxygen and nutrient levels has been confirmed in the legs of patients with CVI (Neumann, van Leeuwen, van den Broek & Berretty 1984).

Extending from the nitric oxide theory, the white blood cell (WBC) trapping hypothesis suggests that once entrapped, the WBCs become activated and release toxic metabolites, TNF-α and proteolytic enzymes (Figure 2.1). These products are then responsible for causing vascular destruction, increased permeability, fibrinogen leakage, and peri-capillary fibrin-cuff formation (Claudy *et al* 1991; Coleridge-Smith, Thomas, Scurr & Dormandy 1988; Thomas, Nash & Dormandy 1988). Increased neutrophil degranulation during experimental venous hypertension in healthy volunteers supports the WBC trapping hypothesis (Shields, Andaz, Abeysinghe, Porter, Scurr & Coleridge Smith 1994), as does the presence of accumulated leucocytes (Thomas, Nash & Dormandy 1988) and toxic oxygen metabolites in the dependent legs of patients with CVI (Whiston, Hallett, Davies, Harding & Lane 1994). While existing theories remain fragmented and do not completely delineate the pathogenesis of VLU, it is almost certain that the cascade of tissue destruction originates from venous hypertension.

2.6 Venous Leg Ulceration: Clinical features

Venous leg ulcers are often defined by their appearance, location and concomitant manifestations. Located in the gaiter area of the lower leg (Collier 1996; Goldstein *et al* 1998; Zimmet 1999), venous ulcers are typically shallow (Collier 1996; Falanga 1993), sloughy (Sibbald 1998) and bordered by erythemic and scaling skin (Lopez & Phillips 1998). Large amounts of serous

exudate are also characteristic of VLU (Collier 1996; Zimmet 1999), as is pain (Hofman *et al* 1997; Sibbald 1998) and surrounding pruritus; lipodermatosclerosis; atrophie blanche; oedema; ochre pigmentation (Lopez & Phillips 1998; Ouahes & Phillips 1995; Sibbald 1988) and telangiectatic veins (Collier 1996; Zimmet 1999). Whilst a diagnosis of venous ulceration may be guided by these clinical manifestations and the location of the wound (Brunk 1999), a classification of VLU should be confirmed by the presence of CVI with either Duplex ultrasonography or plethysmography (Loeb 1994; The Alexander House Group 1992).

2.7 Venous Leg Ulceration: Treatment

The treatment options available for the management of VLU are both diverse and contentious, ranging from conventional alternatives such as topical agents, compression therapy and surgery, to less orthodox treatments such as natural therapies and nutritional intervention. Likewise, the plethora of ancillary measures such as weight reduction, smoking cessation, walking, lymphatic drainage, physical therapy (Zimmet 1999), skin care and leg elevation (Lopez & Phillips 1998), add to the complexity of venous ulcer management. Despite the range of options, there is a paucity of level I and level II evidence to support these treatments (Leach 2004a; Ouahes & Phillips 1995). The exception is for compression therapy, for which some evidence of efficacy is available (Fletcher, Cullum & Sheldon 1997), which may explain why this therapy prevails as the primary treatment of choice for VLU (Callam *et al* 1987b; Falanga 1993; Ouahes & Phillips 1995; Wolfe & Stansby 1998).

2.7.1 Compression Therapy

The use of long-term graduated compression in the management of VLU is advocated by a number of authorities (Dale 1998; Lopez & Phillips 1998; Williams 1996a; Zimmet 1999). This treatment is also supported by findings from a systematic review of twenty-four randomised controlled trials, in which compression therapy, particularly multiple-layer bandaging, was found to increase the healing rate of venous ulceration when compared to non-compression regimes (Fletcher, Cullum & Sheldon 1997). Nevertheless, this evidence was considerably weak, with most trials lacking adequate sample size, randomisation, heterogeneity, consistent bandaging techniques (Baxter & Baxter 2002; Fletcher, Cullum & Sheldon 1997; Nelson 1996), standardised treatments or adequate controls. The efficacy and cost-effectiveness of one type of compression treatment over another also remains unclear (Fletcher, Cullum & Sheldon 1997; Lopez & Phillips 1998).

Whilst compression therapy may be beneficial in addressing the underlying aetiology of the wound (Grindlay & MacLellan 1997), as well as the signs of CVI (Table 2.2), treatment compliance is a fundamental concern (Koch 2002; Ruckley 1992; Sirtori 2001), as poor compliance is often associated with a lower rate of ulcer healing and a higher rate of recurrence (Erickson, Lanza, Karp, Edwards, Seabrook, Cambria, Freischlag & Towne 1995). The reasons why many patients cannot tolerate compression often relate to the long duration of therapy, associated discomfort (Charles 1995), and skin reactions (Greeske & Pohlmann 1996). There are also potentially serious complications associated with compression therapy (Dale 1998; The Alexander House Group 1992). For instance, a 1987 survey of 154 Scottish surgical consultants identified 147

cases of compression-induced injury, of which seven cases required arterial reconstruction, and twelve cases amputation (Callam, Ruckley, Dale & Harper 1987). Without support from other studies, however, the true extent of compression-induced injury is uncertain.

Table 2.2: Therapeutic claims of compression therapy

Reduces:	**Improves:**
• Lipodermatosclerosis	• Calf muscle pump function
• Oedema	• Deep vein blood flow velocity
• Venous reflux	• Local capillary clearance
• Venous hypertension	• Oedema fluid resorption
• Venous dermatitis	• Transcutaneous pO_2
• Superficial vein capacity and pressure	• Venous ejection volume
	• Venous refilling time
	• Plasminogen activator and prostacyclin release

(Lopez & Phillips 1998; Nelson 1996; Ruckley 1992; Zimmet 1999).

2.7.2 SURGERY

Surgery is another treatment option for VLU, and may include sclerotherapy; skin grafting; venous valve reconstruction and transplantation; varicose vein excision, and ligation. However, the effectiveness of many of these surgical procedures is not supported by clinical evidence. The treatment of venous ulceration with split skin grafting, for instance, was not supported in a recent Cochrane review of nine randomised controlled trials (Jones & Nelson 2005). Even so, skin grafting continues to be used as a treatment for leg ulceration (Goldstone 1994). The continuing utilisation of ablative techniques such as venous sclerotherapy and ligation is also controversial, as these procedures often lead to ulcer recurrence in twenty to one hundred percent of cases (Bergan 1993).

Post-subfascial perforator ligation (PSPL) is yet another surgical procedure whose efficacy maybe less than desirable. To illustrate, the three-year ulcer

recurrence rate following PSPL is forty-one percent (Johnson, O'Hara, Corey, Widrich & Nabseth 1985), compared to sixteen percent with compression therapy over 2.5 years (Mayberry, Moneta, Taylor & Porter 1991). Over a five-year period, the VLU recurrence rate with PSPL and compression therapy shifts to fifty-one (Johnson *et al* 1985) and twenty-nine percent, respectively (Mayberry *et al* 1991). Even though compression therapy is likely to provide greater long-term protection from ulcer recurrence than PSPL, a comparative evaluation of the two treatments is required to substantiate this claim.

2.7.3 Topical Therapy

Despite the range of options available, topical agents are often the only form of treatment applied by practitioners. Possible treatments in this category range from ineffectual and traumatic dry dressings (Grindlay & MacLellan 1997) to more effective interventions based on moist-wound healing technology (Winter 1962). In experiments on acute wounds in both animals and humans, moist wound-healing techniques have been shown to produce improvements in collagen synthesis, cell proliferation, macrophage counts, epithelialisation, and granulation (Lopez & Phillips 1998). Moist wound-healing methods have also been found to decrease the inflammatory cell count, debride necrotic tissue, and reduce the pain and cost of wound care (Lopez & Phillips 1998). In spite of these favourable findings, the efficacy of moist wound healing has yet to be proven in chronic wounds, including VLU (Miller 1998; Zimmet 1999). Indeed, few dressings have been proven to enhance venous ulcer healing (Chalmers, Buckenham & Bradbury 2002; Stacey *et al* 1997), and thus, the effectiveness of topical agents in the management of VLU remains debatable.

Despite the controversy around how best to manage VLU, there appears to be consensus that treatment selection should be based on addressing the underlying aetiology of the wound (Ouahes & Phillips 1995; Zimmet 1999). In fact, unless conventional wound management adequately addresses the origin of VLU, ulcer recurrence and chronicity is likely to persist (Goldstone 1994; Zimmet 1999).

2.8 Venous Leg Ulceration: Systemic management

An alternative approach to venous ulcer management is the administration of systemic therapy with venotonic or phlebotonic agents. These agents, such as HCSE, Diosmin and 0-(β-hydroxyethyl)-rutosides (HR), have been shown to produce a range of vascular effects, including a reduction in interstitial exudation and oedema formation (Diehm 1996). The actions of these medications, however, are not akin to those exerted by compression therapy. Firstly, the effects brought about by these agents persist after the cessation of treatment (Frick 2000). Secondly, venotonics specifically target the pathological processes associated with VLU, including poor venous tone, decreased microcirculation, increased capillary permeability and oedema (The Alexander House Group 1992). These agents also reduce inflammation, neutrophil migration, venous damage and growth factor release in hypoxic venous endothelium (Frick 2000). Even though venotonic preparations exert direct venous effects, there is insufficient evidence to indicate superior or inferior activity to compression. Hence, phlebotonic treatment may be utilised as an alternative to compression therapy (Frick 2000), although, combining the two treatments is likely to yield a more beneficial effect (Diehm 1996; Frick 2000). Limited data from two European trials partly support this claim, with a

combination of compression and either HR or Diosmin demonstrating a greater rate of VLU healing than compression alone (Stegmann, Hubner, Deichmann & Muller 1986; Zucarelli, in Diehm 1996). Since HCSE, HR and Diosmin produce similar physiological effects and demonstrate comparable pharmacological activity (Frick 2000), it is argued that HCSE may also parallel the wound healing effects of these agents.

2.9 Horsechestnut: Description

Aesculus hippocastanum, or Horsechestnut, belongs to the Hippocastanaceae family (Wohlmuth 1999) and is one of thirteen species in its genera (Evans 1996; Williams & Olsen 1984). Growing up to thirty metres in height, the Horsechestnut tree is characterised by thick widely spreading branches with wart-like eruptions and horseshoe-like markings. Spiny, light-green seed capsules are located throughout the tree (Krapp & Longe 2001), with each capsule containing between one and four fleshy brown seeds (Figure 2.2) (Bombardelli, Morazzoni & Griffini 1996; Gruenwald, Brendler & Jaenicke 2000; Williams & Olsen 1984). Of all the parts of the Horsechestnut tree, it is these seeds that have been researched the most, primarily in the form of a dried extract known as HCSE.

Figure 2.2 Seed and capsule of *A. hippocastanum*

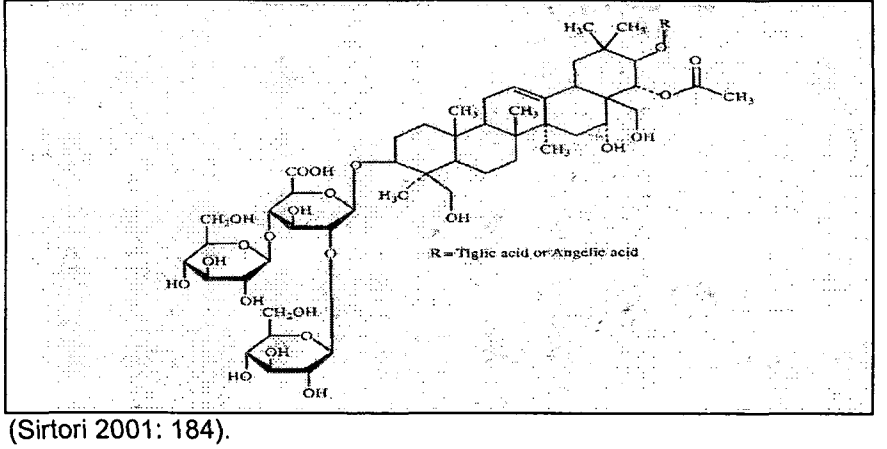


(Bradley 2004).

2.10 HORSECHESTNUT: CHEMICAL PROFILE

The chemical profile of *Aesculus hippocastanum* has been investigated since the nineteenth century (Bombardelli, Morazzoni & Griffini 1996), but the constituent receiving the most attention is a collection of triterpenoid saponins known as aescin (Wohlmuth 1999) (Figure 2.3). Many texts refer to aescin as the active principal of HCSE (Calabrese & Preston 1993), and subsequently, most pharmacological research has been conducted on this constituent rather than the entire extract. However, given that variations in seed cultivation, preparation and storage may alter the level of aescin between three and twenty-eight percent (Bruneton 1995; Mills & Bone 2000; Wohlmuth 1999), it is necessary that extracts of Horsechestnut seed be standardised.

Figure 2.3: Chemical structure of aescin



(Sirtori 2001: 184).

The seeds of Horsechestnut contain a multitude of different flavonoids, which through a series of anti-oxidant, anti-inflammatory and permeability-modifying effects, may be beneficial in vascular conditions (Pengelly 1997). A number of other nutritional constituents are also found in Horsechestnut, including carbohydrates, fatty acids, amino acids, and vitamins D and B-complex (Table 2.3) (Bombardelli, Morazzoni & Griffini 1996; Stankovic, Bastic & Jovanovic 1984).

Table 2.3: Constituents of *Aesculus hippocastanum*

	%	Ref
Major Constituents		
Starch	40-50	(1,2)
Saponins (*includes aescin*)	24-28	(3,4)
Protein	7.25-10.8	(5)
Sugar (saccharose)	7.3-17.5	(5)
Fatty oil	6-8	(1)
Water	1.8-3.5	(5)
Fractionated constituents		
Fatty Acids		
Oleic acid	65-70	(6,7)
Linoleic acid	22.7	(6)
Palmitic acid	4.4	(6)
Stearic acid	3.6	(6)
Linolenic acid	2.2	(6)
Flavonoids		
Astragalin	NA	(8,9)
Isoquercitrin	NA	(8,9)
Leucocyanidin	NA	(8,9)
Rutin	NA	(8,9)
Quercetin	NA	(9,10)
Kaempferol	NA	(9,10)
Quercitrin	NA	(11)
Flavonol glycosides	NA	(1)
Cyclitols	NA	(1)
Oligomeric-proanthocyanidins	NA	(1)
Amino Acids		
Adenine	NA	(9,10)
Adenosine	NA	(9,10)
Guanine	NA	(9,10)
L-lysine	9.4	(12)
L-tryptophan	2.7	(12)
Oligosaccharides		
Glucose	NA	(7)
Glucuronic acid	NA	(7)
Tiglic acid	NA	(7)
1-kestose	NA	(13)
2-kestose	NA	(13)
Stachyose	NA	(13)
Miscellaneous		
Allantoin	NA	(9,10)
Hippocastanine	NA	(12)
Condensed tannins	NA	(9,13)
Uric acid	NA	(14)
Filoguinone	NA	(15)
ά-spinasterol,	NA	(16)
Butyrospermol	NA	(16)
Fridelin	NA	(16)
Triacontane	NA	(16)
Taraxasterol	NA	(16)
Aesculin	NA	(17)
Fraxin	NA	(9,17)
Choline	NA	(9)
Citric Acid	NA	(9)

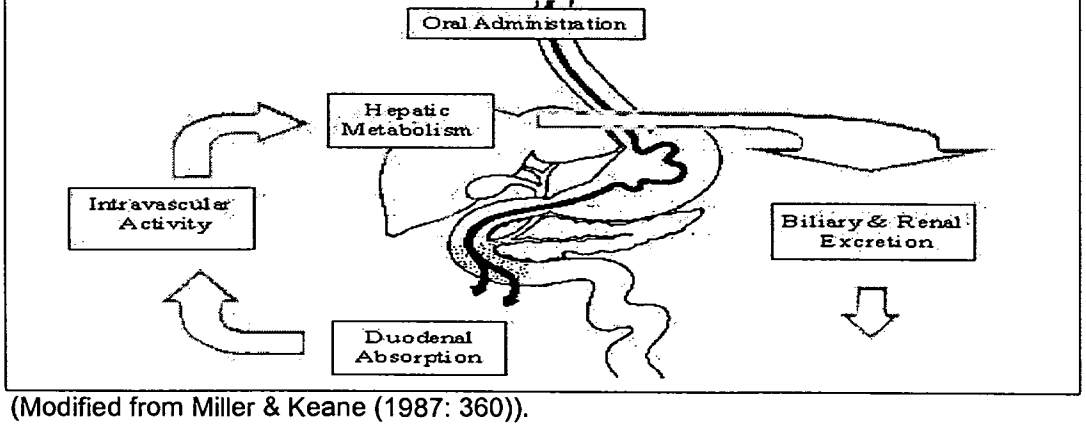
References (Ref): (**1**) Bruneton (1995); (**2**) Wilkinson & Brown (1999); (**3**) Wohlmuth (1999); (**4**) Krueger, in Bombardelli, Morazzoni & Griffini (1996); (**5**) Weinges *et al*, in Bombardelli, Morazzoni & Griffini (1996); (**6**) Kaufmann & Baltes, in Bombardelli, Morazzoni & Griffini (1996); (7) Evans (1996); (**8**) Bisset (2001); (**9**) Barnes & Anderson & Phillipson (2002); (**10**) Mascolo, Borrelli, Capasso, Capasso, Di Carlo, Izzo, Pinto, Castaldo & Longo (1998); (**11**) Wagner, in Bombardelli, Morazzoni & Griffini (1996); (**12**) Beloserky & Dubrowskaya, in Bombardelli, Morazzoni & Griffini (1996); (**13**) Gruenwald, Brendler & Jaenicke (2000); (**14**) Fidler & Hildrebrand, in Stankovic, Bastic & Jovanovic (1984); (**15**) Damm, in Stankovic, Bastic & Jovanovic (1984); (**16**) Allan *et al*, in Stankovic, Bastic & Jovanovic (1984); (**17**) Hoffmann (1996). (NA = Information not available).

2.11 Horsechestnut: Pharmacokinetics

Pharmacokinetic studies on HCSE have directed their attention to the pathway of aescin, and have largely ignored the influence that other constituents may have on the absorption, metabolism or activity of the extract. Even so, the pharmacokinetics of aescin may provide some insight into the pharmacology of HCSE as a whole.

Following the oral administration of aescin, the compound is transported to the intestinal tract, where less than ten percent of the saponins are absorbed (Markwardt 1996; Mills & Bone 2000). This poor level of absorption is attributed to the large molecular size and high polarity of the saponins (Mills & Bone 2000). Food may also interfere with the uptake of these saponins, with absorption likely to be greater during fasting than between-meals (Kunz, Lorkowski, Petersen, Samcova, Schaffler & Wauschkuhn 1998). Once absorbed, the non-metabolised aescin enters the portal vein (Henschler, Hempel, Schultze & Maurer 1971), and progresses through the bloodstream to act exclusively on blood vessel walls (Markwardt 1996; Pengelly 1997). Within one (Meyer-Bertenrath & Kaffarnik 1970) to 2.1 hours, aescin reaches maximum serum concentration (Kunz *et al* 1998), after which the saponins undergo rapid hepatic metabolism (Henschler *et al* 1971), followed by biliary and urinary excretion (Markwardt 1996) (Figure 2.4). With a half-life of twenty hours (Mills & Bone 2000), the elimination of aescin is slow (Kunz *et al* 1998), although a tissue accumulative effect has not been demonstrated (Henschler *et al* 1971). A carryover effect of up to six weeks, however, has been reported with HCSE (Rehn, Unkauf, Klein, Jost & Lucker 1996).

Figure 2.4: Pharmacokinetic pathway of aescin



(Modified from Miller & Keane (1987: 360)).

2.12 HORSECHESTNUT: INDICATIONS AND ACTIONS

Horsechestnut was traditionally used for conditions resulting from poor venous tone (Hoffmann 1996), although several sources suggest that the herb may have also been administered for a number of non-vascular complaints (Table 2.4). Apart from oedema, CVI (Pittler & Ernst 1998), varicose veins, haematoma, contusions and deep vein thrombosis (DVT) (Mills & Bone 2000), however, most of these indications have not been supported by rigorous clinical trials (Gruenwald, Brendler & Jaenicke 2000). In fact, a comprehensive review of HCSE by the German Health Commission resulted in the extract being approved only for the management of CVI (Blumenthal 1998).

Table 2.4: Conditions traditionally treated with Horsechestnut

• Cellulitis	• Intervertebral disc lesions	• Proctitis
• Diarrhoea	• Leg ulceration	• Prostatic hypertrophy
• Dysmenorrhoea	• Musculoskeletal trauma	• Rheumatism
• Enteritis	• Myocardial infarction	• Sunburn
• Gastritis	• Neuralgia	• Uterine haemorrhage
• Haemorrhoids	• Phlebitis	• Varicose veins

(Hoffmann 1996; Mills and Bone 2000; Ozarko 2001; Yoshikawa, Murakami, Matsuda, Yamahara, Murakami & Kitagawa 1996).

The effectiveness of HCSE in various vascular conditions may be attributed to a number of pharmacological effects, including anti-oedema, venotonic (Mills & Bone 2000; Sirtori 2001), anti-inflammatory (Mills & Bone 2000; Sirtori 2001), astringent (Ody 1993), and anti-exudative activity (Bruneton 1995). These effects, as well as the mechanisms of these actions, will now be examined more closely.

2.13 HORSECHESTNUT: ANTI-INFLAMMATORY ACTIVITY

The elevated levels of pro-inflammatory cytokines identified in chronic wounds (Schultz & Mast 1998) indicate that chronic inflammation may be a contributing factor in the development and maintenance of skin ulceration (Yeoh 2000). It is

therefore speculated that a reduction in inflammation could facilitate wound healing. An agent that may effectively lower inflammation is Horsechestnut Seed Extract. To illustrate, the intra-peritoneal administration of β-aescin (5mg/kg) in rats has been found to significantly increase adrenocorticotropic hormone (ACTH) ($p<0.05$), corticosterone ($p<0.01$) and glucose levels ($p<0.001$) (Hiai, Yokohama & Oura 1981). One interpretation of this study is that aescin stimulates the anterior pituitary to release ACTH, and in effect, directs the adrenal cortex to synthesise and release corticosterone (Hiai, Yokohama Oura 1981). Inhibition of the anti-inflammatory effect of aescin after adrenalectomy (Vogel & Uebel 1960) and hypophysectomy (Preziosi & Manca 1965) corroborates this claim.

Aescin may also reduce acute inflammation through anti-histaminic or anti-serotoninergic activity. As demonstrated in a Murine model, oral aescin Ia, Ib, IIa and IIb (50-200 mg/kg) dose-dependently inhibited acetic-acid and histamine-induced vascular permeability, as well as carageenan-induced paw oedema and compound 48/80-induced scratching behaviour (50-200 mg/kg) (Matsuda, Li, Murakami, Ninomiya, Yamahara & Yoshikawa 1997). Excluding fraction Ia, the aescins also dose-dependently inhibited serotonin-induced vascular permeability (50-200 mg/kg). These inhibitory effects on the initial phase of inflammation were consistent with earlier reports (Vogel, Marek & Oertner 1970). Although these studies suggest that aescin may provide acute anti-inflammatory activity, the effect of these saponins in chronic inflammation remains poorly understood. Furthermore, as these studies only examined the effect of aescin, applying these findings to HCSE may be inappropriate as the

overall effect of the extract maybe somewhat different to that of the single constituents.

Components other than aescin are also claimed to be responsible for the anti-inflammatory activity of HCSE, such as the flavonoids (Newall, Anderson & Phillipson 1996). The anti-inflammatory effect of these flavonoids can be attributed to the inhibition of the pro-inflammatory enzymes Lipoxygenase, Cyclooxygenase, phospholipase A2 and phosphodiesterase (Osiecki 1995; Ozarko 2001). One flavonoid identified in HCSE is proanthocyanidin A2, which demonstrates antioxidant, anti-inflammatory and anti-enzymatic activity (Bombardelli, Morazzoni & Griffini 1996; Wilkinson & Brown 1999), which may not only support wound healing (Wilkinson & Brown 1999), but also the regression of CVI (Murray & Pizzorno 1998).

Even though the anti-inflammatory effect of aescin is supported *in vivo*, it may be unsuitable to generalise these findings to HCSE due to the possible interplay of other elements. Studies utilising aescin-free HCSE (Tsutsumi & Ishizuka, in Mascolo *et al* 1998), or comparing HCSE to aescin (Barnes, Anderson & Phillipson 2002), both indicate that the antiinflammatory effect of Horsechestnut is likely to be ascribed to a combination of constituents and not just the saponins (Wohlmuth 1999). Clinical evidence is needed to determine whether the antiinflammatory effect of HCSE is equal to or greater than the effect of its individual components, and whether this antiinflammatory activity is clinically significant.

2.14 Horsechestnut: Anti-oedema activity

The majority of studies investigating the effects of Horsechestnut have focussed their attention on the anti-oedema activity of the plant. This anti-oedema effect is claimed to be the result of a decrease in capillary pore diameter and number (Mascolo *et al* 1998; Vogel, Marek & Oertner 1970); decreased capillary permeability, and a subsequent reduction in interstitial exudation (Rothkopf & Vogel 1976; Vogel, Marek & Oertner 1970). Aescin may also exert an anti-oedema effect by increasing adrenal activity, either through Hypothalamic-Pituitary Axis (HPA) activation; direct adrenal cortex stimulation; metabolism into a corticoid-type compound (Calabrese & Preston 1993), or via a corticomimetic effect (Bombardelli, Morazzoni & Griffini 1996). Some authors also argue that aescin may reduce oedema by promoting diuresis (Vogel & Marek 1962), although clinical findings do not support this claim (Bombardelli, Morazzoni & Griffini 1996). Even though the mechanism for the anti-oedema effect of Horsechestnut is still under investigation, the clinical efficacy of HCSE in the treatment and prophylaxis of oedema is well established.

In a double-blind, crossover, randomised controlled trial (RCT), twenty-two patients with CVI were administered a single 600 mg dose of HCSE, standardised to 100 mg aescin (Bisler, Pfeifer, Kluken & Pauschinger 1986). After three hours, transcapillary filtration in the HCSE group decreased by twenty-two percent, as opposed to a small undisclosed increase in the placebo group. The difference between these groups was statistically significant ($p=0.006$).

In another double-blind, placebo controlled, crossover trial, the oedema reducing effect of HCSE in fifty-two pregnant women was explored (Steiner & Hillemanns 1990). Administered twice daily for two weeks, the 300 mg sustained release preparation of HCSE (standardised to 50 mg aescin) significantly reduced leg oedema ($p<0.01$) and ankle, instep and calf circumference both before and after oedema provocation when compared to placebo. The extract also lessened the severity of leg pain, fatigue, swelling and pruritus in all cases, whilst the placebo had variable results. Nevertheless, these findings should be interpreted with caution given that HCSE demonstrates a carry-over effect of up to six weeks (Rehn *et al* 1996), and that Steiner & Hillemanns (1990) implemented a washout period of only one week. In other words, without an adequate washout period, a crossover design may not be suitable for the investigation of Horsechestnut Seed Extract.

A Cochrane review of HCSE examined the evidence from sixteen well-designed RCTs (Pittler & Ernst 2004). Of these trials, eleven were placebo-controlled and five were compared against reference medications (Table 2.4). Outcome measures included reductions in lower leg volume, calf and ankle circumference, pain, pruritus, and leg fatigue (Pittler & Ernst 1998). HCSE, standardised to 100-150 mg aescin daily, was found to be superior to placebo in all placebo controlled trials, and at least equally effective to reference medications in four out of five studies. In the trial where HCSE was found to be less effective than the reference medication (Koch 2002), the result may have been tainted by the lack of adequate blinding and the introduction of bias from the open design. The use of a different reference medication was also a likely

factor. The superior effect of HCSE over HR in another trial (Erler 1991), however, may have been attributed to the comparatively higher dose of aescin administered (150 mg aescin daily). Findings from a large observation study of 5429 German patients corroborate the improvements reported in this systematic review (Greeske & Pohlmann 1996). Even though there are numerous studies to support the efficacy of HCSE in mild to moderate CVI, there are still no known studies that have examined the effectiveness of HCSE in venous ulceration.

Table 2.5: Randomised controlled trials of HCSE for CVI

Reference	Study design	Sample size	Intervention	Control	Treatment duration	Outcome
Cloarec (1992)	2 parallel arms, DB	30	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	4 weeks	Results of changes in leg circumference, pain and oedema NA (internal report)
Diehm *et al* (1992)	2 parallel arms, DB	40	1 HCSE cap BD (75 mg aescin)	1 placebo cap BD	6 weeks	HCSE significantly reduced leg volume (84mls) when compared to placebo (4mls) ($p<0.01$)
Diehm *et al* (1996)	3 parallel arms, DB	240	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD or compression stockings	12 weeks	Leg volume reduction with HCSE (44mls) and compression (47mls) were significantly greater than placebo (-10 mls) ($p=0.005$)
Erdlen (1989)	2 parallel arms, DB	30	1 HCSE cap BD (50 mg aescin)	Rutosides (dosage not specified)	4 weeks	HCSE significantly reduced ankle circumference (0.4cm) when compared to baseline, yet was equal in effect when compared to rutosides (0.4cm) (no p value)
Erler (1991)	2 parallel arms, DB	40	1 HCSE cap BD (75 mg aescin)	1000 mg HR BD	8 weeks	HCSE significantly reduced ankle and calf girth when compared to baseline (no p value)
Friederich *et al* (1978)	Cross-over, DB	118	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	20 days	HCSE significantly reduced leg oedema ($p<0.05$), pain ($p<0.01$), cramps ($p<0.01$) and fatigue / heaviness ($p<0.05$) when compared to placebo
Kalbfleisch & Pfalzgraf (1989)	2 parallel arms, DB	33	1 HCSE cap daily (50 mg aescin)	50 mg HR daily	8 weeks	Change in leg circumference with HCSE was not significantly different to HR (no p value)
Koch (2002)	2 parallel arms, open	40	1 HCSE cap BD (50 mg aescin)	120 mg Pycnogenol TDS	4 weeks	Pycnogenol was significantly more effective than HCSE in reducing leg circumference ($p<0.001$), heaviness, cramps and nocturnal oedema ($p<0.05$)
Lohr *et al* (1986)	2 parallel arms, DB	80	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	8 weeks	HCSE reduced leg volume by 16.5mls, compared to 3.8mls with placebo (no p value)

Table 2.4 continued

Neiss & Bohm (1976)	2 parallel arms, DB	233	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	20 days	HCSE significantly reduced leg oedema ($p<0.01$), pain ($p<0.01$), pruritus ($p<0.05$) and fatigue ($p<0.05$) when compared to placebo
Paris & Soares (1993)	2 parallel arms, DB	51	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	20 days	HCSE significantly improved disestesy ($p<0.10$), vascular congestion ($p<0.05$), blood ebbling ($p<0.01$), dermatitis ($p<0.01$), burning ($p<0.01$), effort incapacity ($p<0.05$) and pain/pruritus ($p<0.01$) when compared to placebo
Pilz (1990)	2 parallel arms, DB	30	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	20 days	HCSE significantly reduced leg circumference (0.8cm) when compared to placebo (0.1cm) ($p<0.05$)
Rehn *et al* (1996)	3 parallel arms, DB	158	1 HCSE cap BD (50 mg aescin)	500 mg HR or 1000 mg HR daily	12 weeks	HCSE reduced leg volume by 28mls, HR 1000 by 58mls and HR 500 by 40mls (no p value)
Rudofsky *et al* (1986)	2 parallel arms, DB	40	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	4 weeks	HCSE significantly reduced leg volume (44mls) when compared to placebo (34mls) ($p<0.001$). HCSE also significantly improved leg pain ($p<0.05$), fatigue ($p<0.05$), pruritus ($p<0.05$) and tension ($p<0.01$) when compared to placebo
Steiner & Hillemanns (1986)	Cross-over, DB	20	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	2 weeks	HCSE significantly reduced leg volume when compared to placebo ($p<0.001$).
Steiner & Hillemanns (1990)	Cross-over, DB	52	1 HCSE cap BD (50 mg aescin)	1 placebo cap BD	2 weeks	HCSE significantly reduced leg volume when compared to placebo ($p<0.01$)

(Pittler & Ernst 1998; Pittler & Ernst 2004).
BD=Twice daily. DB=Double blind. HCSE=Horsechestnut Seed Extract. HR=Hydroxyethyl-rutosides. TDS=Three times daily. NA= Not available.

Evidence to date suggests that HCSE may be a safe and effective treatment for the prevention and management of leg oedema, particularly at higher standardised doses. Whilst the oedema-reducing effect of HCSE is similar to that reported with compression therapy and other venotonics, the extract demonstrates a comparatively lower incidence of adverse effects and a greater level of treatment compliance (Diehm *et al* 1996; Greeske & Pohlmann 1996; Pittler & Ernst 1998). HCSE is therefore an appropriate and comparable treatment option for chronic venous insufficiency.

2.15 HORSECHESTNUT: VENOTONIC ACTIVITY

As highlighted in previous sections, aescin may assist in the management of CVI and VLU by reducing associated inflammation and oedema. Findings from studies using animal and human models indicate that HCSE may also improve CVI by restoring normal tone in both competent and incompetent veins (Annoni *et al* 1979; Bombardelli, Morazzoni & Griffini 1996; Brunner, Hoffmann & Schuller-Petrovic 2001; Lininger 1999), as well as enhancing capillary resistance, venous and valvular contraction, and venous flow pressure (Guillaume & Padioleau 1994). Whilst these venotonic effects lack clinical support, they partly explain the process by which HCSE may attenuate the pathogenesis of CVI.

The impaired venous tone associated with CVI has been linked to an increase in lysosomal enzyme activity. Given that the level of these enzymes are elevated in patients with CVI (Kreysel, Nissen & Enghofer 1983), and in the exudate of venous ulcers (Schultz & Mast 1998), these enzymes may also be implicated in the pathogenesis of VLU (Frick 2000; Kreysel *et al* 1983). Lysosomal enzymes such as hyaluronidase and elastase are also responsible for extravascular and extracellular matrix degradation (Facino, Carini, Stefani, Aldini & Saibene 1995), which can lead to an increase in capillary permeability, oedema formation, and a delay in wound healing. A reduction in lysosomal enzyme activity may therefore decrease the symptoms of CVI by restoring venous elasticity and contractility through improvements in collagen biosynthesis (Kreysel *et al* 1983) and proteoglycan recovery (Facino, Carini, Stefani, Aldini & Saibene 1995).

HCSE may attenuate overactive lysosomal enzyme activity (Facino *et al* 1995; Hitzenberger 1989; Kreysel *et al* 1983) by shifting the equilibrium between proteoglycan synthesis and degradation, towards net synthesis (Pittler & Ernst 1998; Sirtori 2001). This reduction in enzyme activity against capillary wall mucopolysaccharides may improve vessel wall integrity and subsequently reduce oedema formation (Blumenthal 1998; Gruenwald, Brendler & Jaenicke 2000; Sirtori 2001). Although aescin is claimed to be responsible for the anti-exudative and vascular-tightening effect of HCSE (Blumenthal 1998), other constituents such as proanthocyanidin A2 may also be involved (Facino *et al* 1995). Thus, claims that HCSE exerts greater venotonic activity than aescin alone warrants further investigation (Wilkinson & Brown 1999), as does the clinical implication of this anti-enzymatic effect.

2.16 Horsechestnut: Antioxidant activity

Another process implicated in the pathogenesis of CVI is the peroxidation of venous lipids, and the subsequent production of oxygen free radicals (Guillaume & Padioleau 1994; Masaki, Sakaki, Atsumi & Sakurai 1995). Through the destruction of lipids, proteins, collagen, proteoglycan and hyaluronic acid, these free radicals may also contribute to the generation of VLU (Yeoh 2000). Agents demonstrating significant antioxidant activity may therefore preserve venous tissue and facilitate venous ulcer healing. Hence, the ability of HCSE to decrease enzymatic and non-enzymatic lipid peroxidation *in vitro,* as well as reduce oxygen free radical activity *in vivo,* suggests again that the extract may be conducive to wound healing (Guillaume & Padioleau 1994).

Masaki *et al* (1995) examined the active-oxygen scavenging activity of sixty-five plant extracts *in vitro*. *Aesculus hippocastanum* was found to be more potent than ascorbic acid and α-tocopherol in scavenging superoxide-anions, but less effective than ascorbic acid in scavenging hydroxyl-radicals and inhibiting singlet-oxygen generation (Masaki *et al* 1995). Horsechestnut was also a potent inhibitor of lipid peroxidation. As an indicator of cell protection, Masaki *et al* (1995) also explored the effect that the plant extracts had on fibroblast survival. Horsechestnut was found to increase fibroblast survival four-fold, which was more efficacious than any other extract. As fibroblasts are a major source of collagen, elastin, proteoglycans and matrix metalloproteinases (Schultz & Mast 1998), increasing fibroblast survival is likely to facilitate wound closure. Although the antioxidant and cell-protective activity of Horsechestnut may improve VLU healing, this claim needs to be supported by clinical evidence.

2.17 Horsechestnut: Toxicology

According to authorities, the degree of toxicity in the pericarp (Ody 1993) and the raw fruit of Horsechestnut (Dermarderosian 2000; Krapp & Longe 2001) are at a level high enough to categorize the plant as a poison (Dermarderosian 2000; Mills & Bone 2000; Reynolds 1989). Yet, as these toxins are easily destroyed by heat, the dried seeds are relatively safe (Ozarko 2001). The wide therapeutic index and low toxicity of Horsechestnut reported in multiple animal models further supports the safety of HCSE (Blumenthal 1998; Kunz *et al* 1998; Mills & Bone 2000).

In acute toxicity studies, the oral LD_{50} of HCSE in mice, guinea pigs, rabbits and rats was 990 mg/kg, 1120 mg/kg, 1530 mg/kg and 2150 mg/kg, respectively

(Liehn, Franco, Hampel & Hofrichter 1972). These values equated to between 99 and 215 times the daily human-equivalent dose (Liehn *et al* 1972). In other species, the LD_{50} of a single dose of HCSE was 10.6 mg/g in chicks and 10.7 mg/g in hamsters, whilst two consecutive days of dried powdered seeds in chicks demonstrated an LD_{50} of 6.5 mg/g (Williams & Olsen 1984).

In relation to chronic toxicity, rats administered up to 400 mg/kg of oral HCSE daily for thirty-four weeks demonstrated no signs of clinical, biochemical, morphological or histological adverse effects (Liehn *et al* 1972). The dose administered to rats equated to forty-fold the daily human equivalent dose. Dogs administered up to 40 mg/kg of HCSE daily for thirty-four weeks also failed to yield any adverse reactions. However, dogs did experience vomiting after eight weeks of receiving 80 mg/kg of HCSE. The introduction of an enteric-coated preparation resolved the emesis, indicating that gastric irritation was at cause (Liehn *et al* 1972). Notwithstanding, vomiting is a typical canine response to any foreign substance and may not necessarily be a characteristic reaction to HCSE (Liehn *et al* 1972).

Studies on the reproductive toxicity of HCSE in rats and rabbits failed to demonstrate any teratogenic or embryotoxic effect at oral doses of 300 mg/kg and 100 mg/kg, respectively (Liehn *et al* 1972). HCSE treatment not exceeding ten–fold the human therapeutic dose is therefore unlikely to demonstrate signs of reproductive toxicity. Treatment not exceeding forty–fold the human therapeutic dose is also unlikely to yield symptoms of acute or chronic toxicity.

2.18 Horsechestnut: Adverse effects

Horsechestnut seed extract is a well-tolerated intervention with very few documented adverse effects (Hitzenberger 1989). The reactions typically reported with oral HCSE include mild and infrequent pruritus, nausea, and gastric complaints (Blumenthal 1998). These adverse effects are supported in a systematic review of HCSE, with 8/13 RCTs reporting pruritus, headache, nausea and gastrointestinal symptoms in a collective sample of 859 participants (Pittler & Ernst 1998). The frequency of these adverse drug reactions (ADRs) ranged between 0.9 and three percent. In a large observation study of 5429 patients, however, no more than 0.6 percent of participants manifested ADRs to orally administered HCSE (Greeske & Pohlmann 1996). Even so, the outcome of the latter study may have been favoured by observer bias (Polit & Hungler 1999).

2.19 Horsechestnut: Cautions & Contraindications

According to authorities, there are no contraindications to the use of HCSE (Blumenthal 1998; Lininger 1999; Steiner & Hillemanns 1990), nor are there any adverse interactions between the extract and pharmaceutical agents (Blumenthal 1998). Yet, some authorities still maintain that the extract is unsafe in certain conditions and with certain medications (Barnes, Anderson & Phillipson 2002; Gruenwald, Brendler & Jaenicke 2000; Mascolo *et al* 1998).

Claims that Horsechestnut should be avoided in individuals with bleeding disorders or in those taking anticoagulant medication (Barnes, Anderson & Phillipson 2002; Krapp & Longe 2001) are based on an assumption that Horsechestnut exhibits anti-coagulant activity (Mascolo *et al* 1998). The coumarins responsible for the anticoagulant effect of the plant, however, are

only present in the bark and leaves of Horsechestnut (Bruneton 1995; Gruenwald, Brendler & Jaenicke 2000; Wilkinson & Brown 1999). Therefore, HCSE is unlikely to exhibit an anticoagulant effect, although the interaction between HCSE and anticoagulant therapy warrants further examination.

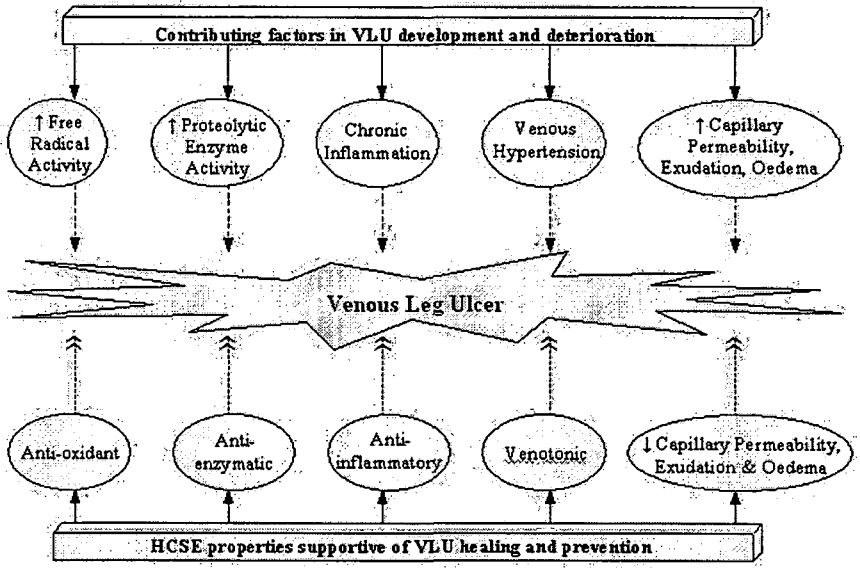
Another contentious contraindication of Horsechestnut use is the presence of renal and hepatic impairment (Gruenwald, Brendler & Jaenicke 2000; Mascolo *et al* 1998; Wohlmuth 1999). However, a review of eighty-three subjects administered intravenous HCSE failed to demonstrate any signs of renal dysfunction in healthy individuals, or worsening of renal function in patients with pre-existing impairment (Sirtori 2001). The source of concern regarding the use of Horsechestnut in patients with hepatic impairment is also uncertain. As there is neither evidence of a nephrotoxic nor hepatotoxic effect associated with the oral administration of HCSE (Lininger 1999), the extract is unlikely to be contraindicated in patients with hepatic or renal insufficiency.

2.20 SUMMARY

The evidence to date indicates that HCSE may be as effective as compression therapy in the management of moderate CVI, although, the level of acceptance, tolerance (Sirtori 2001) and compliance with Horsechestnut treatment is likely to be greater (Greeske & Pohlmann 1996). This increased level of compliance, together with the anti-inflammatory, anti-oxidant, anti-exudative, venotonic and anti-enzymatic effects of HCSE, suggest that the extract may be more effective at facilitating VLU healing than compression therapy (Figure 2.5). HCSE treatment is therefore expected to significantly reduce the financial, psychosocial and physiological burden associated with venous ulceration. Given that the efficacy of HCSE in the management of VLU has yet to be

established, however, the RCT described in the following chapter will be the first study to investigate this unique treatment.

Figure 2.5: The role of HCSE in venous ulcer healing.



CHAPTER 3

STAGE I METHODOLOGY

3.1 Introduction

The previous chapter has highlighted the potential benefits of utilising HCSE in the management of VLU. Yet, given that these effects are speculative, these claims need to be corroborated by sound clinical evidence before HCSE treatment may be incorporated into conventional practice. A randomised controlled trial (RCT) was therefore designed to evaluate the clinical effect of this treatment on venous ulcer healing. Comprehensive discussion and justification of the methodology and methods used to address the hypotheses of the stage I RCT are presented throughout this chapter, beginning with details of the research design.

3.2 Research Design

Randomised controlled trials are 'quantitative, comparative controlled experiments in which an investigator studies two or more interventions in a series of individuals who receive them at random' (Jadad 1998: 2). Considered the gold standard for testing therapeutic interventions (Jolley 1999; Knipschild 1993; Richardson 2000), the RCT is '...the mainstay of modern evidence-based medicine' (Jolley 1998: 213). One reason for this is that the RCT is the most definitive way of determining whether an intervention produces a postulated effect (Evans 2003; Friedman, Furberg & DeMets 1982; Grimm 2002; Portney & Watkins 2000). Characterised by prospective data collection, control groups (Friedman, Furberg & DeMets 1982) and randomisation (Day 1999; Jadad 1998), the RCT controls against major sources of bias (Lloyd-Parks 2001) and attempts to discredit any alternative causal explanation (Polit & Hungler 1999). The clinical trial therefore provides a sound basis for evaluating the efficacy of a therapeutic intervention (Friedman, Furberg & DeMets 1982), by yielding less biased data than any other design (Jolley 1999; Spilker 1991a).

However, the RCT is not appropriate for all interventions. Descriptive studies which hinge on human characteristics that cannot be manipulated are not suitable for investigation using an RCT design (Roberts & Taylor 1999). Interventions with rare or difficult to measure clinical outcomes, or effects that develop over a long period of time, are also difficult to examine in a clinical trial due to the often high rate of withdrawal and the poor level of compliance (Jadad 1998; Vincent & Furnham 1997). RCTs are also costly and laborious to conduct (Grimm 2002; Hudson, Aranda & McMurray 2001), and without sufficient time, personnel and funding, may not always be the most feasible research design.

Opponents of the RCT design also claim that the categorisation of individuals into a common diagnosis does not account for individual variation or disparate patterns of healing (Knipschild 1993; Vincent & Furnham 1997). Another concern is that standardised treatment protocols adopted in clinical trials may not be identical to the procedures utilised in clinical practice (Knipschild 1993; Vincent & Furnham 1997). Lastly, some argue that offsetting the placebo effect in placebo-controlled trials may eliminate the beneficial psychological effect associated with the intervention (Knipschild 1993; Vincent & Furnham 1997). Whilst these aforementioned points are valid, the elimination of these key components in the RCT design, such as the selection criteria, treatment protocols and control groups, would arguably weaken the integrity of the design and subsequently reduce the plausibility of trial findings.

The current study (stage I) was conducted as a prospective, parallel-group, triple-blind, multi-centre, randomised, placebo-controlled trial. As recommended by a collaboration of experts on VLU (The Alexander House Group 1992), this design was necessary to adequately investigate the clinical efficacy of venotonic therapy in venous ulceration. The nature of the trial also demanded the utilisation of a parallel design as opposed to a crossover approach, as similar baseline values could not be foreseen (Spilker 1991a); a longer trial duration may have hampered subject recruitment and compliance, and the carryover effect of HCSE was not well defined. A crossover design was also inappropriate for an ulcer-healing study as baseline data in each arm of the trial was unlikely to be similar, due to the probability of ulcer healing in the first arm (The Alexander House Group 1992). A flow chart of the stage I design is illustrated in Appendix 1.

3.3 Hypotheses

The fundamental purpose of the stage I trial was to determine whether the oral administration of HCSE would influence the healing rate of venous ulceration. The hypotheses of the study were therefore as follows:

Primary Hypothesis

The primary outcome measure in the current study was a 'healed venous leg ulcer'. This outcome was not only clinically relevant, but recommended by the Alexander House Group (1992). Thus, the primary hypothesis for the trial was:

> The oral administration of HCSE is associated with a significant increase in the number of healed venous leg ulcers when compared to placebo at week twelve.

Secondary Hypotheses

The secondary outcome measures in the study were wound size; granulation, epithelial, necrotic and sloughy tissue surface area; pain intensity; wound exudate, and leg oedema. A decrease in these measures, particularly wound size and wound exudate, as well as a transition from necrotic tissue to granulation tissue, were considered effective indicators of progressive wound healing (Bates-Jensen 1997; Xakellis & Frantz 1997). The study therefore tested the following secondary hypotheses:

1. The oral administration of HCSE is associated with a significant reduction in wound dimensions (surface area and volume) when compared to placebo at weeks 4, 8 and 12.
2. The oral administration of HCSE is associated with a significant improvement in wound topography when compared to placebo at weeks 4, 8 and 12, including a decrease in the percentage of necrotic and sloughy tissue and a corresponding increase in the percentage of granulation tissue.
3. The oral administration of HCSE is associated with a significant reduction in adverse venous insufficiency symptoms (level of wound exudate, ankle and calf diameter, and pain score) when compared to placebo at weeks 4, 8 and 12.
4. The oral administration of HCSE is associated with a significant reduction in leg ulcer incidence at four, eight and twelve weeks after the extract is ceased.
5. The oral administration of HCSE is associated with a significant reduction in wound size at four, eight and twelve weeks after the extract is ceased.

Justification for primary hypothesis

The twelve-week VLU healing rate reported with compression therapy ranges between forty and sixty-nine percent (Callam, Harper, Dale, Brown, Gibson, Prescott & Ruckley 1992; Moffatt, Franks, Oldroyd, Bosanquet, Brown, Greenhalgh & McCollum 1992; Thomson, Hooper, Powell & Warin 1996). Given these inconsistent healing rates and the lack of evidence on the wound healing effect of HCSE, a postulated difference between the two treatment groups had to be derived from a similarly designed trial of a comparable agent. An orally administered medication demonstrating properties somewhat similar to HCSE, including improvements in microcirculatory blood flow and a decrease in leucocyte adhesion, is Pentoxifylline (Bertocchi *et al*, in Falanga *et al* 1999; Bougelet, Roland, Ninane, Arnould, Remacle & Michiels 1998; Brennar, in Jull, Waters & Arroll 2001; Pittler & Ernst 1998). Findings from an RCT similar in design to the stage I trial, but utilising Pentoxifylline as the active agent, was therefore claimed to provide adequate justification for the anticipated outcomes of the current study. In one such RCT, forty-nine percent of venous ulcers were healed after eight weeks of Pentoxifylline and compression therapy, compared to twenty-three percent with placebo and compression (Falanga *et al* 1999). The oral administration of HCSE is therefore expected to heal at least forty-nine percent of venous ulcers within twelve weeks, compared to twenty-three percent with placebo.

3.4 VARIABLES & OUTCOME MEASURES

The independent variable or presumed cause of wound healing in the current study (Polit & Hungler 1999) was HCSE. The dependent variables or speculated effects of HCSE (Polit & Hungler 1999), however, were divided into

primary and secondary outcome measures. These measures were conceptualised and operationally defined as follows.

Primary outcome measure

A healed venous leg ulcer was conceptualised as a complete restoration of skin integrity (Miller & Keane 1987). Manifesting as one hundred percent epithelialization (Centre for Medical Education 1993) or a wound surface area of 0 mm^2, ulcer healing was determined by the researcher and the Alfred-Medseed Wound Imaging System (AMWIS) (see section 3.12 for more detail) at weeks zero, four, eight and twelve.

Secondary outcome measures

Wound surface area was defined as the total area of the ulcer surface in mm^2 (Lafferty & Rowe 1993). Planimetric measurements of ulcers were obtained from AMWIS at weeks zero, four, eight and twelve.

Wound volume was defined as the total space of the wound cavity in mm^3 (Miller & Keane 1987) and was measured by multiplying ulcer surface area by wound depth. Wound volume was calculated by AMWIS at weeks zero, four, eight and twelve, and was based on an assumption that the wound base was flat.

Wound exudate was conceptualised as high-protein fluid on the ulcer surface (Centre for Medical Education 1993; Miller & Keane 1987). The level of exudate was assessed and recorded by the researcher at weeks zero, four, eight and

twelve, by using the Wound Assessment Tool (WAT) (see section 3.12 and Appendix 2 for more detail) and associated instructions (Appendix 3).

Ankle and calf diameter, or the circumference of the ankle and calf of the ulcerated leg, were measured in order to quantify changes in leg oedema. Using a flexible measuring tape, ankle and calf girth were assessed at three and eighteen centimetres above the lateral malleolus respectively, and were documented on the WAT at weeks zero, four, eight and twelve.

Pain was conceptualised as the feeling of discomfort at or around the leg ulcer (Miller & Keane 1987). Participants rated the severity of pain using a numerical scale from zero to ten, defining zero as no pain and ten as the worst pain ever experienced. The pain score was assessed by the researcher and documented on the WAT at weeks zero, four, eight and twelve.

Necrotic tissue was defined as full-thickness tissue destruction, manifesting as black eschar on the wound surface (Bates-Jensen 1999). Planimetric measurements of necrotic tissue were calculated by AMWIS and recorded in mm^2 at weeks zero, four, eight and twelve.

Slough was conceptualised as necrotic fat or fascia (Sussman 1998), which presented as soft yellow tissue on the ulcer bed (Bates-Jensen 1999; Sussman 1998). Planimetric measurements of slough were calculated by AMWIS at weeks zero, four, eight and twelve and recorded in mm^2.

Granulation tissue was defined as newly-formed blood vessels and connective tissue (Miller & Keane 1987) that manifested as a spongy red layer of cells on the wound surface (Bates-Jensen 1999). Planimetric measurements of granulation tissue were calculated by AMWIS and recorded in mm^2 at weeks zero, four, eight and twelve.

3.5 SETTING

A large district nursing service within metropolitan Adelaide, South Australia, was the chosen setting for all four studies in the thesis. Employing 323 nurses over three regional centres and twelve nursing clinics (Department of Human Services 2001), the service treated more than 1420 clients with acute and chronic wounds in June 2002, of which 246 of these were venous ulcers (Keane M. 2002 *pers.comm.* 28 June). The provision of data from additional service providers was also sought in order to protect against site bias, as well as improve participant recruitment and sample representation (Spilker 1991a), although attempts to attract participation in these settings were not successful. The solicitation of outpatient leg-ulcer clinics also proved redundant as clinics provided care to clients already managed by the district nursing service. Sites such as acute-care facilities were not approached for the trial, however, due to the estimated high probability of dropouts, attrition and small patient numbers. Despite the lack of participation from other providers, the district nursing service still afforded access to a large number of clients with VLU over a wide geographic region, and across a variety of settings.

3.6 Sample & Selection Criteria

Clients receiving wound care from the district nursing service and meeting the stage I selection criteria were eligible to participate in the trial. Even though inclusion criteria were designed to eliminate confounding variables and maintain homogeneity, admission criteria could not be so restrictive as to compromise recruitment and the generalisability of findings (Polit & Hungler 1999). Variables suspected of delaying wound healing, but not supported by plausible evidence, were therefore omitted from the exclusion criteria. These included cigarette smoking (Thomson *et al* 1996), obesity (Peters 1998), age, gender and diabetes (Erickson *et al* 1995). Other factors known to delay wound healing, such as malnutrition and psychosomatic stress (Sussman 1998), were also excluded from the admission criteria due to an anticipated increase in trial complexity, time and cost. Participants were, however, questioned during pre-screening to ensure clients maintained a diet conducive to wound healing. To determine if clients were eligible to enter the stage I trial, subjects needed to meet the following selection criteria:

1. **Were cognitively capable of providing verbal and written consent**: A person could not legally or ethically provide informed consent if they were cognitively incompetent or senile (Polit & Hungler 1999).
2. **Had a lower leg venous ulcer**: As HCSE is a venotonic (Bombardelli, Morazzoni & Griffini 1996), only ulcers of venous aetiology were expected to respond to the extract. To be classed as a venous ulcer, the wound had to be superficial, exudating and located within the gaiter area of the lower leg. Concomitant signs of CVI also needed to be evident, including the presence of oedema, venous staining or varicose veins.

3. **Had a venous ulcer between one and twenty centimetres in diameter at the widest dimension**: Since wound size may influence the rate of wound healing (Thomson *et al* 1996), ulcer size was limited to avoid extreme cases and distorted findings (Unsworth 1999).
4. **Had a venous ulcer of four weeks duration or longer**: Ulcers of less than four weeks duration demonstrate a significantly greater rate of healing than ulcers of longer duration (Thomson *et al* 1996). Thus, to avoid confounding results (Spilker 1991a), the period of ulceration needed to exceed four weeks.
5. **Had an Ankle-Brachial Pressure Index (ABPI) between 0.8 and 1.3, which was obtained within the last twelve weeks**: The clients' ABPI was assessed by the nursing service using hand-held, continuous-wave Doppler ultrasonography, which provided a prompt and affordable screening tool for arterial insufficiency (Vowden, Goulding & Vowden 1996; The Alexander House Group 1992). An ABPI below 0.8 was suggestive of arterial impairment (Goldstein *et al* 1998), whilst an index above 1.3 indicated non-compressible arteries often of diabetic origin (Lopez & Phillips 1998; Vowden, Goulding & Vowden 1996). Hence, an ABPI between 0.8 and 1.3 reduced the likelihood of a leg ulcer being of arterial or diabetic aetiology, as well as avoiding conditions where compression therapy was contraindicated (Williams 1996b). As ABPI readings may change after three months (Simon, Freak, Williams & McCollum 1991), the reading also had to be no more than twelve weeks old to still be relevant.

6. **Was not receiving oral or topical corticosteroids**: Since corticosteroids impair wound healing (Sussman 1998; Thomas 1995), clients receiving steroid medication had to be excluded to avoid confounding results.
7. **Was not treated with radiotherapy in the last six months**: Radiotherapy destroys fibroblasts and endothelial cells, which subsequently impair wound healing (Sussman 1998). Clients receiving radiotherapy were therefore not eligible to enter the trial due to the probability of distorting findings.
8. **Had not received venotonic therapy in the last six weeks**: Venotonic treatment may ameliorate wound healing. Therefore, recent venotonic use was not permitted because of the likelihood of confounding results.
9. **Had not participated in another wound care trial in the last thirty days**: Interventions from other trials may possess carryover effects (Spilker 1991a) that could influence wound healing. To avoid misconstruing results, recent participation in a wound care trial was not permitted.
10. **Was not allergic to HCSE**: Clients reporting an allergy to HCSE were excluded from the trial to minimise the risk of participant harm.

3.7 Sample size & Power analysis

Power analysis was used to estimate the sample size that was capable of detecting a difference between the two interventions (Burns & Grove 1993; Polit & Hungler 1999). The power of the study, or 1-β, was based on the conventional standard of .80, and was aimed at reducing the risk of committing a type II error (Burns & Grove 1993; Polit & Hungler 1999). Utilising the primary

outcome of 'healed venous ulcer' and the effect size previously reported with oral Pentoxifylline (Falanga *et al* 1999), a sample size of 120 had the power to detect a difference between a treated proportion of 49% and a placebo proportion of 23% (Odds Ratio 3.2) with the alpha (α) level set at 0.05.

3.8 Recruitment

The recruitment of participants is the most arduous process in a clinical trial (McNeely & Clements 1994; Reitemeier 2002; Vickers 2002), with delays in subject accrual often increasing time, costs and resource use (Lloyd-Parks 2001). While many patients may participate in RCTs to contribute to medical knowledge, or to receive superior care (Cunny & Miller 1994; Lovato, Hill, Hertert, Hunninghake & Probstfield 1997; Ross, Grant, Counsell, Gillespie, Russell & Prescott 1999), these reasons are not enough to encourage large numbers of individuals to partake in research trials. Instead, the successful conduct of a clinical trial is dependent on the provision of specific strategies that maximise subject accrual and retention (Lovato *et al* 1997). Protocol considerations designed to improve recruitment in the current study included the elimination of unnecessary admission criteria (Spilker 1991a); the adoption of a multi-centre design (Spilker 1991a); the choice of three dressing protocols, and the collection of data within clinics and patient homes. The provision of explicit information on the safety and efficacy of HCSE, and the benefits of the research, as well as communicating the researcher's intention to release study findings, were also directed at facilitating subject retention (Polit & Hungler 1999).

Recruitment commenced in April 2002 with the posting of flyers (Appendix 4) to all sites. Nursing staff were also provided with a resource booklet and fifteen-minutes of in-service training before being asked to distribute study information sheets (Appendix 5) to all patients with VLU. Clients wishing to participate in the trial were requested to leave a contact name and number on a secure answering service. Within twenty-four hours, clients were telephoned to assess their eligibility against the admission criteria. If all criteria were met, the participant's details, health history and verbal consent were documented (Appendix 6).

The patient's medical practitioner (MP) was then faxed a letter (Appendix 7) requesting written medical consent and treatment authorisation. If medical approval was not received, a follow-up telephone call was placed. If the MP refused to sign the consent form, the patient was withdrawn from the trial. Other practitioners involved in the management of the client's wound were also faxed an information letter (Appendix 7) to minimise the probability of violating the dressing protocol.

After medical consent was obtained, the client was registered on the participant enrolment log (Appendix 8) so that the subject could be efficiently tracked throughout the trial (Cornell 1990). The participant was then randomly assigned to the HCSE or placebo group (see section 3.9 for more detail). At the baseline visit, the subject was supplied with the intervention, data collection forms and further instructions (Appendix 9), after which the participant provided informed

written consent (Appendix 10). The four-month recruitment period was scheduled to cease in August 2002.

The small number (n=2) of participants enrolled in the trial between April and June of 2002 necessitated the implementation of several new recruitment strategies. As well as dispatching continuous reminder notices and information sheets to all staff, a series of advertisements were published in the fortnightly staff newsletter and quarterly client magazine. Furthermore, a staff incentive scheme was introduced in which nurses recruiting clients were entered into a draw to receive a department store voucher. With only four subjects enrolled in the study at the end of August 2002, ethics approval was sought and received for the provision of a list of all clients receiving wound care through the district nursing service. Each nurse was then individually approached to identify which of the nurse's clients met the trial selection criteria. Staff were then requested to distribute information sheets to those clients meeting the criteria. By November 2002, only twenty-eight participants were recruited. Hence, approval for a direct mail-out of information sheets to all 246 clients with VLU was requested from the district nursing service and subsequently granted. By January 2003, a total of forty-two subjects were enrolled.

Interim analysis revealed that greater participant numbers were needed, and as a result, a direct mail-out of information sheets to all 430 clients with both VLU and unclassified wounds was conducted in April 2004. Three large outpatient wound-healing clinics were also sought as additional sites for recruitment, of which the institutional ethics committee approved one. Clinic staff were

consequently informed about the trial and asked to distribute information sheets to all patients with VLU, although this effort did not lead to the recruitment of any additional patients. Other strategies such as mass media advertising, honorariums, recruitment personnel and continuation protocols (Spilker 1991a) were not feasible, however, due to the financial constraints of the trial. By October 2004, a total of fifty-four participants had been recruited through the district nursing service.

3.9 RANDOMISATION

Participants enrolled in the trial had an equal chance of being allocated to the HCSE and placebo group through the use of random assignment (Polit & Hungler 1999). This process was not only central to blinding, but by reducing selection (Spilker 1991a) and volunteer bias (Jolley 1999), was also critical to improving the internal and external validity of the study (Portney & Watkins 2000). Randomisation also reduced the likelihood of systematic bias, and whilst no procedure could balance all extraneous variables between groups (Heard & Harris 1999), randomisation was the most reliable method for creating comparable groups (Polit & Hungler 1999; The Consort Group 2001). In order to balance the size of each group, as well as increase the power of the study, the trial was conducted using a restricted randomisation procedure (Friedman, Furberg & DeMets 1982; The Consort Group 2001).

The allocation of randomisation codes was determined by the block randomisation method using block lengths of four. Thus, for every four subjects enrolled, two participants would be allocated to each of the two groups. These blocks were randomly chosen by an independent party using the lottery method,

and recorded on the randomisation code log (Appendix 11) to allow the selection and completion of 'blocks' to be monitored. A fundamental concern of block randomisation, however, was the increased predictability of the treatment allocation sequence (The Consort Group 2001). Nevertheless, this issue was addressed by masking the interventions (The Consort Group 2001), as described below.

3.10 Masking/Blinding

Blinding is a process in which specific information about data, procedures or interventions are withheld from participants and staff (Day 1999), for the purpose of reducing observer, information and ascertainment bias (Jadad 1998; Jolley 1999; Juhl 1982; Spilker 1991a). With the use of a matching control group, the study was able to blind all study personnel and subjects from treatment allocation throughout the course of the trial. To maintain blinding, the treatment codes were placed in a sealed envelope and held by an independent party. A de-blinding protocol was also developed to manage medical requests for treatment identification (Therapeutic goods administration (TGA) 2000) (Appendix 12), although no such requests were made in the current study. To quantify the efficacy of blinding, clients were asked to speculate about which treatment they received, as well as the level of certainty about receiving that treatment (Spilker 1991a). The Consort Group (2001) argue that when blinding is successful, the ability of participants to identify which treatment they were receiving should be no better than chance.

3.11 Interventions

Participants were randomised to receive HCSE or placebo at a ratio of 2:2. Clients assigned the active intervention were supplied with brown ovoid tablets,

each containing 375 mg HCSE, standardized to 75 mg aescin. This dose was based on the standardised dose reported in previous RCTs (Diehm, Vollbrecht, Amendt & Comberg 1992; Erler 1991). Participants allocated the placebo tablets received an intervention that matched in colour, taste, appearance and odour, which contained the same excipients as the active intervention, yet did not include HCSE. The purpose of the placebo group was to allow for triple-blind conditions and to provide control over major sources of misleading data, including patient and investigator prejudice, extraneous variables, and spontaneous changes in the parameters under investigation (Roberts & Taylor 1999; Spilker 1991a). The use of a placebo also allowed the psychological and non-specific effects of treatment to be corrected (Juhl 1982; The Consort Group 2001), and was therefore able to improve data interpretation by reducing multicausality (Roberts & Taylor 1999; Spilker 1991a).

Both groups self-administered the treatment at a dose of one tablet twice daily with meals until the specified ulcer had healed, for a period not exceeding twelve weeks. The duration of HCSE treatment was guided by previous RCTs (Diehm, Trampisch, Lange & Schmidt 1996; Rehn *et al* 1996) and the need to achieve clinically relevant outcomes. Whilst a longer treatment period was expected to increase the rate of wound healing, this effect was likely to be offset by a probable reduction in subject recruitment and treatment compliance.

Manufacture & Packaging

HCSE and placebo tablets were manufactured, labelled, coded and packaged by Mediherb Pty Ltd, Queensland, in accordance with the Australian code of good manufacturing practice for medicinal products (TGA 2002). The

standardised level of aescin was confirmed by UV-vis spectrophotometry, and quality control was verified by certificates of analysis (Appendix 13). To minimise product deterioration and tampering, tablets were packaged in amber glass bottles with tamper evident lids and stored in a cool secure location away from direct sunlight. At trial completion, all unused bottles of tablets were packaged, sealed and stored in a secure residential facility to allow for further investigation of the extract.

Labelling

Bottles of tablets were labelled in accordance with federal labelling requirements (Spilker 1991a), yet to minimise deblinding, the labels were generic, as illustrated in Figure 3.1.

Figure 3.1: Medication label on stage I treatment bottles.

Horsechestnut and Venous Leg Ulcer Trial

Investigator:	Matthew Leach	Contact:	#### ### ###
Contents:	170 tablets of trial medication		
Instructions:	**take one tablet between 8-10am and one tablet between 6-8 pm** by mouth with food for twelve weeks, or until ulcer heals		
Storage:	Store tablets only in this bottle, away from direct sunlight and below 30^0C.		
Batch No:	AA0027C	Expiry Date:	02 / 2005
Medication code:	000	ID number:	000 - 00 - 000
Warning:	*For clinical trial use only. Keep out of reach of children.*		
Note:	Return bottle and remaining contents at the end of the trial.		

Treatment Compliance

Treatment compliance was measured throughout the study using the participant medication record (Appendix 14), and confirmed by a count of remaining tablets at trial termination. Clients who self-administered less than eighty percent of the trial tablets were considered non-compliant. To minimise the number of non-compliers, participants were provided with written and verbal instructions, and set administration times (Spilker 1991a). Subjects were also telephoned one

week after commencing the study to address any factors that may have hampered compliance (McNeely & Clements 1994).

Dressing Protocol

In addition to the intervention, participants in both treatment groups also received wound care from staff employed by the district nursing service. A standardized dressing protocol was therefore developed to reduce the number of wound treatment variables in the trial (The Alexander House Group 1992). The protocol's compatibility with clinical practice was also reviewed and confirmed by five South Australian wound care experts to minimise practitioner resistance and protocol violation (Burns & Grove 1993; Reitemeier 2002).

The dressing protocol consisted of three treatment plans, with the client's level of tolerance to compression therapy directing the choice of plan. The primary dressing protocol, for instance, consisted of high-level compression, and was recommended to all patients entering the trial. However, to minimise subject attrition, clients unable to tolerate high compression were prescribed the secondary protocol, whilst participants failing to endure any form of compression were allocated the tertiary protocol. A description of the three protocols are presented in Appendix 15.

3.12 INSTRUMENTATION

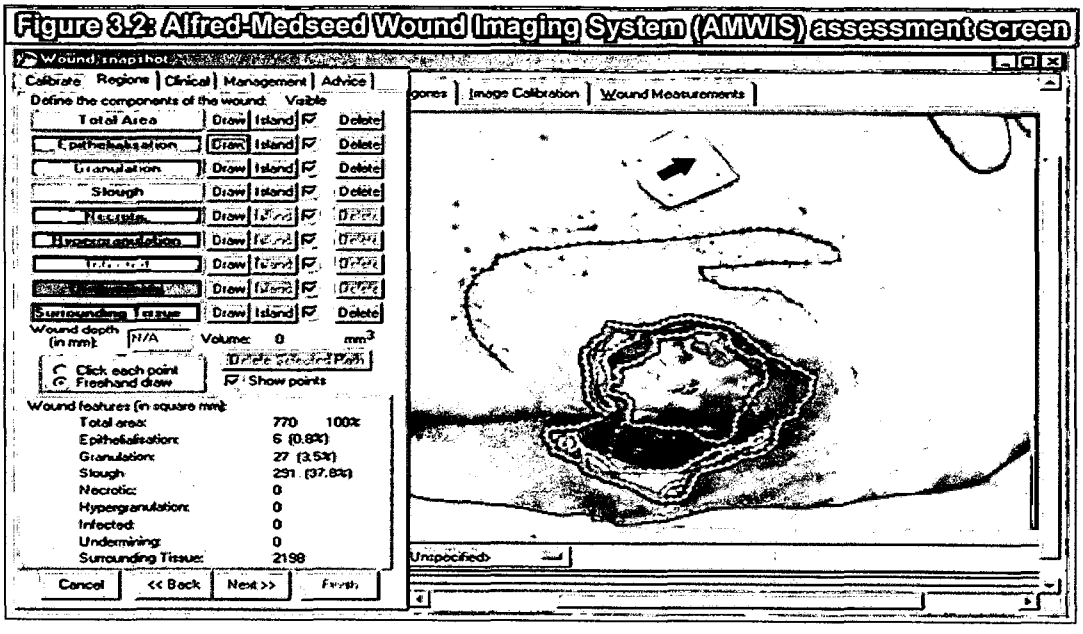
A comprehensive search of MEDLINE and CINAHL between the years 1960 and 2002 was conducted in order to locate a suitable wound assessment instrument for the stage I trial. Seven wound assessment tools were identified, including the Pressure Sore Status Tool (PSST); Sessing scale; Pressure Ulcer

Scale for Healing (PUSH); Sussman Wound Healing Tool (SWHT); Wound Healing Scale (WHS); Wound Care Society Assessment Chart (WCSAC), and the Wound Healing Society Tool (WHST). A review of these instruments found that the PSST and Sessing scale were the most valid and reliable tools to date (Woodbury, Houghton, Campbell & Keast 1999). Yet, the Sessing scale and PSST were not suitable for studies involving repeated measures, as the scales' sensitivity to changes in wound status over time had not been explored (Thomas 1997). Furthermore, measurements from these scales were subjective and were consequently open to significant bias. To avoid these limitations, wound assessments were conducted using the Alfred-Medseed Wound Imaging System (AMWIS).

The Alfred-Medseed Wound Imaging System (AMWIS)

AMWIS was a computerised wound assessment package designed to quantitatively measure the clinical features of a wound. After downloading and calibrating a digital photograph, the researcher used a mouse to outline the perimeter of the lesion and the tissue types within the wound (Figure 3.2). These planimetric measurements allowed AMWIS to calculate the total wound surface area; wound volume, and area of granulation, slough, epithelial, necrotic and infected tissue. These calculations were not only objective, but also internally consistent ($r=0.7$, $p<0.01$) and clinically accurate (99 percent) (Santamaria, Austin & Clayton 2002). Hence, in terms of wound care research, AMWIS was unlikely to be affected by systematic error, and was therefore a valid and reliable tool for measuring serial changes in wound healing. Nonetheless, as AMWIS could not address all the secondary hypotheses

presented above, a comprehensive wound assessment tool (WAT) was developed by the researcher to supplement the software.



The Wound Assessment Tool (WAT)

The Wound Assessment Tool (WAT) (Appendix 2) was a twenty-five-item pencil and paper instrument developed exclusively for the current study. Developed by the researcher, the tool collected data on the appearance of surrounding skin; type and degree of wound exudate; leg ulcer history; wound depth, location and shape; coexisting conditions; wound odour; pain; dressing regime, and frequency of dressing changes. Since the measurement of wound exudate, odour and pain were subject to observer bias, these parameters were measured using the objective response alternatives utilised in AMWIS (Bayside Health & Medseed 2002) and the PSST (Bates-Jensen 1997). Other items in the WAT, however, utilised objective data predominantly from standardised instruments, and were therefore not likely to be subject to misinterpretation or systematic error.

Several other measures were also collected from patients throughout the study. The measurement of parameters unrelated to wound healing, such as blood pressure, allowed the systemic vascular effects of HCSE to be monitored. Similarly, the acquisition of body weight measurements ensured that significant changes in ankle and calf girth were not attributed to a diuretic or anorexiant effect (Simini 1996). Although AMWIS and the WAT provided a comprehensive assessment of all trial outcomes, the WAT was only evaluated for face validity. Nevertheless, the quantifiable measurements and explicit instructions for the tool (Appendix 3), the single-investigator technique, and the adjunctive use of AMWIS, provided reasonable assurance that the data obtained from patients were both rigorous and plausible.

Frequency of assessments

Wound assessments were conducted by the researcher at weeks zero, four, eight and twelve with the use of digital photography, AMWIS and the WAT. Repeated measures, instead of a pre-test post-test design, allowed the wound healing effect of HCSE to be evaluated at different points in time (Polit & Hungler 1999). These monthly time points were based on the frequency of assessments reported in previous trials of HCSE (Diehm *et al* 1996; Rehn *et al* 1996), venous ulceration (Callam *et al* 1992; Mayberry *et al* 1991) and venotonic therapy (Falanga *et al* 1999).

3.13 Procedures & Data collection

Once subjects provided written consent to participate in the trial, the researcher collected data as follows:

1. The lower limb dressings were removed and the ulcerated leg was washed in warm water.

2. The Wound Assessment Tool (WAT) (Appendix 2) was completed. In the case where bilateral leg wounds were evident, the ulcer on the leg with an ABPI nearest 1.0 was chosen, and where multiple wounds were present, the largest wound was selected.
3. A digital photograph of the wound was obtained utilising the Canon IXUS V digital camera as follows:
    a. For wound calibration and orientation, a 10mm arrow was placed on the proximal aspect of the wound facing the head of the client.
    b. To identify the participant, an identification number was placed on the distal aspect of the wound.
    c. For optimum image quality, the flash was set to 'auto' and the shooting mode set to 'macro'.
    d. The camera was positioned fifty centimetres from the wound in a perpendicular fashion, and the photo obtained.
    e. If the photo was clear and adequate, the image was saved. If the photo was unsuitable, however, the photo was deleted and the photographic procedure repeated.
4. Following data collection and for the duration of the trial, the wound was dressed by a district nurse (DN) utilising the designated dressing protocol (Appendix 15).
5. To improve subject retention, participants were telephoned one week after baseline to monitor treatment compliance and adverse effects, as well as address any client concerns (McNealy & Clements 1994).

6. The twenty-minute wound assessments were repeated at weeks four, eight and twelve, with data being entered onto Microsoft Excel data sets within twenty-four hours of collection.
7. Following the final wound assessment, all forms and remaining tablets were collected and the trial termination form completed (Appendix 16).
8. At four, eight and twelve weeks after discharge, participants were telephoned to follow-up any changes in ulcer healing (Appendix 2).
9. Following the completion of data analysis, requesting participants were informed of treatment allocation.

3.14 Adverse Effects

Participants were questioned about the manifestation of adverse effects at week one, and then at each monthly assessment. To improve the accuracy of reports, clients were specifically asked about the presence of headache, nausea, pruritus and dizziness. The manifestation of any unfavourable outcomes was documented on the adverse effect record (Appendix 16). The reporting of mild adverse events necessitated the recommendation of conservative measures only, such as rest. Unfavourable outcomes defined as moderate or serious on the other hand, were processed in accordance with the adverse effect protocol (Appendix 12). As a legislative requirement of the Therapeutic Goods Administration, any severe reaction to HCSE also necessitated completion of the Adverse Drug Reactions Advisory Committee (ADRAC) blue card (Appendix 18).

3.15 Participant discharge, trial termination & follow up

The discharge of participants was finalised through completion of the trial termination form (Appendix 16). Serving four purposes, the termination form

provided a record of returned documents; measured treatment compliance; affirmed participant accuracy with documentation, and quantified the efficacy of blinding (Spilker 1991a). At four, eight and twelve weeks after discharge, subjects were telephoned and asked a set of seven questions (Appendix 2) to evaluate the carry-over effect of HCSE. Responses to these questions provided information on the number of existing and new leg ulcers, the pattern of wound healing, and the utilisation of compression therapy. Completion of the follow-up phase and the stage I trial occurred in February 2005.

3.16 Ethics

To protect the rights of participants, the trial was reviewed and approved by the Human Research Ethics Committees (HREC) of both the district nursing service and the University of South Australia (Appendix 19). The progress and conduct of the trial was monitored by the TGA under the Clinical Trial Notification (CTN) scheme. The current study was also conducted in accordance with TGA guidelines (TGA 2000); the National Health & Medical Research Council (NHMRC) national statement on ethical conduct in research (NHMRC 2001); the clinical trial protocol, and the Declaration of Helsinki (World Medical Association 2000).

Confidentiality

The utilisation of identification codes on data collection forms and computer files eliminated the degree of identifiable data, which minimised the risk of breaching participant confidentiality. Access to these computer files was restricted to the researcher and only made available to the statistical consultant during analysis. Subject profiles and code sheets that contained personal details were withheld

from all third parties and secured in a locked drawer with access limited to the researcher.

Consent

Subjects were fully informed about the stage I trial through the provision of an information sheet (Appendix 5) and a detailed instruction booklet (Appendix 9). Written approbation from the client's MP also assured that there were no unforseen reasons why the subject could not enter the trial (Appendix 7). With sufficient information and an understanding that participation was voluntary, subjects were able to provide both verbal and written consent to partake in the trial (Appendix 10) (Polit & Hungler 1999). To ensure that consent was also valid, both minors and the cognitively impaired were excluded from participating. The current study therefore protected the rights of prospective participants by conducting the trial in accordance with rigorous ethical standards.

3.17 Statistical Analysis

Data were entered into Microsoft Excel by the researcher within twenty-four hours from the point of collection. Data were analysed using the Statistical Analysis System (SAS - version 9.1) and undertaken by a statistician. All analyses were performed on an intention to treat basis. Measures of central tendency and dispersion were used to describe continuous variables with normal distributions, whilst medians and interquartile ranges were used to describe continuous variables whose distributions were sufficiently skewed. For categorical variables, frequency distributions and percentages were used.

Baseline differences between groups were examined using the t-test for independent groups. Outcome differences between the HCSE and placebo groups (between-group effects), differences over time (within-subject effects) and any differential treatment effect at different points in time (interaction effects) were accommodated through the use of repeated measures analysis of variance (RM-ANOVA) (Polit & Hungler 1999). RM-ANOVA was specifically chosen as measures of wound healing were taken at different points in time (Cornell 1990; Polit & Hungler 1999).

Repeated measurements were also analysed using survival analysis, as the duration of healing was of importance (Kalbfleisch & Street 1990). In this context, survival analysis calculated the probability of wound healing occurring in the HCSE and placebo groups from the beginning of the trial to the point of healing (Burns & Grove 1993; Polit & Hungler 1999). The difference between these groups was measured by the Log rank test (SPSS 2001). Survival analysis was also able to model time-to-event data in the presence of censored cases (Polansky & Rijswijk 1994; SPSS 2001). In the current study, this meant that wounds which were not healed at the end of the trial, or at the point the subject was lost to follow-up, were controlled. To adjust for multiple confounders of wound healing, the Cox proportional hazards model was used (Polit & Hungler 1999; SPSS 2001). Categorical measurements not meeting the assumptions of parametric testing, however, were examined using Chi-squared analysis.

Chi-squared (χ^2) analysis was used to determine if differences between the actual and expected number of 'categories' in each treatment group were statistically significant (Munro 1997; Polit & Hungler 1999). In other words, whether the treatment effect on selected categorical outcome variables was greater than that produced by chance (Polit & Hungler 1999). Apart from the need for categorical data, the assumptions of the Chi-squared test required that all categories contain only one entry per subject. It was also desirable that no more than twenty percent of cells had a frequency under five (Burns & Grove 1993; Munro 1997). If the latter assumption could not be met, however, Fishers' exact test was used instead (Polit & Hungler 1999).

The decision to accept or reject the primary and secondary hypotheses was based on the likelihood of random error. Type I errors, for instance, or the rejection of the null hypothesis when a significant difference between groups was not evident, were guarded against by setting the level of significance, or alpha level, at .05 (Polit & Hungler 1999; Roberts & Taylor 1999; Spilker 1991a). Type II errors on the other hand, or the acceptance of the null hypothesis when a significant difference between groups was evident, were controlled by setting the power of the study (1-Beta) at .80 (Polit & Hungler 1999; Roberts & Taylor 1999; Spilker 1991a).

3.18 Summary

The clinical effect of HCSE on venous ulcer healing was examined using a randomised placebo-controlled trial. This design, together with triple-blinding, objective and validated instrumentation, standardised treatment protocols, and intention-to-treat analysis, controlled against major sources of systematic error.

These measures therefore provided a rigorous research design capable of testing the study hypotheses. The following chapter details the results of the trial, as well as the implications of these findings.

CHAPTER 4

STAGE I FINDINGS & DISCUSSION

4.1 INTRODUCTION

The literature to date suggests that HCSE may be useful in the treatment of venous ulceration, although clinical studies have yet to support such a claim. A randomised controlled trial of HCSE was subsequently designed and conducted to examine this assumption. The results of this trial are reported below, including a discussion of the findings in relation to the hypotheses outlined in chapter three. Included in this discussion, are details of the quality and limitations of the study.

4.2 FINDINGS

4.2.1 FLOW OF PARTICIPANTS

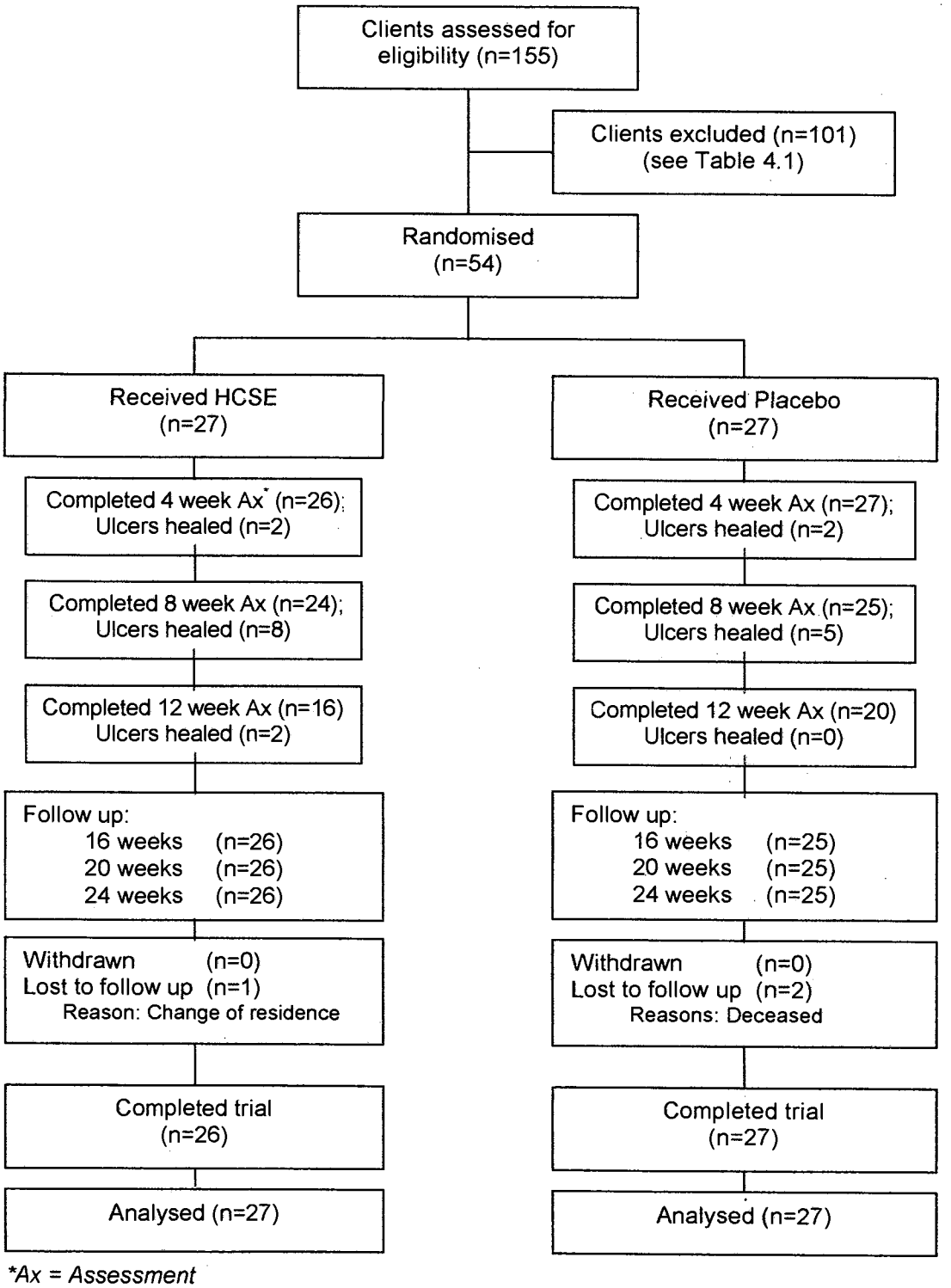
One hundred and fifty-five clients registered their interest in the trial. Of these subjects, fifty-four (35 percent) were randomised into the HCSE (n=27) and placebo groups (n=27). The remaining 101 clients (65 percent) were excluded from the trial, either because the ulcer had healed (46/101), the ABPI was less than 0.8 (17/101), or the client was on prednisolone (12/101). Medical practitioner obstruction, including failure to provide consent (7/101) and delays in approval resulting in eleven healed wounds (11/101), was another leading cause of exclusion. Other reasons for participant exclusion are listed in Table 4.1.

Table 4.1: Reasons for client exclusion from stage I (n=101)	
Reason	**n (%)**
Did not meet inclusion criteria	
Ulcer healed	46 (46)
ABPI < 0.8	17 (17)
Client on prednisolone	12 (12)
Consent refused by medical practitioner	7 (7)
Ulcer < 10 mm diameter	7 (7)
Diabetic or foot ulcer	4 (4)
Other[a]	4 (4)
Skin cancer	2 (2)
Met inclusion criteria but refused to participate	
Client refused to take placebo	2 (2)

a. Other reasons for exclusion included dementia; recent lower leg exposure to radiotherapy; eczema, and recent split-skin graft (SSG) to leg ulcer.

Participant retention in the trial was high, with no clients necessitating withdrawal. A total of three participants were, however, lost to follow-up. In the HCSE group, one subject was lost to follow-up at week four due to a change of residence. Attempts to locate this lost subject were not successful, however. In the placebo group, 2/27 participants were lost to follow-up at week 16 due to death. Despite the loss of three subjects, all fifty-four participants were analysed by intention-to-treat. Figure 4.1 illustrates the flow of participants from recruitment to analysis.

Figure 4.1: Flow of participants through stage I.



**Ax = Assessment*

4.2.2 BASELINE CHARACTERISTICS OF SAMPLE

Participants in the trial were on average, 77.9 years old, overweight (BMI 28.8 ± 5.6), and most likely to be a non-smoker (49/54). Subjects also had an average ABPI of 1.05 ± 0.1, as well as multiple signs of CVI, including ochre pigmentation (46/54), dry skin (40/54) and varicose veins (39/54). There were, however, no statistically significant differences between groups at baseline in terms of demographic or clinical characteristics (Table 4.2).

Table 4.2: Demographic and clinical characteristics of treatment groups at baseline

	HCSE group (*n* = 27)	Placebo group (*n* = 27)	Difference (95% CI)	p value[a]
Mean age ± SD	76.2 ± 9.5	78.9 ± 9.1	-7.9 – 2.3	0.277
Gender, *n* (%)				0.098
Male	19 (70.4)	12 (44.4)	-	-
Female	8 (29.6)	15 (55.6)	-	-
Mean BMI ± SD (kg/m^2)	29.8 ± 6.0	29.0 ± 6.4	-2.6 – 4.2	0.640
Mean blood pressure ± SD (mmHg)				-
Systolic	137.2 ± 17.8	137.0 ± 17.7	-9.5 – 9.9	0.970
Diastolic	70.0 ± 11.0	69.8 ± 13.0	-6.4 – 6.8	0.955
Tobacco smoker, *n* (%)	3 (11.1)	2 (7.4)	-	1.000
Alcohol intake per week, *n* (%)				1.000
0 drinks	14 (51.9)	15 (55.6)	-	-
1-7 drinks	9 (33.3)	9 (33.3)	-	-
>7 drinks	4 (14.8)	3 (11.1)	-	-
Ankle diameter, *n* (%) (cm)				1.000
<23 cm	9 (33.3)	10 (37.0)	-	-
23-28 cm	16 (59.3)	15 (55.6)	-	-
>28 cm	2 (7.4)	2 (7.4)	-	-
Calf diameter, *n* (%) (cm)				0.491
≤27 cm	10 (37.0)	8 (29.6)	-	-
27.1-31 cm	11 (40.7)	9 (33.3)	-	-
>31 cm	6 (22.2)	10 (37.0)	-	-
ABPI ± SD	1.05±0.1	1.04±0.1	-0.1 – 0.1	0.764
Signs of CVI, *n* (%)				
Ochre pigmentation	22 (81.5)	24 (88.9)	-	0.704
Dry skin	22 (81.5)	18 (66.7)	-	0.352
Varicose veins	20 (74.1)	19 (70.4)	-	1.000

SD=Standard Deviation. CI=Confidence Interval. (-)=Not applicable. BMI=Body mass index. ABPI=Ankle brachial pressure index. CVI=Chronic venous insufficiency.
a. p values associated with the mean difference for each variable were calculated with the Fishers exact test for categorical data, and the t-test for independent groups for continuous data.

Wound histories were also similar between groups at baseline (Table 4.3), with the majority of patients manifesting a single venous ulcer (25/54) of less than 36 weeks duration (33/54).

Table 4.3: Wound history of each treatment group at baseline

	HCSE group (*n* = 27) *n* (%)	Placebo group (*n* = 27) *n* (%)	p value[a]
Mean number of existing leg ulcers			0.093
1 ulcer	9 (33.3)	16 (59.3)	-
2 ulcers	8 (29.6)	3 (11.1)	-
3 ulcers	4 (14.8)	6 (22.2)	-
4 or more ulcers	6 (22.2)	2 (7.4)	-
Duration of presenting ulcer			0.366
0-12 weeks	7 (25.9)	4 (14.8)	-
13-24 weeks	3 (11.1)	9 (33.3)	-
25-36 weeks	6 (22.2)	4 (14.8)	-
37-104 weeks	5 (18.5)	5 (18.5)	-
>104 weeks	6 (22.2)	5 (18.5)	-
Number of past ulcer episodes			0.405
1 episode	5 (18.5)	5 (18.5)	-
2 episodes	4 (14.8)	6 (22.2)	-
3 episodes	7 (25.9)	3 (11.1)	-
4 episodes	4 (14.8)	1 (3.7)	-
5 episodes	4 (14.8)	4 (14.8)	-
6 or more episodes	3 (11.1)	7 (25.9)	-
Ulcer history from first to present ulcer			0.835
0-12 months	4 (14.8)	4 (14.8)	-
13-36 months	3 (11.1)	5 (18.5)	-
37-60 months	6 (22.2)	3 (11.1)	-
61-120 months	6 (22.2)	7 (25.9)	-
>120 months	8 (29.6)	8 (29.6)	-

(-)=Not applicable.
a. p values associated with the mean difference for each variable were calculated with the Fishers exact test.

Ninety-one percent (49/54) of patients entering the trial did not require a change to their dressing regime. Wounds at baseline were typically cleaned with warm tap water (34/54), and dressed with a dry inert dressing (28/54) and 18-30 mmHg compression (25/54). The wound dressings applied at baseline were not significantly different between study groups (Table 4.4).

Table 4.4: Wound dressings applied in each treatment group at baseline

	HCSE group (*n* = 27) *n* (%)	Placebo group (*n* = 27) *n* (%)	p value[a]
Dressing protocol			0.117
Primary	12 (44.4)	6 (22.2)	-
Secondary	12 (44.4)	13 (48.1)	-
Tertiary	3 (11.1)	8 (29.6)	-
Wound cleaning agent			0.779
Water	18 (66.7)	16 (59.3)	-
Normal saline	9 (33.3)	11 (40.7)	-
Primary dressing[b]			
Dry inert dressing[c]	16 (59.3)	12 (44.4)	0.410
Zinc impregnated bandage	7 (25.9)	8 (29.6)	1.000
Hydrogel	4 (14.8)	4 (14.8)	1.000
Silver sulphadiazine (SSD) Cream	3 (11.1)	3 (11.1)	1.000
Foam	1 (3.7)	4 (14.8)	0.351
Secondary dressing			
30-40 mmHg compression[d]	12 (44.4)	6 (22.2)	0.182
18-30 mmHg compression[e]	12 (44.4)	13 (48.2)	0.501
Combine	0 (0)	2 (7.4)	0.491
Frequency of dressing change			0.139
Weekly	8 (29.6)	9 (33.3)	-
Two times a week	13 (48.2)	5 (18.5)	-
Three times a week	3 (11.1)	10 (37.0)	-
Alternate daily / daily	3 (11.1)	3 (11.1)	-

a. p values associated with the mean difference for each variable were calculated with Chi-square and Fishers exact test as appropriate.
b. More than one primary dressing was applied to some patients.
c. Inert dressings included Melolin, gauze and Tricotex.
d. 30-40 mmHg compression included Surepress and four-layer Profore.
e. 18-30 mmHg compression included three-layer Profore, Tubigrip and Lestreflex.

Half of participants (27/54) also reported a history of hypertension (Table 4.5), and 35 percent (19/54) had a history of varicose vein ligation (Table 4.6). The mean number of medical conditions (t=-0.82, p=0.422) and surgical procedures (t=-0.10, p=0.924) reported by patients did not differ significantly between groups (Table 20.1, Appendix 20).

Table 4.5: Most frequent medical conditions reported by participants in each treatment group at baseline

	HCSE group (*n* = 27) *n* (%)	Placebo group (*n* = 27) *n* (%)	p value[a]
Hypertension	14 (51.9)	13 (48.2)	1.000
History of childbirth	7 (25.9)	10 (37.0)	0.379
Deep vein thrombosis (DVT)	7 (25.9)	4 (14.8)	0.311
Gout	7 (25.9)	1 (3.7)	0.050
Osteoarthritis	4 (14.8)	6 (22.2)	0.484
Gastro-oesophageal reflux	4 (14.8)	5 (18.5)	1.000
Diabetes mellitus	2 (7.4)	6 (22.2)	0.250

a. p values associated with the mean difference for each variable were calculated with Chi-square and Fishers exact test as appropriate.

Table 4.6: Most frequent surgical procedures reported by participants in each treatment group at baseline

	HCSE group (*n* = 27) *n* (%)	Placebo group (*n* = 27) *n* (%)	p value[a]
Varicose vein ligation	10 (37.0)	9 (33.3)	0.776
Skin grafting	4 (14.8)	8 (29.6)	0.190
Cholecystectomy	4 (14.8)	3 (11.1)	1.000
Hysterectomy	3 (11.1)	6 (22.2)	0.273
Total hip replacement	3 (11.1)	3 (11.1)	1.000
Appendicectomy	3 (11.1)	3 (11.1)	1.000
Inguinal hernia repair	2 (7.4)	3 (11.1)	1.000
Varicose vein sclerotherapy	2 (7.4)	2 (7.4)	1.000
Total knee replacement	2 (7.4)	1 (3.7)	1.000

a. p values calculated with Chi-square and Fishers exact test as appropriate.

The medications most frequently self-administered by subjects were antihypertensives (47/54), nutrient supplements (37/54) and anticoagulants (35/54) (Table 4.7). The difference between groups in terms of the mean number of medications reported was not statistically significant (t=0.14, p=0.890) (Table 20.1, Appendix 20).

Table 4.7: Medications most frequently administered by participants in each treatment group at baseline[a]

	HCSE group (*n* = 27) *n*	Placebo group (*n* = 27) *n*
Antihypertensives	28	19
Nutrient supplements	18	19
Anticoagulants	17	18
Diuretics	16	12
Analgesics	13	12
Antiinflammatories	10	6
Anti-gout agents	8	3

a. Several participants were prescribed more than one agent in the same drug class, thus, overall percentages and differences between groups were not measured.

There were no statistically significant differences between study groups in relation to baseline wound characteristics (Table 4.8). For all participants, the wounds were mostly located in the left (29/54), medial (36/54), posterior (30/54) gaiter (54/54); were less than 400 mm^2 in size (29/54); exudated

moderately (33/54), and contained less than fifty percent granulation tissue (36/54) and more than fifty percent slough (35/54).

Table 4.8: Baseline wound characteristics of treatment groups

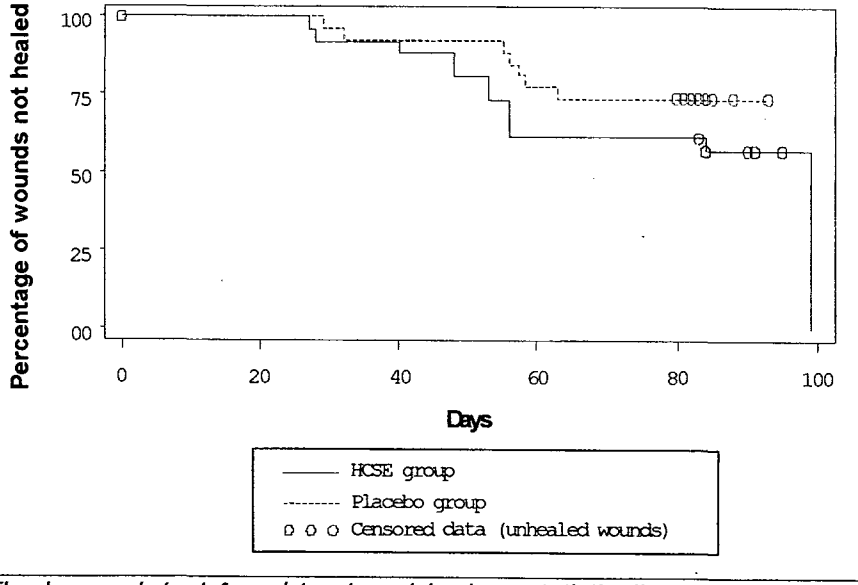
	HCSE group (*n* = 27)	Placebo group (*n* = 27)	Difference (95% CI)	p value[a]
Ulcer location, *n* (%)				-
Gaiter	27 (100)	27 (100)	-	1.000
Medial	18 (66.7)	18 (66.7)	-	1.000
Left	14 (51.9)	15 (55.6)	-	0.785
Posterior	16 (59.3)	14 (51.9)	-	0.584
Ulcer pain ± SD (0-10 scale)	4.6 ± 3.0	4.1 ± 2.7	-1.1 – 2.1	0.543
Wound surface area, *n* (%)				0.294
<100 mm^2	8 (29.6)	5 (18.5)	-	-
100-400 mm^2	10 (37.0)	6 (22.2)	-	-
401-900 mm^2	4 (14.8)	8 (29.6)	-	-
>900 mm^2	5 (18.5)	8 (29.6)	-	-
Wound volume, *n* (%)				0.713
0 mm^3	6 (22.2)	7 (25.9)	-	-
1-200 mm^3	9 (33.3)	6 (22.2)	-	-
201-2000 mm^3	6 (22.2)	9 (33.3)	-	-
>2000 mm^3	6 (22.2)	5 (18.5)	-	-
Wound granulation, *n* (%)				0.691
0-19 %	15 (55.6)	12 (44.4)	-	-
20-49 %	5 (18.5)	4 (14.8)	-	-
50-79 %	5 (18.5)	7 (25.9)	-	-
80-100%	2 (7.4)	4 (14.8)	-	-
Wound slough, *n* (%)				0.149
0-19 %	1 (3.7)	6 (22.2)	-	-
20-49 %	5 (18.5)	7 (25.9)	-	-
50-79 %	6 (22.2)	4 (14.8)	-	-
80-100%	15 (55.6)	10 (37.0)	-	-
Periwound erythema, *n* (%)				0.562
0 mm^2	18 (66.7)	21 (77.8)	-	-
1-2000 mm^2	4 (14.8)	4 (14.8)	-	-
>2000 mm^2	5 (18.5)	2 (7.4)	-	-
Periwound maceration, *n* (%)				0.377
0 mm^2	18 (66.7)	13 (48.2)	-	-
1-200 mm^2	5 (18.5)	7 (25.9)	-	-
>200 mm^2	4 (14.8)	7 (25.9)	-	-
Exudate level, *n* (%)				0.371
Nil	0 (0)	1 (3.7)	-	-
Low	10 (37.0)	5 (18.5)	-	-
Moderate	15 (55.6)	18 (66.7)	-	-
High	2 (7.4)	3 (11.1)	-	-
Exudate type, *n* (%)				0.220
Serous	17 (63.0)	12 (44.4)	-	-
Haemoserous	9 (33.3)	8 (29.6)	-	-
Purulent	1 (3.7)	4 (14.8)	-	-
Haemopurulent	0 (0)	2 (7.4)	-	-
No exudate	0 (0)	1 (3.7)	-	-
Wound odour, *n* (%)				0.170
None	23 (85.2)	17 (63.0)	-	-
Some	3 (11.1)	8 (29.6)	-	-
Offensive	1 (3.7)	2 (7.4)	-	-
Signs of WI present, *n* (%)	3 (11.1)	3 (11.1)	-	1.000
On antibiotics for WI, *n* (%)	3 (11.1)	1 (3.7)	-	0.350

SD=Standard Deviation. CI=Confidence Interval. WI=Wound infection. (-)=Not applicable
a. p values associated with the mean difference for each variable were calculated with Chi-square and Fishers exact test for categorical data, and the t-test for independent groups for continuous data.

4.2.3 RATE OF VENOUS ULCER HEALING

The oral administration of HCSE was associated with a greater percentage of healed venous leg ulcers (12/27) than placebo by week twelve (7/27). The difference in the rate of wound healing between groups was not statistically significant (Log Rank=1.76, p=0.185) (Figure 4.2). Whilst the number of leg ulcers did change significantly over time (F=4.85, p=0.003), there was no evidence of an interaction between treatment and week of assessment (F=1.12, p=0.343). HCSE also had no significant effect on the rate of wound healing after potential baseline confounders, including wound infection and dressing protocol, were controlled in a Cox regression model (Cox Regression=1.34, p=0.247) (Figures 20.1 & 20.2, Appendix 20).

Figure 4.2: Wound-healing curve illustrating the percentage of unhealed wounds in each study group during the twelve-week treatment period



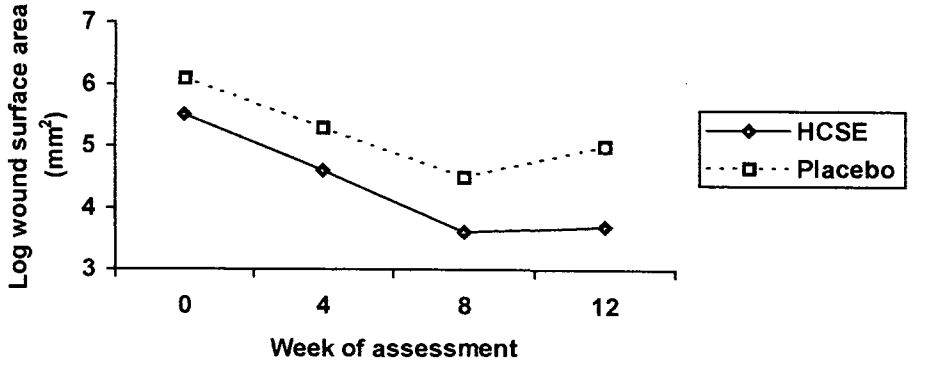
The Log-rank test found treatment had no statistically significant effect on the rate of wound healing over time (Log Rank=1.76, p=0.185).

Participants receiving HCSE participated in the trial for fewer days (67.5 ± 20.8) than subjects on placebo (75.0 ± 16.7). The difference between groups in terms of trial duration was not statistically significant (t=-1.45, p=0.152).

4.2.4 CHANGES IN WOUND DIMENSIONS

For both groups, wound surface area changed significantly over the twelve weeks (F=15.93, p<0.001). Yet, there was no evidence of a significant interaction between treatment and week of assessment for log surface area (F=0.60, p=0.618). Whilst the wound surface area in both groups appeared to fall in the first eight weeks of treatment and increase thereafter (Figure 4.3), these findings should be interpreted with caution. It is likely that the withdrawal of participants with healed wounds and associated lower values may have increased the overall values in each group. This caveat should therefore apply to all graphs that follow a similar pattern.

Figure 4.3: Change in log wound surface area at weeks 0, 4, 8 and 12 for each study group

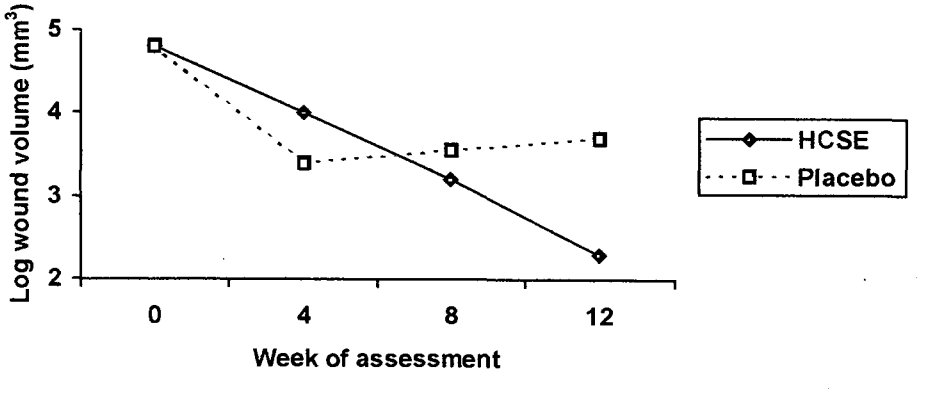


RM-ANOVA found no statistically significant difference between groups in log surface area over time (F=0.60, p=0.618).

A significant change in log wound volume (F=7.18, p<0.001) was evident in both groups over the twelve weeks. The difference in wound volume between groups over time was not statistically significant (F=1.72, p=0.167) (Figure

4.4). Data for wound surface area and volume are presented in Table 20.2 (Appendix 20).

Figure 4.4: Change in log wound volume at weeks 0, 4, 8 and 12 for each study group

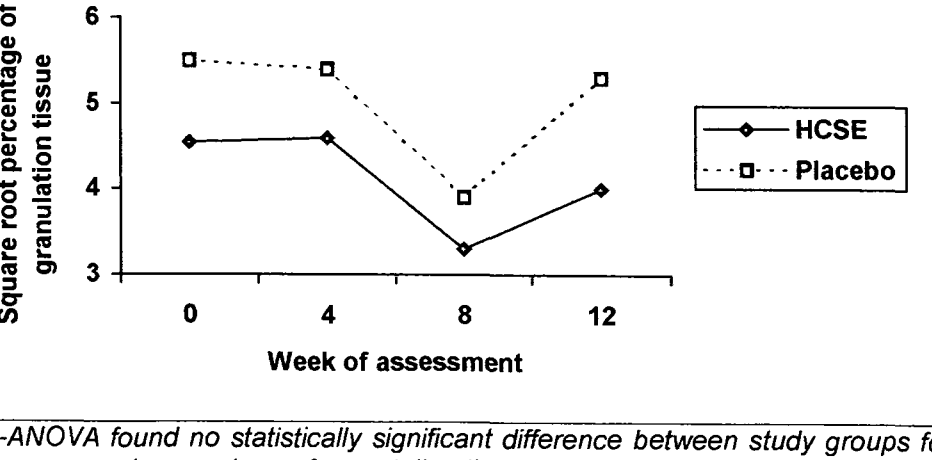


RM-ANOVA found no statistically significant difference between groups in log wound volume over time (F=1.72, p=0.167).

4.2.5 CHANGES IN WOUND TOPOGRAPHY

The square root percentage of wound granulation tissue in the HCSE and placebo group did not change significantly over the twelve weeks (F=2.41, p=0.070), nor was there any evidence of a significant interaction between treatment and time (F=0.10, p=0.962) (Figure 4.5).

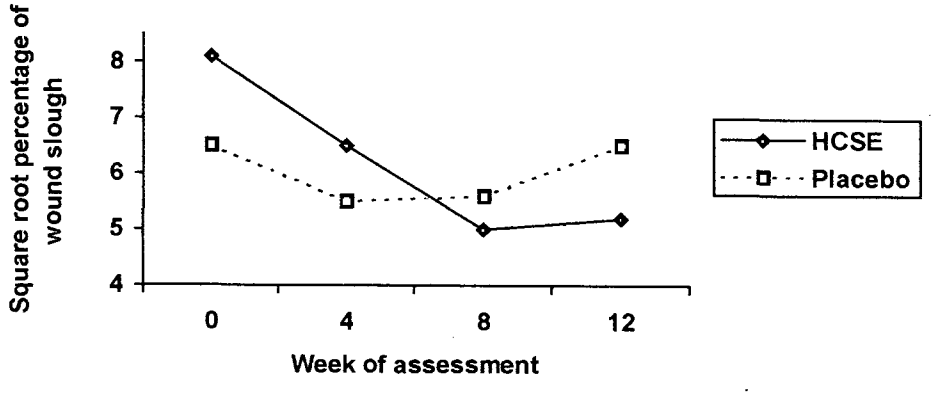
Figure 4.5: Change in the square root percentage of wound granulation at weeks 0, 4, 8 and 12 for each study group



RM-ANOVA found no statistically significant difference between study groups for the square root percentage of granulation tissue over time (F=0.10, p=0.962).

A significant change in the square root percentage of slough over the three months was evident in both groups (F=5.05, p=0.002). The difference between the two study groups in the square root percentage of slough was statistically significant (F=2.76, p=0.045) (Figure 4.6). Post-hoc comparisons revealed that the significant interaction between treatment and time was only evident in the HCSE group, and only between week zero and week four (t=2.27, p=0.025), eight (t=4.04, p<0.001) and twelve (t=3.21, p=0.002). The actual surface area data for slough and granulation tissue are presented in Table 20.4 (Appendix 20).

Figure 4.6: Change in the square root percentage of wound slough at weeks 0, 4, 8 and 12 for each study group

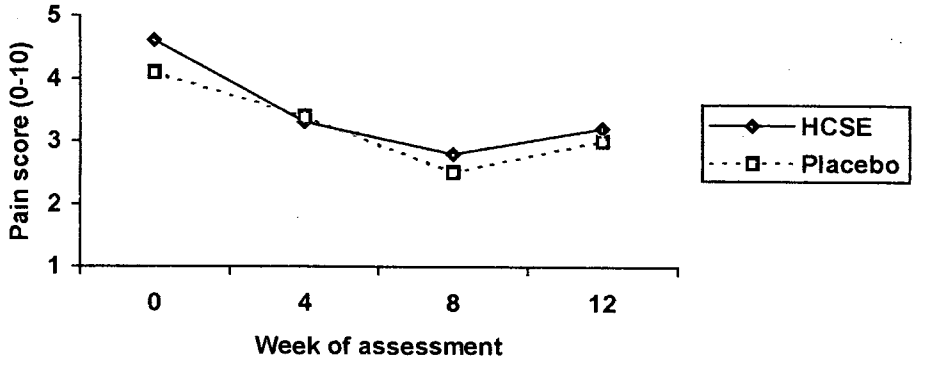


The difference between groups for the square root percentage of slough over time was statistically significant with RM-ANOVA (F=2.76, p=0.045).

4.2.6 Changes in CVI symptoms

The level of ulcer pain reported in each group changed significantly over time (F=8.16, p<0.001). There was, however, no significant interaction between treatment and week of assessment for the degree of wound pain (F=0.27, p=0.847) (Figure 4.7; Table 20.3, Appendix 20).

Figure 4.7: Change in mean pain score at week 0, 4, 8 and 12 for each study group



RM-ANOVA found no statistically significant difference between groups in mean pain score over time (F=0.27, p=0.847).

There was also no statistically significant difference in the level of wound exudate between the two treatment groups at weeks four (Fishers exact=1.59, p=0.777), eight (Fishers exact=3.13, p=0.478) or twelve (Fishers exact=2.43, p=0.565) (Table 4.9).

Table 4.9: Change in wound exudate level at weeks 0, 4, 8 and 12 for each study group

	Week 0[a] *n* (%)	Week 4[b] *n* (%)	Week 8[c] *n* (%)	Week 12[d] *n* (%)
HCSE group				
Nil	0 (0)	2 (7.7)	8 (34.8)	3 (18.8)
Low	10 (37.0)	13 (50.0)	5 (21.7)	4 (25.0)
Moderate	15 (55.6)	10 (38.5)	10 (43.5)	8 (50.0)
Heavy	2 (7.4)	1 (3.9)	0 (0)	1 (6.3)
	(n=27)	(n=26)	(n=23)	(n=16)
Placebo group				
Nil	1 (3.7)	4 (16.0)	7 (28.0)	3 (15.0)
Low	5 (18.5)	9 (36.0)	6 (24.0)	5 (25.0)
Moderate	18 (66.7)	11 (44.0)	9 (36.0)	7 (35.0)
Heavy	3 (11.1)	1 (4.0)	3 (12.0)	5 (25.0)
	(n=27)	(n=25)	(n=25)	(n=20)

Fisher's exact test found no statistically significant difference between groups for the level of wound exudate at weeks zero[a] (Fishers exact=3.83, p=0.371), four[b] (Fishers exact=1.59, p=0.777), eight[c] (Fishers exact=3.13, p=0.478) or twelve[d] (Fishers exact=2.43, p=0.565).

For both groups, ankle (F=0.25, p=0.862) and calf diameter (F=1.81, p=0.149) did not change significantly over the twelve weeks. There were also no

significant differences between the two groups for ankle (F=1.24, p=0.297) and calf (F=1.19, p=0.316) girth over time (Table 4.10).

Table 4.10: Change in ankle and calf girth at week 0, 4, 8 and 12 for each study group

		HCSE group mean ± SD	*n*	Placebo group mean ± SD	*n*
Mean ankle diameter (cm)[a]					
	Week 0	24.2 ± 3.3	27	24.1 ± 2.4	27
	Week 4	24.3 ± 3.4	26	23.8 ± 2.4	25
	Week 8	24.6 ± 3.3	22	24.0 ± 2.3	25
	Week 12	24.4 ± 4.3	16	24.8 ± 2.7	20
Mean calf diameter (cm)[a]					
	Week 0	29.3 ± 4.2	27	30.5 ± 5.6	27
	Week 4	29.5 ± 4.6	26	29.9 ± 4.6	25
	Week 8	29.3 ± 4.2	22	29.3 ± 4.1	25
	Week 12	28.9 ± 4.6	16	28.3 ± 4.3	20

a. RM-ANOVA found no statistically significant difference between groups in mean ankle diameter (F=1.24, p=0.297) or calf diameter over time (F=1.19, p=0.316).

4.2.7 Frequency of dressing changes

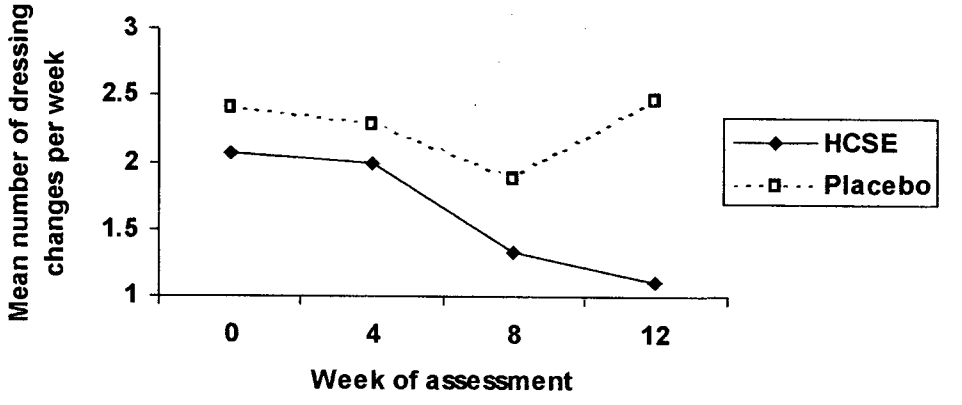
The frequency of dressing changes in the HCSE group decreased from 2.1 per week at baseline to 1.1 at week 12 (Table 4.11). The number of dressing changes in the placebo group increased from 2.4 per week at baseline to 2.5 at week 12 (Figure 4.8). The difference between study groups in the number of dressing changes required at week 12 was statistically significant (t=-2.71, p=0.009) (Table 4.11).

Table 4.11: Mean number of dressing changes per week at weeks 0, 4, 8 and 12

Time point	HCSE (*n*=27) mean ± SD	Placebo (*n*=27) mean ± SD	Mean difference	95% CI	p value
Week 0	2.07 ± 1.24	2.41 ± 1.58	- 0.33	-1.1 – 0.4	0.391
Week 4	2.00 ± 1.69	2.30 ± 1.98	- 0.30	-1.3 – 0.7	0.556
Week 8	1.33 ± 1.54	1.89 ± 1.81	- 0.56	-1.5 – 0.4	0.230
Week 12	1.11 ± 1.09	2.48 ± 2.39	- 1.37	-2.4 - -0.4	0.009

SD=Standard deviation. CI=Confidence interval.

Figure 4.8: Change in the mean number of dressing changes at weeks 0, 4, 8 and 12

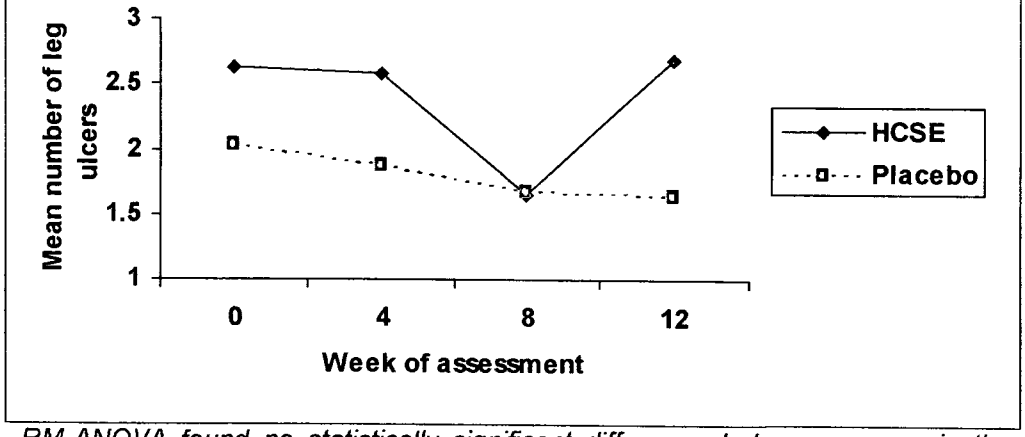


The T-Test for independent groups found the difference between groups in the number of dressing changes required per week was statistically significant at week 12 (t=-2.71, p=0.009).

4.2.8 FOLLOW-UP AFTER CESSATION OF TREATMENT

Twenty seven percent (7/26) of participants in the HCSE group reported a recurrent episode of leg ulceration during the twelve-week follow-up period, compared to 24 percent of subjects (6/25) in the placebo group. The differences between groups in terms of ulcer recurrence (χ^2=0.10, p=1.000) and number of residual ulcers (F=0.45, p=0.721) were not statistically significant (Figure 4.9).

Figure 4.9: Change in the mean number of leg ulcers reported in each group at 4, 8 and 12 weeks follow-up



RM-ANOVA found no statistically significant difference between groups in the number of residual leg ulcers over time (F=0.45, p=0.721).

During the period of follow-up, more participants in the HCSE group reported a decrease in wound size than subjects in the placebo group. The difference between groups, however, was not statistically significant (Table 4.12). On the other hand, a significant association between treatment and change in wound size at four weeks follow-up was evident with protocol-compliant analysis (Fishers exact=9.69, p=0.013). An association at eight (Fishers exact=6.30, p=0.088) and twelve weeks follow up (Fishers exact=3.14, p=0.424), however, was not statistically significant.

Table 4.12: Subjective change in wound size at 4, 8 and 12 weeks after the cessation of treatment

		Healed *n* (%)	Decreased *n* (%)	Unchanged *n* (%)	Increased *n* (%)
Week 4[a]	**HCSE** (n=26)	11 (42)	10 (38)	4 (15)	1 (4)
	Placebo (n=25)	11 (44)	5 (20)	8 (32)	1 (4)
Week 8[b]	**HCSE** (n=26)	14 (54)	10 (38)	2 (8)	0 (0)
	Placebo (n=25)	11 (44)	8 (32)	4 (16)	2 (8)
Week 12[c]	**HCSE** (n=26)	12 (46)	9 (35)	2 (8)	3 (12)
	Placebo (n=25)	10 (40)	5 (20)	9 (36)	1 (4)

Fishers exact test found no statistically significant difference between groups in the change in wound size at four[a] (Fishers exact=2.98, p=0.383), eight[b] (Fishers exact=3.23, p=0.460) and twelve weeks[c] (Fishers exact=6.33, p=0.090) after the cessation of treatment.

4.2.9 Adverse effects of treatment

The number of participants reporting an adverse effect in the HCSE group (17/27) was significantly greater than that reported in the placebo group (8/27) (χ^2=6.03, p=0.014). The difference in the severity of adverse effects between groups was not statistically significant (χ^2=0.78, p=0.714) (Table 4.13).

Table 4.13: Severity of adverse effects reported with each intervention[a]

	HCSE group (n = 17)	Placebo group (n = 8)
Mild	11	6
Moderate	5	2
Severe	6	3

a. Seven participants reported more than one adverse effect. There was no statistically significant difference between groups in the severity of adverse effects reported (χ^2=0.78, p=0.714).

Participants in the HCSE group reported a greater number of adverse events per subject (median=1, inter-quartile range (IQR)=2) than those in the placebo group (median=0, IQR=1). The difference between groups, however, was not statistically significant (Fishers exact=6.90, p=0.193). In the HCSE group, the adverse effects reported were predominantly gastrointestinal in nature (18/21 reports), and in the placebo group, were widely varied (Table 4.14).

Table 4.14: Adverse effects reported in each study group[a]

	HCSE group (n = 17)	Placebo group (n = 8)
Gastrointestinal effects		
Nausea	11	2
Vomiting	5	0
Loose stools	2	2
Constipation	0	1
Miscellaneous effects		
Pruritus	3	1
Visual disturbances	1	0
Headache	0	2
Dyspnoea	0	1
Increased ulcer pain	0	1
Lip sensitivity	0	1

a. Seven participants reported more than one adverse effect.

Most participants reporting an adverse effect from HCSE experienced the symptom for less than twenty-four hours (14/21 reports). Subjects on placebo reported side effects that often persisted for two to four days (5/11 reports) (Table 4.15). The difference between groups in the duration of adverse events was statistically significant (Fishers exact=17.57, p=0.002).

Table 4.15: Duration of adverse effects reported in each study group[a]

	HCSE group (n = 17)	Placebo group (n = 8)
< 1 hour	8	0
1-12 hours	0	2
13-24 hours	6	2
2-4 days	3	5
5-9 days	3	1
>30 days	2	1

a. Seven participants reported more than one adverse effect. The difference in the duration of adverse effects reported between groups was statistically significant (Fishers exact=17.57, p=0.002).

The majority of participants experiencing an adverse reaction to HCSE or placebo did not require pharmaceutical intervention (22/25). Eighty percent (20/25) of subjects did need to reduce the dose of intervention or cease the treatment to resolve the symptom (Table 4.16). The last action reported by patients to resolve the adverse effect did not differ significantly between groups (Fishers exact=2.64, p=0.451).

Table 4.16: The last action reported by participants to resolve the adverse effect of HCSE or placebo[a]

	HCSE group (n = 17)	Placebo group (n = 8)
Cease intervention	7	3
Decrease dose	7	3
No action required	2	0
Use medication	1	2

The Fishers exact test found no statistically significant difference between groups in the actions required to resolve the adverse effects of treatment (Fishers exact=2.64, p=0.451).

4.2.10 COMPLIANCE WITH PROTOCOL AND INTERVENTION

Sixty-seven percent (36/54) of participants were compliant with the dressing protocol. Of the minor protocol deviations, 44 percent (8/18) were attributed to practitioner interference (Table 4.17). The reasons for deviating from the

dressing protocol did not differ significantly between groups (Fishers exact=4.54, p=0.102).

Table 4.17: Reasons for deviating from the dressing protocol

Reason	HCSE group (*n* = 27) *n* (%)	Placebo group (*n* = 27) *n* (%)
Compliant with dressing protocol	20 (74.1)	16 (59.3)
Minor deviations from dressing protocol		
Treatment changed by nurse	4 (14.8)	0 (0)
Treatment refused by participant	2 (7.4)	8 (29.6)
Treatment changed by medical practitioner	1 (3.7)	3 (11.1)

There was no statistically significant difference between groups in the reasons for deviating from the dressing protocol (Fishers exact=4.54, p=0.102).

Sixty-one percent (33/54) of patients were compliant with the intervention (Table 4.18). In the HCSE group, adverse effects were a leading cause of poor treatment compliance (8/27). Factors reducing compliance were not significantly different between groups (Fishers exact=5.41, p=0.314).

Table 4.18: Reasons for poor treatment compliance[a]

	HCSE group (*n* = 27) *n* (%)	Placebo group (*n* = 27) *n* (%)
Compliant with treatment	15 (55.6)	18 (66.7)
Reasons for poor treatment compliance		
Adverse effects	8 (29.6)	2 (7.4)
Hospitalisation	2 (7.4)	3 (11.1)
Ceased by medical practitioner	1 (3.7)	2 (7.4)
Unknown	1 (3.7)	1 (3.7)
Holiday	0 (0)	1 (3.7)

a. Poor treatment compliance was defined as a tablet count of more than twenty percent at trial discharge.
There was no statistically significant difference between groups in the reasons for poor treatment compliance (Fishers exact=5.41, p=0.314).

4.2.11 TESTING OF BLINDING

Most participants in the HCSE (16/26) and placebo group (19/27) were uncertain about the intervention received during the trial. Opinion about treatment received (Fishers exact=3.24, p=0.214) (Table 4.19) and certainty of

opinion (Fishers exact=1.33, p=0.871) (Table 4.20) were not significantly different between groups.

Table 4.19: Participants opinion about the intervention received

	HCSE group (*n* = 26) *n* (%)	Placebo group (*n* = 27) *n* (%)
Do not know	16 (61.5)	19 (70.4)
Received HCSE	10 (37.0)	6 (22.2)
Received placebo	0 (0)	2 (7.4)

There was no statistically significant difference between groups in terms of opinion about treatment received (Fishers exact=3.24, p=0.214).

Table 4.20: Certainty of participants opinion about the intervention received

	HCSE group (*n* = 26) *n* (%)	Placebo group (*n* = 27) *n* (%)
Unsure	16 (61.5)	19 (70.4)
Fifty-fifty	1 (3.8)	0 (0)
Fairly sure	3 (11.5)	3 (11.1)
Almost definite	6 (23.1)	5 (18.5)

There was no statistically significant difference between groups in the certainty about treatment received (Fishers exact=1.33, p=0.871).

4.3 DISCUSSION

The current study reaffirmed that venous leg ulceration is a chronic and recurrent condition (Callam *et al* 1985; Goldstone 1994; Ouahes & Phillips 1995; The Alexander House Group 1992), with many subjects reporting multiple episodes of ulceration over a period often exceeding three years. Participant concerns about VLU (Table 20.5, Appendix 20) were also consistent with reports on the implications of the condition (Charles 1995; Hofman *et al* 1997), such as wound pain, impaired mobility and compromised lifestyle. These findings not only suggest that the conventional management of VLU may be inadequate, but that more effective treatment solutions are

needed. The current study attempted to address some of these issues by examining the clinical efficacy of HCSE.

4.3.1 SAMPLE

The trial sample was similar to the wider population of patients with VLU, particularly with respect to the mean age of participants, wound location, and proportion of ulcers both under and over twelve months duration (Baker & Stacey 1994; Callam *et al* 1987a; Olin, Beusterien, Childs, Seavey, McHugh & Griffiths 1999). The higher ratio of males to females in the HCSE group, however, was inconsistent with previous epidemiological reports (Baker & Stacey 1994; Fowkes 1996; Olin *et al* 1999), yet may just reflect the smaller numbers of female subjects typically found in clinical trials (Lovato *et al* 1997).

The homogeneity of the two study groups suggests that block randomisation was effective in balancing the many variables between groups, and therefore, may improve the internal and external validity of the findings (Portney & Watkins 2000). The major weakness in the current study, however, was the small sample size, leading to low power levels. Failure to achieve adequate sized samples in HCSE and wound care trials is not uncommon. In 11 of 16 (69 percent) well-designed RCTs on HCSE (Pittler & Ernst 2004) and 17 of 24 (71 percent) trials on compression therapy (Fletcher, Cullum & Sheldon 1997), the total sample size did not exceed fifty-three. While factors constraining the recruitment of participants within these studies are unclear, it is likely that a range of practitioner and patient elements were responsible (Leach 2003).

4.3.2 RECRUITMENT

The largest obstacle to the conduct of the stage I trial, and the reason why the study was underpowered, was the difficulty in participant accrual. Whilst the adoption of multiple recruitment strategies, non-restrictive protocols and home visitation were aimed at maximising participant accrual, client and practitioner reservations about the trial limited subject numbers. Such factors may have included concerns about risks; travel; time; level of information; preference toward or against a specific treatment, and aversion to randomisation (Cunny & Miller 1994; Lovato *et al* 1997; Richardson, Post-White, Singletary & Justice 1998; Ross *et al* 1999). Family or clinician opinion about the study or intervention may have also influenced subject participation in the trial (Ross *et al* 1999). Nonetheless, many of these obstacles were addressed by eliminating the need for client travel; providing multiple levels of trial information, and conducting brief and infrequent wound assessments.

Practitioner compliance with the trial protocol, as well as assistance with recruitment, may have also been compromised by time constraints; a lack of incentive; incompatibility with clinical practice, and a lack of interest toward the research question (Benson, Pregler, Bean, Rademaker, Eshler & Anderson 1991; Lovato *et al* 1997; Ross *et al* 1999; Spilker 1991b). Staff may have also viewed the research as less of a priority than existing work commitments (Hudson, Aranda & McMurray 2001) due to increased pressure in the workplace (Emanuel & Warburton 1999). Yet, the trial did not require practitioners to extend upon normal duties or commit additional time to the study.

Strict adherence to the trial protocol may have required some clinicians to modify their practice, which could have led to practitioner resistance, protocol violation and subject withdrawal (Burns & Grove 1993; Reitemeier 2002). Collaboration with the district nursing service wound-specialists and wound management guidelines during the development of the dressing protocols, however, suggests that the trial procedures were compatible with clinical practice. Since many of these barriers to participant accrual were adequately addressed, the difficulties in trial recruitment may have been the result of gate keeping.

Medical practitioners often serve as gatekeepers in clinical trials; the current study was no exception (Gurwitz, Guadagnoli, Landrum, Silliman, Wolf & Weeks 2001; Lovato *et al* 1997; Vickers 2002). The presence of gate keeping was evidenced by MP refusal to bestow consent (7/54), and MP delays in providing consent leading to ulcer healing (11/54). Therefore, the ethics committee's request for written medical consent may have hampered the recruitment of subjects (Gurwitz *et al* 2001). Organizational delays in approving the direct mail-out of information to clients also hindered participant accrual. Thus, in spite of attempts to adequately inform clinicians about the trial and intervention, or avoid clinician involvement in recruitment, gate keeping still occurred (Hudson *et al* 2001).

4.3.3 Rate of ulcer healing & changes in wound dimensions

The current study found insufficient evidence to demonstrate that HCSE was effective in improving the rate of healed VLU, wound surface area, depth and

volume after four, eight and twelve weeks of treatment, although point estimates of these measures highlight the potential efficacy of HCSE. Since the trial was underpowered, however, these non-significant findings may be indicative of a type II error. Two different studies on venotonic therapy support this claim. In one RCT, fifty-five patients with VLU were administered 1000 mg HR or placebo for twelve weeks (Schultz-Ehrenburg & Muller 1993). The rate of wound healing in the HR (12/28) and placebo group (7/27) were identical to that reported in the current study, and likewise, the difference between groups was not statistically significant (p=0.09). A RCT of 107 patients with VLU, however, found that six weeks of treatment with 1000 mg HR and compression therapy was significantly more effective at increasing the rate of wound healing than compression alone (no p value) (Stegmann *et al* 1986). Thus, without evidence from a larger trial, it may be premature to dismiss the value of HCSE in venous ulcer management.

4.3.4 Changes in wound topography

The percentage of ulcer slough and granulation tissue were measured at four-weekly intervals to monitor changes in wound condition. A decrease in slough and a corresponding rise in granulation tissue were indicative of an improvement in ulcer health (Bates-Jensen 1999). Whilst the oral administration of HCSE had a significant effect on wound slough over the twelve weeks, the extract had no effect on ulcer granulation. However, given that the current study was underpowered, this seeming statistical improvement in wound slough may reflect a type I error. On the other hand, a wound de-sloughing effect cannot be ruled out. HCSE may have reduced wound slough through a postulated improvement in local inflammation, oxygenation and

nutrient delivery. This reduction in slough may have also contributed to the significant decline in the number of dressing changes needed in the HCSE group at week twelve. Nevertheless, until this study is replicated with a larger sample, no firm conclusions can be made about the effect of the extract on wound topography.

4.3.5 Changes in CVI symptoms

Many studies have revealed that HCSE is effective in reducing the symptoms of CVI (Pittler & Ernst 2004). Yet, findings from the current study failed to add to this body of evidence, with HCSE treatment changing neither leg oedema, wound pain nor exudation over the twelve weeks. Whilst the ability to detect a significant difference between groups may have been hampered by the small sample, inadequate instrument sensitivity and reliability cannot be ruled out.

A one to ten numerical pain scale was used to quantify the degree of ulcer pain among stage I participants. Despite claims that pain scale measurements lack internal consistency (Sussman 1998), the validity and reliability of pain scales has been well documented (Bergh, Sjostrom, Oden & Steen 2000; Bijur, Silver & Gallagher 2001; Gallagher, Bijur, Latimer & Silver 2002). For instance, the alternative-forms reliability ($r=0.78$-0.92, $p<0.001$) and test-retest reliability ($r=0.75$-0.83, $p<0.001$) of the visual analogue, graphical and numerical scales were rated very high in a study of 167 geriatric patients (Bergh *et al* 2000). Aside from yielding quick and easy-to-analyse data, pain scales also demand less time from participants, and were therefore less likely to affect assessment compliance.

The oedema-reducing effect of HCSE was assessed using serial girth measurements of the ankle and calf. While some authorities argue that calf and ankle circumferences are an invalid and unreliable measure of leg oedema (Bednarczyk, Hershler & Cooper 1992), several trials have correlated these measurements to changes in plethysmographic data (Diehm *et al* 1992; Steiner & Hillemanns 1990). Apart from being a valid measure of oedema, leg diameter measurements were also simple, quick and cost-effective to perform (Perrin & Geux 2000). Even though the utilisation of more sensitive methods were considered in the current study, such as water displacement volumetry (WDV), the increased duration of client assessments was expected to compromise participant accrual, retention and assessment compliance (Cunny & Miller 1994; Lovato *et al* 1997; Ross *et al* 1999).

4.3.6 Follow-up after cessation of treatment

Participants were monitored for twelve weeks after the cessation of treatment in order to examine the carry-over effect and long-term benefit of HCSE therapy. Even though a carry-over effect of up to six weeks has been reported in the literature (Rehn *et al* 1996), HCSE had no effect on leg ulcer recurrence or the number of residual leg ulcerations during the twelve-week follow-up period. However, a greater number of wounds in the HCSE group had decreased in size at four weeks follow-up with protocol-compliant analysis, which suggests that when administered appropriately, HCSE may proffer an extended wound healing effect. Yet, given the likelihood of a type I error, and that changes in wound size were based on clients' subjective observations, this finding must be considered with caution.

4.3.7 ADVERSE EFFECTS OF TREATMENT

The treatment of VLU with Horsechestnut Seed Extract was safe, although frequently yielded mild and transient gastrointestinal effects. The type and nature of adverse events reported in the current study were consistent with the literature (Pittler & Ernst 1998), yet as many as 63 percent of participants reacted to the extract, compared to 30 percent on placebo. The frequency of adverse reactions to HCSE was greater than the 0.9 to 3.0 percent asserted in earlier trials (Pittler & Ernst 1998). One explanation for the higher rate of adverse effects could relate to the increased aescin content of the trial tablets, as aescin is claimed to be a causative factor of gastrointestinal irritation (Barnes, Anderson & Phillipson 2002; Mills & Bone 2000). The lack of adverse event monitoring in studies using HCSE standardised to 75 mg aescin, however, fails to provide data that supports the proposed association between higher aescin levels and the increased frequency of adverse reactions.

To reduce the likelihood of adverse gastrointestinal effects, participants were advised to administer HCSE with meals. This with-meal strategy, however, was not entirely effective in preventing these adverse events. Whilst an enteric-coated formulation could have been employed to reduce the incidence of adverse reactions (Liehn *et al* 1972; Rotblatt & Ziment 2002), to improve treatment compliance, and to improve the treatment effect of HCSE, enteric-coating was costly and was therefore not feasible in the current study.

4.3.8 QUALITY OF THE TRIAL

The random treatment allocation, placebo-control, triple-blinding and parallel group design of the current study, controlled for potential sources of bias and

confounding (Lloyd-Parks 2001). Utilising a single assessor and valid and reliable instrumentation also reduced the probability of observer and ascertainment bias. Thus, the likelihood of alternative causal explanations was minimised (Polit & Hungler 1999). The low attrition rate, homogenous sample and analysis by intention-to-treat also decreased the possibility of misinterpreting results (Spilker 1991a; The Alexander House Group 1992).

The quality of results was also enhanced by quantifying the efficacy of blinding (Spilker 1991a). To determine the success of blinding, a participant's ability to identify the treatment received had to be no better than chance (The Consort Group 2001). As there was no statistically significant difference between groups in terms of opinion and certainty of opinion about treatment received, the blinding conditions of the stage I trial were therefore successful. In other words, the introduction of observer, information and ascertainment bias was highly unlikely (Jadad 1998; Jolley 1999; Juhl 1982; Spilker 1991a). Despite the rigorous study design, however, several limitations hampered the generalisability of these findings.

4.3.9 Limitations

The most notable limitation of the current study, and a problem facing many clinical trials (Dunn & Everitt 1995), was the lack of statistical power. Any significant or non-significant difference between the two study groups may therefore be attributable to a type I or type II error, respectively (Burns & Grove 1993). Given that participant attrition and the scale of the target population were not concerns, it is likely that the sample size was constrained by gate keeping (Leach 2003).

Gate keeping in clinical trials is a common occurrence (Lovato *et al* 1997; Vickers 2002), and in this trial, involved medical and nursing staff, and the participating organization. Woog (1993) argues that gatekeepers, whether they are practitioners or organizations, have no responsibility in controlling participant entry into a trial. Instead, informed written consent should be a deciding factor. Thus, if the subject provides informed consent, and the intent of the research is to benefit individuals, an obstruction of research by gate keeping would not only be inappropriate, but constitute a breach of communitarianism (Hudson *et al* 2001; Woog 1993). It is therefore argued that clinicians have an ethical obligation to provide eligible patients with the opportunity to take part in a trial, with the intention of benefiting the overall community (Reitemeier 2002).

The strategies that were put in place to minimise gate keeping were focussed on building good rapport, as well as improving practitioner understanding about the benefits of HCSE treatment (Hudson *et al* 2001; Lovato *et al* 1997; McNeely & Clements 1994). The strategy that most likely hindered gate keeping, however, was avoiding the use of on-site staff to recruit participants (Hudson *et al* 2001). In particular, the accrual of participants improved when the method of recruitment shifted from staff distribution of information sheets, to the direct mail-out of information.

Another limitation related to the presence of CVI, in particular, the lack of testing to confirm the condition. Given that the presence of CVI was almost essential to treatment success, it is possible that the absence of venous

insufficiency in some patients could have lessened the overall effectiveness of HCSE. Whilst a diagnosis of CVI could have been confirmed by Duplex ultrasonography or plethysmography (Loeb 1994; Ouahes & Phillips 1995; The Alexander House Group 1992), such tests were costly and required medical authorisation. Thus, the financial limitations of the trial, as well as the increased probability of gate keeping, meant that preliminary screening of CVI was not feasible.

4.4 Summary

The stage I trial was the first study to explore the clinical effect of HCSE on venous ulcer healing. Whilst the trial was well designed, the study was unfortunately underpowered. Hence, improvements in the rate of wound healing and in most secondary outcomes did not reach statistical significance. HCSE did, however, significantly affect the percentage of wound slough and the frequency of dressing changes over the twelve weeks. Given that these outcomes could have a positive impact on staff workload, organisational costs and wound health, these effects warrant further investigation to determine whether HCSE is suitable for future VLU management. Adopting the strategies outlined in this chapter may help to minimise gate keeping and practitioner interference in these future trials, as well as increase subject recruitment and statistical power. Confirmation of CVI utilising Duplex ultrasonography or plethysmography, along with the enteric-coating of tablets, may also improve the treatment effect of HCSE in prospective studies. Improved rates of wound healing may also be achieved in future trials by identifying the types of individuals that are most likely to respond to HCSE treatment, which the following chapter brings to light.

CHAPTER 5

STAGE II COMPARATIVE CASE STUDY

5.1 INTRODUCTION

Earlier chapters have explored in detail the many implications of venous ulceration, as well as the potential benefits of utilising HCSE in this chronic condition. In recent chapters, the clinical efficacy of HCSE was examined. As with many wound trials, however, it is often unclear exactly which types of patients the investigated treatment may benefit. Hence, the current study used a comparative multiple-case design to identify the factors that may predict wound healing among patients receiving HCSE and placebo, and to illustrate to clinicians the typical response patterns that may be observed among clients treated with these interventions.

5.2 DESIGN

The case study is 'an empirical inquiry that...investigates a contemporary phenomenon within its real-life context, especially when...the boundaries between phenomenon and context are not clearly understood' (Yin 2003: 13). This level of inquiry is often achieved by examining an entire case in detail (Hooker 1991; Polit & Hungler 1999). Thus, unlike experimental designs that focus on specific sets of variables, case studies examine a wide range of factors within the context of a given phenomenon to better understand why individuals progress in a particular manner (Bergen & While 2000; Keyzer 2000; Yin 2003). Such an approach is therefore capable of capturing the complex and interactive elements of the human experience.

Thoughtful and systematic case studies can answer a multitude of clinical questions, as well as clarify concepts, develop theories and generate insights into previously unsuspected relationships (Bryar 1999; Keyzer 2000; McKee

2004; Polit & Hungler 1999; Whitney 2000). Case studies can therefore assist in identifying and understanding the important and complex variables that influence patient care (Bryar 1999; Hooker 1991; McKee 2004), particularly when the nature of a situation is unique, intricate or dynamic (Fitzgerald 1999; Yin 2003). In wound management for instance, a case study design may identify elements that facilitate or hinder wound healing that were previously overlooked or rejected. In other words, case studies may provide researchers and practitioners with an opportunity to take a fresh new look at a phenomenon (McKee 2004).

Even though findings from case studies can be generalised to theories, the results cannot be generalised to the wider population (Bryar 1999; Bergen & While 2000; Yin 2003). One reason for the difficulty in extrapolating findings is that case studies cannot establish cause and effect relationships (Hooker 1991), but instead, only attempt to understand a relationship (Jensen & Rodgers 2001). This limitation may explain why case studies are situated in a lower position (level IV) in the hierarchy of evidence (see Table 1.1). Nevertheless, case studies are a valid research methodology with high internal validity, and therefore should not be viewed as a reflection of flawed experimental design (Keyzer 2000; Whitney 2000).

A well-executed case study is characterised by the following elements: a prospective approach; repeated measures; a consistent clinical protocol; overt selection criteria; comparative cases; multiple data collection sources, and a comprehensive description of participants (Bryar 1999; Fitzgerald 1999;

Whitney 2000; Yin 2003). The use of a comparative multiple case design, as well as the sourcing of data from the stage I trial, meant that most of these criteria were achieved, and that the stage II study was rigorous in design.

5.3 Objectives

The primary purpose of the stage II study was to understand why venous ulcer healing had occurred in less than half of patients receiving HCSE and placebo. Thus, the objectives of the current study were to:

1. Identify the factors that predict venous ulcer healing and non-healing among stage I participants receiving HCSE and conventional treatment
2. Identify the factors that predict venous ulcer healing and non-healing among stage I subjects receiving placebo and conventional treatment
3. Present four cases that were characteristic of venous ulcer healing and non-healing in both the HCSE and placebo groups, and
4. Discuss the types of patients that may benefit from the use of HCSE in the management of venous ulceration.

5.4 Sample

Participants considered for selection in the current study were required to have had a venous leg ulcer that was previously treated with either HCSE or placebo (Chapter 3), and managed using one of three dressing protocols (Appendix 15). These conditions, in addition to the selection criteria outlined in Chapter three, reduced the number of variables that could have influenced wound healing, and therefore, enabled the researcher to isolate factors that best predicted a patient's response to treatment. Of the 53 stage I participants who met these criteria, four archetypal cases were chosen. These cases were characteristic of a VLU healer and non-healer from both the HCSE and

placebo groups in the stage I trial. As asserted by Yin (2003), the use of representative cases was necessary to minimise the risk of misinterpretation.

Logistic regression was initially used to guide the selection of cases by identifying the factors that predicted venous ulcer healing (Polit & Hungler 1999). The small sample and insufficient variability of data, however, did not support a logistic regression, with all coefficients found to be insignificant. Instead, the selection of cases was guided by the comparison of means and medians. In particular, the subject who most closely matched the medians and means of each group, particularly the variables that were significantly related to wound healing, was selected as the characteristic case for that group. For example, the archetypal healer in the HCSE group reported a venous ulcer duration of 30 weeks (Median for healed group=21 weeks); an ulcer history of 18 months (Median for healed group=42 months); a wound surface area of 118mm^2 (Median for healed group=153 mm^2); the use of psychotropic medication, and no history of skin grafting (Table 5.1). The case most characteristic of a non-healer in the HCSE group, however, did not use psychotropic medication, but reported a venous ulcer duration of 52 weeks (Median for non-healed group=51 weeks); a leg ulcer history of 60 months (Median for non-healed group=96 months), and a wound surface area of 430mm^2 (Median for non-healed group=430 mm^2) (Table 5.1).

Table 5.1: Baseline differences in characteristics between the healed and unhealed wounds in the HCSE group (n=27)

	Healed group (*n* = 12)	Unhealed group (*n* = 15)	Difference (95% CI)	p value[a]
Median age, *years* (IQR)	76.0 (10.0)	79.0 (8.0)	-5.1 – 10.2	0.504
Gender, *n* (%)			-	1.000
Male	8 (66.7)	11 (73.3)		
Female	4 (33.3)	4 (26.7)		
Tobacco smoker, *n* (%)	0 (0.0)	3 (20.0)	-	0.231
Median alcohol consumption, *n per day* (IQR)	0.5 (12.3)	0.0 ± (7.0)	-6.1 – 2.2	0.337
ABPI ± SD	1.1 ± 0.1	1.1 ± 0.1	-0.1 – 0.1	0.850
Ulcer location, *n* (%)				
Gaiter	12 (100.0)	15 (100.0)	-	1.000
Medial	8 (66.7)	10 (66.7)	-	1.000
Left	8 (66.7)	6 (40.0)	-	0.252
Posterior	7 (58.3)	9 (60.0)	-	1.000
Median duration of presenting ulcer, *weeks* (IQR)	20.5 (36.3)	51.0 (132.0)	-15.8 – 197.1	0.092
Median total of all ulcer episodes, *n* (IQR)	3.0 (3.5)	3.0 (3.0)	1.0 – 2.5	0.401
Median ulcer history from first to present ulcer, *months* (IQR)	42.0 (126.0)	96.0 (180.0)	-16.0 – 195.2	0.092
Mean blood pressure ± SD (mmHg)				
Systolic	138.3 ± 16.0	136.3 ± 19.6	-16.4 – 12.4	0.778
Diastolic	70.8 ± 10.6	69.3 ± 11.6	-10.4 – 7.4	0.732
Mean BMI ± SD (kg/m^2)	29.9 ± 6.8	29.7 ± 5.4	-5.0 – 4.7	0.951
Median ankle diameter, *cm* (IQR)	23.0 (2.4)	23.5 (5.5)	-0.7 – 4.5	0.150
Median calf diameter, *cm* (IQR)	28.5 (4.8)	31.0 (6.0)	-2.0 – 4.7	0.424
Median number of existing leg ulcers, *n* (IQR)	2.0 (1.8)	2.0 (3.0)	-0.9 – 2.0	0.466
Median wound depth, *mm* (IQR)	0.5 (2.0)	1.0 (2.0)	-0.5 – 1.8	0.280
Pain score of ulcer± SD (0-10 scale)	5.1 ± 2.8	4.1 ± 3.3	-3.4 – 1.5	0.431
Dressing protocol, *n* (%)			-	0.398
Primary	7 (58.3)	5 (33.3)		
Secondary	4 (33.3)	7 (46.7)		
Tertiary	1 (8.3)	3 (20.0)		
Median frequency of dressing changes, *n per week* (IQR)	2.0 (1.8)	2.0 (1.8)	-0.8 – 1.3	0.746
Median wound surface area, mm^2 (IQR)	153.0 (254.8)	430.0 (1035.0)	-292 – 1797.7	0.150
Uses psychotropic medication, *n* (%)	4 (33.3)	0	-	0.028
Uses nutritional supplements, *n* (%)	6 (50.0)	7 (46.7)	-	1.000
Has a history of skin grafting, *n* (%)	0	4 (26.7)	-	0.078
Compliant with HCSE treatment, *n* (%)	5 (41.7)	10 (66.7)	-	0.258

SD=Standard Deviation. (-)=Not applicable. ABPI=Ankle brachial pressure index. BMI=Body mass index.
a. p values associated with the mean difference for each variable were calculated with the Fishers exact test or χ^2 test for categorical data, and the t-test for independent groups for continuous data.

The case that typified a healer in the placebo group presented with an anterior leg ulcer of four weeks duration (Median for healed group=15 weeks); a wound surface area of 175 mm^2 (Median for healed group=118 mm^2); an ankle diameter of 22.5 cm (Median for healed group=22.7cm); had used psychotropic medication; was female, and had no history of skin grafting (Table 5.2). The case that characterised a non-healer in the placebo group on the other hand, presented with a posterior lower-leg ulcer of 24 weeks duration (Median for non-healed group=37 weeks); a wound surface area of 387 mm^2 (Median for non-healed group=711 mm^2); a history of skin grafting, and an ankle diameter of 25.5 cm (Median for non-healed group=24.6 cm) (Table 5.2).

Table 5.2: Baseline differences in characteristics between the healed and unhealed wounds in the placebo group (n=27)[a]

	Healed group (*n* = 8)	Unhealed group (*n* = 19)	Difference (95% CI)	p value[a]
Median age, *years* (IQR)	81.0 (21.0)	78.5 (13.0)	-10.2 – 5.8	0.570
Gender, *n* (%)			-	0.236
Male	2 (25.0)	10 (52.6)		
Female	6 (75.0)	9 (47.4)		
Tobacco smoker, *n* (%)	1 (12.5)	1 (5.3)	-	0.513
Median alcohol consumption, *n per day* (IQR)	2.0 (7.0)	0.0 (3.3)	-6.2 – 3.2	0.522
ABPI ± SD	1.0 ± 0.1	1.1 ± 0.1	-0.1 – 0.2	0.454
Ulcer location, *n* (%)				
Gaiter	8 (100)	19 (100)	-	1.000
Medial	3 (37.5)	15 (78.9)	-	0.072
Left	4 (50.0)	11 (57.9)	-	1.000
Posterior	2 (25.0)	12 (63.2)	-	0.103
Median duration of presenting ulcer, *weeks* (IQR)	15.0 (12.0)	37.0 (106.3)	-83.8 – 275.9	0.282
Median total of all ulcer episodes, *n* (IQR)	3.0 (6.0)	3.5 (4.5)	-4.5 – 2.7	0.625
Median ulcer history from first to present ulcer, *months* (IQR)	72.0 (114.0)	64.5 (298.5)	-159 – 202.0	0.809
Mean blood pressure ± SD (mmHg)				
Systolic	138.8 ± 12.2	136.3 ± 19.9	-18.1 – 13.2	0.751
Diastolic	72.5 ± 12.8	68.7 ± 13.3	-15.3 – 7.6	0.498
Median BMI (IQR) (kg/m^2)	28.9 (7.7)	27.4 (6.2)	-7.1 – 4.2	0.603
Mean ankle diameter ± SD (cm)	22.7 ± 2.6	24.6 ± 2.2	-0.0 – 3.9	0.053
Median calf diameter, *cm* (IQR)	30.5 (5.5)	30.5 (8.0)	-6.4 – 3.4	0.539
Median number of existing leg ulcers, *n* (IQR)	1.0 (2.0)	1.0 (2.0)	-3.1 – 0.3	0.111
Median wound depth, *mm* (IQR)	1.0 (2.0)	1.0 (2.0)	-1.3 – 0.8	0.578
Pain score of ulcer± SD (0-10 scale)	3.2 ± 3.2	4.4 ± 2.5	-1.1 – 3.6	0.287
Dressing protocol, *n* (%)			-	0.598
Primary	1 (12.5)	5 (26.3)		
Secondary	4 (50.0)	6 (31.6)		
Tertiary	3 (37.5)	8 (42.1)		
Mean frequency of dressing changes ± SD	3.9 ± 1.1	3.6 ± 1.3	-1.4 – 0.8	0.571
Median wound surface area, *mm*^{2} (IQR)	118.0 (246.0)	710.5 (1245.0)	-170 – 1735.5	0.103
Uses psychotropic medication, *n* (%)	5 (62.5)	2 (10.5)	-	0.011
Uses nutritional supplements, *n* (%)	3 (37.5)	7 (36.8)	-	1.000
Has a history of skin grafting, *n* (%)	0	8 (42.1)	-	0.061
Compliant with placebo, *n* (%)	4 (50.0)	14 (73.7)	-	0.653

SD=Standard Deviation. (-)=Not applicable. ABPI=Ankle brachial pressure index. BMI=Body mass index.
a. p values associated with the mean difference for each variable were calculated with the Fishers exact test or χ^2 test for categorical data, and the t-test for independent groups for continuous data.

5.5 DATA COLLECTION

Once the four cases were selected, patient data were extracted from the trial documents and data sets. The most useful sources of information were the participant details form (Appendix 6), wound assessment tool (Appendix 2) and AMWIS. Further details regarding these instruments, as well as the process of data collection, are made explicit in chapter three. Photographs of participant's wounds that were imported into AMWIS can be found in Appendix 21.

5.6 STATISTICAL ANALYSIS

Data were analysed using SPSS, version 11.0. Baseline differences between the healers and non-healers in each treatment group were calculated using Chi-Square analysis (χ^2) or Fisher's exact test for categorical data, and the t-test for independent groups for continuous data. Frequency distributions and percentages were used to describe the categorical data. Measures of central tendency and variability were used for descriptive data where values were normally distributed, while medians and the interquartile range were used to describe continuous data with skewed distributions.

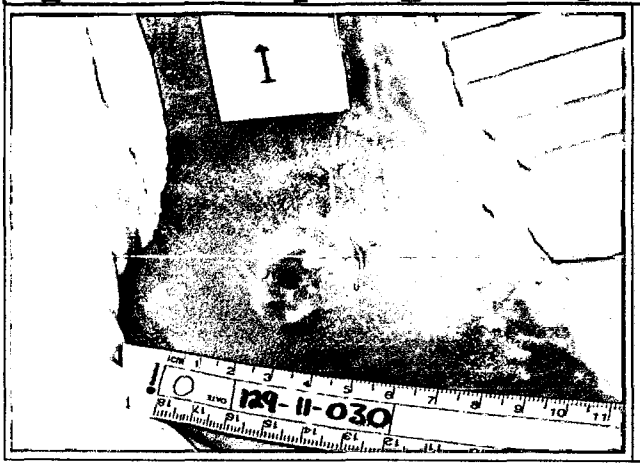
Each of the four cases was described and individually analysed using a narrative approach known as explanation building (Yin 2003). The patterns of commonality and disparity across cases were also examined (Jensen & Rodgers 2001). The four cases selected for discussion are presented below.

5.7.1 CASE STUDY 1: HCSE GROUP, ULCER HEALED

Client history: Colin was a 53 year-old married man living in the northern Adelaide suburbs. Over the past eighteen months, Colin had reported two episodes of leg ulceration of which the most recent, which was the ulcer under investigation, had been active for twenty-five weeks. The client also reported a history of asbestosis; obesity (BMI=37); deep vein thromboses (DVT); epilepsy; hypertension; a bilateral patellectomy, and an appendicectomy. Medications administered for the management of these conditions included Morphine 10 mg daily; Celecoxib 200 mg mané; Aspirin 100 mg daily; Sodium valproate 400 mg BD; Trandolapril 2 mg daily; Verapamil 2.5 mg mané, and Mirtazipine 45 mg nocté. Although a non-smoker, Colin was a consumer of two standard alcoholic drinks a day.

Baseline assessment: The client initially presented with a linear-shaped ulcer to the right, antero-lateral gaiter. This wound was deep (5 mm), sloughy (55%) and painful (6/10), and was surrounded by dry, macerated and erythematous skin (Figure 5.1). Based on the location of the wound, the moderate level of serous exudate, the presence of lower limb pigmentation, the history of knee surgery and DVT, and an ABPI of 1.0, the ulcer was most likely to be of venous origin.

Figure 5.1: Case study 1 - Image and description of wound at week 0.



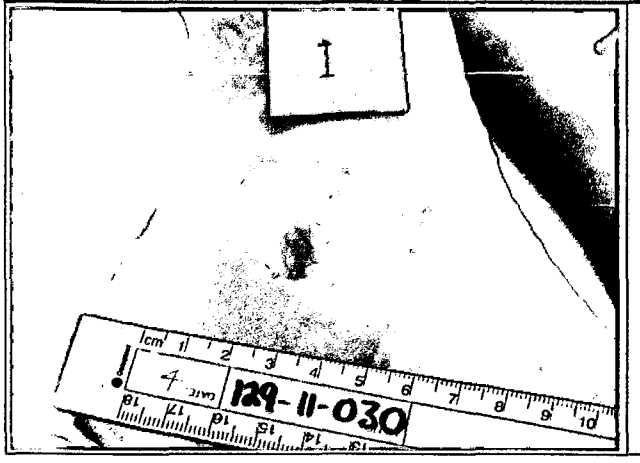
Wound surface area:	118 mm^2
Wound volume:	590 mm^3
Granulation tissue:	45%
Sloughy tissue:	55%
Exudate amount:	Moderate
Exudate type:	Serous
Wound odour:	None
Wound pain:	6 / 10
Surrounding Erythema:	980 mm^2
Surrounding maceration	183 mm^2

Once all stage I selection criteria were satisfied, Colin was enrolled in the trial and commenced on HCSE twice daily. The wound was also dressed in accordance with the primary dressing protocol, consisting of a bi-weekly application of Tricotex and four-layer Profore.

Week four assessment: After four weeks of HCSE treatment, ulcer surface area increased to 156 mm^2, wound pain rose to 7/10, and the exudate became haemopurulent. Apart from a wound infection, these signs were indicative of increased autolytic activity. In support of the latter, wound slough had decreased by 71 percent, while the percentage of granulation tissue had increased 2.6 fold. Other indicators of improvement were also evident, including a 47 percent reduction in wound volume; a 46 percent decrease in surrounding erythema; a decline in the amount of exudate, and the resolution of periwound maceration (Figure 5.2). Systemic changes were also noted, including a 20 mmHg fall in systolic blood pressure (to 140/80), a five-kilogram loss of body weight (to 110 kg) and a consequent decrease in the body mass index (to 35). In relation to the dressings applied, the only change made over the four weeks was the replacement of Tricotex with Biatain. Given

the low level of exudate, however, it is unclear why a foam dressing usually reserved for moderate to heavy exudating wounds was applied by the nurse.

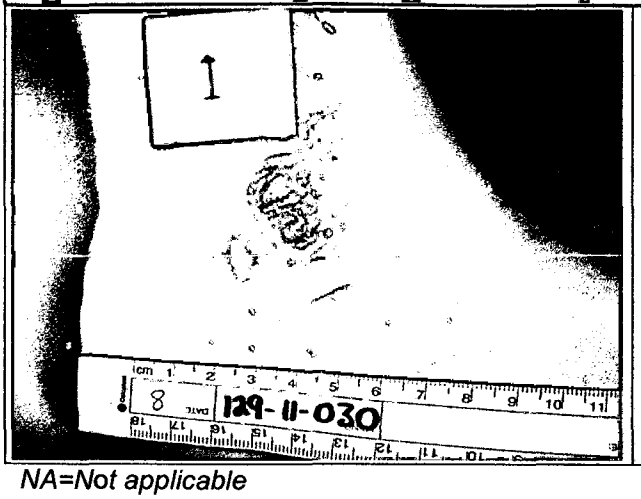
Figure 5.2: Case study 1 - Image and description of wound at week 4.



Wound surface area:	156 mm^2
Wound volume:	312 mm^3
Granulation tissue:	88%
Sloughy tissue:	12%
Exudate amount:	Low
Exudate type:	Haemopuruler
Wound odour:	None
Wound pain:	7 / 10
Surrounding Erythema:	531 mm^2
Surrounding maceration	0 mm^2

Week eight assessment: By this point in the trial, both leg ulcers had healed, systolic blood pressure had decreased by 5 mmHg (to 135/80), wound pain had fallen to 2/10, and surrounding erythema had dropped a further 27 percent (Figure 5.3). Yet, complete wound closure had occurred one-week prior, and because of this, compression therapy was ceased at week seven. This may explain why the ankle diameter increased from 23 cm at week four to 27.5 cm at week eight, and why the calf circumference rose from 32 cm to 33 cm over the same period. Even so, it is uncertain whether the increase in leg oedema, and the development of a new ulcer four-weeks after trial discharge, had occurred by chance, or had been a direct result of ceasing HCSE and compression therapy. Given that the client was compliant with HCSE treatment, it is unlikely that inadequate serum aescin levels were a factor.

Figure 5.3: Case study 1 - Image and description of wound at week 8.



Wound surface area:	0 mm^2
Wound volume:	0 mm^3
Granulation tissue:	0%
Sloughy tissue:	0%
Exudate amount:	None
Exudate type:	NA
Wound odour:	None
Wound pain:	2 / 10
Surrounding Erythema:	264 mm^2
Surrounding maceration	0 mm^2

NA=Not applicable

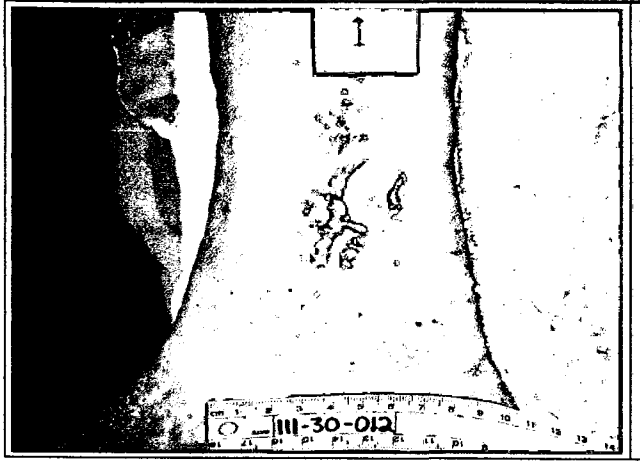
5.7.2 Case study 2: HCSE group, ulcer not healed

Client history: Another client who received HCSE during the stage I trial, but whose ulcer did not heal, was Samuel. Living in the southern Adelaide suburbs, Samuel was a 76 year-old married man who neither smoked nor consumed alcohol, but was overweight (BMI=33). The client also had a history of atrial fibrillation (AF); benign prostatic hypertrophy; eczema; lymphoedema; a bilateral angioplasty, and a right shoulder repair. Apart from being prescribed Aspirin 150 mg daily and Sotalol 320 mg mané for the management of AF, Samuel also self-administered 1000 mg Paracetamol nocté and one multivitamin daily.

Baseline assessment: On first examination, the client was found to have a shallow (1mm), circular wound to the right medio-posterior gaiter. This ulcer was predominantly sloughy (89 percent), caused little pain (3/10), and was surrounded by dry and macerated tissue (Figure 5.4). The presence of moderate serous exudate, ochre pigmentation, dry skin, varicose veins and an ABPI of 1.0 suggested that the wound was of venous origin. This wound

was also one of three presenting ulcers that had been active for the past twelve months, and one of eight ulcer episodes that had developed over the last five years.

Figure 5.4: Case study 2 - Image and description of wound at week 0.



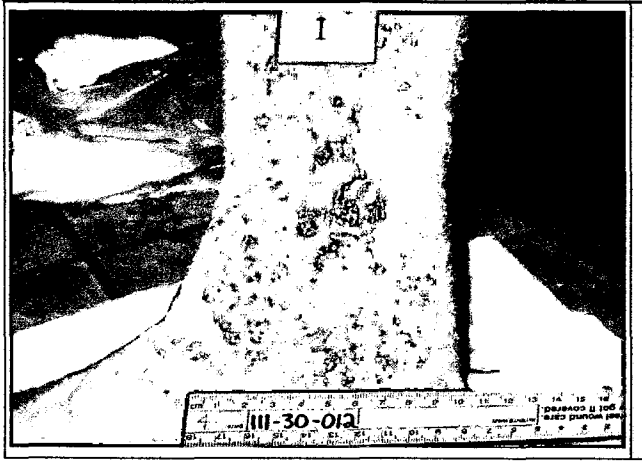
Wound surface area:	430 mm^2
Wound volume:	430 mm^3
Granulation tissue:	11%
Sloughy tissue:	89%
Exudate amount:	Moderate
Exudate type:	Serous
Wound odour:	None
Wound pain:	3 / 10
Surrounding maceration	162 mm^2
Surrounding excoriation	0 mm^2

After the baseline assessment was completed, the wound was cleaned with warm tap water and dressed in accordance with the secondary dressing protocol, which included the biweekly application of Silver Sulfadiazine (SSD) cream, zinc paste bandaging and three layer Profore. The use of SSD cream was requested by the client's general practitioner due to the presence of heavy wound colonisation with *Pseudomonas aeruginosa*, a gram-negative bacteria often associated with chronic wound infection (Berkow 1992).

Week four assessment: After the first four weeks of treatment, the ulcer showed little sign of improvement. In fact, wound surface area had risen by nine percent, slough had increased by eight percent, and ankle (28 cm) and calf girth (31 cm) had remained unchanged. There was also no change in the type or amount of wound exudate, or in the dressings applied. Yet, the periwound maceration had resolved, wound depth had decreased by 1 mm (to

0 mm), ulcer pain had fallen to 1/10, and the surface area of granulation tissue had increased by thirteen percent (Figure 5.5). Samuel had also experienced a six-kilogram drop in body weight (to 116 kg) and a fall in blood pressure, from 155/80 at baseline to 120/60 at week four.

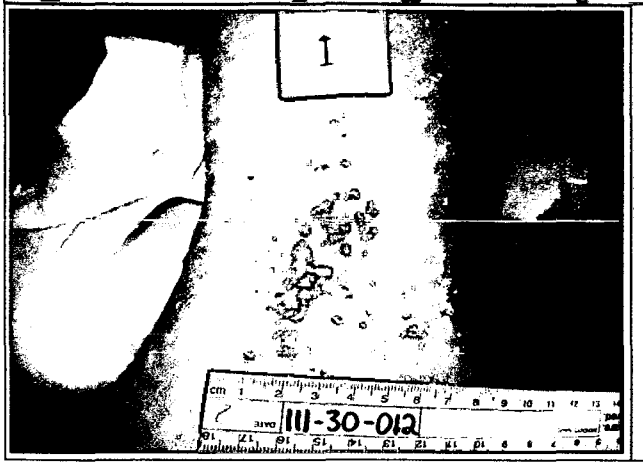
Figure 5.5: Case study 2 - Image and description of wound at week 4.



Wound surface area:	467 mm^2
Wound volume:	0 mm^3
Granulation tissue:	11%
Sloughy tissue:	89%
Exudate amount:	Moderate
Exudate type:	Serous
Wound odour:	None
Wound pain:	1 / 10
Surrounding maceration	0 mm^2
Surrounding excoriation	0 mm^2

Week eight assessment: At week eight, the dressing regime, blood pressure (120/60), body weight (116 kg) and degree of wound pain (1/10) had remained unchanged, although signs of ulcer deterioration continued. Surface area, for instance, had increased a further fifteen percent, wound slough had risen by another seven percent, and ulcer depth had returned to 1 mm. Although the type and degree of exudate remained the same, the surrounding maceration returned. Ankle and calf diameter had also increased to 28.5 cm and 34.5 cm, respectively. The only notable sign of improvement at this time point was a 83 percent rise in wound granulation since week four (Figure 5.6).

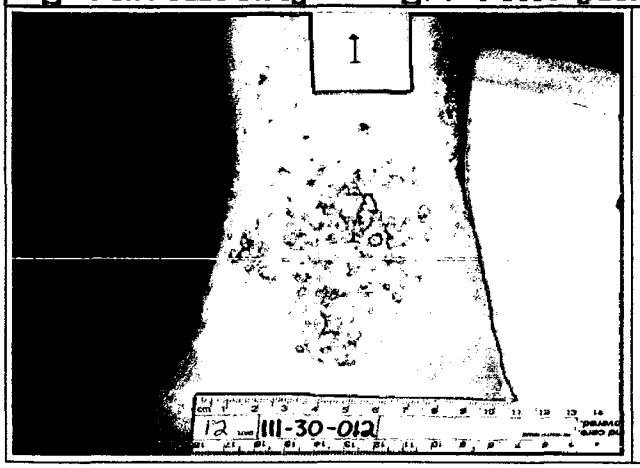
Figure 5.6: Case study 2 - Image and description of wound at week 8.



Wound surface area:	538 mm^2
Wound volume:	538 mm^3
Granulation tissue:	18%
Sloughy tissue:	82%
Exudate amount:	Moderate
Exudate type:	Serous
Wound odour:	None
Wound pain:	1 / 10
Surrounding maceration	212 mm^2
Surrounding excoriation	0 mm^2

Week twelve assessment: By week twelve, the ulcer surface area had reduced by 31 percent, wound slough had fallen by 25 percent, and calf diameter had dropped by 1 cm (to 33.5 cm). Other signs, however, were less promising, including a sixty percent reduction in granulation tissue, a 1 mm increase in wound depth (to 2 mm), and the emergence of another leg ulcer, bringing the total number of ulcers to four. Systemically, a rise in blood pressure (to 140/70) and body weight (to 120 kg) were evident. The presence of heavy, green purulent exudate; surrounding excoriation; increased ulcer pain (to 6/10); a rise in ankle diameter (to 30 cm), and an 18-fold increase in periwound maceration were suggestive of heavy wound colonisation with *P.aeruginosa* (Figure 5.7). Since Samuel was compliant with treatment, and compression therapy was utilised, it is likely that the presence of wound infection hindered ulcer healing. Throughout the follow-up period, however, the main ulcer demonstrated signs of improvement, and at twelve weeks follow-up, two of the four ulcers had healed.

Figure 5.7: Case study 2 - Image and description of wound at week 12.



Wound surface area:	370 mm^2
Wound volume:	740 mm^3
Granulation tissue:	11%
Sloughy tissue:	89%
Exudate amount:	Heavy
Exudate type:	Purulent
Wound odour:	None
Wound pain:	6 / 10
Surrounding maceration	3944 mm^2
Surrounding excoriation	2944 mm^2

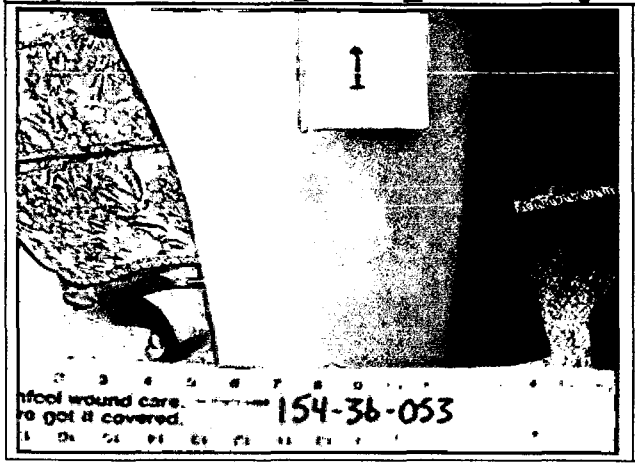
5.7.3 Case study 3: Placebo group, ulcer healed

Client history: Joyce was an 81 year-old married woman who resided in the southern Adelaide suburbs. Living a relatively active life, Joyce was of normal weight (BMI=29), never smoked, and consumed no more than one glass of wine a day. Apart from macular degeneration, for which the client self-administered one antioxidant tablet daily (BioACE), the client had no other relevant medical history.

Baseline assessment: During the baseline assessment, a single circular-shaped ulcer to the left medio-anterior gaiter was identified. This wound had been present for four weeks, and was the first and only episode of ulceration reported by the client. Given the ulcer location, percentage of slough (71%), ochre pigmentation, dry skin, history of five pregnancies, and an ABPI of 1.0, underlying CVI was likely, and thus, the wound was classified as venous. The small percentage of granulation tissue (29 percent) and the shallow nature of the wound (0 mm) supported this classification, albeit the absence of ulcer pain and exudate did not (Figure 5.8). Since the client could not tolerate compression, the wound was dressed in accordance with the tertiary dressing

protocol, in which the ulcer was cleaned with normal saline and dressed with Duoderm gel, Jelonet and Melolin three times a week.

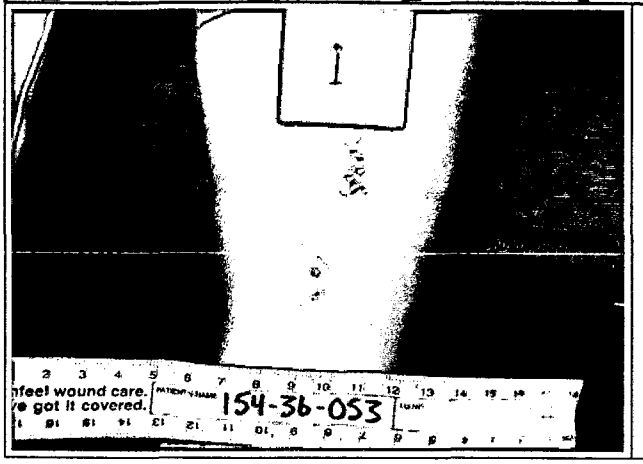
Figure 5.8: Case study 3 - Image and description of wound at week 0.



Wound surface area:	175 mm^2
Wound volume:	0 mm^3
Granulation tissue:	29%
Sloughy tissue:	71%
Exudate amount:	Nil
Exudate type:	None
Wound odour:	None
Wound pain:	0 / 10
Surrounding tissue:	Healthy & intac

Week four assessment: After four weeks of treatment with placebo, the wound had improved. This included a 45 percent reduction in ulcer surface area, a 40 percent decrease in wound slough, and the resolution of both leg and periwound dryness. There were also no adverse changes to wound depth (0 mm), exudate level (nil), pain score (0/10), blood pressure (130/60) or body weight (58 kg) since baseline. The only deleterious signs at this time point were a one-centimetre rise in ankle diameter (to 23.5 cm), a three-centimetre increase in calf diameter (to 29 cm), and a 56 percent reduction in granulation tissue (Figure 5.9). The latter sign, however, may be attributed to Joyce's decision to change the moist wound healing dressing to a cotton Tubifast stocking.

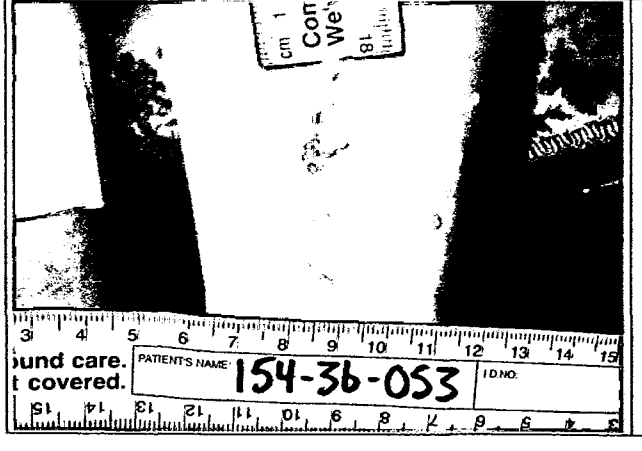
Figure 5.9: Case study 3 - Image and description of wound at week 4.



Wound surface area:	97 mm^2
Wound volume:	0 mm^3
Granulation tissue:	23%
Sloughy tissue:	77%
Exudate amount:	Nil
Exudate type:	None
Wound odour:	None
Wound pain:	0 / 10
Surrounding tissue:	Healthy & intac

Week eight assessment: In just eight weeks, the leg ulcer had completely healed. While poor dressing compliance may have been expected to hinder wound healing, the patient's brief ulcer history, active lifestyle and limited medical history instead favoured the wound. Other improvements were also evident at this time point, including a five-millimetre decrease in ankle diameter (to 23 cm) and a one-kilogram drop in body weight (to 57 kg). All other parameters remained unchanged, such as ochre pigmentation, calf diameter (29 cm), blood pressure (130/60) and wound pain (0/10) (Figure 5.10). The final assessment revealed that Joyce was compliant with the placebo intervention and experienced no adverse reactions. There were also no signs of ulcer recurrence during the twelve-week follow-up period.

Figure 5.10: Case study 3 - Image and description of wound at week 8.



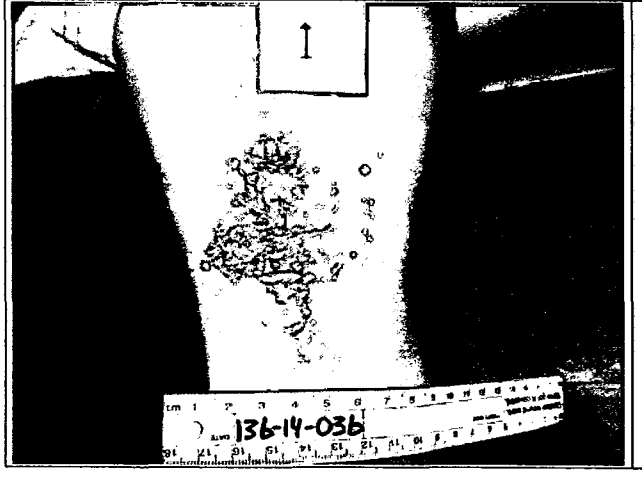
Wound surface area:	0 mm^2
Wound volume:	0 mm^3
Granulation tissue:	0%
Sloughy tissue:	0%
Exudate amount:	Nil
Exudate type:	None
Wound odour:	None
Wound pain:	0 / 10
Surrounding tissue:	Healthy & intac

5.7.4 CASE STUDY 4: PLACEBO GROUP, ULCER NOT HEALED

Client history: Peter was a 55 year-old, morbidly obese (BMI=45.5) man who lived alone in the northern Adelaide suburbs. Even though a non-drinker, Peter was a heavy smoker of forty cigarettes a day. The client also reported a history of psoriasis, stroke, non-insulin dependent diabetes mellitus (NIDDM), and a left leg skin graft. For the management of these conditions, the client administered Metformin 500 mg daily; Aspirin 150 mg mané; Clopidogrel 75 mg daily, and Lisinopril 10 mg mané.

Baseline assessment: Peter initially presented with a 2 mm deep, irregular-shaped wound to the right latero-posterior gaiter. Present for the past six months, this wound was one of three ulcers currently active. The wound was also the fifth episode of ulceration reported by the client over the last three years. On closer examination, the wound was found to be covered by soft eschar (73%), slough (23%) and granulation tissue (4%) (Figure 5.11).

Figure 5.11: Case study 4 - Image and description of wound at week 0.



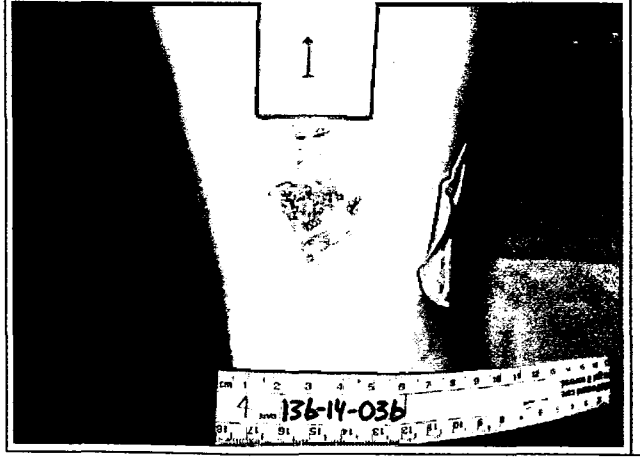
Wound surface area:	387 mm^2
Wound volume:	774 mm^3
Granulation tissue:	4%
Sloughy tissue:	23%
Eschar:	73%
Exudate amount:	Low
Exudate type:	Serous
Wound odour:	None
Wound pain:	5 / 10
Surrounding tissue:	Dry

The moderate level of pain (5/10), low level of serous exudate, ABPI of 0.91, and the presence of ochre pigmentation, dry skin and varicose veins pointed

toward a diagnosis of venous ulceration. Whilst the primary and secondary dressing protocol were encouraged, the client could not tolerate compression therapy. Hence, Peter was commenced on the tertiary dressing protocol, which included cleaning the wound with warm normal saline, and applying Duoderm gel, Melolin and Hyperfix tape three times a week.

Week four assessment: Within four weeks of commencing the placebo, the wound surface area had decreased by 34 percent, granulation tissue had increased-1.6 fold, pain had reduced to 3/10, and the eschar had completely resolved. Systemic changes were also noted, including a 2 kg drop in body weight (to 128 kg) and a 10 mmHg decrease in systolic blood pressure (to 130/80). These signs of improvement, however, were offset by a 2.5-fold increase in wound slough, a one-millimetre rise in wound depth (to 3 mm), and a three-centimetre widening in calf diameter (to 37 cm) (Figure 5.12). Yet, there was no corresponding change in ankle diameter or wound exudation, and no change in the dressing regime.

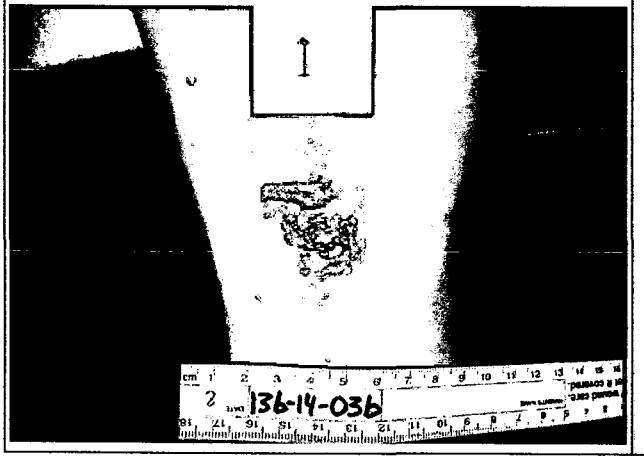
Figure 5.12: Case study 4 - Image and description of wound at week 4.



Wound surface area:	255 mm^2
Wound volume:	765 mm^3
Granulation tissue:	10%
Sloughy tissue:	90%
Exudate amount:	Low
Exudate type:	Serous
Wound odour:	None
Wound pain:	3 / 10
Surrounding tissue:	Healthy & intac

Week eight assessment: Signs of wound healing continued through to week eight, including a 35 percent reduction in ulcer surface area, a 71 percent drop in wound slough, and a two-fold increase in granulation tissue (Figure 5.13). Wound depth had also decreased by one millimetre, together with a 25 mmHg fall in systolic blood pressure (to 105/70) and a 6 kg drop in body weight (to 122 kg). Whilst the decrease in calf circumference (to 37 cm) and the resolution of surrounding dry skin were indicative of improvements in CVI, this claim was countered by a one-centimetre rise in ankle diameter (to 26.5 cm).

Figure 5.13: Case study 4 - Image and description of wound at week 8.

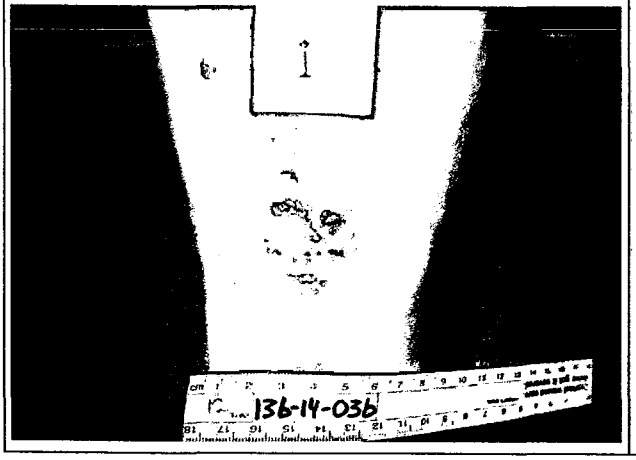


Wound surface area:	121 mm^2
Wound volume:	242 mm^3
Granulation tissue:	45%
Sloughy tissue:	55%
Exudate amount:	Low
Exudate type:	Serous
Wound odour:	None
Wound pain:	3 / 10
Surrounding tissue:	Healthy & intac

Even though the trial dressing protocol had been put in place, signs of heavy wound colonisation at week seven influenced the nurse to change the primary dressing to Acticoat, a silver impregnated dressing commonly used for wound infection. At the week eight assessment, however, there had been no change in the level of ulcer pain or in the type or degree of wound exudate when compared to the previous assessment to indicate that heavy wound colonisation was present.

Week twelve assessment: By week twelve, wound granulation had increased by forty percent, which corresponded with a 49 percent reduction in wound slough. Ulcer surface area had also fallen by three percent, together with a one-millimetre reduction in wound depth (to 1 mm), and a one-centimetre decrease in both ankle (to 25.5 cm) and calf diameter (to 36 cm) (Figure 5.14). On the other hand, wound pain had increased to 6/10 and body weight had risen to 123 kg. Even so, there were no changes to the dressing regime or level of wound exudate that could explain these findings, nor were there any issues relating to treatment compliance or adverse effects. The improvements in wound healing that were evident over the twelve weeks continued throughout follow-up, and at eight weeks, all three leg ulcers had healed. By twelve weeks follow-up, however, two leg ulcers had recurred.

Figure 5.14: Case study 4 - Image and description of wound at week 12.



Wound surface area:	111 mm^2
Wound volume:	111 mm^3
Granulation tissue:	69%
Sloughy tissue:	31%
Exudate amount:	Low
Exudate type:	Serous
Wound odour:	None
Wound pain:	6 / 10
Surrounding tissue:	Healthy & intac

5.8 Discussion

The current study has identified a number of factors that may predict venous ulcer healing in patients receiving HCSE or placebo. These factors, if controllable, may be used to improve treatment decisions and patient outcomes by providing a more tailored approach to wound care, and by

determining if alternative treatments are warranted (Falanga & Sabolinski 2000). If uncontrollable, these predictors may be used to plan for appropriate ongoing care. The process of explanation building was used to uncover these predictors by describing four characteristic cases of VLU healing and non-healing, and through the presentation of these cases, illustrate to clinicians the typical response patterns that may be observed among clients treated with HCSE and placebo. The following section examines these factors further by discussing the patterns of commonality and disparity between the four cases.

The factors that predicted wound healing in all four cases, both significantly and non-significantly, were wound surface area, ulcer duration, use of psychotropic medication, and history of skin grafting. There is no evidence, however, that skin grafting and psychotropic agents influence wound closure directly. Even so, it is possible that the anxiolytic and antidepressant effects of some psychotropic medications may address the adverse effects that anxiety, stress and depression might otherwise have on wound healing (Leach 2004a).

The impact that wound surface area has on ulcer closure is also controversial. Whilst smaller wounds would be expected to heal more rapidly than larger wounds, as observed in the four case studies, studies testing this assumption have led to conflicting results. For example, a retrospective review of 260 patient records from a Pennsylvanian cutaneous ulcer clinic found an increase in wound surface area was significantly associated with failure to heal ($p<0.001$) (Margolis *et al* 1999). In three earlier and possibly underpowered

studies, however, the correlation between surface area and wound healing was not statistically significant (Erickson *et al* 1995; Mayberry *et al* 1991; Rijswijk & Polansky 1994). Hence, these abovementioned and largely unrecognised predictors of wound healing warrant further investigation.

The chronicity, or period of ulceration, was also identified as a possible predictor of wound healing, with the duration of ulceration in both unhealed cases more than doubling that in the healed cases. This finding was similar to that reported by Margolis *et al* (1999). Margolis *et al* (1999) also reported a significant association between wound duration and venous ulcer healing ($p=0.002$) after a review of 260 patient histories from a Pennsylvanian ulcer clinic. An analysis of 119 client records from a Californian vascular clinic reported similar findings, with patients demonstrating a significant delay in the rate of VLU healing when ulcer duration exceeded nine months ($p=0.02$) (Mayberry *et al* 1991). This inverse relationship between wound chronicity and ulcer healing suggests that the aggressive treatment of venous ulceration in the early stages of development may be critical to treatment success.

The only predictor of wound healing that was exclusive to the HCSE group was the history of ulceration, with healers demonstrating a shorter ulcer history on average, than non-healers. One possible explanation for this relationship is that the history of ulceration may be correlated with the severity of CVI. To support this claim, two separate studies have found that the efficacy of HCSE (n=143, no p value) (Ottillinger & Greeske 2001) and the rate of venous ulcer healing (n=71, $p=0.039$) (Erickson *et al* 1995) both

reduce as the severity of venous insufficiency increases. Thus, Horsechestnut Seed Extract may be most effective in patients with mild to moderate CVI. Venotonic therapy should therefore be recommended to patients in the early stages of venous insufficiency to not only reduce the need for compression therapy, but also minimise the associated impact on quality of life (Ottillinger & Greeske 2001).

In the placebo group, the factors that predicted wound healing were gender, ankle diameter and ulcer location. However, none of these variables have been shown to influence wound healing in studies to date (Erickson *et al* 1995; Margolis, Berlin & Strom 1999; Mayberry *et al* 1991). Whilst the greater proportion of females in the healed group may have occurred by chance, it is possible that female patients were more receptive to the placebo effect. In support of this claim, a randomised controlled trial of twenty-two patients with citric-acid induced coughing indicated that females were more responsive to placebo than males ($p<0.025$) (Rostami-Hodjegan, Abdul-Manap, Wright, Tucker & Morice 2001). Yet, in trials on dental pain (n=596) (Averbuch & Katzper 2001) and major depression (n=876) (Casper, Tollefson & Nilsson 2001), gender did not predict placebo response. Thus, further investigation is needed to determine whether gender groups may need to be examined separately in future wound care trials.

The most prominent feature to emerge from the two non-healing cases was the presence of heavy wound colonisation. Some authorities suggest that this inverse relationship between microbial load and ulcer healing may be the

result of increased inflammation and local tissue destruction (Gilchrist 1994; Thomson 2000). Apart from systemic factors, the microbial load of an ulcer is likely to be influenced by the presence of wound slough (Rijswijk, Harding, Bacilious, Bolton, Ennis, Seaman, Siegal, Staiano-Coico & Thomson 2000). Thus, treatments that decrease ulcer slough, such as HCSE (chapter 4), may reduce the probability of wound infection, and in turn, foster ulcer healing (Rijswijk *et al* 2000). While case one (HCSE-healed case) supported this assumption, inconsistent changes in wound slough in the remaining cases did not. Therefore, the association between slough, infection and wound healing warrants further investigation.

Even though all four cases were compliant with treatment, and compliance did not differ significantly between groups, several studies have reported that treatment compliance is a significant predictor of wound healing. For instance, a retrospective analysis of 71 patient records from a Wisconsin venous ulcer clinic found the rate of wound healing was significantly greater among clients who were strictly compliant with compression therapy ($p \leq 0.02$) (Erickson et al 1995). Similarly, non-compliance with compression stockings significantly predicted delayed VLU healing in a retrospective analysis of 119 client records from a Californian vascular clinic ($p<0.001$) (Mayberry *et al* 1991). Practitioners may therefore improve treatment success and ameliorate patient outcomes by adopting measures that facilitate treatment compliance, as well as utilising interventions that reduce wound colonisation and ulcer surface area.

5.9 SUMMARY

By utilising a comparative case design, the stage II study has identified a number of variables that may predict venous ulcer healing, ranging from potential predictors such as gender, psychotropic medication and skin grafting, to more plausible factors such as wound surface area, ulcer duration, treatment compliance and wound infection. The study has also established that treating VLU with placebo may be most effective in female patients with smaller, less chronic wounds, and in those without signs of heavy wound colonisation. For patients treated with HCSE, treatment may be most effective in those with mild to moderate CVI, smaller, less chronic wounds, a shorter history of ulceration, and in those without signs of wound infection. Yet, given the limitations of the case study design and the lack of statistically significant predictors in the case selection process, such claims cannot be generalised to the wider population. The current study has instead, used patterns of commonality and disparity to add to existing theories, and highlighted areas for further research (Fitzgerald 1999) in order to improve future study design, treatment success, patient care and quality of life. In the following chapter, the social impact of HCSE treatment will be explored by examining the cost-effectiveness of the therapy.

CHAPTER 6

STAGE III COST-BENEFIT ANALYSIS

6.1 INTRODUCTION

The preceding chapters have highlighted the clinical implications of using HCSE as a treatment for venous ulceration. In this chapter, the cost-benefit of using HCSE over other wound treatments will be presented. In view of rising budgetary restraints; staff shortages; scarcer resources; spiralling health care expenses, and the costs of managing leg ulceration, the relative expense of adopting alternative wound treatments needs to be considered (McIntosh, Donaldson & Ryan 1999; Stone 2002; Stone, Curran & Bakken 2002). Studies comparing conventional treatments to complementary therapies should also consider the cost-effectiveness of each intervention to test the assumption that alternative therapies are less expensive than conventional treatments (Brazier & Morgan 2002). Therefore, to address the dearth of economic evaluation in nursing and wound care (Franks & Bosanquet 2004; Olin, Beusterien, Childs, Seavey, McHugh & Griffiths 1999; Stone, Curran & Bakken 2002), and to provide a better understanding of the societal benefit of using HCSE as an adjunctive wound care treatment, the current study will compare the cost-effectiveness of HCSE and conventional treatment to conventional treatment alone.

6.2 DESIGN

Cost-benefit analysis (CBA) examines the costs and benefits of alternative interventions from a societal perspective (Anderson & Lloyd 2001). Estimating the total cost of administering an intervention and comparing that to the benefits the treatment creates (Chang, Price & Pfoutz 2001) can inform stakeholders of the inherent worth of an intervention. Such comparisons may then facilitate the selection of competing treatment alternatives (Drummond, O'Brien, Stoddart &

Torrance 1997; Warner & Luce 1982). A CBA therefore does not prescribe what decision makers should do but merely highlights the choices that are available (Leplege 1992; Stone 2002; Stone, Curran & Bakken 2002). As with evidence-based practice, decisions regarding the allocation of resources can be also be guided by cost-benefit analysis (Maynard 1997; McIntosh, Donaldson & Ryan 1999).

The values produced from a CBA are quantified in monetary terms to better compare the net benefit of one intervention or service over another (Drummond et al 1997; Robinson 1993; Watson 1997). Whilst many benefits remain difficult to express in fiscal terms (Leplege 1992; Robinson 1993; Stone 2002; Stone, Curran & Bakken 2002), cost-benefit analyses continue to be the preferred choice of economic evaluation (McIntosh, Donaldson & Ryan 1999). It is likely that this tendency for CBA is attributed to its comprehensive, theoretically sound and powerful design (Robinson 1993).

A common assumption of cost-benefit analysis is that the proposed treatment alternative is effective (Drummond *et al* 1997). The efficacy of an intervention should therefore be determined by good quality evidence before a CBA is conducted. It is for this reason that the stage I trial preceded the stage III study, as illustrated in Appendix 1. Cost-benefit analyses also provide clinical trials with richer data in order to facilitate the integration of research findings into clinical practice. Taking into consideration the economic impact and clinical efficacy of an intervention can therefore aid evidence-based decisions and contribute to ethical and responsible practice (Maynard 1997; Stone 2002;

Stone, Curran & Bakken 2002). Whilst Gray, Russell, Flett and Cooper (2002) warn that cost reductions should not be made at the expense of clinical standards, practitioners utilising CBA within an EBP framework may instead identify opportunities where wound care costs can be reduced without compromising client outcomes (Gray *et al* 2002).

Despite the proclaimed benefits of CBA, there are still very few economic evaluations of nursing practice (Stone, Curran & Bakken 2002) and wound management (Franks & Bosanquet 2004; Olin *et al* 1999). As a result, the integration of new and effective interventions into clinical practice may be hindered or delayed. The stage III CBA was therefore developed to contribute to this body of knowledge and to ascertain the societal benefit of using HCSE in the treatment of VLU.

6.3 Methodology

The current study was initially designed to compare the cost-benefit of treating venous ulceration with either HCSE or placebo. However, the evaluation of the benefits or results of these interventions (Chang, Price & Pfoutz 2001), such as improvements in morbidity, mortality, wellbeing and productivity (Chang, Price & Pfoutz 2001; McIntosh, Donaldson & Ryan 1999; Warner & Luce 1982), were not only difficult to quantify, but were beyond the scope of the study (Stone, Curran & Bakken 2002). Furthermore, the clinical benefits associated with the two treatments, such as improvements in ulcer healing, wound topography and the frequency of dressing changes, were already measured and discussed in the stage I trial. Thus, the current study focussed on the relative costs of treating venous ulceration with HCSE and conventional therapy in comparison

to placebo and conventional treatment, without attempting to cost intangible benefits to the patient or the service provider. To understand the context of these costs, the sample and setting need to be described.

Sample and Setting

Home health care accounts for 69 percent of the cost of managing venous ulceration (Olin *et al* 1999). Thus, viewing the stage III CBA from the perspective of a large metropolitan community nursing service is apposite. Given that the sample and setting for the current study match that of the stage I trial, these details will not be revisited. Instead, further information about the sample and setting can be located in chapter three, whilst baseline characteristics of subjects can be found in chapter four.

Variables

The costs or inputs in a CBA are the resources used to deliver a service or intervention (Chang, Price & Pfoutz 2001), such as labour, supplies, equipment, transportation, capital and social service costs (Anderson & Lloyd 2001; Warner & Luce 1982). In relation to wound care, appropriate economic evaluations need to consider the expense of dressing materials, practitioner time and travel costs (Kerstein 2003; Young 1997). Therefore, the total outlay of managing VLU in the community should include the cost of staff salaries, organizational infrastructure, Workcover, superannuation, travel, dressing materials and HCSE. Definitions of these CBA inputs are detailed below.

- HCSE: The HCSE tablets produced for the stage I trial were manufactured by Mediherb Pty Ltd, in Warwick, Queensland. The cost to

consumers for the purchase of HCSE was estimated at AUD$20 per bottle of sixty tablets. Given that HCSE is administered at a dosage of one tablet twice daily, one bottle of tablets was sufficient to provide thirty days of treatment.

- Dressing materials: All dressing materials applied to the ulcers of trial participants, including all primary and secondary dressings, were individually costed and calculated as dressing costs per visit. Due to the discounted prices offered to the community nursing service, however, these costs were relatively conservative.
- Service costs: Nurses employed by the nursing service were paid in accordance with state award rates. Since four different levels of nurses visited clients in the community, the hourly rate of pay ranged between AUD$15.36 and AUD$25.56 per hour (Australian Industrial Relations Commission 2004). The rate of pay used by the nursing service in order to calculate visit costs was not disclosed, but was incorporated into an overall fee of AUD$69 per client visit, irrespective of visit duration. This fee was also inclusive of organizational infrastructure, Workcover, superannuation and travel cost.

6.4 STATISTICAL ANALYSIS

Upon completion of the stage I trial, all costs associated with the management of VLU were calculated in 2004 Australian dollars. To improve the precision of these findings, all inputs were micro costed. In other words, the cost of each resource was calculated for each participant (Drummond *et al* 1997). Means and standard deviations were used to describe variables with normal distributions, whilst medians and interquartile ranges were used to describe

variables whose distributions were significantly skewed. Differences between group means were then evaluated using the *t*-test for independent groups (TTIG). In particular, the difference in total costs between the HCSE and placebo groups were calculated and tested for statistical significance.

Sensitivity analysis

Sensitivity analyses were also conducted to test the assumptions of the CBA to determine whether variations in the input variables would alter the conclusions made from the analysis (Chang, Price & Pfoutz 2001; Nielson & Fiore 2000). More specifically, one-way sensitivity analyses were performed on staffing costs and dressing costs, with only one expense manipulated at a time, and all other costs remaining constant (Nielson & Fiore 2000). To ascertain if total expenditure was sensitive to variations in the base-case estimates of staffing and dressing costs, each expense was generously varied by fifty percent above and below the mean.

Discounting

Discounting is a strategy used in CBA to convert future costs into present values (Chang, Price & Pfoutz 2001). However, the current analysis did not predict the expense of either treatment beyond twelve weeks. The costs of each treatment were therefore only measured in the short term and did not necessitate discounting.

6.5.1 STAFFING COSTS

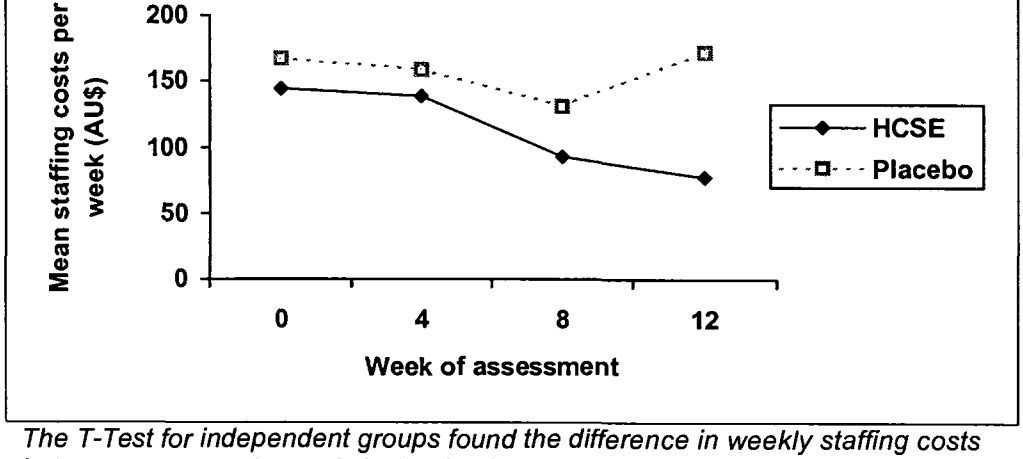
The weekly staffing costs associated with the treatment of VLU consistently decreased in the HCSE group from $144 at baseline to $77 at week 12 (Table 6.1). Staffing costs in the placebo group, however, fluctuated, with costs initially decreasing in the first eight weeks from $167 at baseline to $131 at week 8, but then escalating to $172 at week 12 (Figure 6.1). The difference in staffing costs between groups at baseline was not significant (p=0.159). However, a cost saving of $95 per patient receiving HCSE was statistically significant at week 12 (p=0.004).

Table 6.1: Mean weekly staffing costs for treating patients in the HCSE and placebo groups ± SD

Time point	HCSE (*n*=27) $ ± SD	Placebo (*n*=27) $ ± SD	Cost saving[a] $	Difference (95% CI)	p value
Week 0	144.15 ± 86.04	167.32 ± 109.48	-23.17	-76.9 – 30.6	0.159
Week 4	139.00 ± 117.25	159.59 ± 137.41	-20.59	-90.4 – 49.2	0.237
Week 8	92.67 ± 107.32	131.28 ± 125.42	-38.61	-102.4 – 25.1	0.517
Week 12	77.22 ± 75.48	172.46 ± 166.23	-95.24	-165.7 – -24.7	0.004

a = cost saving calculated by subtracting mean HCSE costs from mean placebo costs (a minus value indicates a cost saving in favour of HCSE).
SD = Standard deviation. CI=Confidence interval.

Figure 6.1: Change in weekly staffing costs between groups at week 0, 4, 8 & 12



The T-Test for independent groups found the difference in weekly staffing costs between groups to be statistically significant at week 12 (p=0.004).

6.5.2 DRESSING COSTS

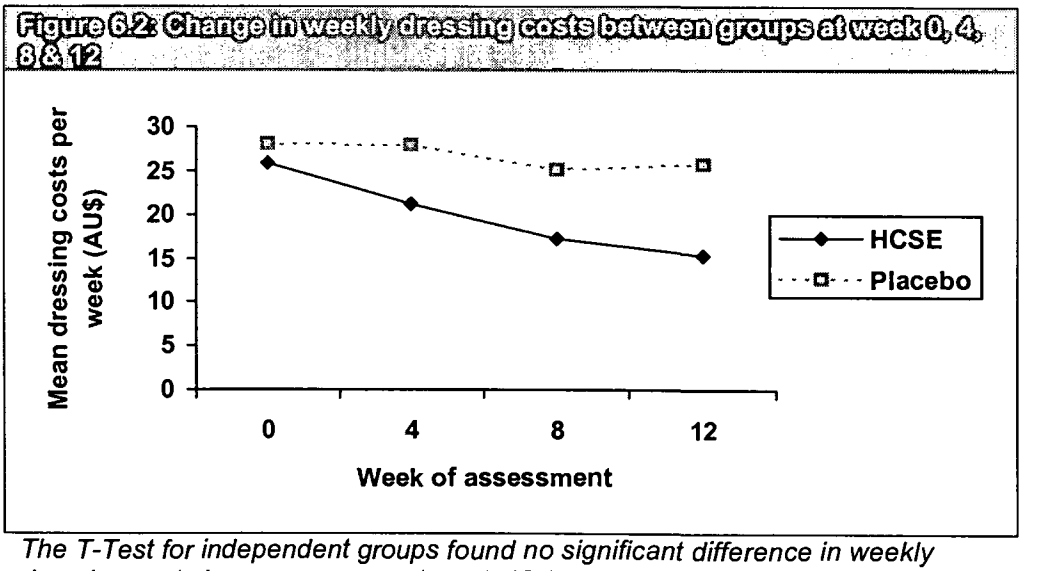
The weekly cost of dressing materials in the HCSE group consistently declined over the twelve weeks, from $26 at baseline to $15 at week 12 (Table 6.2). The placebo group, however, demonstrated a much smaller reduction in dressing costs over time, decreasing from $28 at baseline to $26 at twelve weeks (Figure 6.2). Despite an average weekly cost saving of $10 for each patient in the HCSE group at week twelve, the difference in the cost of dressing materials between groups was not statistically significant at this time point (p=0.342) or at any other week of assessment.

Table 6.2: Mean weekly dressing costs for treating patients in the HCSE and placebo groups ± SD

Time point	HCSE (*n=27*) $ ± SD	Placebo (*n=27*) $ ± SD	Cost saving[a] $	Difference (95% CI)	p value
Week 0	25.85 ± 18.77	28.07 ± 42.71	-2.22	-20.2 – 15.8	0.441
Week 4	21.15 ± 15.26	27.87 ± 43.68	-6.72	-24.6 – 11.2	0.255
Week 8	17.32 ± 17.75	25.15 ± 43.81	-7.83	-26.1 – 10.4	0.484
Week 12	15.34 ± 18.14	25.69 ± 44.57	-10.35	-28.9 – 8.2	0.342

a = cost saving calculated by subtracting mean HCSE costs from mean placebo costs (a minus value indicates a cost saving in favour of HCSE).
SD = Standard deviation. CI=Confidence interval.

Figure 6.2: Change in weekly dressing costs between groups at week 0, 4, 8 & 12



The T-Test for independent groups found no significant difference in weekly dressing costs between groups at week 12 (p=0.358).

6.5.3 TOTAL WOUND MANAGEMENT COSTS

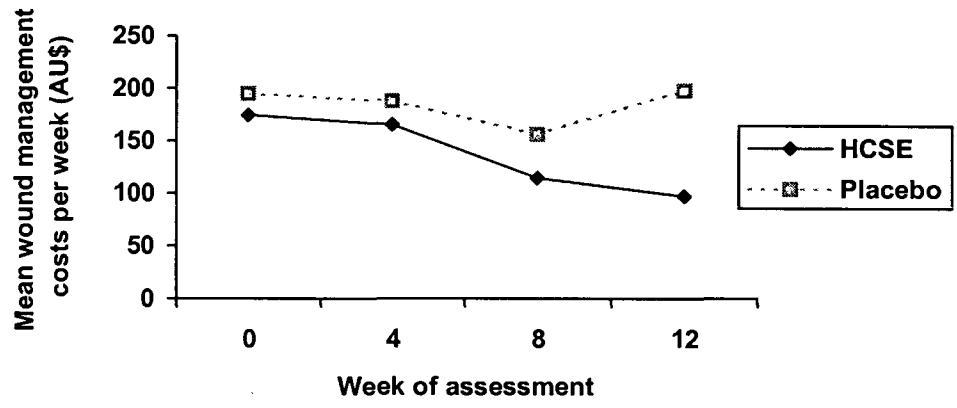
The total weekly cost of managing VLU in the HCSE group, including staffing, dressing and intervention costs, decreased from $175 at baseline to $97 at week 12 (Table 6.3). Total costs in the placebo group also declined in the first eight weeks, from $195 at baseline to $156 at week 8, but increased thereafter to $198 at week 12 (Figure 6.3). Whilst total wound care costs at baseline were slightly higher in the placebo group, the difference between groups was not statistically significant (p=0.238). The difference between groups at week twelve, however, was statistically significant (p=0.011), saving an average of $101 per patient in the HCSE group. These wound management costs and savings were also insensitive to variations in staffing costs (Table 22.1 & 22.2, appendix 22) and dressing costs (Table 22.3 & 22.4, appendix 22) within the range of ± 50 percent, and remained statistically significant at week 12.

Table 6.3: Mean total weekly wound management costs for treating patients in the HCSE and placebo groups ± SD

Time point	HCSE (*n*=27) $ ± SD	Placebo (*n*=27) $ ± SD	Cost saving[a] $	Difference (95% CI)	p value
Week 0	175.00 ± 98.93	195.39 ± 137.99	-20.39	-86.0 – 45.2	0.238
Week 4	164.97 ± 118.49	187.46 ± 167.09	-22.49	-101.6 – 56.6	0.210
Week 8	114.61 ± 121.53	156.43 ± 155.53	-41.81	-118.0 – 34.4	0.485
Week 12	97.20 ± 88.75	198.15 ± 189.86	-100.96	-181.9 - -20.0	0.011

a = cost saving calculated by subtracting mean HCSE costs from mean placebo costs (a minus value indicates a cost saving in favour of HCSE).
SD = Standard deviation. CI=Confidence interval.

Figure 6.3: Change in mean total weekly wound management costs for each group after 4, 8 & 12 weeks treatment



The T-Test for independent groups found the difference in total weekly wound management costs between groups to be statistically significant at week 12 (p=0.011).

6.6 Discussion

The management of venous leg ulceration consumes a large number of resources, including dressing materials, staff and infrastructure (Franks & Bosanquet 2004). In fact, these resources are estimated to cost Australia between AUD$554 and AUD$655 million annually. Even so, there has been little deliberation in Australia about the cost of treating VLU on an individual basis. Recent overseas studies have, however, shed some light on these costs. In the UK for instance, treating patients with venous ulceration for twenty-four weeks using two layer and four layer compression bandaging cost an estimated AUD$2319 and AUD$2218 per patient, respectively (Moffatt, McCullagh, O'Connor, Doherty, Hourican, Stevens, Mole & Franks 2003). In contrast, the cost of treating venous ulcers at home for only twelve weeks with a hydrocolloid dressing and high compression bandaging amounted to AUD$1588 in France and AUD$2240 in Europe for each wound healed (Meaume & Gemmen 2002). The management of VLU for twelve weeks in the current study also totalled between AUD$1740.52 per individual treated in the HCSE group, and

AUD$2159.88 per individual in the placebo group. In spite of the different types of primary and secondary dressings applied, the total costs in the stage III CBA were consistent with those previously reported by Meaume & Gemmen (2002). The discrepancy between these findings and those reported in the UK study (Moffatt *et al* 2003), however, may be explained by differences in the costs of dressing materials and the frequency of nursing visits.

From a health care provider perspective, HCSE was a more cost-effective treatment of venous ulceration than placebo. To illustrate, the total cost of treating VLU with placebo and conventional care for twelve weeks amounted to AUD$2159.88 per patient, in comparison to AUD$1740.52 per individual receiving HCSE and conventional care. The difference between these values represented a twenty-four percent cost saving in favour of the extract. Moreover, these savings were insensitive to wide variations in the base-case estimates of staffing and dressing costs, and were therefore robust to plausible explanations (Nielson & Fiore 2000). Furthermore, as there were no significant cost differences between groups at baseline, it is unlikely that these savings were the result of heterogenous costs at week zero. Adopting Horsechestnut as a treatment of venous ulceration may therefore ease health care expenditure and in turn, increase the availability of essential resources.

In view of current budgetary constraints, however, some organizations may be cautious about procuring new and unconventional interventions. In spite of these reservations, integrating HCSE into the management of VLU is likely to save the health care provider around $101 per patient per week, with an

average saving of $95 in costs to the organisation, and $10 in dressing expenditure. Given the greater rate of wound healing reported in chapter four, HCSE may also avoid further costs to the organization by reducing demand on scarce health care resources. These conservative savings therefore suggest that the treatment of venous ulceration with HCSE is likely to improve the efficiency of community health care services.

The most expensive component of wound management is the cost of nursing care, a claim not only supported by the current study, but also by Meaume & Gemmen (2002). Therefore, any intervention that reduces the need for nursing visits is likely to produce substantial cost savings for the health care provider, and furthermore, allow organizations to better accommodate staff shortages. Since all CBA expenses were multiplied by the frequency of nursing visits, any variations in the rate of dressing changes subsequently affected the total cost of wound care. Thus, the significant decline in total wound management costs, particularly staffing costs, may be attributed to a reduction in the number of nursing visits. It should also be noted that the greater improvements in wound healing in the HCSE group could have contributed to the significant decrease in nursing visits, as no significant difference in visit frequency was evident between groups when healed ulcers were excluded from the analysis ($p=0.108$). Alternatively, the need for fewer dressing changes in the HCSE group may have been influenced by greater reductions in wound slough, as illustrated in Figure 4.7.

6.7 QUALITY AND LIMITATIONS OF STAGE III

The stage III CBA represents the first known Australian study to compare the costs of two alternate treatments of venous ulceration. Aside from highlighting the costs of managing VLU in the community, the current study also identified a novel intervention that may potentially decrease wound management expenditure. The precision and robustness of these findings were enhanced by utilising a CBA design and by micro-costing a range of inputs. Sensitivity analyses also confirmed that the validity of the CBA was not threatened by the cost assumptions of the study (Nielson & Fiore 2000). Even so, the current study was not without limitations.

Firstly, the small sample in the current study limited the extent to which the CBA findings could be generalised. Strategies to improve participant recruitment and increase sample size, however, have already been highlighted in chapter four, and will therefore not be discussed in this section. The twelve-week duration of the trial was also a limitation of stage III, in that the long-term benefit of using HCSE in the treatment of VLU still remains unclear. Whilst the current study illustrates the short-term costs of HCSE treatment, future research needs to examine the long-term benefit of the extract by utilising extended intervention periods; by calculating cost savings over the fiscal year; and by costing benefits.

Due to the difficulty in quantifying indirect costs such as pain, impaired mobility and lost productivity (Stone, Curran & Bakken 2002), these expenses could not be incorporated into the current CBA. Thus, the development of valid and appropriate instrumentation that is capable of measuring the indirect costs of

wound care interventions in monetary terms, is needed to more comprehensively examine the impact of such treatments.

Despite the small sample, short-term duration and the absence of indirect costings, the current study provided the first step towards examining the economic impact of HCSE treatment. Future studies are now warranted to comprehensively explore the long-term cost-effectiveness of treating venous ulceration with HCSE, for both the client and the health care system, to determine whether use of the extract is beneficial to society as a whole (Brazier & Morgan 2002).

6.8 SUMMARY

Cost-benefit analysis '...provides an estimate of the value of resources used up by each programme compared to the value of resources the programme might save or create' (Drummond *et al* 1997: 14). In the stage III CBA, the cost of treating VLU with either HCSE or placebo was compared. Assuming equal benefit, the difference between groups in relation to the cost of treating venous ulceration was in favour of HCSE. In other words, HCSE was more cost-effective in the management of venous ulceration than placebo. Thus, in accordance with the EBP paradigm, these findings provide economic justification for the decision to use HCSE in clinical practice. Moreover, this CBA suggests that the health and wellbeing of consumers, and the efficiency of service provider operations, may be enhanced through the use of HCSE by increasing the rate of wound healing, decreasing the frequency of nursing visits, and allowing more clients to be treated at an equivalent cost (Franks &

Bosanquet 2004). The following section builds on these findings, and determines whether HCSE therapy would be feasible in clinical practice.

STAGE IV

DESCRIPTIVE SURVEY

CHAPTER 7

STAGE IV LITERATURE REVIEW

7.1 Introduction

The preceding section has investigated the clinical efficacy, cost benefit and clinical application of HCSE in venous ulceration. In the following section, the clinical feasibility of Horsechestnut treatment will be explored in order to complete the four components of the EBP paradigm (Figure 1.2). Given that public use and attitude toward complementary medicine may be influenced by a clinician's point of view (Fitch, Gray, Greenberg, Labrecque & Douglas 1999), establishing a practitioner's opinion of natural medicine, venotonic therapy and HCSE may identify how patients are informed and ultimately exposed to these therapies, and whether treatments such as HCSE would be feasible in clinical practice. A critical review of the literature on public and practitioner use and attitude toward natural medicine will provide a foundation on which this stage IV study is premised.

7.2 Public use of natural therapies

The level of natural therapy use throughout the western world has received significant attention, with claims that the use of these modalities is increasing worldwide (Easthope, Tranter & Gill 2000; Norred 2002). In the United States (US) for example, the use of alternative medicine has increased significantly ($p=0.001$), from thirty four percent (520/1539) of the population in 1990, to forty two percent (865/2055) in 1997 (Eisenberg, Davis, Ettner, Appel, Wilkey, Rompay & Kessler 1998). The therapies demonstrating the greatest rise in popularity were herbal medicine, massage and nutrient supplementation. Consistent with other studies (Emslie, Campbell & Walker 2002; Hall & Giles-Corti 2000; MacLennan, Wilson & Taylor 1996; Shumay, Maskarinec, Gotay, Heiby & Kakai 2002; Sirois & Gick 2002; Thomas, Nicholl & Coleman 2001),

alternative therapy use was most frequent among tertiary-educated, high income earning, female Caucasians within the age range of 35 to 49 years. The level of natural therapy use recorded in the US was similar to that reported in South Australia (MacLennan, Wilson & Taylor 1996), England (Thomas, Nicholl & Coleman 2001), and North East Scotland (Emslie, Campbell & Walker 2002).

A population survey of one thousand Japanese adults, however, revealed a comparatively higher rate of natural therapy use to that reported in previous studies (Yamashita, Tsukayama & Sugishita 2002). The Japanese study found seventy-six percent (760/1000) of participants had used a complementary modality during the twelve months preceding the survey, while no more than sixty-six percent (660/1000) of residents had used orthodox medicine. Yet, the annual out-of-pocket cost of using natural therapies was half that of orthodox medicine, with complementary and conventional treatment amounting to AUD$281 and AUD$565 per resident, respectively (Yamashita *et al* 2002). Of the therapies used, respondents were particularly favourable of nutritional and tonic drinks, dietary supplements and health-related appliances. Health promotion and disease prevention were among the main reasons for selecting these treatments. The twenty-three percent (1000/4292) response rate and the possible introduction of recall bias, however, limit the generalisability of these findings.

Recent studies in the United States suggest that natural therapy use may have increased further since Eisenberg's *et al* (1998) study in 1998. In a study of 6852 randomly selected pre-operative patients from sixteen US institutions for

instance, complementary therapy use was reported by sixty-seven percent (4591/6852) of participants (Norred 2002). Of the modalities used, vitamin supplementation (3700/6852), mineral supplementation (2672/6852) and herbal medicine (1850/6852) were the most popular. As with earlier reports, educated, Caucasian females were the most likely to use these therapies, although, users of alternative medicine were more likely to be over forty years of age. Whilst these findings may be isolated to preoperative patients, it is also possible that the disparity in these characteristics could be attributed to the increased age of participants in the study.

In another recent US study, eighty-five percent of 567 outpatients surveyed reported the use of at least one complementary modality, with particular preference for manual healing, dietary management, and mind and body control techniques (Boutin, Buchwald, Robinson & Collier 2000). Despite the high percentage of users, however, many patients believed they were inadequately informed about complementary medicine. Thus, some consumers may not be conversant with the principles of evidence-based practice.

A 2001 study of 416 randomly selected Ontario residents on the other hand, revealed a much lower rate of complementary therapy use, with only thirty-seven percent (154/416) of respondents found to be using these therapies, in particular, chiropractic, massage and herbal medicine (Lewis, Paterson, Beckerman & Sandilands 2001). Given that these findings were comparable to reports in British Columbia (Cook, Frighetto, Marro & Jewesson 2002), but dissimilar to findings in other countries, it is likely that global variations in natural

therapy use are present. One explanation for these differences may be attributed to the political and cultural disparity between countries.

In a South Australian study, natural therapy use was reported among forty-eight percent (1442/3004) of respondents, with the majority of users preferring vitamin supplementation (1130/3004) and herbal medicine (297/3004) (MacLennan, Wilson & Taylor 1996). The annual cost to the population for using these medicines amounted to AU$51 million in South Australia and AU$621 million nationally. This expenditure exceeded the AU$360 million spent on pharmaceutical medications in the same year. MacLennan, Wilson and Taylor (1996) argue that this shift toward complementary medicine may be attributed to a growing focus on illness prevention, with the majority of natural medicine users exercising regularly, being of normal weight, and demonstrating an optimistic outlook on life.

Worldwide statistics indicate that one half of individuals in the industrial world are utilising natural medicine, particularly ingestive modalities such as nutrient supplementation and herbal medicine. Although limited data is available, figures from the US and Scotland suggest that this degree of use is likely to rise and surpass the level of use of orthodox medicine. Further research is needed to understand why this shift toward natural medicine is occurring, and why patients with chronic conditions may be turning to these modalities (Sirois & Gick 2002).

7.3 Nurse use of natural therapies

Nurses are among a number of practitioners expressing a widespread interest in natural medicine, and as an integral part of the health care system, are in a

unique position to introduce these modalities to a wide spectrum of the community. Apart from increasing patient choice, the integration of these modalities into mainstream health care may also improve patient care by providing new strategies that address long-standing clinical issues (Hancock 1995). Nevertheless, the reasons for turning to these modalities, as well as the types of therapies nurses use, have yet to be consistently defined.

In Connecticut for instance, 61 of 202 (30%) nurse practitioners surveyed reported the use of complementary medicine, in particular, meditation and guided imagery (Hayes & Alexander 2000). Of the seventy-three percent (202/276) of nurses who responded to the survey, thirty-one percent (63/202) had received training in a natural therapy, although the level of education was not illuminated. In the UK on the other hand, nurses were more likely to engage in massage, aromatherapy and reflexology (Hayes & Cox 1999; Rankin-Box 1997; Trevelyan 1996), with most nurses holding at least one qualification in natural medicine, primarily at certificate and diploma level.

A moderate level of natural therapy use was also evident in a study of 56 South Australian district nurses, although the modalities most frequently employed were massage, nutrition and relaxation (Leach 2002). Even though two-thirds of staff had received training in natural medicine, the level of education often did not exceed one day. This inadequate level of training was confirmed by a poor level of knowledge on these therapies, a finding also reported elsewhere (Vinker, Nakar, Amir, Lustman & Weingarten 2002). Thus, given that the safe and effective delivery of natural medicine requires adequate training (Myers

2003), and that many nurses do not possess appropriate qualifications in complementary medicine, it is likely that some practitioners are adopting new modalities which they may be ill equipped to use (Richardson 2001).

Studies to date suggest that up to 58 percent of nurses may be integrating natural therapies into the clinical setting (Trevelyan 1996), with a particular preference for massage and aromatherapy (Hayes & Cox 1999; Leach 2002; Rankin-Box 1997; Trevelyan 1996). However, most of these studies are not of high quality, in that many are flawed by sampling bias and poorly established instrument validity and reliability (Leach 2002). Natural therapy use in nursing practice therefore warrants further investigation.

7.4 Medical practitioner use of natural therapies

The extent to which patients are exposed to complementary therapies is partially dependent on the medical practitioners use of these modalities, and the level of referrals the clinician makes to natural therapists. Thus, as gatekeepers of medical services and key stakeholders in legislative change (British Medical Association, in Botting & Cook 2000), MPs are likely to influence both consumer and practitioner use of natural medicine. As with nurses, however, it is still unclear which therapies the medical profession may favour, as well as the reasons for selecting these modalities, due to inconsistencies in the literature.

Reports of natural therapy use amongst general practitioners (GPs) in the UK for example, range between thirteen and thirty-two percent (Lewith, Hyland & Gray 2001; Perkin, Pearcy & Fraser 1994; Perry & Dowrick 2000; White, Resch & Ernst 1997), with acupuncture, homeopathy, chiropractic and osteopathy

being the most frequently employed. Of the physicians engaging in these therapies, thirteen to thirty-eight percent had received natural therapy training (Lewith, Hyland & Gray 2001; Perry & Dowrick 2000; Wharton & Lewith 1986), although the level of education in these studies was not defined.

Alike UK physicians, sixteen percent (32/200) of Canadian GPs also reported the use of alternative therapies, with many of the 200 practitioners surveyed favouring the use of acupuncture and hypnosis (Verhoef & Sutherland 1995). The GPs practising natural modalities were predominantly young, male, and educated in alternative medicine. Yet, the twenty percent (40/200) of respondents who had received training in complementary medicine had obtained their education predominantly through lectures and seminars. It is therefore unlikely that Canadian and UK GPs engaging in natural medicine hold formal qualifications for these modalities. This claim of insufficient training is corroborated by findings from a similar study of Quebec GPs (Goldszmidt, Levitt, Duarte-Franco & Kaczorowskim 1995).

Physicians in the United States on the other hand, seldom report the use of acupuncture. Instead, these practitioners are more likely to prescribe nutritional supplementation. Preferences for other therapies, however, are inconsistent across the US. The use of herbal medicine is one such example, with herbal use ranging from zero percent (0/85) in Washington (Boutin, Buchwald, Robinson & Collier 2000) to thirty-five percent (105/300) in Wisconsin (Rooney, Fiocco, Hughes & Halter 2001). Even though political differences may explain the discrepancy in these findings, the comparatively small sample and poor

response rate in the Washington study suggests that sampling error may also be a contributing factor.

The level of alternative therapy use among Australian medical practitioners is consistent with practices in the UK, with 100 of 282 (36%) Perth GPs surveyed reporting the use of natural medicine, particularly acupuncture (Hall & Giles-Corti 2000). These findings replicate reports from GPs in Auckland (Marshall *et al* 1990) and Victoria, Australia (Pirotta, Farish, Kotsirilos & Cohen 2002). The level of training in natural medicine on the other hand varied between practitioner groups, with twenty-four percent (59/249) of Auckland GPs (Marshall *et al* 1990) and forty-seven percent (132/282) of Perth GPs (Hall & Giles-Corti 2000) receiving formal training in complementary medicine. However, as highlighted elsewhere (Berman, Singh, Lao, Singh, Ferentz & Hartnoll 1995), disparate definitions of alternative medicine in the Auckland survey may have led to inconsistent practitioner responses.

Studies exploring physician use of natural modalities, as with surveys on patient and nurse use, are often compromised by poor response rates and undemonstrable tool validity and reliability. These flaws are reflected by significant variation in the levels of natural therapy use reported world wide, ranging between thirteen and fifty percent in Australia, New Zealand, the US and UK, to ninety-five percent in Germany (Himmel, Schulte & Kochen 1993). Apart from methodological differences, variations in findings between countries may be explained by geographical and political disparity. Practitioner preference toward the use of acupuncture, however, was consistent across the globe,

except for the US. The level of training in natural therapies on the other hand remains a concern, as many individuals approach MPs to make an informed choice about complementary medicine (Botting & Cook 2000). Since adequate training is needed to practice a natural modality both safely and competently (Stone 1999), poor MP training may increase the risk of patient harm, as well as compromise the client's ability to make an informed decision about their care.

7.5 Public attitude toward natural therapies

Population based studies to date have limited their investigation to the use of natural medicine and have largely ignored the attitude of individuals toward this alternative approach (Sirois & Gick 2002). Of the few studies that have examined these attitudes, most have focussed their attention on individuals' opinions of single therapies. Even so, findings from such research may begin to explain the surging interest in complementary medicine (Klepser, Doucette, Horton, Buys, Ernst, Ford, Hoehns, Kautzman, Logemann, Swegle, Ritho & Klepser 2000). For instance, a survey of 794 randomly selected Iowa residents found users of herbal medicine were more positive toward the safety and efficacy of medicinal plants, yet less favourable of the safety of prescription drugs than non-users. This inverse relationship between natural therapy use and the espousal for allopathic medicine is also reported elsewhere (Shumay *et al* 2002; Sirois & Gick 2002). As well as the dissatisfaction with mainstream health care, individuals may be turning to natural medicine in order to find a cure, to better manage one's symptoms, or to improve well-being (James 1999). Whether these factors apply to patients with chronic leg ulcers, however, is uncertain.

7.6 NURSE ATTITUDE TOWARD NATURAL THERAPIES

Nurses are at the forefront of informing clients about strategies that may support individual health and wellbeing, including advice on the use of both conventional and natural treatments. However, the attitudes of nurses toward complementary medicine are likely to influence the level of patient exposure to these modalities. To illustrate, a survey of 92 Finnish oncology nurses found practitioners using natural therapies in clinical practice were more supportive of complementary medicine than non-users ($p=0.005$) (Salmenpara, Suominen & Lauri 1998). Thus, the previously highlighted deviations in natural therapy use could be attributed to global variations in nurse's attitudes.

In the abovementioned study of Finnish oncology nurses, most respondents believed that complementary therapies were neither safe nor beneficial, involved unknown risk factors, and were offered by quacks for financial gain (Salmenpara, Suominen & Lauri 1998). By contrast, a large survey of 467 Ohio registered nurses found most clinicians were favourable of complementary medicine, as well as the integration of these therapies into mainstream practice (King, Pettigrew & Reed 1999). These supportive attitudes were shared among fifty-six South Australian district nurses, with those surveyed agreeing that complementary therapies were safe and effective, and resulted in positive patient outcomes (Leach 2002). Furthermore, over one-half of respondents believed that nurses should have a basic knowledge of natural modalities and that these therapies could and should be utilised within nursing practice. Nurses with a positive attitude toward complementary treatments also held a greater level of knowledge on these therapies ($p=0.04$). This finding corroborates that reported by Kreitzer, Mitten, Harris and Shandeling (2002), who identified a

more positive attitude toward natural medicine among clinicians with higher levels of complementary therapy training. Hence, increased knowledge, training and use of complementary medicine are likely to improve a practitioner's stance on natural therapies.

A generally positive attitude toward complementary medicine is evident among nurses in the US and Australia. While the reasons for this supportive attitude are not well defined, it is possible that many nurses may support and engage in these therapies in order to improve job satisfaction, client health and well-being (McCabe 1996), and nursing practice (Taylor 1996). It is still uncertain, however, whether these attitudes are likely to have a significant impact on client care.

7.7 Medical practitioner attitude toward natural therapies

Individuals planning to use natural therapies may also solicit the opinion of a physician before formulating a decision. The practitioner's attitude toward complementary medicine, however, is likely to influence the choice that an individual makes. Thus, physicians who exhibit a negative attitude toward natural medicine may in effect limit the range of treatment options they make available to clients.

In a meta-analysis of twelve surveys on physician's opinions about the efficacy of alternative medicine (Table 7.1), most practitioners believed that complementary therapies were moderately effective, with manipulative techniques, acupuncture and homeopathy considered to be the most useful (Ernst, Resch & White 1995). More recent surveys on Canadian and UK GPs

corroborate these findings (Perry & Dowrick 2000; Verhoef & Sutherland 1995). Even though the opinion of physicians on the efficacy of complementary medicine may reflect a moderate level of acceptance of these modalities, the perceived usefulness of natural therapies should not be confused with clinical efficacy (Ernst, Resch & White 1995). Instead, treatment decisions should be guided by the highest level of evidence available, such as that produced from randomised controlled trials.

Table 7.1: Surveys investigating medical practitioner perception of the efficacy of complementary medicine

Author	Year	Study location	Sample size	Practitioner type	Outcome
Anderson & Anderson	1987	UK	n=222, rr=81%	GPs	-Patient referrals to CPs: manipulation (50%), Acupuncture (20%), & Homeopathy (18%). -Therapy believed to have a valid basis: manipulation (35%), Acupuncture (15%), & Homeopathy (7%).
Cameron-Blackie & Mouncer	1993	UK	n=101, rr=43%	GPs	Therapies that would be used for ten specified conditions: acupuncture (30%), osteopathy (13%), homeopathy (13%), & chiropractic (6%)
Hadley	1989	NZ	n=166, rr=77%	GPs	60% of GPs indicated acupuncture, chiropractic and hypnosis were useful
Himmel *et al*	1993	Germany	n=40, rr=56%	GPs	63% of GPs believed CM was better than or equal to OM
Knipschild *et al*	1990	Netherlands	n=293, rr=74%	GPs	The most efficacious therapies were believed to be manual therapy (6.4/10), homeopathy (4.6/10), acupuncture (3.9/10)
Lynoe & Svensson	1992	Sweden	n=330, rr=79%	GPs	Positive attitudes were most evident toward manual therapy (47%) & acupuncture (43%)
Marshall *et al*	1990	NZ	n=171, rr=67%	GPs	30% of GPs practiced CM and 69% referred patients to CPs
Perkin *et al*	1994	UK	1. n=87, rr=81% 2. n=81, rr=81%	1. GPs 2. Hospital physicians	Patient referrals for CM: 1. osteopathy (78%), acupuncture (66%) & homeopathy (49%) 2. acupuncture (58%), osteopathy (52%) & homeopathy (21%)
Reilly	1983	UK	n=86, rr=86%	GP trainees	Therapies claimed to be useful were acupuncture (76%), homeopathy (45%), osteopathy (39%) & chiropractic (16%)
Schachter *et al*	1993	Israel	n=89, rr=89%	Physicians	54% of physicians believed CM was useful
Visser *et al*	1992	Netherlands	n=71, rr=70%	Rheumatologists	Positive attitudes were most evident toward manipulation (49%), acupuncture (37%) & homeopathy (23%)
Wharton & Lewith	1986	UK	n=145, rr=73%	GPs	86% of GPs believed CM was useful, particularly manipulation, acupuncture & homeopathy

(Modified from Ernst, Resch & White 1995)
CM=complementary medicine, CP=Complementary practitioners, GP=General practitioners, n=number, NZ=New Zealand, OM=orthodox medicine, rr=response rate, UK=United Kingdom

In a later study of 2748 UK physicians, attitudes toward natural medicine were once again found to be positive, particularly among young female practitioners specialising in palliative medicine (Lewith, Hyland & Gray 2001). Despite the

favourable attitude, however, the majority of practitioners agreed that natural therapies should be subject to further scientific testing before orthodox physicians accept these modalities. Furthermore, many practitioners believed that complementary therapies acted by way of a placebo effect; were less effective than allopathic medicine, and could prevent individuals from obtaining conventional treatment. Physicians in Minneapolis exhibited similar constraint, with most MPs failing to facilitate open discussion about complementary therapies (Boucher & Lenz 1998). Instead, these clinicians chose to highlight the harmful effects of natural medicine (Boucher & Lenz 1998). Whilst these findings indicate that some physicians are cautious about utilising natural therapies within mainstream practice, support for an integrative approach by practitioners in Liverpool and Israel suggest that this trepidation may not be widespread (Schachter, Weingarten & Kahan 1993; Vinker *et al* 2002).

Studies investigating physicians' attitudes toward natural medicine have uncovered a generally positive position throughout the western world, particularly among younger clinicians and those espousing the safety and efficacy of these modalities (Easthope, Tranter & Gill 2000). While practitioners are particularly optimistic about the efficacy of acupuncture and manipulative therapies, there is conflicting support for the use of other complementary modalities. These attitudes, as well as the safety, efficacy and familiarity of these modalities (Marshall *et al* 1990; Verhoef & Sutherland 1995), may explain why physicians are more likely to integrate acupuncture and manipulative therapies into medical practice than any other modality.

7.8 SUMMARY

Public acceptance of natural medicine is almost certainly on the increase in the western world. Whilst the public demonstrate a predilection for herbal medicine and nutrition, these therapies are not compatible with practitioner preference. Instead, nurses are more likely to practice massage and aromatherapy, with physicians preferring to engage in acupuncture. It is unclear, however, why differences in treatment preference are evident between practitioners and patients, and whether treatment choices continue to vary in specific clinical areas such as wound management.

There is also a dearth of information on the level of use and support for HCSE and other venotonic agents in the management of CVI. Whilst the level of public acceptance of natural medicines and the availability of English language publications may influence the degree of espousal for phlebotonics, these barriers to venotonic, HCSE and natural therapy use warrant further investigation to ensure that suitable treatment options for VLU are not withheld from patients. The following chapter describes a study that not only addresses this need, but also highlights the level of use and perceived usefulness of these interventions among nurses, medical practitioners and patients.

CHAPTER 8

STAGE IV METHODOLOGY

8.1 INTRODUCTION

The literature in the previous chapter suggests that public and clinician interest in natural medicine is on the rise. Although reasons for the shift toward complementary medicine have been identified for a number of client groups, there is a paucity of data about the use of alternative therapies among patients with chronic wounds. To address this concern and in particular, explore the feasibility of using HCSE as a treatment for VLU, required the development of a descriptive survey. Comprehensive discussion of the methods and methodology used for the survey are described throughout this chapter, beginning with details of the stage IV study design.

8.2 STUDY DESIGN

The fourth stage of the thesis utilised a descriptive survey methodology to investigate the feasibility of using HCSE as a treatment for venous ulceration. The descriptive survey design was not only useful for exploring subject preferences and attitudes toward stage IV concepts (Polit & Hungler 1999), but had the potential of improving the honesty and quality of participant responses by maintaining subject anonymity (de Vaus 1999; Roberts & Taylor 1999) and by avoiding interviewer bias (Polit & Hungler 1999). A posted questionnaire also permitted greater access to a larger sample (Burns & Grove 1993; Polit & Hungler 1999) by demanding less time and expense than any other design (Polit & Hungler 1999; Roberts & Taylor 1999).

Postal surveys, however, are not without limitations. For instance, questionnaires can discriminate against individuals who are illiterate, blind and cognitively impaired (Polit & Hungler 1999). Even so, the pre-screening of

patients during the stage I trial, as well as the clinician's capacity to practice, ensured that all participants were literate and cognitively competent.

Surveys can also be limited by poor response rates, misinterpretation and missing data (Polit & Hungler 1999). Strategies to increase participant responses were therefore employed, including the provision of reply-paid envelopes; pre-survey notification (McAvoy & Kaner 1996), and the inclusion of two rounds of follow-up (Burns & Grove 1993; de Vaus 1999). The potential for misinterpretation on the other hand was reduced by tailoring the questionnaire to each stratum; advising participants on how to contact the investigator if concerns arise, and by creating clear and unambiguous questions (Polit & Hungler 1999). As described in section 8.7, the clarity of questioning was reviewed and confirmed by a medical practitioner (MP); two academic researchers; three wound care specialists, and the district nursing-client reference group.

8.3 Aims

The aims of the current study were to:

1. Establish whether natural medicine, venotonic therapy and HCSE are being utilised by district nurses, medical practitioners, and clients with VLU.
2. Ascertain district nurse, medical practitioner and client opinion of natural medicine, venotonic therapy and HCSE.
3. Determine whether district nurses and medical practitioners would recommend natural medicine, venotonic therapy or HCSE to clients with venous ulceration, and

4. Identify the factors that facilitate and constrain the utilisation of HCSE in clinical practice.

8.4 Research Questions

To address the aims of the stage IV study, the following questions were investigated:

1. Do district nurses, medical practitioners and clients believe natural therapies and HCSE are safe and effective?
2. Do district nurses, medical practitioners and clients believe venotonic therapy and HCSE are suitable treatment options for the management of venous ulceration?
3. Are district nurses and medical practitioners currently recommending natural therapies, venotonic therapy or HCSE to clients with venous ulceration?
4. Do district nurses and medical practitioners plan to recommend natural modalities, venotonic agents or HCSE to clients with venous ulceration?
5. Are clients utilising natural therapies, venotonic agents or HCSE in the management of venous ulceration?
6. Do clients plan to utilise natural modalities, venotonic agents or HCSE in the management of venous ulceration?
7. Is there any association between participant age, gender and profession and the clinical application of natural medicine, venotonic therapy and HCSE?
8. Is there any association between subject opinion of natural medicine and the clinical application of venotonic therapy and HCSE?

9. Is there any association between participant opinion of venotonic therapy and the clinical application of HCSE?

8.5 Setting & Sample

Participants selected for the stage IV study needed to be exposed to information on venotonic therapy and HCSE in order to adequately complete the questionnaire. Hence, individuals not informed about the stage I trial and not living within metropolitan Adelaide were excluded from the survey. Practitioners selected for participation also had to be exposed to VLU in clinical practice. Thus, a convenience sample of 122 Adelaide district nurses was invited to participate in the stage IV study, including five Clinical Nurse Consultants (CNC), twelve Clinical Nurses (CN), and 105 Registered (RN) and Enrolled Nurses (EN). MPs on the other hand were less likely to be exposed to clients with VLU, and therefore, only those clinicians expected to have treated venous ulcers were approached. However, of the 1624 GPs, 24 dermatologists and 10 vascular specialists working in South Australia in the year 2000 (Australian Institute of Health & Welfare (AIHW) 2004), no more than 85 were directly informed about HCSE and the stage I trial. A random sample of seventy-five GPs, six vascular specialists and four dermatologists were subsequently invited to participate in the stage IV study.

Clients on the other hand were informed about HCSE through the stage I information sheets. Even though a proportion of these patients registered their interest in the stage I study, no more than 35 percent were eligible to participate in the trial. The four major reasons for stage I exclusion were an ABPI outside the 0.8 to 1.3 range; corticosteroid use; failure to obtain medical consent; and

wound closure (Table 4.1). Whilst the former reason eliminated patients with ulcers that were primarily non-venous, the other factors did not necessitate exclusion from the stage IV study. A convenience sample of sixty-three clients was therefore invited to participate in the survey, including forty-seven stage I participants and sixteen non-participants with contact details. The flow of participants through the stage IV study is further illustrated in Appendix 1.

8.6 Selection Criteria

To fulfil the aims of the stage IV study, and to ensure that each subject possessed prior knowledge of HCSE and the stage I trial, only those individuals meeting the following selection criteria were invited to participate.

Clients:

1. Resided in metropolitan Adelaide in the last twelve months
2. Obtained leg ulcer management from the district nursing service within the last year
3. Reported a history of active venous leg ulceration in the past twelve months, supported by an ABPI between 0.8 and 1.3
4. Registered their interest in the stage I trial, and
5. Was cognitively capable of accurately completing the questionnaire

Medical Practitioners:

1. Resided in metropolitan Adelaide in the last twelve months
2. Was contacted during stage I for medical consent, and
3. Practiced as a General Practitioner, Dermatologist or Vascular specialist in the past twelve months

Nurses:

1. Was employed by the Adelaide district nursing service
2. Practiced nursing in a clinical capacity, and
3. Practiced as an EN, RN, CN, or CNC in wound care.

8.7 INSTRUMENTATION

Development

A comprehensive search of MEDLINE, CINAHL and AMED between the years 1960 and 2002 endeavoured to locate a research instrument that addressed the aims of the stage IV study. Although many surveys examined the use and opinion of natural medicine among practitioners and patients, no single instrument comprehensively addressed all the aims of the current study. Consequently, a new tool needed be developed.

A three-page pencil and paper self-administered questionnaire was developed to support the aims of the stage IV survey. Two versions of the instrument were created, including a seventeen-item tool for clients and a twenty-item survey for practitioners (Appendix 23). Other than question one which utilised a three point Likert scale, all items in the survey utilised a five-point Likert format to quantify the direction and intensity of responses (de Vaus 1999). To enhance the richness of information, the survey also integrated ten items for open comment (Polit & Hungler 1999).

The stage IV instrument was divided into four sections to improve readability and to simplify data analysis. Section one explored the participant's opinion of natural modalities and the current and projected use of these therapies for VLU.

Parts two and three identified the level of venotonic and HCSE use among subjects, respectively, as well ascertaining the attitude of participants toward these treatments. The final section provided details of subject demographics, including the level of exposure to both VLU and the stage I trial. Although the first section included modified items from a previous instrument (Leach 2002), the remaining questions were developed exclusively for the stage IV study. On that account, the validity and reliability of the tool needed to be established to minimise measurement error.

Validity & Reliability

To ensure the stage IV questionnaire adequately captured the participant's opinion and use of natural therapies, venotonics and HCSE, the validity and reliability of the tool had to be established (Roberts & Taylor 1999). In collaboration with the statistical consultant and two professorial supervisors, the face validity of the instrument was confirmed. Nevertheless, face validity fails to provide sufficient evidence of an instrument's ability to adequately measure the construct under investigation (Burns & Grove 1993). Consequently, the content validity of the tool was measured to determine if all content areas of importance were sufficiently represented (Greenwood 1999). To ascertain the content validity (CV) of the two surveys, six experts in wound care, district nursing, natural medicine and allopathic medicine (Table 8.1) were invited to rate the relevance of each instrument item from 1=not relevant to 4=very relevant. The mean percentage of items with a score of three or four was calculated as 0.82, with good content validity defined as an index of 0.8 or above (Polit & Hungler 1999).

Table 8.1: Panel of experts who reviewed the content validity of the stage IV questionnaire.

	Position	Years in position	Qualifications	Experience
1	a. CEO of research & development (Mediherb) b. Herbalist	a. 19 years b. 15 years	BSc., Dip.Phytotherapy.	Experienced herbalist; researcher
2	a. Medical Practitioner b. Researcher	a. 35 years b. 30 years	BM.	Founder of ACCMER
3	a. Clinical Nurse Consultant (RDNS) b. District nurse	a. 12 years b. 29 years	RN., Grad.Cert. Management.	Specialist in wound care
4	a. Clinical Nurse Consultant (RDNS) b. Registered nurse	a. 3 years b. 8 years	RN., BN., Grad.Cert.Soc.Sc., M.Nurs.Sc (Nurse Practitioner).	Specialist in wound care
5	a. Advanced Wound Specialist (RDNS) b. Registered nurse	a. 18 months b. 18 years	RN., BN., Cert.Hyperbaric nursing., Cert.Orthopaedic nursing.	Specialist in wound care
6	Research manager (Mediherb)	9 years	B.App.Sc., PhD.	Researcher in herbal medicine

ACCMER=Australian Centre for Complementary Medicine Education & Research; BM=Bachelor of Medicine; BN=Bachelor of Nursing; BSc=Bachelor of Science; RDNS=Royal District Nursing Service; RN=Registered Nurse.

A particularly useful method for evaluating the reliability of attitude scales is Cronbach's alpha (Thomas 1990). This reliability index was therefore selected to test the internal consistency of each item in the stage IV questionnaire (Polit & Hungler 1999; Thomas 1990). Testing thirteen items within sections one, two and three of the client and practitioner surveys using SPSS (version 11.0), yielded a Cronbach's alpha of 0.93 and 0.96, respectively. Hence, the stage IV survey was reliable as these values were well above the 0.70 needed for group-level comparisons (Polit & Hungler 1999). Therefore, the stage IV questionnaire demonstrated a high degree of validity and reliability in measuring client and practitioner use and opinion of natural therapies, venotonics and HCSE.

Coding

Each instrument was coded prior to distribution in order to track respondents and minimise follow-up expenditure. Upon receipt of the completed

questionnaire, the three-digit code was matched with the number on the questionnaire log (Appendix 24) and recorded as returned. Any participants with outstanding questionnaires were then mailed reminder notices and additional surveys during consecutive rounds of follow-up.

8.8 Procedures & Data Collection

Stage I subjects and eligible non-participants were informed of the survey during trial discharge and trial exclusion respectively. District nursing staff, however, were notified about the stage IV study through round flyers, while MPs were informed via facsimiled letters. Client and practitioner questionnaires were then dispatched by mail in April 2003 and again in November 2004 to all individuals meeting the selection criteria. Participants not responding to the survey within fourteen days were posted a reminder letter and an additional questionnaire. A second series of reminder notices were then posted to remaining non-respondents two weeks after the first round of follow-up. Data collection for the stage IV study was subsequently completed by December 2004.

8.9 Ethical Considerations

The stage IV study was reviewed and approved by the ethics committees of both the district nursing service and the University of South Australia (Appendix 25). To protect the rights of participants, the study was also conducted in accordance with the approved research plan and the NHMRC 'national statement on ethical conduct involving humans' (NHMRC 2001).

Confidentiality

Participant anonymity in the current study could not be guaranteed due to the coding procedure previously described. Subject confidentiality on the other

hand was safeguarded by restricting access to all study data and by securing all documentation within a locked cabinet inside a secure residential facility.

Consent

All participants were adequately informed about the stage IV survey through the study information sheet (Appendix 26). Whilst completion of the questionnaire satisfied implied consent for most respondents, HREC ruling required clients to also provide written consent (Appendix 27). Therefore, in view of local and national guidelines, the stage IV study was conducted in a respectful, fair and beneficent manner.

8.10 Statistical Analysis

Responses from questionnaires were coded and entered onto SPSS (version 11.0) for data cleaning and statistical analysis. Qualitative material from open-ended questions, however, required quantification using content analysis (Polit & Hungler 1999). In other words, key themes needed to be identified from participant comments and grouped into positive and negative responses. Once categorised data were coded, data were then descriptively analysed using measures of central tendency and variability.

The relationship between ordinal-level variables were examined using Kendall's tau correlation coefficient (T) as the assumptions of parametric testing could not be met (Burns & Grove 1993; Polit & Hungler 1999). Serving two purposes, Kendall's Tau indicated both the strength and the direction of the relationship between variables, with –1.00 denoting a strong negative correlation and +1.00 a strong positive correlation (Burns & Grove 1993; SPSS 2001). In terms of the strength of the association between variables, these were defined as very high

>0.8; high 0.6-0.8: moderate 0.3-0.59; and small <0.3 (Hough 1999). To reduce the likelihood of these results being attributed to random error or chance, the significance level, or alpha level, was set at 0.05 (Hicks 1990; Roberts & Taylor 1999).

8.11 Summary

The stage IV descriptive survey was designed to examine client and practitioner use and opinion of natural therapies and venotonic agents in the management of VLU. Utilising a questionnaire with established validity and internal consistency, the stage IV survey ascertained if patients and clinicians would utilise these aforementioned modalities and whether these therapies were feasible for the future treatment of venous ulceration. The subsequent chapter details the results of this survey and discusses the implications of the study findings.

CHAPTER 9

STAGE IV FINDINGS & DISCUSSION

9.1 INTRODUCTION

The literature cited in earlier chapters has indicated that HCSE may be of use in the treatment of venous ulceration. A four-phase investigation exploring the efficacy and clinical application of HCSE was therefore designed and conducted to examine this assumption. Findings from the first three stages have already been presented, with the results of the fourth stage reported below. These findings are discussed in accordance with the research questions outlined in chapter eight. Details of the quality and limitations of the stage IV study are also presented.

9.2 FINDINGS

9.2.1 DEMOGRAPHICS OF SAMPLE

Sixty-three clients were invited to participate in the stage IV study. After two rounds of follow-up, a total of 50/63 questionnaires were returned, providing a response rate of 79 percent. As illustrated in Table 9.1, the majority of these respondents were males over the age of seventy years who had participated in the stage I trial.

Table 9.1: Demographics of clients (n=50)

		Number	%
Age	50-59 years	3	6
	60-69 years	7	14
	70-79 years	20	40
	80+ years	15	30
	Missing	5	10
Gender	Male	32	64
	Female	18	36
Participated in stage I	Yes	36	72
	No	14	28

Medical practitioners (MPs) on the other hand were less responsive than clients, with only 28/85 MPs (33 percent) completing the questionnaire. Of the practitioners responding to the survey, most were male GPs under the age of fifty years. The majority of these MPs also had more than eleven years of medical experience; had frequently treated patients with VLU, and had been exposed to participants in the stage I trial (Table 9.2).

Table 9.2: Demographics of medical practitioners (n=28)

		Number	%
Age	30-39 years	8	28.6
	40-49 years	9	32.1
	50-59 years	8	28.6
	Missing	3	10.7
Gender	Male	22	78.6
	Female	6	21.4
Type of practitioner	GP	26	92.9
	Dermatologist	2	7.1
Medical experience (years)	7-8 years	1	3.6
	9-10 years	3	10.7
	11 years and over	21	75.0
	Missing	3	10.7
Frequency of treating VLU	Infrequently	7	25.0
	Monthly	6	21.4
	Weekly	11	39.3
	Daily	2	7.1
	Missing	2	7.1
Exposure to participant in stage I	Yes	18	64.3
	Unsure	3	10.7
	No	7	25.0

GP=General practitioner

Of the 122 nurses approached for the stage IV survey, 39 responded (32 percent). As illustrated in Table 9.3, these nurses were most likely to be female; registered; aged between thirty and fifty-nine years, and have had more than eleven years of nursing experience. The majority of the nurses responding to the survey were also exposed to participants in the stage I trial, and had treated VLU on a daily basis.

Table 9.3: Demographics of nurses (n=39)			
		Number	%
Age	20-29 years	6	15.4
	30-39 years	10	25.6
	40-49 years	12	30.8
	50-59 years	10	25.6
	Missing	1	2.6
Gender	Female	36	92.3
	Male	2	5.1
	Missing	1	2.6
Type of practitioner	RN	22	56.4
	CN	12	30.8
	EN	3	7.7
	CNC	1	2.6
	Missing	1	2.6
Nursing experience (years)	5-6 years	2	5.1
	7-8 years	5	12.8
	9-10 years	3	7.7
	11 years and over	28	71.8
	Missing	1	2.6
Frequency of treating VLU	Daily	24	61.5
	Weekly	14	35.9
	Missing	1	2.6
Exposure to participant in stage I	Yes	23	59.0
	No	15	38.5
	Missing	1	2.6

CN=Clinical nurse; CNC=Clinical nurse consultant; EN=Enrolled nurse; RN=Registered nurse

9.2.2 Do Clients believe that natural therapies are safe and effective?

Clients with VLU were generally uncertain about the safety (Table 9.4) and efficacy (Table 9.5) of natural therapies, particularly homeopathy and aromatherapy.

Table 9.4: Do clients believe natural therapies are safe? (n=50)			
	Agree (%)	Unsure (%)	Disagree (%)
Massage	24 (48)	25 (50)	1 (2)
Vitamin & mineral supplementation	23 (46)	25 (50)	2 (4)
Meditation & relaxation	19 (38)	27 (54)	4 (8)
Herbal medicine	15 (30)	32 (64)	3 (6)
Acupuncture & acupressure	13 (26)	31 (62)	6 (12)
Aromatherapy	7 (14)	37 (74)	6 (12)
Touch & spiritual healing	7 (14)	28 (56)	15 (30)
Homeopathy	6 (12)	40 (80)	4 (8)
Mean response	14.3	30.6	5.1

Table 9.5: Do clients believe natural therapies are effective? (n=50)			
	Agree (%)	**Unsure (%)**	**Disagree (%)**
Vitamin & mineral supplementation	15 (30)	32 (64)	3 (6)
Massage	15 (30)	32 (64)	3 (6)
Meditation & relaxation	14 (28)	32 (64)	4 (8)
Herbal medicine	12 (24)	35 (70)	3 (6)
Acupuncture & acupressure	11 (22)	32 (64)	7 (14)
Touch & spiritual healing	6 (12)	29 (58)	15 (30)
Homeopathy	5 (10)	42 (84)	3 (6)
Aromatherapy	3 (6)	41 (82)	6 (12)
Mean response	10.1	34.4	5.5

Clients were also unclear whether natural modalities should be incorporated into mainstream medicine (Table 9.6), in particular, the integration of aromatherapy, homeopathy, touch and spiritual healing.

Table 9.6: Do clients believe natural therapies should be incorporated into mainstream medicine? (n=50)			
	Agree (%)	**Unsure (%)**	**Disagree (%)**
Massage	21 (42)	27 (54)	2 (4)
Vitamin & mineral supplementation	19 (38)	28 (56)	3 (6)
Herbal medicine	17 (34)	30 (60)	3 (6)
Meditation & relaxation	14 (28)	32 (64)	4 (8)
Acupuncture & acupressure	12 (24)	32 (64)	6 (12)
Homeopathy	6 (12)	39 (78)	5 (10)
Touch & spiritual healing	5 (10)	29 (58)	16 (32)
Aromatherapy	3 (6)	39 (78)	8 (16)
Mean response	12.1	32	5.9

9.2.3 Do Clients use natural therapies in the management of VLU?

The majority of clients responding to the questionnaire had never used complementary therapies in the management of venous ulceration (Table 9.7), possibly because of insufficient evidence (4/50) and a lack of opportunity (5/50). Of the modalities employed, however, nutrient supplementation and herbal medicine were the most favoured, with over twenty percent (11/50) of clients using these therapies on a daily basis (Table 9.7). Eight of the fifty patients (16%) indicated that the use of these modalities were recommended by a health care professional. A moderate positive correlation between natural

therapy use and participation in stage I was also evident (τ=0.41, p=0.016). Factors such as age (τ=-0.21, p=0.211) and gender (τ=-0.1, p=0.562) on the other hand were not found to be associated with the use of complementary medicine.

Table 9.7: Are clients using natural therapies in the management of venous ulceration? (n=50)

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Vitamin & mineral supp.	13 (26)	0 (0)	1 (2)	0 (0)	36 (72)
Herbal medicine	11 (22)	2 (4)	1 (2)	4 (8)	32 (64)
Meditation & relaxation	6 (12)	2 (4)	0 (0)	2 (4)	40 (80)
Homeopathy	3 (6)	0 (0)	0 (0)	1 (2)	46 (92)
Massage	2 (4)	3 (6)	1 (2)	2 (4)	42 (84)
Touch & spiritual healing	1 (2)	2 (4)	0 (0)	1 (2)	46 (92)
Acu-puncture / pressure	1 (2)	0 (0)	0 (0)	1 (2)	48 (96)
Aromatherapy	0 (0)	0 (0)	0 (0)	0 (0)	50 (100)
Mean response	4.6	1.1	0.4	1.4	42.5

The projected use of natural therapies for the treatment of VLU increased across all modalities except meditation. Clients willing to try alternative therapies, particularly massage, herbal medicine and nutrient supplementation, may do so in an attempt to ameliorate wound healing (4/50) and improve peripheral circulation (3/50). Most participants, however, were doubtful about the prospective use of complementary medicine (Table 9.8), with 7/50 (14%) concerned about the dearth of clinical evidence.

Table 9.8: Do clients plan to use natural therapies for venous ulceration in future? (n=50)

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
Herbal medicine	6 (12)	13 (26)	26 (52)	2 (4)	3 (6)
Massage	6 (12)	11 (22)	24 (48)	5 (10)	4 (8)
Vitamin & mineral supp.	5 (10)	14 (28)	28 (56)	1 (2)	2 (4)
Meditation & relaxation	3 (6)	6 (12)	31 (62)	6 (12)	4 (8)
Homeopathy	1 (2)	4 (8)	37 (74)	5 (10)	3 (6)
Acu-puncture / pressure	1 (2)	4 (8)	33 (66)	6 (12)	6 (12)
Touch & spiritual healing	0 (0)	5 (10)	30 (60)	7 (14)	8 (16)
Aromatherapy	0 (0)	3 (6)	36 (72)	5 (10)	6 (12)
Mean response	2.8	7.5	30.6	4.6	4.5

St.=Strongly

9.2.4 Do Clients believe that venotonic therapy is suitable for the management of VLU?

Thirty-eight percent (19/50) of patients believed that venotonic therapy was suitable for the treatment of VLU (Table 9.9), with previous success influencing twenty percent (10/50) of opinions. Clients not supporting the administration of venotonics, however, articulated concerns about the availability of information (2/50) and evidence on these agents (2/50).

Table 9.9: Client opinion of venotonics as a treatment for VLU (n=50).

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
Venotonics are suitable for VLU	8 (16)	11 (22)	28 (56)	3 (6)	0 (0)
Would consider using venotonics for VLU in future	13 (26)	11 (22)	22 (44)	3 (6)	1 (2)

St.=Strongly

Whilst no relationship was evident between a client's opinion of venotonic therapy and a subjects gender (τ=-0.06, p=0.723) and participation in stage I (τ=0.22, p=0.241), opinion was negatively correlated with age (τ=-0.36, p=0.006). Clients demonstrating a positive attitude toward venotonic agents were also more supportive of the safety (τ=0.41, p=0.003) and efficacy of herbal medicine (τ=0.43, p=0.004); the integration of herbal therapies into mainstream practice (τ=0.46, p=0.001); the use of nutrient supplementation (τ=0.32, p=0.024), and the use of herbal medicine for the future treatment of VLU (τ=0.41, p=0.016).

9.2.5 Do Clients use venotonic therapy in the management of VLU?

Fifty-two percent (26/50) of clients utilised venotonic agents in the daily management of VLU, although HCSE was the only product listed. Forty-eight percent (24/50) of patients on the other hand had never used venotonic therapy beyond the trial, with previous adverse events (3/50) and uncertainty about treatment efficacy (3/50) constraining the use of these agents. Yet, 24/50 (48%) clients considered using these agents in future (Table 9.9), because of previous treatment success (10/50). A moderate positive correlation between venotonic use and participation in stage I was present (τ=0.56, p=0.047). The current use of venotonic therapy (τ=-0.32, p=0.017) and the intention to utilise these agents in future (τ=-0.33, p=0.015) were, however, negatively associated with client age.

9.2.6 Do Clients believe that HCSE is safe, effective and suitable for the management of VLU?

Although most clients believed that HCSE was safe (30/50), only 20/50 (40%) agreed that the extract was effective (Table 9.10). Fifty two percent (26/50) of clients were also uncertain about the integration of HCSE into mainstream medicine, explained to some degree by concerns about the lack of evidence (3/50). Of the 20/50 (40%) clients who believed that HCSE should be incorporated into orthodox medicine, twelve percent (6/50) were influenced by previous treatment success.

Table 9.10: Client opinion of Horsechestnut Seed Extract (HCSE) (n=50).

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
HCSE is safe	17 (34)	13 (26)	18 (36)	1 (2)	1 (2)
HCSE is effective for venous insufficiency	14 (28)	6 (12)	26 (52)	4 (8)	0 (0)
HCSE should be incorporated into MM	8 (16)	12 (24)	26 (52)	4 (8)	0 (0)
HCSE is suitable for VLU	9 (18)	10 (20)	27 (54)	4 (8)	0 (0)
Will consider using HCSE based on current information	13 (26)	11 (22)	22 (44)	3 (6)	1 (2)
Will consider using HCSE based on positive research findings	14 (28)	11 (22)	21 (42)	2 (4)	2 (4)
Mean responses	12.5	10.5	23.3	3.0	0.7

St.=Strongly. MM=Mainstream medicine

Fifty-four percent (27/50) of clients were also uncertain whether HCSE was suitable as a treatment for VLU (Table 9.10), with 3/50 (6%) patients once again expressing concern about the lack of evidence. Patients who believed that HCSE was suitable, however, may have been inspired by previous success (7/50) or an associated improvement in leg oedema and leg pain (4/50).

Previous treatment success (9/50) and a willingness to try anything (3/50) may motivate 48 percent (24/50) of clients to consider HCSE treatment (Table 9.10), while positive research findings may influence fifty percent (25/50) of patients to use the extract in future (Table 9.10). Of the 22/50 (44%) clients who were reluctant to use HCSE, however, four percent (2/50) were concerned about the efficacy of the extract, and another four percent (2/50) required support from a General Practitioner.

Client attitudes toward HCSE were not associated with age (τ=-0.26, p=0.089), gender (τ=-0.12, p=0.521) or participation in stage I (τ=0.01, p=0.832), but were positively correlated with support for the safety (τ=0.56, p<0.001) and efficacy of herbal medicine (τ=0.67, p<0.001), and the integration of herbal medicine into mainstream health care (τ=0.68, p<0.001). Patient opinion of HCSE was also positively correlated with support for the safety (τ=0.37, p=0.026) and efficacy of nutrient supplementation (τ=0.48, p=0.004), and the integration of nutrient supplements into conventional practice (τ=0.37, p=0.034). Likewise, attitudes toward HCSE were positively associated with the use of herbal medicine (τ=0.34, p=0.011) and the administration of nutrient supplements (τ=0.33, p=0.034), as well as the future use of herbal medicine (τ=0.48, p<0.001). Client use and opinion of HCSE were also significantly correlated with the intention to use venotonics in future (p<0.001), and a belief that venotonics are a suitable treatment option for VLU (p<0.001) (Table 28.1, Appendix 28).

9.2.7 Do clients use HCSE in the management of VLU?

Forty of the fifty clients (80%) did not use HCSE as a treatment for venous ulceration. Of the remaining patients, 18 percent (9/50) used the extract on a daily basis, and two percent (1/50) on an infrequent basis. The main sources of information on HCSE were found to be the stage I trial (13/50) and the district nurse (4/50).

9.2.8 Do Medical practitioners believe that natural therapies are safe and effective?

The majority of MPs agreed that meditation, relaxation, massage and acupuncture were safe and effective (Table 9.11). Yet, very few believed that homeopathy and aromatherapy were useful (Table 9.12).

Table 9.11: Do medical practitioners believe natural therapies are safe? (n=28)

	Agree (%)	Unsure (%)	Disagree (%)
Meditation & relaxation	27 (96.4)	0	1 (3.6)
Massage	25 (89.3)	2 (7.1)	1 (3.6)
Acupuncture & acupressure	19 (67.9)	8 (28.6)	1 (3.6)
Aromatherapy	17 (60.7)	5 (17.9)	5 (17.9)
Vitamin & mineral supplementation	15 (53.6)	9 (53.6)	4 (14.3)
Touch & spiritual healing	15 (53.6)	6 (21.4)	7 (25.0)
Homeopathy	9 (32.1)	11 (39.3)	7 (25.0)
Herbal medicine	2 (7.1)	19 (67.9)	6 (21.4)
Mean response	16.1	7.5	4.0

Table 9.12: Do medical practitioners believe natural therapies are effective? (n=28)

	Agree (%)	Unsure (%)	Disagree (%)
Meditation & relaxation	22 (78.6)	2 (7.1)	4 (14.3)
Massage	19 (67.9)	5 (17.9)	3 (10.7)
Acupuncture & acupressure	14 (50.0)	10 (35.7)	4 (14.3)
Vitamin & mineral supplementation	7 (25.0)	13 (46.4)	8 (28.6)
Touch & spiritual healing	4 (14.3)	11 (39.3)	13 (46.4)
Herbal medicine	2 (7.1)	15 (53.6)	9 (32.1)
Aromatherapy	1 (3.6)	12 (42.9)	14 (50.0)
Homeopathy	1 (3.6)	11 (39.3)	15 (53.6)
Mean response	8.8	9.9	8.8

Practitioner support for the integration of natural therapies into mainstream medicine related only to the modalities MPs believed were safe and effective (Table 9.13).

Table 9.13: Do medical practitioners believe natural therapies should be incorporated into mainstream medicine? (n=28)

	Agree (%)	Unsure (%)	Disagree (%)
Meditation & relaxation	22 (78.6)	1 (3.6)	5 (17.9)
Massage	19 (67.9)	5 (17.9)	3 (10.7)
Acupuncture & acupressure	11 (39.3)	7 (25.0)	10 (35.7)
Vitamin & mineral supplementation	6 (21.4)	15 (53.6)	7 (25.0)
Herbal medicine	2 (7.1)	10 (35.7)	14 (50.0)
Touch & spiritual healing	2 (7.1)	7 (25.0)	19 (67.9)
Aromatherapy	1 (3.6)	6 (21.4)	20 (71.4)
Homeopathy	0	6 (21.4)	21 (75.0)
Mean response	7.9	7.1	12.4

9.2.9 Do medical practitioners recommend natural therapies to clients with VLU?

Concerns about the lack of clinical evidence (10/28) may explain why most MPs were disinclined to recommend natural therapies to patients with VLU (Table 9.14). On the other hand, a belief that these modalities improve wound healing (4/28) may drive one in four practitioners to endorse massage and nutrient supplementation on a frequent basis (Table 9.14).

Table 9.14: Do medical practitioners recommend natural therapies to patients with venous ulceration? (n=28)

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Massage	5 (17.9)	3 (10.7)	1 (3.6)	5 (17.9)	14 (50.0)
Meditation & relaxation	1 (3.6)	1 (3.6)	2 (7.1)	2 (7.1)	22 (78.6)
Vitamin & mineral supp.	0	3 (10.7)	4 (14.3)	10 (35.7)	11 (39.3)
Acu-puncture / pressure	0	1 (3.6)	1 (3.6)	3 (10.7)	23 (82.1)
Herbal medicine	0	0	4 (14.3)	2 (7.1)	22 (78.6)
Aromatherapy	0	0	1 (3.6)	0	27 (96.4)
Homeopathy	0	0	0	2 (7.1)	26 (92.9)
Touch & spiritual healing	0	0	0	0	28 (100)
Mean response	0.8	1.0	1.6	3.0	21.6

The majority of MPs did not intend to use natural modalities for the future management of VLU, with particularly little support for homeopathy, aromatherapy, touch and spiritual healing (Table 9.15). The reluctance to use these therapies may have related to concerns about the paucity of clinical

evidence (8/28). Thirteen of the 28 MPs (46%) did agree, however, to endorse massage or nutrient supplementation in the future management of VLU.

Table 9.15: Do medical practitioners plan to recommend natural therapies to patients with venous ulceration in future? (n=28)

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
Vitamin & mineral supp.	3 (10.7)	10 (35.7)	6 (21.4)	4 (14.3)	5 (17.9)
Massage	3 (10.7)	10 (35.7)	6 (21.4)	3 (10.7)	6 (21.4)
Meditation & relaxation	1 (3.6)	4 (14.3)	5 (17.9)	9 (32.1)	9 (32.1)
Acu-puncture / pressure	1 (3.6)	2 (7.1)	6 (21.4)	8 (28.6)	11 (39.3)
Herbal medicine	0	5 (17.9)	7 (25.0)	10 (35.7)	6 (21.4)
Aromatherapy	0	0	4 (14.3)	12 (42.9)	12 (42.9)
Touch & spiritual healing	0	0	4 (14.3)	11 (39.3)	13 (46.4)
Homeopathy	0	0	2 (7.1)	13 (46.4)	13 (46.4)
Mean response	1.0	3.9	5.0	8.8	9.4

St.=Strongly

9.2.10 Do medical practitioners believe that venotonic therapy is suitable for the management of VLU?

Forty-six percent (13/28) of MPs believed that venotonic agents were a suitable treatment option for VLU, while 36 percent (10/28) remained uncertain and 18 percent (5/28) disagreed. The espousal for venotonic therapy was partly based on a belief that these agents address the underlying cause of VLU (2/28) and that phlebotonics are supported by clinical evidence (2/28). Medical practitioners who believed that venotonics were unsuitable, however, claimed there was insufficient clinical evidence (4/28). Whilst MP opinion of venotonic therapy was not found to be associated with practitioner type (τ=-0.008, p=0.973), age (τ=0.18, p=0.241), gender (τ=-0.21, p=0.209), years of experience (τ=0.03, p=0.883) or exposure to patients with VLU (τ=0.19, p=0.268), clinician attitude was positively correlated with stage I participant contact (τ=0.33, p=0.022). Practitioner opinion of venotonic agents was also positively associated with the recommendation of massage (τ=0.27, p=0.038),

herbal medicine (τ=0.32, p=0.033), nutrient supplementation (τ=0.4, p=0.001), meditation (τ=0.36, p=0.013) and acupuncture (τ=0.40, p=0.011). There was also evidence of a positive correlation between a clinician's attitude toward venotonics and the intention to recommend massage (τ=0.43, p=0.004), herbal medicine (τ=0.48, p<0.001), meditation (τ=0.38, p=0.009) and acupuncture to patients with VLU in future (τ=0.36, p=0.008).

9.2.11 Do medical practitioners recommend venotonic therapy to clients with VLU?

Fifteen of the 28 MPs (54%) had never prescribed venotonic therapy as a treatment for VLU, partly because of concerns about insufficient evidence (5/28) and knowledge (2/28). Thirty-nine percent (11/28) of practitioners were also uncertain about utilising these agents in future (Table 9.16) for the same aforementioned reasons. Of the 32 percent (9/28) of clinicians likely to endorse venotonic therapy (Table 9.16), however, the availability of evidence was a motivating factor (3/28). The projected use of venotonic agents was also positively associated with the recommendation of nutrient supplementation (τ=0.33, p=0.023), meditation (τ=0.37, p=0.015) and acupuncture (τ=0.42, p=0.012), and a belief that HCSE should be incorporated into mainstream medicine (τ=0.45, p=0.006). The current use of venotonic agents on the other hand was positively correlated with the recommendation of massage (τ=0.35, p=0.030) and herbal medicine (τ=0.51, p=0.013).

Table 9.16: Do medical practitioners plan to recommend venotonics as a treatment for venous ulceration in future? (n=28)

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
Would consider recommending venotonics to patients with VLU in future	0	9 (32.1)	11 (39.3)	4 (14.3)	3 (10.7)

St.=Strongly

9.2.12 Do medical practitioners believe that HCSE is safe, effective and suitable for the treatment of VLU?

Forty-six percent (13/28) of MPs believed that HCSE was safe, although 71 percent (20/28) were uncertain about the efficacy of the extract in the management of CVI (Table 9.17). Eighteen of the 28 practitioners (64%) were also dubious about the suitability of Horsechestnut treatment, explained to some extent by a lack of information (4/28) and evidence (3/28) on the extract. Many MPs were also doubtful about the assimilation of HCSE into mainstream medicine. For instance, eleven percent (3/28) of those supporting an integrative approach believed there was sufficient evidence, while eighteen percent (5/28) of opponents argued to the contrary. A favourable attitude toward HCSE was positively associated with the use of herbal medicine (τ=0.29, p=0.043) and a belief that venotonic therapy was suitable for the treatment of VLU (τ=0.37, p=0.036).

Table 9.17: Medical practitioner opinion of Horsechestnut Seed Extract (HCSE) (n=28).

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
HCSE is safe	2 (7.1)	11 (39.3)	14 (50.0)	1 (3.6)	0
HCSE is effective for CVI	0	6 (21.4)	20 (71.4)	1 (3.6)	0
HCSE should be incorporated into MM	0	8 (28.6)	16 (57.1)	4 (14.3)	0
HCSE is suitable for VLU	0	7 (25.0)	18 (64.3)	2 (7.1)	1 (3.6)
Will consider recommending HCSE based on current information	0	6 (21.4)	15 (53.6)	5 (17.9)	1 (3.6)
Will consider recommending HCSE based on positive research findings	3 (10.7)	18 (64.3)	5 (17.9)	1 (3.6)	0
Mean responses	0.8	9.3	14.7	2.3	0.3

St.=Strongly. MM=Mainstream medicine.

9.2.13 Do medical practitioners recommend HCSE to clients with VLU?

The majority of MPs (26/28) had never recommended HCSE for the treatment of VLU, with a lack of information (6/28) and a paucity of evidence (2/28) hampering the use of the extract. Practitioners likely to use HCSE, however, including 3.6 percent (1/28) monthly and 3.6 percent (1/28) weekly, did so based on clinical evidence (2/28). A lack of existing information on the other hand (6/28) may explain why 54 percent (15/28) of MPs were uncertain about recommending the extract to patients. Yet, the presence of positive research findings may motivate 75 percent (21/28) of practitioners to use HCSE in future (Table 9.17).

9.2.14 Do nurses believe that natural therapies are safe and effective?

Overall, most nurses believed that natural therapies were safe and effective, with more than 79 percent (31/39) of clinicians espousing the safety and efficacy of massage, nutrient supplementation and meditation. By contrast, no

more than 33 percent (13/39) of nurses agreed that homeopathy was safe and effective (Table 9.18 & 9.19).

Table 9.18: Do nurses believe natural therapies are safe? (n=39)

	Agree (%)	Unsure (%)	Disagree (%)
Massage	35 (89.7)	4 (10.2)	0
Meditation & relaxation	35 (89.7)	4 (10.2)	0
Vitamin & mineral supplementation	33 (84.6)	6 (15.4)	0
Aromatherapy	29 (74.4)	7 (17.9)	3 (7.7)
Acupuncture & acupressure	28 (71.8)	11 (28.2)	0
Touch & spiritual healing	24 (61.5)	13 (33.3)	2 (5.1)
Herbal medicine	18 (46.2)	20 (51.3)	1 (2.6)
Homeopathy	13 (33.3)	24 (61.5)	2 (5.1)
Mean response	26.9	11.1	1.0

Table 9.19: Do nurses believe natural therapies are effective? (n=39)

	Agree (%)	Unsure (%)	Disagree (%)
Massage	33 (84.6)	6 (15.4)	0
Meditation & relaxation	33 (84.6)	6 (15.4)	0
Vitamin & mineral supplementation	31 (79.5)	8 (20.5)	0
Acupuncture & acupressure	24 (61.5)	15 (38.5)	0
Aromatherapy	21 (53.8)	13 (33.3)	5 (12.8)
Herbal medicine	18 (46.2)	19 (48.7)	2 (5.1)
Touch & spiritual healing	16 (41.0)	19 (48.7)	4 (10.3)
Homeopathy	11 (28.2)	26 (66.7)	2 (5.1)
Mean response	23.4	14	1.6

More than 71 percent (28/39) of nurses believed that massage, nutrient supplementation and meditation should be incorporated into mainstream medicine, while less than 31 percent (12/39) agreed to the integration of homeopathy (Table 9.20).

Table 9.20: Do nurses believe natural therapies should be incorporated into mainstream medicine? (n=39)

	Agree (%)	Unsure (%)	Disagree (%)
Massage	31 (79.5)	8 (20.5)	0
Vitamin & mineral supplementation	30 (76.9)	8 (20.5)	1 (2.6)
Meditation & relaxation	28 (71.8)	11 (28.2)	0
Acupuncture & acupressure	24 (61.5)	14 (35.9)	1 (2.6)
Aromatherapy	21 (53.8)	13 (33.4)	5 (12.8)
Herbal medicine	15 (38.5)	23 (59.0)	1 (2.6)
Touch & spiritual healing	14 (35.9)	17 (43.6)	8 (20.5)
Homeopathy	12 (30.8)	24 (61.5)	3 (7.7)
Mean response	21.9	14.8	2.4

9.2.15 Do nurses recommend natural therapies to clients with VLU?

More than 64 percent (25/39) of nurses had recommended massage and nutrient supplementation to patients with VLU (Table 9.21). Of the clinicians utilising these therapies, thirteen percent (5/39) did so to promote wound healing. A lack of knowledge (10/39) and a paucity of sufficient evidence (4/39) on the other hand, may explain why most nurses did not recommend homeopathy, acupuncture, aromatherapy, touch or spiritual healing to clients (Table 9.21).

Table 9.21: Do nurses recommend natural therapies to patients with venous ulceration? (n=39)

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Vitamin & mineral supp.	4 (10.3)	12 (30.8)	11 (28.2)	9 (23.1)	3 (7.7)
Aromatherapy	2 (5.1)	2 (5.1)	3 (7.7)	7 (17.9)	25 (64.1)
Meditation & relaxation	2 (5.1)	3 (7.7)	7 (17.9)	9 (23.1)	18 (46.2)
Herbal medicine	1 (2.6)	3 (7.7)	5 (12.8)	11 (28.2)	19 (48.8)
Massage	1 (2.6)	1 (2.6)	15 (38.5)	8 (20.5)	14 (35.9)
Acu-puncture / pressure	1 (2.6)	1 (2.6)	1 (2.6)	6 (15.4)	30 (76.9)
Touch & spiritual healing	1 (2.6)	0	2 (5.1)	6 (15.4)	30 (76.9)
Homeopathy	1 (2.6)	0	1 (2.6)	4 (10.3)	33 (84.6)
Mean response	1.6	2.8	5.6	7.5	21.5

The majority of nurses were also inclined to recommend nutrient supplementation, massage and meditation to clients in future (Table 9.22). Greater familiarity with these therapies was a reason for endorsing these modalities (2/39). Uncertainty about the future recommendation of homeopathy, aromatherapy and acupuncture, however, may have related to concerns about insufficient knowledge (9/39) and clinical evidence (2/39).

Table 9.22: Do nurses plan to recommend natural therapies to patients with venous ulceration in future? (n=39)

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
Vitamin / mineral supps	12 (30.8)	23 (59.0)	4 (10.3)	0	0
Meditation / relaxation	3 (7.7)	19 (48.7)	12 (30.7)	4 (10.3)	1 (2.6)
Herbal medicine	3 (7.7)	12 (30.8)	17 (43.6)	5 (12.8)	2 (5.1)
Aromatherapy	2 (5.1)	7 (17.9)	22 (56.4)	6 (15.4)	2 (5.1)
Touch / spiritual healing	2 (5.1)	7 (17.9)	18 (46.1)	9 (23.1)	3 (7.7)
Massage	1 (2.6)	25 (64.1)	13 (33.3)	0	0
Acupuncture / pressure	1 (2.6)	7 (17.9)	23 (58.9)	6 (15.4)	2 (5.1)
Homeopathy	1 (2.6)	5 (12.8)	22 (56.4)	7 (17.9)	4 (10.3)
Mean response	3.1	13.1	16.4	4.6	1.8

St.=Strongly

The recommendation of natural therapies to patients with VLU, both presently and in the future, was not correlated with a nurse's age ($p>0.630$), gender ($p>0.059$), position ($p>0.291$), years of experience ($p>0.211$) or contact with patients with VLU ($p>0.460$). Endorsing complementary modalities was, however, significantly associated with exposure to participants in stage I ($T=0.27$, $p=0.040$).

9.2.16 Do nurses believe that venotonic therapy is suitable for the management of VLU?

Twenty of the 39 nurses (51%) believed that venotonics were suitable for the management of VLU (Table 9.23). The support for these agents was to some extent attributed to a belief that venotonics increase treatment choice (3/39) and that the therapy was backed by clinical evidence (2/39). Conversely, of the 49 percent (19/39) of nurses who were uncertain about the suitability of venotonic therapy, thirteen percent (5/39) were concerned about the lack of experience with these agents, and eight percent (3/39) with the paucity of evidence.

Table 9.23: Do nurses believe venotonics are a suitable treatment for venous ulceration? (n=39)

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
Venotonics are a suitable treatment for VLU	2 (5.1)	18 (46.2)	19 (48.8)	0	0

St.=Strongly

Nurses attitudes toward venotonics were significantly associated with stage I participant contact (τ=0.44, p=0.001); a belief that nutrient supplementation (τ=0.34, p=0.028) and homeopathy were safe (τ=0.34, p=0.033); that homeopathy was effective (τ=0.50, p=0.001), and that aromatherapy (τ=0.32, p=0.024) and therapeutic touch should be incorporated into mainstream medicine (τ=0.36, p=0.009). There was also evidence of a significant correlation between a nurse's espousal for venotonic treatment and the recommendation of massage (τ=0.28, p=0.044) and aromatherapy (τ=0.40, p=0.008), and the intent to recommend herbal medicine (τ=0.30, p=0.018), homeopathy (τ=0.36, p=0.001) and aromatherapy to clients with venous ulceration in future (τ=0.34, p=0.002).

9.2.17 Do nurses recommend venotonic therapy to clients with VLU?

Fifty-one percent (20/39) of nurses endorsed venotonic therapy as a treatment for venous ulceration, although the level of use was largely infrequent (Table 9.24). Addressing the underlying aetiology of the wound was one reason for recommending these agents to patients (2/39). A nurse's endorsement of venotonic therapy was also significantly correlated with exposure to both stage I participants (τ=0.49, p<0.001) and patients with VLU (τ=0.32, p=0.026).

Insufficient knowledge (9/39) and experience (6/39) on the other hand prohibited 39 percent (15/39) of nurses from advocating the therapy.

Table 9.24: Do nurses recommend venotonics for the treatment of venous ulceration? (n=39)

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Currently recommends venotonics to patients with VLU	1 (2.6)	3 (7.7)	1 (2.6)	15 (38.5)	19 (48.7)

Nineteen of the 39 nurses (49%) intended to recommend venotonic agents to patients in future (Table 9.25). In 23 percent (9/39) of cases, endorsement was dependent upon the provision of additional evidence and information. The intent to recommend venotonic therapy in future was also moderately associated with stage I participant exposure (τ=0.41, p=0.004). By contrast, uncertainty about the future application of venotonic therapy was related to a lack of evidence (3/39), information (2/39) and experience (3/39) with these agents.

Table 9.25: Do nurses plan to recommend venotonic therapy as a treatment for venous ulceration in future? (n=39)

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
Would consider recommending venotonics to patients with VLU in future	1 (2.6)	18 (46.2)	17 (43.6)	3 (7.7)	0

St.=Strongly

9.2.18 Do nurses believe that HCSE is safe, effective and suitable for the treatment of VLU?

Although 67 percent (26/39) of nurses believed that HCSE was safe, only 49 percent (19/39) agreed that the extract was effective (Table 9.26). Fifty-one percent (19/39) of nurses were also doubtful about the integration of HCSE into mainstream medicine (Table 9.26), partly because of concerns about the paucity of evidence (2/39). Among the 46 percent (18/39) of nurses who

espoused an integrative approach (Table 9.26), however, ten percent (4/39) believed that the therapy was supported by research.

Table 9.26: Nurses opinion of Horsechestnut Seed Extract (HCSE) (n=39).

	St.Agree (%)	Agree (%)	Unsure (%)	Disagree (%)	St.Disagree (%)
HCSE is safe	3 (7.7)	23 (59.0)	13 (33.4)	0	0
HCSE is effective for CVI	4 (10.3)	15 (38.5)	19 (48.8)	1 (2.6)	0
HCSE should be incorporated into MM	3 (7.7)	15 (38.5)	20 (51.3)	1 (2.6)	0
HCSE is suitable for VLU	3 (7.7)	15 (38.5)	20 (51.3)	1 (2.6)	0
Would consider recommending HCSE based on current info	3 (7.7)	16 (41.0)	17 (43.6)	3 (7.7)	0
Would consider recommending HCSE based on positive research findings	11 (28.2)	20 (51.3)	8 (20.5)	0	0
Mean responses	4.5	17.3	16.2	1.0	0

St.=Strongly. MM=Mainstream medicine.

Uncertainty about the suitability of HCSE treatment was articulated by 51 percent (20/39) of nurses, which in part, related to concerns about the lack of evidence (1/39). However, of the 46 percent (18/39) of nurses who believed that HCSE was an appropriate treatment for VLU, eight percent (3/39) were motivated by alleged wound healing effects and a further eight percent (3/39) by observed benefits.

Nurses opinions of HCSE were negatively correlated with age (τ=-0.33, p=0.011) and positively associated with stage I participant exposure (τ=0.5, p<0.001). A favourable attitude toward HCSE was also associated with the recommendation of meditation (τ=0.25, p=0.043) and aromatherapy (τ=0.39, p<0.001). There was also evidence of a significant correlation between the use and opinion of HCSE, and the recommendation and opinion of venotonic therapy (Table 28.2, Appendix 28).

9.2.19 Do nurses recommend HCSE to clients with VLU?

Nineteen of the 39 nurses (49%) recommended HCSE as a treatment for VLU, with claims that the therapy was justified (1/39) and capable of reducing wound-healing time (3/39). Fifty-one percent (20/39) of nurses on the other hand did not recommend the extract to patients (Table 9.27), of which five percent (2/39) were constrained by a lack of information.

Table 9.27: Do nurses recommend HCSE as a treatment for venous ulceration? (n=39)

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Currently recommend HCSE for VLU treatment	0	3 (7.7)	2 (5.1)	14 (35.9)	20 (51.3)

Exposure to positive research findings may inspire eighty percent (31/39) of nurses to recommend Horsechestnut therapy to patients in future (Table 9.25), while support from MPs and the employing organization may drive five percent (2/39) of clinicians to use the extract. Of the 8/39 (21%) nurses who were reluctant to endorse HCSE treatment (Table 9.26), five percent (2/39) were concerned by the lack of information.

9.3 Discussion

9.3.1 Demographics of sample

The demographic characteristics of stage IV participants were generally consistent with the wider population. For instance, nurses participating in the stage IV study were demographically similar to those reported in the annual South Australian (SA) nursing survey (Baldock 2002). The characteristics of stage IV MPs were also consistent with data from the Australian Institute of

Health and Welfare (AIHW) medical labour force study (AIHW 2004). Clients in the current study, however, differed from the average patient with VLU (Callam *et al* 1987a), in that most were males. Yet, given that 47/63 (75%) clients were subjects from the stage I trial, and 57 percent (27/47) of these were male, this disparity is likely to reflect the characteristics of the stage I sample and the predominance of male subjects typically reported in clinical trials (Lovato *et al* 1997).

The rate of response from client's to the stage IV survey exceeded the response rates of earlier studies on natural therapy use (Emslie *et al* 2002; Klepser *et al* 2000; Shumay *et al* 2002; Yamashita, Tsukayama & Sugishita 2002). The practitioners response rate on the other hand was relatively small, which supports claims that GPs are poor responders of questionnaires (McAvoy & Kaner 1996). Therefore, whilst patient use and opinion of complementary medicine may replicate that in the wider community, the opinions of nurses and MPs cannot be generalised.

9.3.2 Client use and attitude toward natural therapies.

Patients with venous leg ulceration were found to be infrequent users of natural medicine. The lack of opportunity, practitioner influence, and concerns about clinical evidence limited the extent to which clients used these modalities. Indeed, the paucity of clinical evidence to support the use of complementary therapies in the management of VLU (Leach 2004a) corresponds with patient concerns.

The relationship between a practitioner's opinion and a patient's use of alternative medicine is supported by the literature (Salmenpara, Suominen & Lauri 1998), and may explain how clinician support for nutrient supplementation and herbal medicine could have influenced a client's use of these therapies. Yet, practitioner support for massage and meditation did not affect a patient's use of these treatments, suggesting that the utilisation of nutritional and herbal products may be induced by other factors. One such reason may be the increasing number of complementary medicines that are now available to consumers. This increase in product availability, as well as the willingness of individuals with chronic conditions to seek new treatments (Sirois & Gick 2002), particularly alternative therapies (Berg & Arnetz 1998; Ernst 2000; Jensen 1990), may explain why the use of herbal medicine among patients with VLU was three times that reported by South Australians in 1996 (MacLennan, Wilson & Taylor 1996).

The projected rise in natural therapy use amongst stage IV clients was consistent with the trend reported overseas (Eisenberg *et al* 1998; Johnson, Wootton, Kimzey, McCullagh, Wesley, Byrd, Singh, Rubino & Pucino 2000; Norred 2002). Apart from the abovementioned factors, a client's decision to turn to complementary therapies may also be driven by the inadequate treatments offered by conventional medicine (Coates & Jobst 1998; White 2003), such as surgery and topical therapy. To address these shortfalls of orthodox health care, and to facilitate the integration of alternative therapies into mainstream practice, may therefore require the provision of sound clinical evidence and a corresponding increase in practitioner acceptance.

9.3.3 CLIENT USE AND ATTITUDE TOWARD VENOTONIC AGENTS.

Even though one-third of clients supported the use of venotonic agents in the management of VLU, this espousal was frequently based on unfounded claims of previous success. For the majority of patients for instance, previous success related to participation in the stage I trial, and yet, stage I subjects were adequately blinded from treatment allocation. Thus, any claims of former success remain tenuous. The theoretical rationale for venotonic therapy may have instead been a more impelling reason for clients to use and support these agents. Consequently, some patients may be utilising venotonic agents without justification from sound clinical evidence.

Individuals using natural modalities are relatively more open to trying new treatments than users of orthodox medicine (Sirois & Gick 2002). This willingness to engage in new therapies may explain why clients most favourable of herbal medicine and nutrient supplementation were most supportive of venotonic agents. It is also likely that the association between venotonics and the abovementioned modalities related to the comparable elements of the three therapies.

The support for venotonic therapy was greatest amongst middle-aged clients, in much the same way that natural medicine is favoured by middle-aged women (Cook *et al* 2002; MacLennan, Wilson & Taylor 1996). Yet, gender had no significant effect on a patient's attitude toward venotonic agents or complementary medicine. Even so, it is possible that the discrepancy in these

findings was attributed to the overrepresentation of males in the stage IV sample.

The lack of information and the infrequent exposure to venotonic therapy generated patient concerns about the usefulness of these agents. Given that phlebotonics are infrequently used outside Europe (Coleridge-Smith 1996), however, it was foreseen that most clients would be unfamiliar with venotonic therapy. It was also anticipated that few patients would use venotonic agents in future because of insufficient evidence and previous adverse effects, despite forty-eight percent of clients indicating otherwise. Indeed, the lack of evidence to support the use of venotonics in the management of VLU, and the degree of adverse events reported in the stage I trial, corroborate these concerns.

Although fifty-two percent of patients reported the use of venotonic agents, it is likely that many participants included the stage I intervention as previous therapy. Therefore, it remains unclear if clients are utilising these agents in the management of VLU. It is apparent from the stage IV findings, however, that patients with venous ulceration may be vulnerable to trying new treatments, including venotonic therapy. This vulnerability should highlight to practitioners why clients with VLU should be adequately informed before embarking on new therapies.

9.3.4 Client use and opinion of HCSE

The majority of patients neither used nor supported HCSE in the management of VLU because of concerns about the dearth of evidence. Clients who did

support Horsechestnut therapy, however, were often driven by anecdotal reports and perceived treatment success. Yet, in view of stage I blinding, these claims of former success maybe inappropriate.

Another factor likely to influence the future use of HCSE is MP approval. Given the level of gate keeping in the stage I trial, however, and the degree of physician uncertainty about Horsechestnut therapy, it is unlikely that many MPs would encourage clients to use HCSE in future. Instead, the provision of plausible evidence, improvements in practitioner attitude, and client instruction about evidence-based practice may be required to facilitate the integration of HCSE into mainstream practice.

9.3.5 MEDICAL PRACTITIONER USE AND ATTITUDE TOWARD NATURAL THERAPIES.

The majority of medical practitioners agreed that natural medicine was safe, although alike Netherlands physicians (Knipschild, Kleunen & Riet 1990), many believed that complementary therapies were ineffective and should not be incorporated into mainstream practice. The primary reason for the marginal level of use and espousal for alternative medicine related to concerns about the paucity of clinical evidence. These opinions not only corresponded with earlier reports (Lewith, Hyland & Gray 2001; Marshall *et al* 1990), but were consistent with findings from a recent review of natural therapies in wound care (Leach 2004a). Whilst it appeared that many MPs were engaging in evidence-based practice, a number of practitioners were still recommending natural modalities to clients with VLU. Thus, some MPs may be endorsing complementary medicine without sufficient justification (Schachter, Weingarten

& Kahan 1993). Even though several physicians may have turned to these therapies to better meet client needs (Snyderman & Weil 2002), further research is needed to corroborate these claims and to determine whether other factors are likely to influence a practitioner's use of complementary medicine.

9.3.6 MEDICAL PRACTITIONER USE AND ATTITUDE TOWARD VENOTONIC AGENTS.

Despite the moderate level of support for venotonic therapy, very few physicians used or planned to recommend the agents to clients in future. The factors most likely to constrain the use of these agents were a lack of knowledge and a paucity of clinical evidence. Although concerns about limited evidence were plausible, several practitioners continued to believe that venotonics were a justifiable treatment for venous ulceration. Hence, many MPs maybe engaging in practice that is not evidence-based, and in effect, may increase the risk of client harm and the cost of client care. Nevertheless, since MPs did not specify the treatments prescribed, it is unclear if the recommended agents were complementary medicines or pharmaceuticals.

A factor found to be significantly associated with a practitioner's opinion of venotonic therapy was the degree of exposure to stage I participants. On that account, it is likely that the conduct of the stage I trial inadvertently influenced the attitudes of many clinicians. A practitioner's use and opinion of venotonic therapy was also found to be positively correlated with the use of massage, herbal medicine, nutrient supplementation, meditation and acupuncture. Whilst the association with herbal medicine and nutrition may be explained by the

similar elements of these treatments, the connection between venotonics and other modalities remains unclear. As with client attitudes, however, it is conceivable that practitioners using natural therapies may be more open to trying new interventions. Even so, further investigation is needed to confirm that these factors do in fact shape a clinician's opinion of venotonic treatment, and the subsequent integration of this therapy into mainstream practice.

9.3.7 MEDICAL PRACTITIONER USE AND OPINION OF HCSE

In support of earlier claims (Diehm 1996), most practitioners were hesitant about recommending HCSE to patients with venous ulceration. Whilst the provision of clinical evidence and the support for venotonic therapy and herbal medicine are likely to improve the utilisation of the extract in future (Bielanski & Piotrowski 1999), client exposure to the therapy may still be limited by MP prejudice. For example, even though there is sound clinical evidence to support the use of HCSE in venous insufficiency (Pittler & Ernst 2004), and MPs were informed of this evidence, most practitioners were still doubtful about the efficacy of the extract in CVI. Therefore, the anticipated rise in Horsechestnut use following the release of positive stage I findings remains debatable. To determine whether factors other than evidence are likely to hinder a practitioner's use of HCSE, and whether some practitioners maybe withholding suitable treatment options from clients, requires further investigation.

9.3.8 NURSE USE AND ATTITUDE TOWARD NATURAL THERAPIES.

Unlike some medical practitioners, nursing staff were generally supportive of natural medicine, with most affirming the safety, efficacy and integration of these therapies into mainstream practice. The favourable attitude of nurses

toward massage, nutrient supplementation and meditation in particular, coincided with an increased use of these therapies. The modalities that clinicians recommended (Hayes & Cox 1999; Leach 2002; Rankin-Box 1997; Tattam 1995; Trevelyan 1996), the attitudes toward these therapies (King, Pettigrew & Reed 1999; Leach 2002), and the disparity between nurse and medical staff opinion (Kreitzer, Mitten, Harris & Shandeling 2002; Rooney, Fiocco, Hughes & Halter 2001) were consistent with the literature.

The therapies least likely to be recommended by nurses for the management of VLU were the same as those eluded by MPs. As with earlier reports (Hayes & Cox 1999; Leach 2002), the reasons for avoiding these therapies related to reservations about insufficient evidence and limited knowledge. Previously listed concerns about the invasive nature of these modalities; the likelihood of treatment interactions, and the need for collegial and institutional support on the other hand, were not corroborated by the stage IV study (Leach 2002). Nonetheless, further investigation is needed to clarify why nurses may only welcome certain modalities in wound management, and whether improvements in complementary therapy research and nursing education could increase the use of these modalities among nurses and patients in future.

9.3.9 Nurse use and attitude toward venotonic agents.

The current study indicates that many nurses are endorsing venotonic therapy as a treatment for VLU in spite of the paucity of evidence to support the practice. Whilst the source of this contention is unknown, some clinicians may have been influenced by the stage I literature. Therefore, a number of

practitioners may be basing the use of venotonic therapy on experimental research findings and pathophysiologic rationale, and not on clinical evidence.

The favourable attitudes toward venotonic treatment were significantly associated with the use and support of natural modalities, particularly aromatherapy and homeopathy. Yet, these therapies were among the least favoured and used by nurses, as well as the least comparable to venotonics. Therefore, the correlation between these natural modalities and a nurse's opinion of venotonic treatment may be coincidental.

A number of other factors were also found to be significantly associated with a nurse's use and support for venotonic therapy. The correlation with stage I participant exposure for instance, suggests that nurses opinions of venotonic agents may have been influenced by the stage I trial, in a similar manner that subject contact influenced MP attitudes. On the other hand, the association between the use of venotonics and the treatment of VLU remains unclear. One possible interpretation of this relationship is that repeated exposure to chronic and recurrent wounds may have driven nurses to seek out alternative treatments to better meet client needs. Indeed, further research is needed to determine whether existing interventions are effectively addressing client and practitioner needs, and whether venotonic therapy may proffer a more complete wound care solution.

9.3.10 Nurse use and opinion of HCSE

Even though nurse's attitudes toward HCSE were more optimistic than MPs and clients, few intended to use the extract. The lack of evidence, information

and familiarity with HCSE prevented many clinicians from endorsing the treatment. On the other hand, support from health care organizations and medical practitioners may increase the use of Horsechestnut therapy among nurses in future. Yet, as HCSE treatment does not require medical authorisation, this need for MP support may reflect a nurse's fear of criticism or litigation (James 1999). Such trepidation may also explain why several nurses coveted approval from the employing organization before recommending HCSE. According to an earlier survey, this need for workplace support may not only apply to the integration of Horsechestnut, but to a range of natural therapies (Leach 2002).

Another factor that may have influenced the use of HCSE was the release of positive stage I findings. Since the stage I results were inconclusive, however, and most MPs would only support the extract if trial findings were positive, it is expected that few nurses would recommend HCSE in future. A number of clinicians on the other hand, still believed that there was sufficient evidence to support the use of Horsechestnut therapy in the management of VLU. Thus, it is probable that some practitioners maybe using the theoretical rationale of stage I to justify the use of HCSE, rather than basing the decision on sound clinical evidence.

As with physicians, many nurses were also doubtful about the efficacy of HCSE in chronic venous insufficiency, even though numerous clinical trials have supported this application (Pittler & Ernst 2004). Whilst the origin of this uncertainty is unclear, one possible explanation may the degree of

unfamiliarity with the treatment, particularly as most nurses were not aware of the extract prior to the stage I trial.

A more positive attitude toward HCSE was also evident among younger aged nurses, though the source of this relationship is uncertain, as age did not influence a practitioner's view of other therapies. The association between a clinician's opinion of Horsechestnut and other unrelated modalities, such as meditation and aromatherapy, was unexplainable as well, but as with MPs, may have been indicative of individual variance within the small sample (Unsworth 1999). Nurses recommending and supporting venotonic therapy were also more likely to favour and use HCSE, which may have been attributed to the similarity of the two treatments.

The need to be informed about a range of therapeutic options from a variety of disciplines is every patient's right. Yet, since many practitioners were unfamiliar with venotonic therapy and HCSE, a number of clinicians may not be equipped to inform patients about these treatments. Therefore, the provision of sound clinical evidence and the dissemination of these findings to health care providers may be needed to increase the future use of HCSE among patients with venous ulceration.

9.3.11 Quality and Limitations of Stage IV

The stage IV survey was the first known study to explore client and practitioner use and opinion of venotonic therapy and HCSE, as well as the factors that hinder and facilitate the use of these therapies in the treatment of venous ulceration. The current study was also one of few surveys to investigate the

use of complementary medicine with valid and reliable instrumentation. Yet, several limitations hampered the generalisability of these findings.

Despite the demographic similarities between clinicians and the wider population, the poor response rate and likelihood of refusal and sampling bias suggests that the opinion of practitioners may not be entirely representative of the target population (de Vaus 1999; Polit & Hungler 1999). In fact, subjects responding to the survey may have been more supportive of natural medicine and HCSE, and in effect, may have yielded a more positive view of these therapies. While strategies such as preliminary notification; reply-paid envelopes; response incentives and multiple rounds of follow-up were employed to maximise the return of completed surveys, these measures were not enough. A reduction in questionnaire length also may have improved the response rate (de Vaus 1999), although such a strategy was undesirable as a reduction in the quality of responses was foreseen.

Subjects invited to participate in the current study were expected to have some prior knowledge of venotonic therapy and HCSE. This small target population unfortunately limited the size of the sample and the generalisability of the stage IV findings. Even though the provision of balanced information on HCSE and venotonic therapy may have permitted greater access to a larger randomised sample, such a strategy was unfeasible due to financial constraints, but also unfavourable because of the potential introduction of response bias. Any further investigation into the use of venotonic therapy may

therefore need to be examined through a more comprehensive study of natural medicine use in wound management.

Another limitation of the stage IV study was the influence of the stage I trial, with the treatment provided in the trial likely to have overestimated the level of venotonic and HCSE use reported by subjects in the current study. Thus, questions specifying the use of these therapies outside the trial may have generated results that were more accurate.

A series of open-ended questions were incorporated into the survey to understand why participants used natural medicine, venotonic therapy and HCSE in the management of VLU. Although few subjects responded to these questions, a moderate rate of incomplete replies was expected (de Vaus 1999). The use of closed-ended questions to explicate the use of these modalities on the other hand was not suitable due to the lack of recognized alternative responses and the likelihood that participant's views may have been distorted (de Vaus 1999).

The current study has provided some insight into the possible behaviours of district nurses, MPs and patients with regards to the use of natural therapies in wound management. While the abovementioned limitations hindered the generalisability of the stage IV results, these shortfalls may be used to assist researchers in designing future studies on complementary medicine use.

9.4 SUMMARY

The stage IV study was the final component of a four-stage investigation into the feasibility of HCSE treatment. Of the three groups surveyed, nurses were the most likely to support and use HCSE, venotonic agents, and other natural modalities in the management of VLU, while clients were the most amenable to using these therapies in future. However, since many participants based the use of these treatments on a false perception of plausible evidence, a number of these individuals may require supplementary education on EBP. Several participants, on the other hand, expressed concerns about using HCSE and other natural modalities because of the paucity of evidence, and may only be driven to use these therapies through the provision of valid research findings. Even so, practitioner bias, gate keeping and a lack of knowledge may continue to hamper the integration of these therapies into orthodox practice. Apart from depriving patients of suitable treatment options, these obstacles may compromise a patient's ability to make an informed choice about their care (Adams, Cohen, Eisenberg & Jonsen 2002). Whilst the aims of the current study were addressed, the modest response rate and the small sample of clinicians suggests that further investigation is needed to corroborate these findings. In the following chapter, the main conclusions of the four-stage investigation are presented, as well as the recommendations for further research.

CHAPTER 10

CONCLUSION & RECOMMENDATIONS

10.1 Introduction

The clinical efficacy and feasibility of using HCSE in the treatment of venous ulceration was explored across four separate investigations. In the first study (stage I), a randomised, triple-blind, placebo-controlled trial was employed to examine the effect of HCSE on venous ulcer healing. Four representative cases of VLU healing and non-healing, in both the HCSE and placebo groups, were then selected from the trial and explored in a comparative case study (stage II). Data from the trial were also used to carryout a cost-benefit analysis of HCSE therapy (stage III). In the final study (stage IV survey), the feasibility of HCSE treatment, venotonic therapy and other natural modalities was examined. In this final chapter, the major findings of the four stages are revisited and summarised, and the recommendations for clinical practice and further research are presented.

10.2 Main Conclusions

Venous leg ulceration is a chronic and recurrent condition that affects around 0.6 percent of the western population (Nelzen, Bergqvist & Lindhagen 1996). Apart from the physical manifestations, VLU is associated with significant psychosocial and financial implications, such as depression, anxiety, social isolation, immobility and unemployment. It is therefore necessary that venous ulceration be effectively managed to not only improve patient health and wellbeing, but to decrease health care expenditure and the burden on community resources. While compression therapy remains the cornerstone of VLU treatment in most western countries, the efficacy of this therapy is debatable. Moreover, patient compliance with compression therapy is poor, which suggests that a more effective and well-tolerated treatment of venous ulceration needs to be sought.

In the area of complementary medicine, several therapies are demonstrating potential benefit in the treatment of chronic wounds (Leach 2004a), of which HCSE is one. This extract has been found to produce a range of pharmacological effects that target the pathological processes which lead to venous insufficiency. Since CVI is a precursor of venous ulceration (Callam *et al* 1987b; Goldstein *et al* 1998; Koch 2002; The Alexander House Group 1992; Thomas, Nash & Dormandy 1988), and the clinical efficacy of HCSE in the treatment of venous insufficiency is already established (Pittler & Ernst 1998), it is argued that the extract would significantly improve VLU healing.

The evidence-based practice paradigm provided a framework that underpinned the examination of the clinical efficacy, cost-effectiveness, clinical relevance and feasibility of HCSE treatment in venous ulceration. Exploring these different aspects of the therapy was aimed at assisting practitioners in making an informed decision about HCSE treatment. These aspects of the therapy were therefore examined in four separate stages to determine whether HCSE should be integrated into mainstream practice.

Findings from the four-stage investigation revealed that HCSE may be useful in the management of venous ulceration. Even though improvements in the rate of wound healing and in most secondary outcomes were not statistically significant between groups in the stage I trial, HCSE significantly affected the percentage of wound slough. This improvement in wound topography may have decreased the need for regular dressing changes, which could have led

to the decline in the number of nursing visits needed in the HCSE group at week twelve, and the subsequent reduction in organisational costs. In fact, twelve weeks of Horsechestnut therapy was found to save the district nursing service up to twenty-four percent in VLU treatment costs. These results suggest that HCSE therapy may be beneficial to health care providers, as well as clients with mild to moderate CVI, smaller, less chronic wounds, a shorter history of ulceration, and in those without signs of wound infection. However, given that the trial findings were inconclusive; that this was the first study of its kind, and that many patients and practitioners may require further evidence before they consider HCSE therapy, it is unlikely that Horsechestnut Seed Extract will be integrated into conventional care until new evidence emerges.

10.3 Recommendations & implications for clinical practice

This thesis has highlighted a need for further research into the effects of HCSE on venous ulcer healing. To improve the quality of such studies, the following recommendations are advised.

- Future trials on HCSE should incorporate measures that minimise gate keeping and practitioner resistance. Such strategies may not only increase sample size and statistical power, but also improve the generalisability of findings. Using on-site clinical staff to recruit participants, for instance, should be avoided (Hudson *et al* 2001). However, if on-site personnel are required, it is essential that well-informed trusting relationships be developed between staff and the research team (Hudson *et al* 2001; Lovato *et al* 1997; McNeely & Clements 1994).

- Even though the duration of the stage I trial was based on suitable healing rates from previous studies, a duration of twelve weeks may not be adequate for trials on HCSE and VLU. Therefore, to aim for a healing rate between 57 and 83 percent, and to account for the slow and increasing effect of HCSE over time (Diehm *et al* 1996; Frick 2000), future trials may need to adopt an intervention period of no less than twenty-four weeks (Falanga *et al* 1999; Mayberry *et al* 1991; Moffatt *et al* 1992; Thomson *et al* 1996).
- The financial limitations of the stage I study meant that the enteric coating of tablets was not feasible. Yet, it is recommended that future studies on HCSE utilise enteric-coated formulations to reduce the incidence of adverse gastrointestinal effects, to improve treatment compliance, and to maximise the treatment effect of the extract.
- Given that venous ulcers may only respond to HCSE in the presence of mild to moderate CVI, any further investigation of the extract will need to confirm the presence of low-grade venous insufficiency during participant screening. Other factors that are likely to influence the treatment effect of HCSE, such as the history of ulceration and the presence of wound infection, will also need to be considered in future trial selection criteria.
- The prevention of venous ulceration in susceptible individuals warrants further investigation due to the recurrent nature of the condition. Future studies of HCSE should therefore examine the long-term safety and efficacy of the extract in the prevention of VLU.

- The stage II study examined the short-term cost-effectiveness of treating venous ulceration with HCSE. Future studies are now needed to evaluate the long-term cost-effectiveness of HCSE therapy, which incorporate both the direct and indirect benefits of treatment.
- A comprehensive nationwide survey of wound care practitioners and clients with chronic wounds may elucidate the extent to which natural modalities are being employed in wound management. The clinical efficacy of the treatments identified in the survey could then be investigated to evaluate the feasibility of using these therapies within mainstream practice.
- Despite the recent shift toward evidence-based practice, some practitioners maybe using therapies that are not supported by plausible evidence (Leach 2004a; Schachter, Weingarten & Kahan 1993). Instead, clinicians may be basing treatment decisions on theories or experimental research findings. Practitioners may therefore require further training in EBP in order to better evaluate the plausibility of presenting claims, to justify clinical decisions, and to improve patient care.

10.4 Closing Summary

The escalating incidence of venous ulceration, as well as the climate of increasing health care expenditure, indicates that new and effective treatments of VLU are needed. Although HCSE may encumber the pathogenesis of CVI and perpetuate venous ulcer healing, the stage I trial did not support such a claim. However, taking into account the small sample and insufficient power of the stage I trial, and the significant improvement in wound

slough, visit frequency and organisational costs, it appears that HCSE may be useful in the management of VLU. The clinical efficacy and feasibility of using HCSE in the treatment of venous ulceration therefore warrants further investigation. High quality evidence from such trials may motivate clinicians to use venotonic agents in clinical practice, and in turn, expose patients to a unique therapeutic approach that specifically targets the aetiology of VLU. Apart from improving client health, wellbeing and quality of life, adopting such an approach may potentially reduce health care expenditure and resource utilisation.

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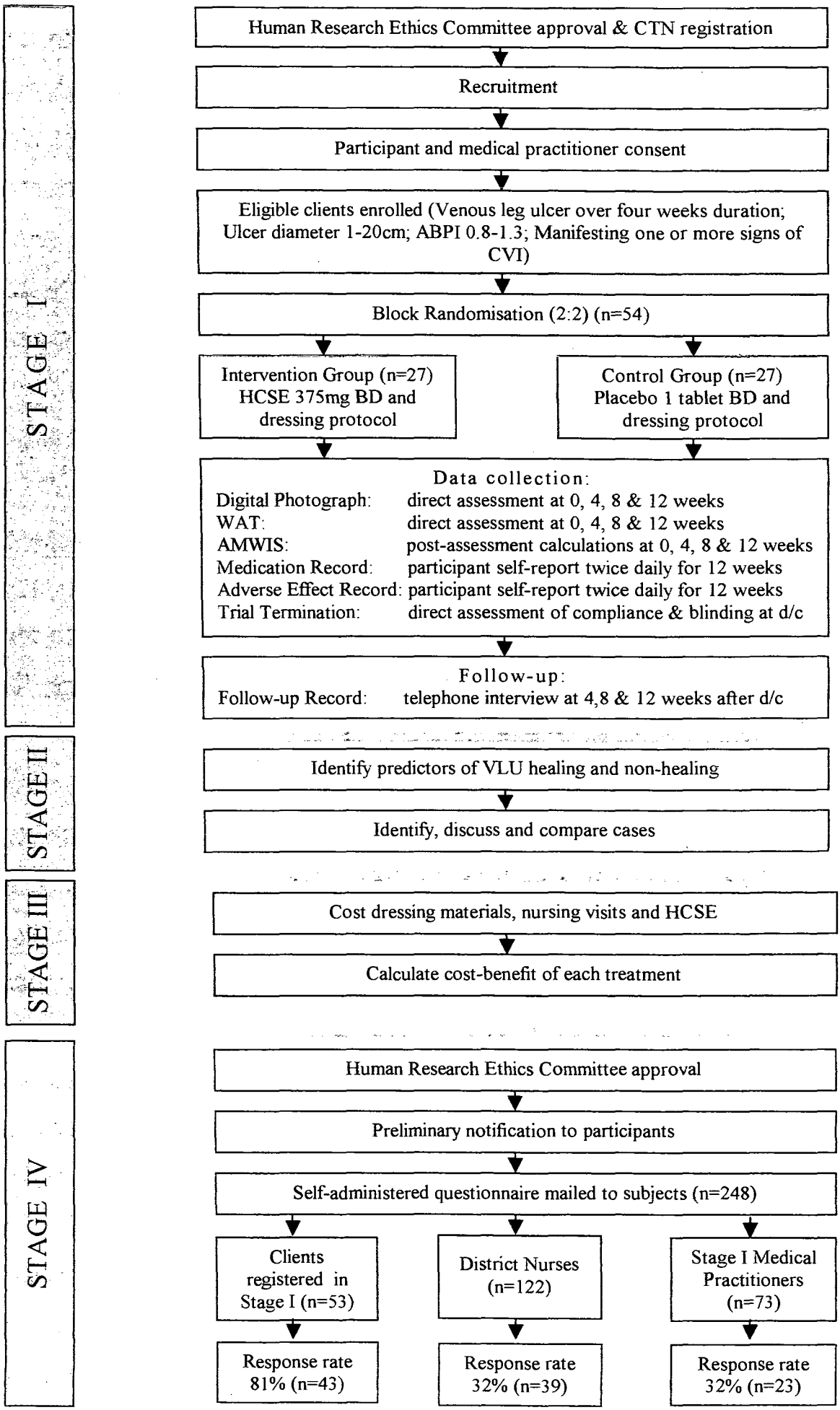
Appendix 1

Flow chart of study design

FLOW CHART OF STUDY DESIGN



Appendix 2



Wound assessment tool (WAT)



WOUND ASSESSMENT TOOL (WAT)

Trial Name:	Horsechestnut and Venous Leg Ulcer Trial	ID NUMBER:	
Chief Investigator:	Mr Matthew Leach		
Organisation:	University of SA, City East campus.	Baseline Date:	
Telephone:	8302 1020	Date ulcer healed:	

. Ulcer Location. (circle **all** that apply)

.Left or 2.Right leg. | 1.Medial or 2.lateral. | 1.Anterior or 2.Posterior. | 1.Foot or 2.Gaiter or 3.Calf or 4.Other.....

. Ulcer Shape. (circle only **one**)

.Irregular. | 2.Round/oval. | 3.Square/rectangular. | 4.Linear/elongated. | 5.Bowl/boat. | 6.Butterfly. | 7.Other.....

. Duration of presenting ulcer:	*weeks*
. Total of all leg ulcer episodes:	*episodes*
. Total duration since appearance of first leg ulcer:	*months*

Measurement		Baseline	Week 4	Week 8	Week 12
	Time: / Date:	(/ /)	(/ /)	(/ /)	(/ /)
. ABPI	(An ABPI conducted anytime in the last 12 weeks is valid)				
. BP (sitting)		/	/	/	/
. Height (cm)					
. Weight (kg)					
0. BMI	BMI=Weight (kg) / Height (m)^2 **1** = <18 **2** = 18-19.9 **3** = 20-24.9 **4** = 25-29.9 **5** = >30				
1. Ankle diameter(cm)	(Measure 3cm above lateral ankle of treatment leg)				
2. Calf diameter (cm)	(Measure 18cm above lateral ankle of treatment leg)				
3. Total number of leg ulcers	(Count all leg ulcers between toes and knee on both legs)				
4. Coexisting conditions	(Write **all** that apply) 1 = Ocre / brown pigmentation 2 = Dry / scaling skin 3 = Varicose veins 4 = Erythema				
5. Wound Depth (mm)	(Measure from deepest part of wound bed to highest wound edge)				
6. Exudate Amount	1 = Nil (wound bed dry) 2 = Low (wound bed moist. < 25% dressing wet) 3 = Moderate (wound bed saturated. > 25% to < 75% dressing wet) 4 = Heavy (wound bed bathed in fluid. > 75% dressing wet)				

		Baseline	Week 4	Week 8	Week 12
17. **Exudate Type**	**1** = None **2** = Serous: thin, watery, clear **3** = Haemoserous: thin, watery, pale red/pink **4** = Purulent: thin or thick, opaque, tan/yellow **5** = Haemopurulent: thin or thick, opaque, brown/orange **6** = Blood: thick, opaque, bright/dark red				
18. **Wound Odour**	**1** = None **2** = Some: mild odour; dissipates quickly **3** = Offensive: strong odour; persists in room				
19. **Surrounding tissue**	**(Write <u>all</u> that apply)** **1** = Healthy / intact **2** = Dry / scaling **3** = Excoriated **4** = Erythema **5** = Oedematous **6** = Macerated **7** = Eczema / Dermatitis **8** = Venous staining **9** = Fibrotic/scarred **10** = Other (specify)				
20. **Pain score (0 - 10)**	(0=no pain, up to 10=worst pain experienced)				
21. **Onset of Pain**	**(Write <u>all</u> that apply)** **1** = Not applicable / No pain **2** = Only at intervention **3** = Intermittent / No pattern **4** = Constant **5** = Nocturnal **6** = Other (specify)				
22. **Dressing Protocol**	**1** = Primary dressing protocol **2** = Secondary dressing protocol **3** = Tertiary dressing protocol				
23. **Cleaning agent**	**(Write <u>all</u> that apply)** **1** = Water **2** = Normal saline **3** = Other (specify)				
24. **Dressings applied (primary/secondary)**	**(Write <u>all</u> that apply)** **1** = Gel **2** = Melolin **3** = Tricotex **4** = Foam **5** = Profore **6** = Combine **7** = Tubigrip **8** = Other (specify)				
25. **Frequency of dressing changes**	**(Write only <u>one</u> that applies)** **1** = daily **2** = q 2 days **3** = q 3 days **4** = q 4 days **5** = q 5 days **6** = q 6 days **7** = q 7 days **8** = Other (specify)				
26. **Comments**					
Signature (surname)		( )	( )	( )	( )

NOTE: Complete assessment using instruction sheet. <u>Do not fill in shaded areas</u>.

FOLLOW-UP RECORD

		Week 4	Week 8	Week 12
	Date:	(/ /)	(/ /)	(/ /)
1. Is ulcer healed?	**1** = Yes **2** = No			
2. Date ulcer healed	dd/mm/yy **99** = Not healed			
3. Number of leg ulcers	Number of ulcerations in total to both legs			
4. Any new ulcerations?	**1** = Yes **2** = No			
5. Is compression being applied?	**1** = No compression **2** = Lestreflex **3** = Surepress **4** = Three layer Profore **5** = Four layer Profore **6** = Compression stockings **7** = Tubigrip			
6. Subjective change in wound size.	**1** = Not applicable/Healed **2** = Decreased **3** = Unchanged **4** = Increased			
7. Any new issues / concerns	Any events, treatments, or issues relating to the leg ulcer over the last four weeks (text)			

Appendix 3



Instructions for WAT



INSTRUCTIONS FOR USING THE WOUND ASSESSMENT TOOL (WAT)



University of
South Australia

Division of Health Sciences ♦ School of Nursing and Midwifery

'Horsechestnut and Venous Leg Ulcer Trial'

Researcher: Mr Matthew Leach RN. BN(Hons). ND.

General Instructions

The wound assessment tool will be used to evaluate the effects of the Horsechestnut treatment on wound healing. Please note that only one ulcer will be assessed throughout the whole trial. If there are multiple leg ulcers, please select the largest ulcer. The selected ulcer will be referred to as the 'treatment ulcer/leg' throughout these instructions. It is vital that you understand the definitions of each section and complete every section completely and accurately. The WAT is estimated to take ten minutes to complete. In addition, the time each wound assessment is conducted must be similar, for example 0900-1200 only or 1200-1500 only. Areas that are shaded do not need to be completed. Following the initial baseline assessment, an assessment is required every month for three months. Once the week 12 assessment has been completed, or if the ulcer heals beforehand, all trial material (wound assessment tool, medication record, adverse effect record, consent form, and bottle of remaining tablets) are to be collected for data entry.

Specific Instructions

1. ULCER LOCATION

Remember that only one ulcer will be assessed throughout the whole trial. If there are multiple leg ulcers, please select the largest ulcer. Circle which applies for each option. For example, circle left or right leg, *then* circle medial or lateral, *then* circle anterior or posterior. For the last option, if the location is not best described by any of these options, please specify under 'other'.

2. ULCER SHAPE

Circle only one option that best describes the shape of the leg ulcer. If no options best describe the shape of the ulcer, please specify under 'other'.

3. DURATION OF PRESENTING ULCER

Record the number of weeks the 'treatment ulcer' has been present.

4. TOTAL OF ALL LEG ULCER EPISODES

Record the number of leg ulcer episodes the participant has experienced in their lifetime.

5. TOTAL DURATION SINCE APPEARANCE OF FIRST LEG ULCER

Record the total number of months between the presentation of the first leg ulcer to the most recently presented leg ulcer.

6. ABPI

The Ankle-Brachial Pressure Index is used to determine whether the patient may have signs of arterial disease, thus determining whether compression therapy is appropriate. The ABPI will have been conducted before the trial is commenced, and is therefore not required throughout the remainder of the trial period. An ABPI conducted within twelve weeks of starting the trial will be valid.

7. BLOOD PRESSURE (BP)
The BP will determine whether participants entering the trial have similar baseline characteristics. The BP needs to be taken with the patient sitting down for a minimum of five minutes, or after the dressing is changed.

8. HEIGHT (cm)
The height will be utilised to calculate the participants Body Mass Index (BMI) at the end of the trial period to determine whether participants have similar baseline characteristics. The participant should have their heels, buttocks, shoulders and head against a wall and the height obtained at the highest point of the head.

9. WEIGHT (kg)
The weight will determine whether participants have similar baseline characteristics. The weight needs to be taken at approximately the same time for each assessment, for example between 0900-1200 or 1200-1500 every assessment. The weight should be obtained with loose clothing and no shoes.

10. BMI (Body Mass Index)
BMI is an indicator of body fat stores and body size. BMI is calculated by dividing weight (kg) by height (m^2). A BMI <18 = very underweight; 18-19.9 = underweight; 20-24.9 = acceptable; 25-29.9 = overweight; >30 = morbid obesity.

11. ANKLE DIAMETER
Measure the circumference 3cm above the lateral ankle of the 'treatment ulcer/leg'.

12. CALF DIAMETER
Measure the circumference 18cm above the lateral ankle of the 'treatment ulcer/leg'.

13. TOTAL NUMBER OF ULCERS
Count all leg ulcers that are present between the toes and knee of each leg including the 'treatment ulcer.'

14. COEXISTING CONDITIONS
Record all conditions that are present on the 'treatment leg' only. For example, if all conditions are present, you will write 1, 2, 3, 4.

15. WOUND DEPTH
Use measuring tape or ruler to measure the depth of the 'treatment ulcer', measuring from the deepest part of the wound bed to the highest wound edge in millimetres (mm).

16. EXUDATE AMOUNT
Visualise the wound into four quarters, with each quarter representing 25% of the wound. This will help determine the percentage of the wound involved. Use these additional descriptions as a guide.

- Nil = wound tissues dry
- Low = wound tissues moist; moisture evenly distributed in wound; drainage involves $\leq$ 25% dressing.
- Moderate = wound tissues saturated; drainage may or may not be evenly distributed in wound; drainage involves > 25% to $\leq$ 75% dressing.
- Large = wound tissues bathed in fluid; drainage freely exposed; may or may not be evenly distributed in wound; drainage involves > 75% of dressing.

17. EXUDATE TYPE
Some dressings interact with wound drainage to produce a gel or trap liquid. Before assessing exudate type, gently cleanse wound with normal saline or tap water (as per protocol). Pick the exudate type that is predominant in the wound according to colour and consistency.

18. WOUND ODOUR
Assess wound odour according to its initial smell and its persistence in the environment. Use these additional descriptions as a guide.

- None = no odour present.
- Some = mild odour; odour dissipates quickly; odour localised to dressing.
- Offensive = strong odour; persists in room/environment.

19. SURROUNDING TISSUE

Use these additional descriptions as a guide.

➢ Healthy/Intact	=	tissue resembles intact skin of leg
➢ Dry/scaling	=	dry, rough, scaling skin
➢ Excoriated	=	redness of the skin without excess heat, but with a scratched/abrasion appearance
➢ Erythema	=	redness of the skin without excess heat
➢ Oedematous	=	skin is shiny and taught; indentation appears after 5 seconds of firm finger pressure
➢ Macerated	=	white, mottled 'water-logged' skin
➢ Eczema/dermatitis	=	skin inflammation (heat; erythema; crusting, blisters, pruritis)
➢ Venous staining	=	ochre-brown pigmentation
➢ Fibrotic, scarred	=	hard, rigid to touch

20. PAIN SCORE

Whilst the patient is at rest and sitting, and before the dressing is taken down, ask the patient to score their level of pain in the 'treatment leg' ranging between 0 and 10 (0= no pain, up to 10= the worst pain ever experienced) according to onset.

21. ONSET OF PAIN

Ask patient to score their level of pain according to its onset. Use these additional descriptions as a guide.

➢ Not applicable / No pain	=	no complaint of pain with activity nor dressing changes
➢ Only at intervention	=	experiences wound pain only with dressing changes
➢ Intermittent / No pattern	=	experiences wound pain at varying times of the day; with no established pattern. May or may not be effected by activity; may or may not be effected by dressing changes
➢ Constant	=	experiences pain constantly; during dressing changes and changes in activity. May require regular analgesia.
➢ Nocturnal	=	experiences wound pain only at night when sleeping

22. DRESSING PROTOCOL

Record whether the 'treatment leg' was managed using the primary, secondary or tertiary dressing protocol.

23. CLEANING AGENT

Record all cleaning agents that were utilised on the 'treatment leg' only. For example, if both water and normal saline was used, you will write 1, 2.

24. DRESSINGS APPLIED

Record all dressing materials applied to the 'treatment ulcer/leg.' For example, if Gel, Melolin and Profore were applied to the 'treatment ulcer/leg', you will write 1, 2, 5. If a dressing other than that specified in the dressing protocol is used, please specify the product name.

25. FREQUENCY OF DRESSING CHANGES

Record the period between dressing changes (only one) that best applies to the 'treatment ulcer/leg'.

26. COMMENTS

Factors that may influence wound healing, such as wound infection, antibiotic therapy, or changes in dressing protocol need to be documented.

NOTE: Some parts of the wound assessment instructions have been adopted from Bates-Jensen BM. (1997) 'The pressure sore status tool. A few thousand assessments later.' *Adv Wound Care* 10(5): 65-73.

APPENDIX 4

STAGE I FLYER

University of South Australia

Division of Health Sciences

◆

School of Nursing and Midwifery

DO YOU HAVE A LEG ULCER ?

Volunteers Needed

Horsechestnut and Venous Leg Ulcer Trial (HAVLUT).

Leg ulcers effect one percent of the population, characterised by slow healing and recurrent episodes. As a district nurse and PhD candidate, Matthew Leach has been looking at ways to improve the healing rate of leg ulcers. Matthew is currently conducting a major research study on the wound healing effects of a herbal extract in patients with chronic leg ulcers.

This study aims to evaluate the claim that Horsechestnut can assist in venous leg ulcer healing. The anticipated benefits for participants are an increase in leg ulcer healing, and a decrease in the long-term discomfort, anxiety, inconvenience, financial costs and complications often associated with chronic leg ulcers.

Matthew is looking for **clients with leg ulcers** who receive care from the ##### District Nursing Service to enrol in this study anytime between **22nd April & 30th December 2002**. If you:

~ Are aged between 18 and 90 years,

~ Have a lower leg ulcer and,

~ Are not taking steroid medication or pentoxifylline

your participation in the study would be *greatly valued*.

You will be asked to take a tablet twice a day for twelve weeks (*at no charge*) and your ulcer will be assessed every four weeks within this period. Please ask your district nurse for an information sheet, or contact Matthew for more information.

Researcher:
Mr Matthew Leach RN. BN(Hons). ND.

Position:
PhD Candidate.
School of Nursing & Midwifery
University of SA: City East
North Terrace Adelaide 5000

Contact:
Telephone: 8302 1020 (answering machine).
Mobile: [redacted] (7 days a week).
Email:
matthew.leach@postgrads.unisa.edu.au

Appendix 5

Stage I information sheet

INFORMATION SHEET



University of
South Australia

Division of Health Sciences ◆ School of Nursing and Midwifery

'Horsechestnut and Venous Leg Ulcer Trial'

Researcher: Mr Matthew Leach RN. BN(Hons). ND.

Leg ulcers effect one percent of the population, characterised by slow-healing and recurrent episodes. As a PhD candidate, naturopath and district nurse, Matthew Leach has been looking at ways to improve the healing rate of leg ulcers. Matthew is currently conducting a major research study on the wound healing effects of a herbal extract known as Horsechestnut in patients with leg ulcers.

This study aims to evaluate the claim that Horsechestnut can improve venous leg ulcer healing. The anticipated benefits for participants are an *increase* in the healing rate of leg ulcers, and a *decrease* in the long-term discomfort, anxiety, inconvenience, financial costs and complications often associated with leg ulcers.

Many studies have found Horsechestnut to be effective in improving leg swelling, leg itching and leg pain. Horsechestnut is also well tolerated with 0.6 percent of people experiencing only mild and transient itching, dizziness, nausea, or headache. These effects were not any more frequent than in those taking an inactive placebo.

Matthew is looking for volunteers receiving leg ulcer care through the ##### District Nursing Service to participate in this trial. You can enter the trial anytime between **22nd April 2002 and 30th December 2002**. You are invited to participate in this study if you:

~ Are aged over 18 years,

~ Have a lower leg ulcer or wound that is located between the knee and the ankle, and has been present for at least four weeks, and

~ Are not taking steroid medication, such as prednisolone & cortisone

Participation in this study is voluntary, and you have the right to withdraw from the study at any time. However, your ongoing participation is important for the outcome of this study. The study has been reviewed and supported by the University of South Australia and the district nursing service. The results of this

study, together with some wound photographs, will be published in the researchers thesis, clinical nursing journals and conference proceedings. Research findings will also be made available to all district nursing staff and participants at completion of the trial. All participants will also remain confidential. Names, personal details and identifiable information will not appear in any publications, reports or documents.

To comply with Australian Freedom of Information legislation, all data obtained in the study will be retained for a minimum period of seven years in secured compactors at the University of South Australia, City East campus.

In relation to the treatment, the tablets that you will be provided may be either the Horsechestnut herb or an inactive placebo. The purpose of using a placebo is to better evaluate the effectiveness of the Horsechestnut treatment. You will have the opportunity to be notified of your treatment at the completion of the trial. Participants will be asked to take one tablet twice a day for twelve weeks and record this on a medication sheet. Both the provision of tablets and the participation in the trial is *free*.

A digital photograph of the ulcer and a brief wound assessment will be conducted four times over a twelve-week period, unless your leg ulcer heals beforehand, either at your home or in a nursing centre. As part of the nursing care of your leg ulcer, compression bandaging will be advised. However, if you cannot tolerate compression therapy, another non-compression dressing will be available.

Your support in this trial will be *greatly valued* as it will provide the necessary information to potentially improve current wound care practice and patient health and wellbeing.

If you are interested in participating in this clinical trial, please contact:

8302 1020

and leave your name and contact telephone number on the secure answering service. Matthew will contact you to answer your questions and assess whether you are suitable for the trial. If you have any urgent questions, please contact Matthew Leach on [redacted]. If you have concerns relating to the conduct of this project, the Chair of the district nursing service Human Research Ethics Committee, Ms Anne Maddock, can be contacted on 1300 364 264.

Thank-you greatly for your interest.

Appendix 6

Stage I participant details & admission criteria form

PARTICIPANT DETAILS

Trial Name:	Horsechestnut and Venous Leg Ulcer Trial	**Date:**	
Chief Investigator:	Mr Matthew Leach	**ID Number:**	- -
Organisation:	University of SA, City East campus.	**Site:**	
Telephone:	8302 2071	**TreatmentCode:**	
		Verbal Consent:	Y / N
Title:	Mr / Ms / Miss / Mrs / Dr	**Written Consent:**	Y / N
Surname:		**GP Fax Consent:**	Y / N
First Name:		**GP Confirmation:**	Y / N
Address:		**Approved / Not Approved**	
Suburb:		**Post Code:**	
Telephone:	( )	**Age:**	*years* (/ /)
Other Contact:		**Sex:**	1. Male 2. Female
Visit Schedule:	*day(s):*	*time(s):*	
GP Name:	Dr	**GP Telephone:**	**Fax:**

Medical History:

Surgical History:

Medications:

Smoking: *Cigs/day* **Alcohol:** *drinks/wk*

ABPI: *Date of ABPI ( )*

ADMISSION CRITERIA

The applicant must satisfy all the following selection criteria to be admitted into this trial.

Y	N		
☐	☐	1	Is mentally capable of providing verbal and written consent
☐	☐	2	Has a lower leg venous ulcer
☐	☐	3	Has one or more signs of CVI (oedema; venous staining; VV)
☐	☐	4	Ulcer diameter is between 1cm and 20cm
☐	☐	5	Ulcer duration exceeds 4 weeks
☐	☐	6	Has an ABPI between 0.8 and 1.3
☐	☐	7	Is not receiving oral or topical corticosteroids
☐	☐	8	Has not been treated with radiotherapy in the last six months
☐	☐	9	Has not received venotonic therapy in the last six weeks
☐	☐	10	Has not participated in another wound trial in the last 30 days
☐	☐	11	Is not allergic to HCSE

Appendix 7

Stage I practitioner consent forms

CONFIDENTIAL:
HAVLUT MEDICAL PRACTITIONER CONSENT

University of South Australia

TO: Dr

FROM: Mr Matthew Leach RN. BN(Hons). ND.
Chief Investigator / PhD Candidate
School of Nursing & Midwifery
University Of South Australia: City East Campus
North Terrace SA 5000
Tel: (08) 8302 2071 / Mob: [redacted] / Fax: (08) 8381 1821

RE: ***Horsechestnut and Venous Leg Ulcer Trial (HAVLUT).***

DATE:

Dear Dr .....,

As a matter of professional courtesy, I wish to inform you that ..... has enrolled to participate in a randomised, placebo-controlled, double blind trial approved by the ##### District Nursing Service Ethics Committee; the University of South Australia Human Research Ethics Committee; and registered under the Therapeutic Goods Administration (TGA). The trial will examine the efficacy of orai Horsechestnut Seed Extract (HCSE) as an additional treatment for chronic venous leg ulceration.

Horsechestnut, or Aesculus hippocastanum, is a tall deciduous tree native to Western Asia and South-east Europe. The principle component of Horsechestnut is aescin, which is believed to be responsible for reducing leg oedema and improving venous blood flow[1]. Horsechestnut also reduces proteolytic enzyme destruction of capillary walls, thus reducing the exudation of protein, electrolytes and water into the interstitium[1]. A systematic review of Horsechestnut seed extract (HCSE) evaluated thirteen double-blind randomised controlled trials, eight of which were placebo-controlled, and five of which were controlled against reference medications. All studies found Horsechestnut to be superior to placebo in reducing lower leg volume, calf and ankle circumference, pain, itching, and leg fatigue in chronic venous insufficiency[2]. In comparison to conventional treatment, HCSE was as effective as compression therapy in decreasing the symptoms of venous insufficiency, with a far less degree of adverse effects and with greater compliance[3]. The only adverse drug reactions (ADR) documented in these studies were mild and transient episodes of pruritis, headache, dizziness, nausea or unspecified gastrointestinal tract symptoms[2]. The frequency of these ADR were between 0.9 and three percent. In three of these studies, ADR frequency to Horsechestnut was not significantly different to placebo[2]. With no reported drug interactions or contraindications, HCSE is arguably a safe and effective treatment for the management of chronic venous insufficiency.

Participants in the Horsechestnut trial will self-administer an oral Horsechestnut or placebo tablet twice daily for twelve weeks. Wound care will continue to be provided by the designated nursing service, with wound assessments being conducted every four weeks for a maximum duration of twelve weeks by the chief investigator. ..... has voluntarily enrolled in HAVLUT as he/she meets the following selection criteria: has a leg ulcer of venous aetiology; is currently not taking oral or topical corticosteroid medication; and is cognitively capable of providing informed consent. To ensure there are no reasons why ..... could participate in HAVLUT, could you please sign the acknowledgement below.

I, Dr ....., have no clinical reasons why ..... (DOB: .....) should not participate in the Horsechestnut and Venous Leg Ulcer Trial HAVLUT). This includes the self-administration of oral Horsechestnut Seed Extract (HCSE) or Placebo at a dose of one tablet BD, until the ulcer heals or for a period not exceeding twelve weeks.

Signature:..... Date:.....

If however, if you have any reasons why ..... should not participate in HAVLUT, please tick the following box ☐, and comment below:

.....

Please return this completed document and fax back within 24 hours. The information provided in this letter is strictly confidential and restricted to the chief investigator. If you have any concerns or questions, the chief Investigator can be contacted as above. Your time and acknowledgement is greatly appreciated. *Thankyou.*

Mr Matthew Leach RN. BN(Hons). ND.

References:
1. Blumenthal, M., (ed). (1998) *The complete German commission E monographs: therapeutic guide to herbal medicines.* American Botanical Council, Texas.
2. Pittler M. Ernst (1998) 'Horse-chestnut seed extract for chronic venous insufficiency. A criteria based systematic review.' *Archives of Dermatology,* 134(Nov): 1356-1360.
3. Diehm, C. Trampisch, H. Lange, S. Schmidt, C. (1996) 'Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency.' *The Lancet*, 347(8997): 292-294.

Office Use Only:
Sent: .....
Received: .....
Outcome: .....

CONFIDENTIAL:
HAVLUT PRACTITIONER INFORMATION

University of South Australia

TO:

FROM: Mr Matthew Leach RN. BN(Hons). ND.
Chief Investigator / PhD Candidate
School of Nursing & Midwifery
University Of South Australia: City East Campus
North Terrace SA 5000
Tel: (08) 8302 1020 / Mob: [redacted] / Fax: (08) 8381 1821

RE: ***Horsechestnut and Venous Leg Ulcer Trial (HAVLUT).***

DATE:

Dear .....,

As a matter of professional courtesy, I wish to inform you that ..... has enrolled to participate in a randomised, placebo-controlled, double-blind trial approved by the ##### District Nursing Service Ethics Committee; the University of South Australia Human Research Ethics Committee; the #### CNC generalists/wound specialists forum; and registered under the Therapeutic Goods Administration (TGA). The trial will examine the efficacy of oral Horsechestnut Seed Extract (HCSE) as an additional treatment for venous leg ulceration.

Horsechestnut, or Aesculus hippocastanum, is a tall deciduous tree native to Western Asia and South-east Europe. The principle component of Horsechestnut is aescin, which is believed to be responsible for reducing leg oedema and improving venous blood flow[1]. Horsechestnut also reduces enzyme destruction of proteins in capillary walls, thus reducing the leakage of protein, electrolytes and water into the interstitium[1]. A systematic review of Horsechestnut seed extract (HCSE) evaluated thirteen double-blind randomised controlled trials, eight of which were placebo-controlled, and five of which were controlled against reference medications. All studies found Horsechestnut to be superior to placebo in reducing lower leg volume, calf and ankle circumference, pain, itching, and leg fatigue in chronic venous insufficiency [2]. In comparison to conventional treatment, HCSE was as effective as compression therapy in decreasing the symptoms of venous insufficiency, with a far less degree of adverse effects and with greater compliance[3]. The only adverse drug reactions (ADR) documented in these studies were mild and transient episodes of pruritis, headache, dizziness, nausea or unspecified gastrointestinal tract symptoms[2]. The frequency of these ADR were between 0.9 and three percent. In three of these studies, ADR frequency to Horsechestnut was not significantly different to placebo[2]. With no reported drug interactions or contraindications, HCSE is arguably a safe and effective treatment for the management of chronic venous insufficiency.

Participants in the Horsechestnut trial will self-administer an oral Horsechestnut or placebo tablet twice daily for twelve weeks and wound care will continue to be provided by ####. The use of compression therapy is however recommended during participation in HAVLUT. Wound assessments will be conducted every four weeks for a maximum duration of twelve weeks by the chief investigator. If you have any concerns or questions, the chief Investigator can be contacted as above. Your time and support is greatly appreciated. Thankyou.

Matthew Leach.

References:
1. Blumenthal, M., (ed). (1998) *The complete German commission E monographs: therapeutic guide to herbal medicines.* American Botanical Council, Texas.
2. Pittler M. Ernst (1998) 'Horse-chestnut seed extract for chronic venous insufficiency. A criteria based systematic review.' *Archives of Dermatology,* 134(Nov): 1356-1360.
3. Diehm, C. Trampisch, H. Lange, S. Schmidt, C. (1996) 'Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency.' *The Lancet,* 347(8997): 292-294.

APPENDIX 8

STAGE I ENROLMENT LOG

STAGE I ENROLMENT LOG

Trial Name:	Horsechestnut and Venous Leg Ulcer Trial (HAVLUT)
Chief Investigator:	Mr Matthew Leach
Organisation:	University of SA, City East campus.
Telephone:	8302 2071

ID Number	Surname	Enrolment Date	Baseline Data Date	First Assessment Date	Second Assessment Date	Third Assessment Date	Discharged
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Appendix 9



Stage I participant instruction booklet



PARTICIPANT INSTRUCTION BOOKLET



University of
South Australia

Division of Health Sciences ♦ School of Nursing and Midwifery

'Horsechestnut and Venous Leg Ulcer Trial'

Researcher: Mr Matthew Leach RN. BN(Hons). ND.

Thank-you for your participation in this clinical trial. The instruction sheet will provide you with more details about the trial, forms, wound assessments, dressing regime, lifestyle considerations, treatment details, dose schedule, and important contacts.

TRIAL SUMMARY

The purpose of this study is to examine how Horsechestnut seed extract (HCSE) influences the healing rate of chronic venous leg ulcers. The duration of this trial is twelve weeks, commencing from the first wound assessment.

MATERIALS

The documents and materials required for the trial include:

- Participant Instruction sheet
- Consent Form
- Medication Record
- Adverse Effect Record
- Two Bottles of Trial Tablets

It is important that you keep all the following documents within the included plastic sleeve to prevent any documents from being damaged or mislaid. In addition, please keep these documents stored in a safe place, out of the reach of others.

WRITTEN CONSENT FORM

During your discussion with the chief investigator, all questions and concerns about the trial should have been resolved. You should have also been informed about the need to sign a consent form before you can proceed with the trial. The consent form should be signed before your first wound assessment. You will be provided with a copy of this form once signed.

WOUND ASSESSMENTS

The chief investigator (Matthew) will conduct an assessment of your leg ulcer on the first visit, week 4, week 8, and week 12, whilst in the presence of a nurse. These assessments will evaluate the healing rate of your leg ulcer. If

you have more than one ulcer, please ensure that the same ulcer is assessed each time. Each wound assessment will measure:

- Ankle and calf diameter
- Pain score (with 0 being no pain and 10 being the worst pain ever)
- Body weight
- Blood pressure
- Wound depth
- Condition of surrounding skin

The chief investigator will also obtain a digital photograph of your wound during each wound assessments to accurately calculate your wound size.

DRESSING REGIME

During this trial there will be three dressing regimes. It is advised that you commence the primary dressing protocol, as compression will be necessary to reduce ankle swelling and improve venous blood flow. The nurse that normally provides your wound care will follow the 'primary dressing protocol' for the treatment of your leg ulcer. However, if you cannot tolerate the primary protocol, you can try the secondary dressing protocol. If you cannot tolerate any level of compression, you can ask the nurse to follow the 'tertiary dressing protocol'. The dressing protocols are outlined as follows:

Primary Dressing Protocol:
The leg with the ulcer will be cleaned with warm tap water. Following this, sorbolene cream will be applied to the effected leg from toe to knee, avoiding all ulcerations. If the ulcer is dry or exuding only a small amount of fluid, then a non-stick dressing called Tricotex will be applied. However, if the wound is exuding a large amount of fluid, a foam dressing called Biatain will be applied. Profore (four-layers) or Surepress (two-layers) compression bandaging will then be applied. These dressings will be changed once or twice a week until the ulcer is healed.

Secondary Dressing Protocol:
The leg with the ulcer will be cleaned with warm normal saline. Following this, sorbolene cream will be applied to the effected leg from toe to knee, avoiding all ulcerations. If the ulcer is dry or exuding only a small amount of fluid, then a non-stick dressing called Tricotex will be applied. However, if the wound is exuding a large amount of fluid, a foam dressing called Biatain will be applied. Profore (three-layers), Lestreflex (one-layer) or Tubigrip (stocking) compression will then be applied. These dressings will be changed once or twice a week until the ulcer is healed.

Tertiary Dressing Protocol:
The leg with the ulcer will be cleaned with warm normal saline. Following this, sorbolene cream will be applied to the effected leg from toe to knee, avoiding all ulcerations. If the ulcer is dry or exuding only a small amount of fluid, gel and a non-stick dressing (Melolin) will be applied to the ulcer. However, if the wound is exuding a large amount of fluid, Biatain or Mesorb will be applied. The dressing will then be secured with tape and/or a Tubiform stocking. These dressings will be changed every two to three days.

It is important not to interfere with your dressings as this may impair wound healing. To keep your dressing dry, wrap your leg with a plastic bag when you shower.

LIFESTYLE CONSIDERATIONS

To maximise the benefits of this trial, it is important that you follow the listed lifestyle considerations.

- Walk on a regular basis: this will stimulate the flow of blood from your legs back to your heart by contracting your calf muscles.
- Avoid standing in one place for long periods: this will cause fluid to collect in your legs and delay wound healing.
- Elevate your legs: whenever you are sitting, raise your feet to the height of your heart to prevent fluid collecting in your legs. Whilst elevating your feet, also move your feet up and down to stimulate the flow of blood from your legs back to your heart by contracting your calf muscles.
- Eat a well-balanced diet: to promote wound healing, eat foods rich in vitamins and minerals, including a wide range of fruits and vegetables. Avoid fatty foods, salt, and sugar as these can alter your nutrient levels.

REVIEW OF HORSECHESTNUT

Horsechestnut, or Aesculus hippocastanum, is a tall deciduous tree native to Western Asia and South-east Europe. The principle component of Horsechestnut is aescin, which is believed to be responsible for reducing leg swelling and improving venous blood flow (Blumenthal 1998). Horsechestnut also reduces enzyme destruction of proteins in the walls of small blood vessels. Thus reducing the leakage of protein, electrolytes and water into the tissue of the leg (Blumenthal 1998). A systematic review of Horsechestnut seed extract (HCSE) evaluated thirteen double-blind randomised controlled trials, eight of which were placebo-controlled, and five of which were controlled against reference medications. All studies found Horsechestnut to be superior to placebo in reducing lower leg volume, calf and ankle circumference, pain, itching, and leg fatigue (Pittler and Ernst 1998). In comparison to conventional treatment, HCSE was as effective as compression therapy in decreasing the symptoms of venous insufficiency, with a far less degree of adverse effects and with greater compliance (Diehm, Trampisch, Lange and Schmidt 1996). The adverse drug reactions (ADR) documented in eight of these studies were mild and transient itching, headache, nausea and gastrointestinal tract symptoms. The frequency of these ADR were between 0.9 and three percent. In three of these studies, ADR frequency to Horsechestnut was not significantly different to placebo (Pittler and Ernst 1998). Therefore, with no reported contraindications of oral Horsechestnut treatment, the relative safety and efficacy of HCSE in the management of CVI is well established.

DOSE SCHEDULE AND MEDICATION RECORD

You will be issued with two bottles of tablets which may be the Horsechestnut seed extract or an inactive placebo. You will not be informed as to which treatment you will receive. The purpose of using a placebo is to better evaluate the effectiveness of the Horsechestnut treatment. You will have the opportunity to be notified of your treatment at the completion of the trial. It is important to remember that Horsechestnut is slow-acting and treats the cause of venous leg ulcers not the symptoms, therefore you may not notice any improvement for several weeks.

You will be required to take one tablet in the morning between 8-10am and one tablet in the evening between 6-8pm with food. You are then required to tick in the medication record that you have taken the tablet.

Tablets need to remain within the bottle provided, and must be stored in a dark, cool place. There is no known interaction between Horsechestnut and other medications, so please continue taking prescribed medications as normal. However, it is recommended that you do not consume alcohol when taking your tablets. Failure to take the tablet on time every day for the duration of the trial may impair the full benefit of your treatment.

ADVERSE EFFECT RECORD

If you experience any symptoms other than what you normally experience, please document the following:

1. Date: the date the symptom occurred
2. Time: the time the symptom started
3. Description of the symptom: describe the symptom, its location, when it gets worse and when it gets better.
4. Severity: write down if the symptom was Mild (you can still continue with your daily activities), Moderate (you had to limit your daily activities) or Severe (you could not continue with your daily activities).
5. Duration: write down how many minutes, hours or days the symptom persisted for, from the time it started to the time it ended.
6. Relationship to study tablet: write down whether you believe the study tablet caused your symptom. Only include one of the following responses: no (a definite no); possible (you are unsure); probable (you are reasonably sure) or definite (you are confident that the study tablet caused your symptom).
7. Action taken: write down what you did to relieve the symptom. This may include lying down; administering a medication; consulting a health care professional.

In the case where a severe symptom may occur, seek medical advice immediately. Please inform the treating doctor that you are participating in a clinical trial. The treating doctor may request the identity of your treatment if they believe the study tablets may have caused the symptoms. If this occurs, the chief investigator can be contacted to inform the treating doctor of your treatment, and you will be subsequently withdrawn from the trial. Once your condition is improved, you will need to write the details of your symptom on

the adverse effect record, then contact the chief investigator to collect all remaining stock and documentation.

COMPLETION OF TRIAL

Following the final wound assessment at week 12, or if the ulcer heals beforehand, all trial documents included in this package, together with the bottle of remaining tablets, will be collected by the chief investigator. Matthew will then complete a trial discharge form and determine your satisfaction with the trial. Once the trial is completed, you will have the opportunity to be informed of which treatment group you were randomly allocated to. Matthew will also contact you at 4, 8 and 12 weeks after discharge to follow-up any changes. The results of this trial are anticipated to be published in 2005.

IMPORTANT CONTACTS

Your participation in this trial is very important and greatly valued, therefore any questions, concerns, comments or complaints need to be addressed promptly. All your concerns can be directed to the chief investigator, Matthew Leach. However, if you feel there is a matter you wish to discuss with someone impartial, Professor Jan Pincombe or Dr Gigi Foster can be contacted as below.

1. **Matthew Leach**
   School of Health Sciences
   University of SA: City East campus
   North Terrace Adelaide SA 5000
   Telephone: 8302 2071
   Mobile: [redacted]
   Email: matthew.leach@ unisa.edu.au

2. **Professor Jan Pincombe**
   School of Nursing & Midwifery
   University of SA: City East campus
   North Terrace Adelaide SA 5000
   Telephone: 8302 2027
   Email: jan.pincombe@unisa.edu.au

3. **Dr Gigi Foster**
   School of Commerce
   University of SA: City West campus
   North Terrace Adelaide SA 5000
   Telephone: 8302 0821
   Email: jennifer.foster@unisa.edu.au

References:

Blumenthal, M., (ed). (1998) *The complete German commission E monographs: therapeutic guide to herbal medicines.* American Botanical Council, Texas.

Diehm, C. Trampisch, H. Lange, S. Schmidt, C. (1996) 'Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency.' *The Lancet*, 347(8997): 292-294.

Pittler, M. Ernst, E. (1998) 'Horse-chestnut seed extract for chronic venous insufficiency. A criteria based systematic review.' *Archives of Dermatology*, 134(Nov): 1356-1360.

Appendix 10



Stage I consent form



Chief Investigator's Copy

CONSENT FORM

Project Title **Horsechestnut and venous leg ulcer trial**

Chief Investigator: **Matthew Leach**
School of Health Sciences
University of South Australia: City East
North Terrace Adelaide SA 5000
Tel: 8302 2071 Mob: [redacted]

Supervisor names: **Prof Jan Pincombe & Dr Gigi Foster**

- I have received written and verbal information about this research project.
- I understand the purpose of the research project and my involvement in it.
- I understand that I may withdraw from the research project at any stage.
- I understand that while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
- I understand that my wound will be digitally photographed throughout the trial

Name of participant .....

ID Number: .....-.....-.....

Signed ..... **Date** .....

I have provided information about the research to the research participant and believe that he/she understands what is involved.

Researcher's signature and date .....

Consent form

Participants Copy

CONSENT FORM

Project Title **Horsechestnut and venous leg ulcer trial**

Chief Investigator: **Matthew Leach**
School of Health Sciences
University of South Australia: City East
North Terrace Adelaide SA 5000
Tel: 8302 2071 Mob: [redacted]

Supervisor names: **Prof Jan Pincombe & Dr Gigi Foster**

- I have received written and verbal information about this research project.
- I understand the purpose of the research project and my involvement in it.
- I understand that I may withdraw from the research project at any stage.
- I understand that while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
- I understand that my wound will be digitally photographed throughout the trial

Name of participant .....

ID Number: .....-.....-.....

Signed ..... **Date** .....

I have provided information about the research to the research participant and believe that he/she understands what is involved.

Researcher's signature and date .....

APPENDIX 11

STAGE I RANDOMISATION CODE LOG

RANDOMISATION CODE LOG

Trial Name:	Horsechestnut and Venous Leg Ulcer Trial (HAVLUT)
Chief Investigator:	Mr Matthew Leach
Organisation:	University of SA, City East campus.
Telephone:	8302 2071

Date	Block selected	(Date when code provided) and full ID Code				Block complete
		1	2	3	4	☑
	- - -	( ) - -	( ) - -	( ) - -	( ) - -	
	- - -	( ) - -	( ) - -	( ) - -	( ) - -	
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Appendix 12



Stage I adverse effect & de-blinding protocol



ADVERSE EFFECT & DE-BLINDING PROTOCOL



University of
South Australia

Division of Health Sciences ♦ School of Nursing and Midwifery

'Horsechestnut and Venous Leg Ulcer Trial'

Researcher: Mr Matthew Leach RN. BN(Hons). ND.

The presence of any adverse effects to the stage I intervention should be clearly documented on the adverse effect record. The severity of the adverse event reported will then determine which action is necessary to manage the symptom.

MILD ADVERSE EFFECTS

If the adverse effect is mild, or the client can continue with their daily activities, conservative measures should be recommended. For example, if a client reports mild headache with the treatment, bed rest or paracetamol should be advised.

MODERATE ADVERSE EFFECTS

If the client reports a moderate adverse event, or the client's daily activities become limited, the following strategies should be employed sequentially:

1. Assess the dose, frequency and manner of the delivered intervention, and re-educate the client if administration of the treatment deviates from the trial protocol.
2. If the adverse effect continues, withhold trial medication for twenty-four hours and then resume as per protocol.
3. If the adverse effect persists, decrease the frequency of trial medication to one tablet daily.
4. On the condition where the adverse effect continues, cease trial medication.

SEVERE ADVERSE EFFECTS

The reporting of serious or unexpected adverse effects, where the subject cannot continue with any daily activity, necessitates implementation of the following procedure:

1. The client should seek immediate assessment and treatment from a general practitioner or hospital.
2. If the adverse effect is believed to be attributed to the trial intervention, and the MP requests the release of participant treatment details, the intervention code should be requested from the independent party reserving the treatment allocation schedule and relayed back to treating MP.
3. By violating blinding conditions, the participant should be withdrawn from the trial.
4. The chairpersons of the #### and University of South Australia Ethics committees should be informed of the serious adverse event and the necessary action undertaken.
5. The ADRAC blue card should be completed and forwarded to the TGA within seven days from the onset of the event.
6. If the treating MP determined the adverse effect to be unrelated to the treatment and the code was not revealed, the participant had the choice to either continue or withdraw from the trial.
7. Seven days after the manifestation of a serious adverse event, the participant should be contacted to evaluate treatment compliance, trial continuation and the recurrence of adverse effects.

Appendix 13



Stage I certificates of analysis



MEDI HERB
ACN 006 454 717

CERTIFICATE OF ANALYSIS

Horsechestnut Tablets

Product Name:	Horsechestnut Tablets
Product Code:	HORXTBCT
Batch Number:	002701
Preparation Type:	Tablet
Coating:	Brown film coated
Storage:	Below 30°C. Protect from light.
Expiry:	3 years from date of manufacture.

TEST	SPECIFICATION		RESULTS
Colour:	Brown tablet		Complies
Shape:	Medium oval tablet		Complies
Length:	18.8 mm – 19.2 mm		18.946 mm
Weight (mean):	750.5 mg – 829.5 mg		787 mg
Thickness:	5.9mm – 6.3 mm		6.089 mm
Friability:	< 1.0%		Complies
Disintegration:	NMT 30 Minutes		Complies
Active Level	375mg of Horsechestnut Extract equivalent to 75mg of aescin		Complies
Microbiological Contamination:	Total Plate Count:	≤ 1.0×10^4 cfu/g	< 1.0×10^4 cfu/g
	E. Coli:	Not detected/g	Not detected/g
	Salmonella:	Not detected/10 g	Not detected/10 g
	Total Yeast & Mould:	≤ 1.0×10^1 cfu/g	< 1.0×10^1 cfu/g

Authorised By: 19/4/2002
on behalf of
Reg Lehmann
Research Manager

PO Box 713
Warwick Qld 4370 AUSTRALIA
Telephone: +61 7 4661 0700 Fax: +61 7 4661 0788

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MEDI HERB
ACN 006 454 717

CERTIFICATE OF ANALYSIS

Horsechestnut Placebo Tablets

Product Name:	Horsechestnut Placebo Tablets
Product Code:	PLACEBOHC
Batch Number:	002702
Preparation Type:	Tablet
Coating:	Brown film coated
Storage:	Below 30°C. Protect from light.
Expiry:	3 years from date of manufacture.

TEST	SPECIFICATION		RESULTS
Colour:	Brown tablet		Complies
Shape:	Medium oval tablet		Complies
Length:	18.8 mm – 19.2 mm		19.04 mm
Weight (mean):	910 mg – 990 mg		978 mg
Thickness:	5.9mm – 6.3 mm		6.289 mm
Friability:	< 1.0%		Complies
Disintegration:	NMT 30 Minutes		Complies
Microbiological Contamination:	Total Plate Count:	≤ 1.0×10^4 cfu/g	< 1.0×10^4 cfu/g
	E. Coli:	Not detected/g	Not detected/g
	Salmonella:	Not detected/10 g	Not detected/10 g
	Total Yeast & Mould:	≤ 1.0×10^1 cfu/g	< 1.0×10^1 cfu/g

Authorised By: 19/4/2002

on behalf of

Reg Lehmann

Research Manager

PO Box 713
Warwick Qld 4370 AUSTRALIA
Telephone: +61 7 4661 0700 Fax: +61 7 4661 0788

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Appendix 14



Stage I medication record



MEDICATION RECORD

Trial Name:	Horsechestnut and Venous Leg Ulcer Trial
Chief Investigator:	Mr Matthew Leach
Organisation:	University of SA, City East campus
Telephone:	8302 2071

ID NUMBER: - -

Commencement Date: / /

Completion Date: / /

First Assessment Date: / /

	Week 1	Week 2	Week 3	Week 4
8-10am				
6-8pm				

Week 4 Assessment Date: / /

	Week 5	Week 6	Week 7	Week 8
8-10am				
6-8pm				

Week 8 Assessment Date: / /

	Week 9	Week 10	Week 11	Week 12
8-10am				
6-8pm				

Final Assessment Date: / /

NOTE: Starting from the shaded box (week 1), tick in each consecutive box every time you take a treatment tablet. It is important that you administer the treatment tablets at the recommended times (one tablet at 8-10am and one tablet at 6-8pm). If you forget to take a tablet and if it is *over* 4 hours before your next dose, take the treatment tablet as soon as you remember. If it *less* than four hours before your next dose, do not take the missed dose and write an X in the appropriate box.

Stage I medication record

Appendix 15



Stage I dressing protocol



DRESSING PROTOCOL

University of
South Australia

Division of Health Sciences ♦ School of Nursing and Midwifery

'Horsechestnut and Venous Leg Ulcer Trial'

Researcher: Mr Matthew Leach RN. BN(Hons). ND.

WOUND ASSESSMENT DATES			
Baseline:	**Week 4:**	**Week 8:**	**Week 12:**

TRIAL SUMMARY

The purpose of this study is to determine whether Horsechestnut seed extract (HCSE) influences the healing rate of venous leg ulcers. The duration of the trial is twelve weeks, or less if the ulcer heals beforehand. The trial will commence for the participant following the baseline wound assessment.

CONTACT:

Your participation in this trial is very important and greatly valued; therefore any questions, concerns, comments or complaints need to be addressed promptly to the chief investigator as below:

Mr Matthew Leach
School of Nursing & Midwifery
University of South Australia: City East
North Terrace Adelaide SA 5000
Tel: 8302 1020 Mob: [redacted]
Email: matthew.leach@postgrads.unisa.edu.au

DRESSING INSTRUCTIONS

The dressing protocol is a detailed outline of how the venous ulcer should be cleaned and treated whilst the client is participating in this trial. It is important that this protocol is strictly followed to avoid unnecessary variables in the study. This protocol was developed from the current literature, incorporating moist wound healing principles, measures to prevent tissue injury, and measures to preserve client comfort. This protocol has also been supported by five Adelaide wound care experts.

Wound assessments will be conducted by the chief investigator every four weeks for a maximum period of twelve weeks. These assessments will be conducted in conjunction with the scheduled dressing change to avoid unnecessary exposure of the wound. Therefore, please determine whether a wound assessment is due prior to commencing wound care (see above). Each client admitted to the study will be asked to commence the primary dressing protocol. However, in participants where high compression cannot be tolerated, the secondary protocol is advised. In those participants where any form of compression cannot be tolerated, the tertiary dressing protocol is to be implemented. The protocol for each group is outlined below. Matthew thanks you for your time and valuable support.

COMPLETION OF TRIAL

Following completion of the week 12 assessment, the client will be discharged from the clinical trial. Therefore, there will be no further obligation to continue with the dressing protocol. Matthew thanks you for your time and valuable support.

☐ PRIMARY DRESSING PROTOCOL (HIGH COMPRESSION - 30-40MMHG)

1. Clean selected leg from toe to knee in a bowl of warm tap water using a clean face washer.
   (Rationale: Water is an appropriate, non-toxic agent for wound cleansing (Glide 1992; Young 1995) and must be applied warm to avoid compromising macrophage activity (Young 1995)).
2. Apply sorbolene cream to selected leg from toe to knee but avoiding all ulcerations.
   (Rationale: Moisturisers are beneficial in improving concomitant venous eczema in VLU (Lopez & Phillips 1998)).
3. Apply primary dressing as follows:
   a. If ulcer exudate amount = *None, Small or Scant* (wound is wet; exudate soils less than 25% of dressing), apply Tricotex (Smith & Nephew) over the entire wound with at least 5mm of Tricotex covering the wound perimeter.
      (Rationale: Tricotex is a non-stick dressing provided with Profore (Smith & Nephew) which prevents adherence of the secondary dressing to the wound).

      OR

   b. If ulcer exudate amount = *Moderate or Large* (wound is saturated; exudate soils 25% or more of dressing), apply Biatain (Coloplast) or Mesorb (SSL) dressing over the entire wound with at least 5mm of dressing covering the wound perimeter.
      (Rationale: an absorbent dressing absorbs excess exudate and prevents maceration of surrounding skin).

      OR

   c. If the surrounding skin is dry, flaking and friable, apply zinc oxide impregnated bandage (Viscopaste, Smith & Nephew) from toe to knee in a spiral configuration with 50% overlap. In addition, every turn of the bandage should fold back on itself in a pleat over the anterior surface of the leg.
      (Rationale: Zinc oxide impregnated bandage is claimed to improve surrounding skin integrity by facilitating collagen synthesis (Linder 1991).
4. Apply Softban (Smith & Nephew) in spiral configuration fifty percent overlap and no stretch.
5. In order of preference, apply high level compression therapy as follows:
   a. Apply Four-layer Profore (Smith & Nephew) compression bandaging to selected leg from toe to knee as per manufacturers instructions. All bandages should be applied with 50% overlap and include *Profore #2* (spiral configuration with no stretch); *Profore#3* (figure of eight configuration with 50% stretch); and *Profore#4* (spiral configuration with 50% stretch).

      OR

   b. Apply Surepress (Convatec) compression bandaging to selected leg from toe to knee, utilising spiral configuration with 50% stretch and 50% overlap.
      (Rationale: Compression is recommended for venous ulceration to reduce venous hypertension and facilitate wound healing (Harris, Brown-Etris & Troyer-Caudle 1996)).
6. Change dressing every seven days.

☐ SECONDARY DRESSING PROTOCOL (MODERATE COMPRESSION – 18-29MMHG)

1. Clean selected leg from toe to knee in a bowl of warm tap water using a clean face washer.
   (Rationale: Water is an appropriate, non-toxic agent for wound cleansing (Glide 1992; Young 1995) and must be applied warm to avoid compromising macrophage activity (Young 1995)).
2. Apply sorbolene cream to selected leg from toe to knee but avoiding all ulcerations.
   (Rationale: Moisturisers are beneficial in improving concomitant venous eczema in VLU (Lopez & Phillips 1998)).
3. Apply primary dressing as follows:
   a. If ulcer exudate amount = *None, Small or Scant* (wound is wet; exudate soils less than 25% of dressing), apply Tricotex (Smith & Nephew) over the entire wound with at least 5mm of Tricotex covering the wound perimeter.
      (Rationale: Tricotex is a non-stick dressing provided with Profore (Smith & Nephew) which prevents adherence of the secondary dressing to the wound).

      OR

   b. If ulcer exudate amount = *Moderate or Large* (wound is saturated; exudate soils 25% or more of dressing), apply Biatain (Coloplast) or Mesorb (SSL) dressing over the entire wound with at least 5mm of dressing covering the wound perimeter.
      (Rationale: an absorbent dressing absorbs excess exudate and prevents maceration of surrounding skin).

      OR

   c. If the surrounding skin is dry, flaking and friable, apply zinc oxide impregnated bandage (Viscopaste, Smith & Nephew) from toe to knee in a spiral configuration with 50% overlap. In addition, every turn of the bandage should fold back on itself in a pleat over the anterior surface of the leg.
      (Rationale: Zinc oxide impregnated bandage is claimed to improve surrounding skin integrity by facilitating collagen synthesis (Linder 1991).
4. Apply Softban (Smith & Nephew) in spiral configuration fifty percent overlap and no stretch.
5. In order of preference, apply moderate level compression therapy as follows:
   a. Apply Modified Profore compression bandaging to selected leg from toe to knee as per manufacturers instructions. All bandages should be applied with 50% overlap and include *Profore #2* (Crepe: spiral configuration with no stretch); and *Profore#4* (Co-Plus: spiral configuration with 50% stretch).

      OR

   b. Apply Lestreflex (Seton Healthcare) compression bandage to selected leg from toe to knee in spiral configuration as per manufacturers instructions.

      OR

   c. Apply appropriate sized graduated Tubigrip (Seton Healthcare) stocking to selected leg from toe to knee.
6. Change dressing once or twice a week.

☐ TERTIARY DRESSING PROTOCOL (NO COMPRESSION)

1. Clean selected leg from toe to knee in a bowl of warm tap water using a clean face washer.
   (Rationale: Water is an appropriate, non-toxic agent for wound cleansing (Glide 1992; Young 1995) and must be applied warm to avoid compromising macrophage activity (Young 1995)).
2. Apply sorbolene cream to selected leg from toe to knee but avoiding all ulcerations.
   (Rationale: Moisturisers are beneficial in improving concomitant venous eczema in VLU (Lopez & Phillips 1998)).
3. Apply primary dressing as follows:
   a. If ulcer exudate amount = *None, Small or Scant* (wound is wet; exudate soils less than 25% of dressing), apply Hydrogel to wound bed as follows: 5 cent size of gel for wounds with a diameter less than 5cm; 10 cent size of gel for wounds with a 6-12cm diameter; 20 cent size of gel for wounds exceeding a 12cm diameter. Apply Melolin (Smith & Nephew) over the entire wound with at least 5mm of Melolin covering the wound perimeter.
   (Rationale: Hydrogels are soothing, decrease pain and decrease dressing adhesion (Crisp & Taylor 2001). Hydrogels also support wound healing by providing a moist environment that promotes epithelial cell growth; rehydrates devitalised tissue; and facilitates debridement (Crisp & Taylor 2001; Glide 1992).

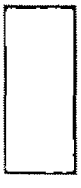
   OR

   b. If ulcer exudate amount = *Moderate or Large* (wound is saturated; exudate soils 25% or more of dressing), apply Biatain or Mesorb over the entire wound with at least 5mm of dressing covering the wound perimeter.
4. Secure dressing with paper tape.
5. Support dressing by applying blue or yellow Tubiform stocking (SSL) ensuring the tubiform covers 10cm above and below dressing.
   (Rationale: stockings provide support for the wound product and also maintain cleanliness of the dressing).
6. Change dressing every two to three days.

Appendix 16



Stage I adverse effect record



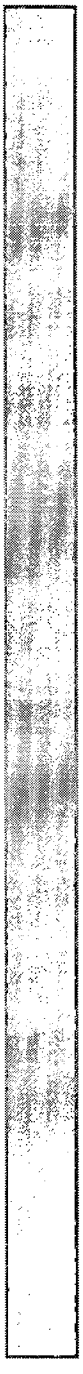
ADVERSE EFFECT RECORD

	Trial Name:	Horsechestnut and venous leg ulcer trial	**ID NUMBER:**
	Chief Investigator:	Mr Matthew Leach	
Commencement Date:	**Organisation:**	University of SA, City East campus.	
Completion Date	**Telephone:**	8302 2071	

Date	Time	Sign or Symptom	Severity of symptom (Mild/moderate/severe) 1 2 3	Duration of symptom (Days/hours/minutes)	Do you believe your symptom was related to the study tablet? (No/Possible/Probable/Definite) 1 2 3 4	Action taken to treat symptom

Note: Please complete record every time a side effect occurs. Please keep all documents in plastic sleeve. Contact chief investigator if adverse effects are moderate or severe.

APPENDIX 17



ADRAC BLUE CARD



Report of Suspected Adverse Reaction to Drugs and Vaccines

*(See **reverse for statement about use of personal information**)*

Patient *(Initials or Record No. only)*

Date of Birth: / /

Sex: M / F Weight: _ _ _kg

Adverse Reaction Description:

Date of Onset of Reaction: / /

All Drug Therapy /Vaccines Prior to Reaction *(please use trade names)*	**Daily Dosage** *(Dose No for vaccines, e.g. 1st DTP etc)*	**Date Begun**	**Date Stopped**	**Reason for Use**

Treatment *(of reaction)* :

Outcome: Recovered ☐ Date of Recovery: / / Not Yet Recovered ☐

Unknown ☐ Fatal ☐ Date of Death: / /

Sequelae: No ☐ Yes ☐ *(describe)*

Severity: Life threatening ☐ Hospitalised ☐ Required a visit to Doctor ☐

Comments *(eg. relevant history, allergies, previous exposure to this drug)*:

Reporting Doctor, Pharmacist, etc:

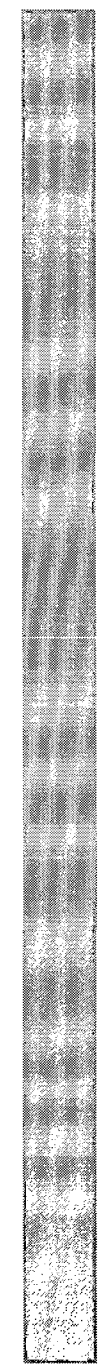
Name: Postcode _ _ _ _

Address:

Signature _____ / /

ADRAC blue card

Appendix 18



Stage I trial termination form

TRIAL TERMINATION FORM

Trial Name:	Horsechestnut and Venous leg Ulcer Trial	**DATE:**	/ /
Chief Investigator:	Mr Matthew Leach	**ID NUMBER:**	- -
Organisation:	University of SA, City East campus.	**Date commenced:**	/ /
Telephone:	8302 2071	**Date completed:**	/ /
		Notify of Rx group:	Yes / No
		Date notified:	/ /

1. Which forms were returned?

	Y	N	
1	☐	☐	2 Adverse effect record
	☐	☐	Medication record

2. Was the bottle of tablets returned?

	Y	N	
1	☐	☐	2

3. What was the final tablet count?

_____ / 170 tablets ☐ %

4. How many days did the subject participate?

_____ / 84 days ☐ %

5. Follow-up questions

a. Which treatment group do you believe you were in?

1 ☐ HCSE
2 ☐ Placebo
3 ☐ Don't know

b. How sure are you that you were in this group?

1 ☐ Almost definite
2 ☐ Fairly sure
3 ☐ Fifty-fifty
4 ☐ Unsure

c. Comments about the treatment or trial?

_____

_____

_____

Declarations

Chief Investigator: I, the chief investigator, have received and reviewed all documentation for completion, and discussed any relevant matters with the participant about the trial:

(signature).....*(date)*.....

Participant: I, the participant, have accurately completed all documentation relevant to the horsechestnut and venous ulcer trial as per details outlined in the participant instruction sheet and by the chief investigator:

(signature).....*(date)*.....

Appendix 19

Stage I ethics approval

University of South Australia

School of Nursing and Midwifery

Educating Professionals • Creating and Applying Knowledge • Serving the Community

12 February 2002

Dear Matthew

Re: Ethics Protocol P294/01 - "The clinical efficiency of Horsechestnut Seed Extract (HSECE) in patients with chronic venous leg ulceration: a double-blind, randomised, placebo-controlled, multicentre trial".

Thank you for providing the additional information requested by the Human Research Ethics Committee in its letter to you dated 12 December 2001.

I am pleased to advise that your ethics protocol is approved.

Please regard this email as official notification of approval and note that as requested I have copied this email to your supervisor, Professor Jan Pincombe.

Please contact me if I may be of further assistance.

I wish you well as you progress through your research.

Regards, Vicki

Vicki Allen
Ethics Officer
Research Services
University of South Australia
Mawson Lakes Campus
Mawson Lakes Boulevard
Mawson Lakes SA 5095
Telephone: + 61 8 8302 3118
Fax: +61 8 8302 3921
Email: vicki.allen@unisa.edu.au

21 April 2004

Dear Matthew,

Re: Application to extend ethics approval a further 12 months - Ethics Protocol P294/01 " The clinical efficiency of Horsechestnut Seed Extract (HCSE) in patients with chronic venous leg ulcerations: a double-blind, randomised, placebo-controlled, multicentre trial"

I am pleased to advise that your ethics approval has been extended. The new expiry date is 1 March 2005. Please note that further applications for extension must be made prior to the expiry date for projects.

Please regard this email as formal notification of extension approval.

Best wishes for your research

Regards,

Vicki Allen
Ethics Officer
Research Services
University of South Australia
Mawson Lakes Campus
Mawson Lakes Boulevard
Mawson Lakes SA 5095
Telephone: + 61 8 8302 3118
Fax: +61 8 8302 3921
Email: vicki.allen@unisa.edu.au

THE EDUCATION CE
Home and Community Healthcare Studies

6 March 2002

31 Flemington Street, Glenside
South Australia 5065
PO Box 247 Glenside
South Australia 5065
Telephone +61 8 8206 0066
Facsimile +61 8 8206 0067
A business unit of Royal District
Nursing Service of South Australia

Mr Matthew Leach
School of Nursing & Midwifery
University of South Australia: City East
North Terrace
Adelaide SA 5000

Dear Mr Leach,

The RDNS Ethics Committee at its meeting on 21 February 2002 considered your protocol –

The clinical efficacy of Horsechestnut Seed Extract (HCSE) in patients with chronic venous leg ulceration: a double-blind, randomised, placebo-controlled, multicentre trial

It was the Committee's opinion that there were no ethical objections to the project being undertaken.

The procedures outlined in the protocol must be adhered to.

The NHMRC Statement on Human Experimentation "Supplementary Note 1" states that Institutional Ethics Committee (IEC) must provide surveillance of research projects until completion of the protocol.

In accordance with these guidelines, approval for the protocol is given on the understanding that you will provide the Committee with a progress report of not more than one page in length on your research by later than 21 February 2002.

Approval has been given for one year and renewal is contingent upon the provision of the progress report.

Yours sincerely,

Julie Black,
Chairperson,
RDNS Ethics Committee.

H/Education/Ethicom/ Approval M Leach 6/3/02.doc

RDNS

Royal District Nursing
Service of SA Inc

ABN 21 588 603 824

Business Centre
31 Flemington Street
Glenside
South Australia 5065
PO Box 247 Glenside
South Australia 5065
Telephone 08 8206 0000
Facsimile 08 8206 0011
www.rdns.net.au
callcentre@rdns.sa.gov.au

7th May 2004

Matthew Leach
Lecturer in Naturopathy
School of Health Sciences
University of South Australia
North Terrace
Adelaide SA 5000

Dear Matthew,

Thank you for your request for approval of extension for the following project:

'The clinical efficacy of Horsechestnut Seed Extract (HCSE) in patients with chronic venous leg ulceration: a double-blind, randomized, placebo-controlled, multicentre trial.'

The Committee has considered your request and has approved the extension for this project due for reporting on 7th May 2005.

Yours sincerely,

Anne Maddock
Chairperson
RDNS Ethics Committee

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ACCREDITED BY THE AUSTRALIAN COUNCIL ON HEALTHCARE STANDARDS

Appendix 20

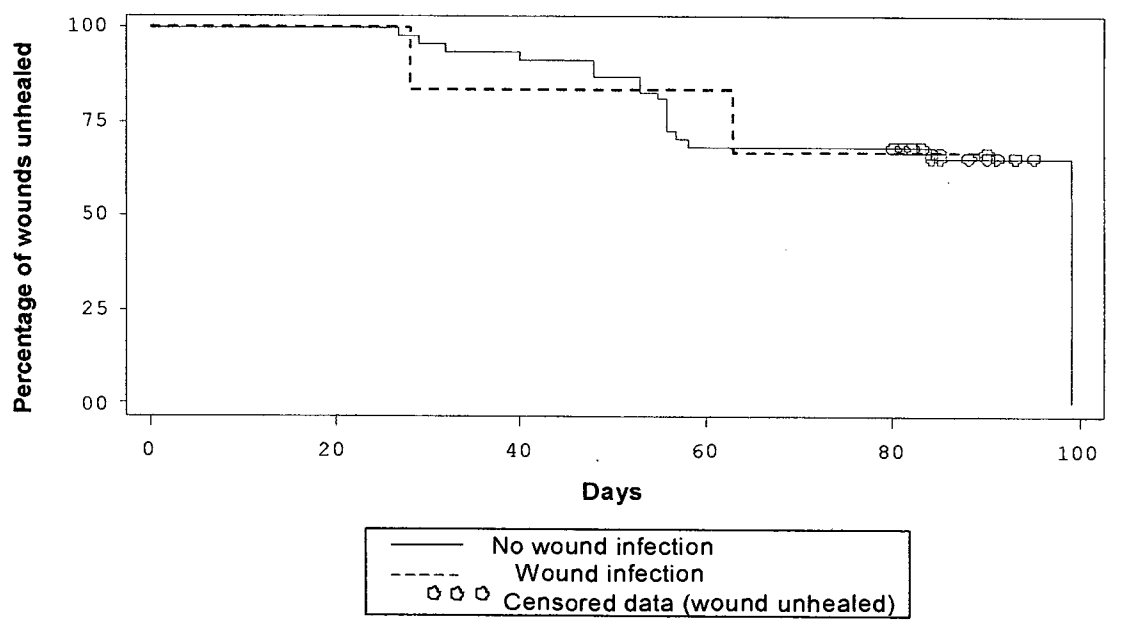
Additional stage I results

Table 20.1: Mean number of medical conditions, surgical procedures and medications in each group at baseline

	HCSE group (n = 27) mean ± SD	Placebo group (n = 27) mean ± SD	95% CI	p value[a]
Mean number of medical conditions	3.11 ± 2.03	3.59 ± 2.29	-1.7 – 0.7	0.422
Mean number of previous surgical procedures	1.93 ± 1.24	1.96 ± 1.40	-0.8 – 0.7	0.924
Mean number of medications currently taking	5.93 ± 3.15	5.81 ± 2.69	-1.5 – 1.7	0.890

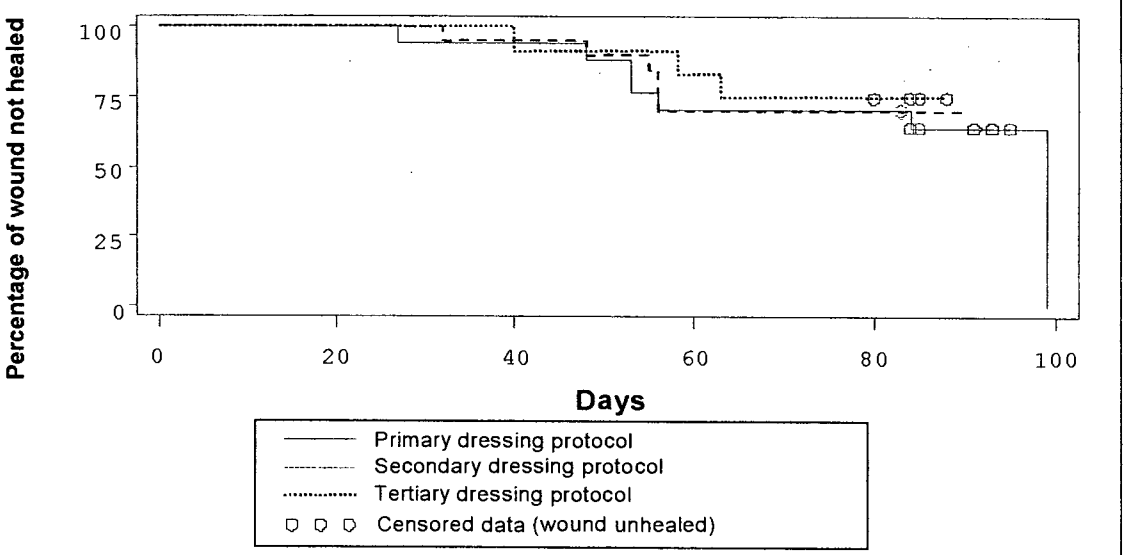
a. p values calculated with the t-test for independent groups..

Figure 20.1: Wound-healing curve showing the number of wounds not healed over the twelve-week trial period for participants with and without wound infection



The Log-rank test found wound infection had no significant effect on the rate of wound healing over time (Log rank=0.002, p=0.966).

Figure 20.2: Wound-healing curve showing the number of wounds not healed over the twelve-week trial period for participants on each dressing protocol



The Log-rank test found the three dressing protocols had no significant effect on the rate of wound healing over time (Log rank=0.43, p=0.810).

Table 20.2: Change in wound dimensions at weeks 0, 4, 8 and 12

	HCSE group median (IQR)	*n*	Placebo group median (IQR)	*n*
Median surface area (mm^2)[a]				
Week 0	204 (682)	27	509 (1414)	27
Week 4	115 (577)	26	290 (655)	25
Week 8	128 (598)	22	239 (1154)	25
Week 12	260 (1167)	16	482 (1425)	20
Median wound volume (mm^3)[a]				
Week 0	193 (1085)	27	236 (1456)	27
Week 4	92 (500)	26	15 (758)	25
Week 8	74 (661)	22	24 (1193)	25
Week 12	159 (1536)	16	282 (1540)	20

RM-ANOVA found no statistically significant difference between groups for log wound surface area (F=0.60, p=0.618) or volume (F=1.72, p=0.167) over time.

Table 20.3: Change in pain score at weeks 0, 4, 8 and 12

	HCSE group mean ± SD	*n*	Placebo group mean ± SD	*n*
Mean pain score (0-10 pain scale)[a]				
Week 0	4.6 ± 3.0	27	4.1 ± 2.7	27
Week 4	3.3 ± 2.9	26	3.4 ± 3.3	25
Week 8	2.8 ± 3.4	22	2.5 ± 2.6	25
Week 12	3.2 ± 3.5	16	3.0 ± 2.7	20

a. RM-ANOVA found no statistically significant difference between groups for the change in pain score over time (F=0.27, p=0.847).

Figure 20.3: Level of wound exudate in the HCSE group at week 0, 4, 8 & 12

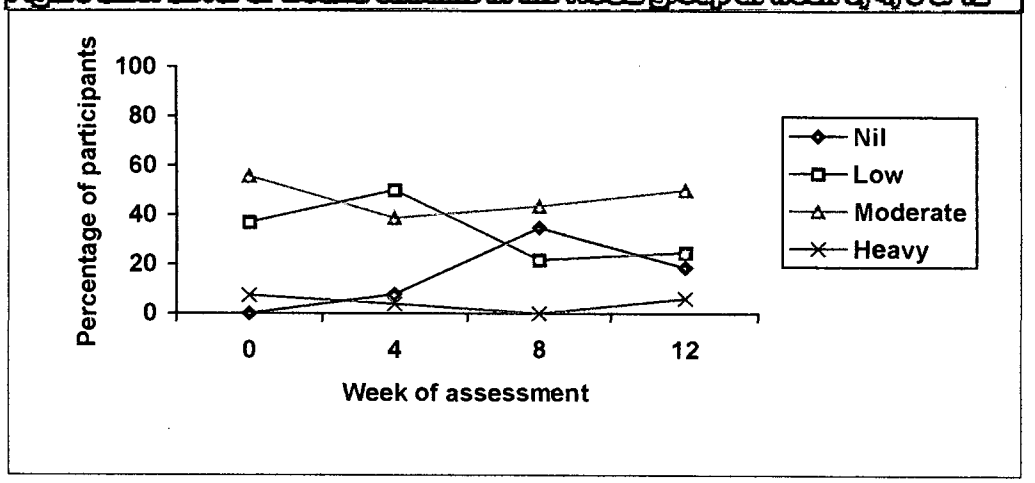


Figure 20.4: Level of wound exudate in the placebo group at week 0, 4, 8 & 12

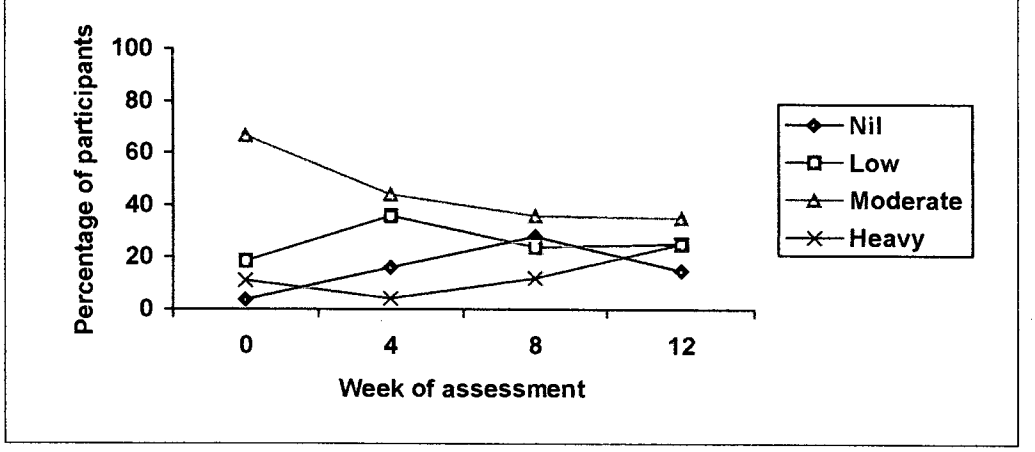


Table 20.4: Change in wound topography at weeks 0, 4, 8 and 12

	HCSE group median (IQR)	*n*	Placebo group median (IQR)	*n*
Median granulation tissue (IQR) (mm^2)[a]				
Week 0	31.0 (597.3)	27	119.0 (510.0)	27
Week 4	47.5 (88.5)	26	188.0 (362.0)	25
Week 8	78.0 (367.8)	22	77.0 (396.0)	25
Week 12	22.5 (44.5)	16	93.0 (330.0)	20
Median sloughy tissue (IQR) (mm^2)[a]				
Week 0	416.5 (653.5)	27	183.0 (1232.0)	27
Week 4	320.5 (699.8)	26	170.0 (277.0)	25
Week 8	300.0 (596.5)	22	285.0 (785.0)	25
Week 12	237.5 (923.8)	16	182.0 (1146.0)	20

a. *RM-ANOVA found no statistically significant difference between groups for the change in log granulation tissue (F=0.63, p=0.594) or log slough over time (F=2.13, p=0.099).*

Table 20.5: Participants primary concern about having a venous leg ulcer

Concern	HCSE group (*n*=27) *n* (%)	Placebo group (*n*=27) *n* (%)
Ulcer pain	13 (48)	9 (33)
Compression bandaging	6 (22)	7 (26)
Compromised lifestyle	5 (19)	4 (15)
Ulcer duration	1 (4)	2 (7)
Impaired mobility	1 (4)	2 (7)
General nuisance	1 (4)	1 (4)
Pruritus	0 (0)	2 (7)

There was no statistically significant difference between groups for the concerns reported about venous ulceration (X^2=3.58, p=0.731).

Appendix 21

Photographs of participant's wounds (see attached CD)

Appendix 22

Additional stage III results

Table 22.1: Adjusted[a] mean weekly staffing costs for treating patients in the HCSE and placebo groups ± SD

Time point	HCSE (*n*=27) $ ± SD	Placebo (*n*=27) $ ± SD	Cost saving[a] $	Difference (95% CI)	p value
Week 0	72.07 ± 43.02	83.66 ± 54.74	-11.58	-38.5 – 15.3	0.159
Week 4	69.50 ± 58.63	79.80 ± 68.70	-10.30	-45.2 – 24.6	0.237
Week 8	46.33 ± 53.66	65.64 ± 62.71	-19.31	-51.2 – 12.6	0.517
Week 12	38.61 ± 37.74	86.23 ± 83.12	-47.62	-82.9 - -12.4	0.004

a. Base-case staffing costs were reduced by fifty percent.

Table 22.2: Adjusted[a] mean total weekly wound management costs for treating patients in the HCSE and placebo groups ± SD

Time point	HCSE (*n*=27) $ ± SD	Placebo (*n*=27) $ ± SD	Cost saving[a] $	Difference (95% CI)	p value
Week 0	187.92 ± 106.04	209.42 ± 154.72	-21.50	-93.9 – 50.9	0.294
Week 4	175.73 ± 119.45	201.39 ± 184.04	-25.66	-110.4 – 59.1	0.207
Week 8	123.64 ± 128.47	169.00 ± 172.80	-45.36	-128.5 – 37.8	0.466
Week 12	105.24 ± 95.42	211.00 ± 204.32	-105.76	-192.8 - -18.7	0.021

a. Base-case staffing costs were increased by fifty percent.

Table 22.3: Adjusted[a] mean weekly dressing costs for treating patients in the HCSE and placebo groups ± SD

Time point	HCSE (*n*=27) $ ± SD	Placebo (*n*=27) $ ± SD	Cost saving[a] $	Difference (95% CI)	p value
Week 0	12.93 ± 9.38	14.04 ± 21.36	-1.11	-10.1 – 7.9	0.441
Week 4	10.58 ± 7.63	13.93 ± 21.84	-3.36	-12.3 – 5.6	0.255
Week 8	8.66 ± 8.87	12.65 ± 21.87	-3.99	-13.1 – 5.1	0.493
Week 12	7.67 ± 9.07	12.85 ± 22.29	-5.17	-14.5 – 4.1	0.342

a. Base-case dressing costs were reduced by fifty percent.

Table 22.4: Adjusted[a] mean total weekly wound management costs for treating patients in the HCSE and placebo groups ± SD

Time point	HCSE (*n*=27) $ ± SD	Placebo (*n*=27) $ ± SD	Cost saving[a] $	Difference (95% CI)	p value
Week 0	247.07 ± 141.63	279.04 ± 191.42	-31.97	-123.9 – 60.0	0.202
Week 4	234.65 ± 176.53	267.26 ± 234.71	-32.60	-146.0 – 80.8	0.213
Week 8	161.32 ± 174.66	222.07 ± 217.07	-60.75	-168.3 – 46.8	0.489
Week 12	136.18 ± 125.76	284.39 ± 271.67	-148.21	-263.8 - -32.6	0.007

a. Base-case dressing costs were increased by fifty percent.

Appendix 23

Stage IV questionnaires

HORSECHESTNUT AND VENOUS ULCER TRIAL – HAVLUT
STAGE IV PRACTITIONER QUESTIONNAIRE

ankyou for your support in the Horsechestnut and Venous Leg Ulcer Trial (HAVLUT). The following questionnaire will identify rrent opinion on natural medicine, systemic venous therapy and Horsechestnut Seed Extract (HCSE). Your support in completing s questionnaire is important and greatly appreciated. For each question, please indicate how you feel at the time by ticking inside e box only to prevent misinterpretation. Please also try to avoid answering 'unsure' unless you really are uncertain. Some questions o ask for further comments that you are encouraged to write. This questionnaire is estimated to take less than eight minutes to mplete. *Please return the completed questionnaire using the attached reply paid envelope by* ***Monday 14th April 2004***. Thankyou.

ATURAL MEDICINE /THERAPIES

tural medicine is the use of any practice that supports the healing process by methods other than pharmaceutical medicines and gery. Natural medicine includes massage, reflexology, homeopathy, meditation, acupuncture, aromatherapy, relaxation, ch/spiritual healing, herbal medicine and nutrition.

Please answer for each therapy, whether you believe the therapy is generally safe, effective, and should be incorporated into instream medicine:

	...is a safe therapy	**...is an effective therapy**	**...should be incorporated into mainstream medicine**
Massage	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Herbal medicine	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Vitamin/Mineral supplements	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Homeopathy	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Aromatherapy	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Meditation / relaxation	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Acupuncture / acupressure	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Touch or spiritual healing	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree

I currently recommend the following therapies to patients with venous leg ulcers: (please tick only one box per therapy)

	Often (daily)	**Frequently (weekly)**	**Sometimes (monthly)**	**Occasionally (infrequently)**	**Never**
Massage					
Herbal medicine					
Vitamin/Mineral supplements					
Homeopathy					
Aromatherapy					
Meditation / relaxation					
Acupuncture / acupressure					
Touch or spiritual healing					

2b. ***Please explain why you do (including names of specific treatments) or do not recommend any of the above therapies to patients with venous leg ulcers?***.....

.....

will consider recommending the following therapies to patients with venous leg ulcers in future: (please tick only one box herapy)

	Strongly Agree	**Agree**	**Unsure**	**Disagree**	**Strongly Disagree**
Massage					
Herbal medicine					
Vitamin/Mineral supplements					
Homeopathy					
Aromatherapy					
Meditation / relaxation					
Acupuncture / acupressure					
Touch or spiritual healing					

3b. *Please explain why you may (including names of specific treatments) or may not recommend the use of any of the above therapies in future:* .....

.....

YSTEMIC VENOUS THERAPY

n alternative approach to conventional venous ulcer management is Systemic Venous Therapy (SVT) with venotonic agents, which ossess anti-exudative and oedema-protective properties. Systemic Venous Therapy is often administered orally, in contrast to topical erapy which is applied directly to the wound bed. Examples of Systemic Venous Therapy are Paroven, Proflo & Horsechestnut Seed.

. **I believe systemic venous therapy is a suitable treatment option for patients with venous leg ulcers:** (please tick one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

4b. *Please explain why systemic venous therapy is a suitable or unsuitable treatment for venous leg ulcers:* .....

.....

. **I currently recommend systemic venous therapy to patients with venous leg ulcers:** (please tick only one box)

Daily ☐ Weekly ☐ Monthly ☐ Infrequently ☐ Never

5b. *Please explain why you do (including generic names) or do not recommend systemic* **venous** *therapy to patients with venous leg ulcers:* .....

. **I will consider recommending systemic venous therapy to patients with venous leg ulcers in future:** (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

6b. *Please explain why you would or would not use systemic* **venous** *therapy in future:* .....

.....

ORSECHESTNUT SEED EXTRACT (HCSE)

e such systemic venous therapy is the herbal preparation Horsechestnut Seed Extract (HCSE). Since 1960, numerous studies have plored the use of HCSE in venous insufficiency, leg oedema, varicose veins, haematomas and deep vein thrombosis (DVT). Based the information you have been provided on the Horsechestnut trial:

believe HCSE is safe: (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

believe HCSE is effective in managing venous symptoms (for example leg oedema, leg pain) : (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

I believe HCSE should be incorporated into mainstream medicine: (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

9b. *Please explain why HCSE should or should not be incorporated into mainstream medicine:*. .....

.....

I currently recommend HCSE to patients with venous leg ulceration: (please tick only one box)

Daily ☐ Weekly ☐ Monthly ☐ Infrequently ☐ Never

10b. *If you currently recommend HCSE, from whom or what did you first find out about HCSE?* .....

.....

I believe HCSE is a suitable treatment option for venous leg ulceration: (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

11b. *Please explain why you do/do not believe HCSE is a suitable treatment option for clients with venous leg ulcers:*

.....

12a. Based on the information provided for the Horsechestnut trial, I would recommend HCSE to clients with venous leg ulcers: (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

12b. *Please explain why you would/would not currently recommend HCSE to clients with venous leg ulcers:* .....

.....

13a. If the results of the Horsechestnut trial find HCSE to be significantly more effective than placebo in improving the rate of venous ulcer healing, I would recommend HCSE to patients with venous leg ulceration: (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

13b. *Please explain why you would/would not recommend HCSE to clients with venous leg ulcers:* .....

.....

.....

DEMOGRAPHICS

14. Please tick the box which indicates your age-group:

19 and under	☐	40-49 years
20-29 years	☐	50-59 years and over
30-39 years	☐	60 years and over

15. Please tick the box indicating your Gender:

Male ☐ Female

16. What position do you currently hold?

EN	☐	CNC
RN	☐	General / Medical practitioner
CN	☐	Other (please specify).....

17. How many years of nursing/medical experience have you had in total since being enrolled / registered?

1-2	☐	7-8
3-4	☐	9-10
5-6	☐	11 years and over

18. How frequently do you treat patients with venous leg ulcers?

Daily ☐ Weekly ☐ Monthly ☐ Infrequently ☐ Never

19. Were you involved in the care of a client whom participated in the Horsechestnut & Venous Leg Ulcer Trial (HAVLUT)?

Yes ☐ Unsure ☐ No

20. Please write down your home post-code?

|___|___|___|___|

Thankyou for your time and valuable input in completing this questionnaire.

Please return the completed questionnaire using the attached reply paid envelope

---

Chief investigator: Mr Matthew Leach RN. BN(Hons). ND.
PhD Candidate / Chief Investigator
School of Nursing & Midwifery
University of South Australia: City East
North Terrace Adelaide SA 5000
Tel: (08) 8302 1020 Mob: [redacted] Fax: (08) 8381 1821

HORSECHESTNUT AND VENOUS ULCER TRIAL – HAVLUT
STAGE IV PARTICIPANT QUESTIONNAIRE

Thankyou for your support in the Horsechestnut and Venous Leg Ulcer Trial (HAVLUT), which examined the use of Horsechestnut Seed Extract in treating venous leg ulcers. The following questionnaire will identify your opinion on natural medicine, venotonics and Horsechestnut Seed Extract (HCSE). Your support in completing this questionnaire is important and greatly appreciated. For each question, please indicate how you feel at the time by ticking inside one box only to prevent misinterpretation. Please also try to avoid answering 'unsure' unless you really are uncertain. Some questions also ask for further comments that you are encouraged to write. This questionnaire is estimated to take less than eight minutes to complete. *Please return the completed questionnaire using the attached reply paid envelope by* ***Monday 4th April 2004***. Thankyou.

NATURAL MEDICINE

Natural medicine is the use of any practice that supports healing by methods other than medically prescribed medicines and surgery. Natural medicine includes massage, reflexology, homeopathy, meditation, acupuncture, aromatherapy, relaxation, touch/spiritual healing, herbal medicine and nutrition.

1. Please answer for each therapy, whether you believe the therapy is generally safe, effective, and should be incorporated into mainstream medicine:

	...is a safe therapy	...is an effective therapy	...should be incorporated into mainstream medicine
Massage	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Herbal medicine	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Vitamin/Mineral supplements	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Homeopathy	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Aromatherapy	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Meditation / relaxation	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Acupuncture / acupressure	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree
Touch or spiritual healing	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree	☐Agree ☐Unsure ☐Disagree

2a. I have used or currently use the following therapies for my leg ulcer: (please tick only one box per therapy)

	Often (daily)	Frequently (weekly)	Sometimes (monthly)	Occasionally (infrequently)	Never
Massage					
Herbal medicine					
Vitamin/Mineral supplements					
Homeopathy					
Aromatherapy					
Meditation / relaxation					
Acupuncture / acupressure					
Touch or spiritual healing					

2b. ***Please explain why you used (including names of specific treatments) or avoided the use of any of the above therapies?***.....
.....

. **I would consider using the following therapies for my leg ulcer:** (please tick only one box per therapy)

	Strongly Agree	Agree	Unsure	Disagree	Strongly Disagree
Massage					
Herbal medicine					
Vitamin/Mineral supplements					
Homeopathy					
Aromatherapy					
Meditation / relaxation					
Acupuncture / acupressure					
Touch or spiritual healing					

3b. ***Please explain why you might use (including names of specific treatments) or avoid the use of any of the above therapies?*** .....

.....

ENOTONICS

alternative approach to treating leg ulcers is the use of venotonic agents. These agents possess vein toning effects and -swelling reducing properties. Venotonics are often administered by mouth, and include Paroven, Proflo, rsechestnut Seed Extract.

. **I believe venotonics are a suitable treatment option for my leg ulcer?** (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

4b. ***Please explain why venotonics are a suitable or unsuitable treatment for your leg ulcer:*** .....

.....

. **I have used or currently use venotonics for my leg ulcer?** (please tick only one box)

Daily ☐ Weekly ☐ Monthly ☐ Infrequently ☐ Never

5b. ***If you have used venotonics for your leg ulcer, what was the name of the therapy(s)?***

.....

. **I would consider using venotonics for my leg ulcer in future?** (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

6b. ***Please explain why you would or would not use venotonics in future:*** .....

.....

RSECHESTNUT SEED EXTRACT (HCSE)

e such venotonic is Horsechestnut Seed Extract (HCSE). Since 1960, numerous studies have explored the use of HCSE leg swelling, varicose veins, bruising and deep vein thrombosis (DVT). Based on the information you have been vided on the Horsechestnut trial:

believe HCSE is safe? (please tick only one box)

trongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

believe HCSE is effective for managing symptoms of poorly functioning veins (For example leg swelling, leg n)? (please tick only one box)

trongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

I believe HCSE should be incorporated into mainstream medicine? (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

9b. *Please explain why HCSE should or should not be incorporated into mainstream medicine:*.....

.....

. I currently use HCSE for my leg ulcer? (please tick only one box)

Daily ☐ Weekly ☐ Monthly ☐ Infrequently ☐ Never

10b. *If you currently use HCSE, who recommended HCSE to you?* .....

.....

. I believe HCSE is a suitable treatment option for my leg ulcer? (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

11b. *Please explain why you do/do not believe HCSE is a suitable treatment option for your leg ulcer?*

.....

. Based on the information provided for the Horsechestnut trial, I would consider using HCSE for an existing future leg ulcer? (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

12b. *Please explain why you would/would not currently consider using HCSE for your leg ulcer?* .....

.....

. If the results of the Horsechestnut trial find HCSE to be effective in improving ulcer healing, I would consider ng HCSE for an existing or future leg ulcer? (please tick only one box)

Strongly Agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly Disagree

13b. *Please explain why you would/would not consider using HCSE for your leg ulcer in future?* .....

.....

.....

MOGRAPHICS

Please tick the box which indicates your age-group:

19 years and under	☐	50-59 years
20-29 years	☐	60-69 years
30-39 years	☐	70-79 years
40-49 years	☐	80 years and over

Please tick the box indicating your Gender:

Male
Female

Did you participate in the recent Horsechestnut & Venous Leg Ulcer Trial (HAVLUT)?

Yes
No

Please write down your home post-code?

|___|___|___|

Thankyou for your time and valuable input in completing this questionnaire.

Please return the completed questionnaire using the attached reply paid envelope

---

Chief investigator: Mr Matthew Leach RN. BN(Hons). ND.
PhD Candidate / Chief Investigator
School of Nursing & Midwifery
University of South Australia: City East
North Terrace Adelaide SA 5000
Tel: (08) 8302 1020 Mob: [redacted] Fax: (08) 8381 1821

Appendix 24

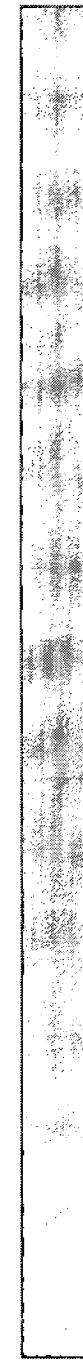
Stage IV questionnaire log

Stage IV Questionnaire Log

Study Name:	Stage IV feasibility study
Chief Investigator:	Mr Matthew Leach
Organisation:	University of SA, City East campus.
Telephone:	8302 1020

Participant Name	Code	Date of Dispatch	Date Received	Date of First Follow-up	Date Received	Date of Second Follow-up	Date Received	Received

Appendix 25



Stage IV ethics approval



University of South Australia

Human Research Ethics Committee
Telephone: + 618 8302 3118
Facsimile: + 618 8302 3921
Email: Vicki.Allen@unisa.edu.au

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19 December 2002

Matthew Leach
20 Marrington Circuit
MORPHETT VALE SA 5162

Dear Matthew

Thank you for submitting your ethics protocol **(P334/02) - Horsechestnut and Venous Leg Ulcer Trial Stage II: Utilisation and attitudes towards natural therapies, systemic therapy & HCSE.**

The University's Human Research Ethics Committee (HREC) was pleased to consider this at its meeting on 16/12/02 and to approve it, subject to you:

1. Submitting a Consent Form for participants who are not anonymous given their previous involvement in Stage 1 of this research.
2. Amending the Information Sheet by redrafting the second paragraph. Currently it implies that the results of the trial were positive and that participants are aware of the results. Also, removing all references to anonymity and including HREC contact details (refer Ethics Officer details below).
3. Obtaining written approval from the organisations where the research will be undertaken.

Please note that HREC considered medical advice in its assessment of this protocol.

So that we can expedite approval, please submit **one** copy of the information requested above to:

Vicki Allen
Ethics Officer
Research Services
Mawson Lakes Campus

Email Vicki.allen@unisa.edu.au
phone +61 8 8302 3118 fax +61 8 8302 3921

Under the national guidelines, you must not begin your research before receiving final approval. Once you have submitted the necessary amendments, and they have been accepted, your approval will be finalised and you may commence your research.

Ethics approval is always made on the basis of a number of conditions detailed in the attachment; it is important that you are familiar with, and abide by, these conditions. It is also essential that you conduct all research according to UniSA guidelines, which can be found at http://www.unisa.edu.au/orc/ethics/index.htm. These guidelines should assist you with the formulation of necessary papers such as the information sheet and the consent form.

We look forward to receiving your amendments in the near future. In the meantime, please contact Vicki Allen if you have any questions

Yours sincerely

Associate Professor Eimear Muir-Cochrane
Chair, HREC

Enc
Cc Professor Jan Pincombe (NRC – City East), Professor David Wilkinson (HSO – City East)

RDNS

Royal District Nursing
Service of SA Inc

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RDNS Fleet Management

Mr Matthew Leach
20 Marrington Circuit
MORPHETT VALE SA 5162

Dear Matthew,

In response to your submission dated the 30 January 2003, regarding your resubmission for ***"Horsechestnut and Venous Leg Ulcer Trial: Stage II"***, the Ethics Committee unanimously agreed that the concerns had been well addressed.

On behalf of the Ethics Committee I wish you all the best with your research.

Yours sincerely,

Anne Maddock
Chairperson, RDNS Ethics Committee
Quality Manager

ACCREDITED BY THE AUSTRALIAN COUNCIL ON HEALTHCARE STANDARDS

APPENDIX 26

STAGE IV INFORMATION SHEET

QUESTIONNAIRE INFORMATION SHEET



University of
South Australia

Division of Health Sciences ◆ School of Nursing and Midwifery

'Horsechestnut and Venous Leg Ulcer Trial (Stage IV)'

Researcher: Mr Matthew Leach RN. BN(Hons). ND.

The stage I Horsechestnut and venous leg ulcer trial (HAVLUT) is now complete, which examined the healing effect of oral Horsechestnut Seed Extract (HCSE) on venous leg ulcers. Your support in the clinical trial was greatly appreciated.

The results of HAVLUT are still being processed. However, to determine whether the use of HCSE may be supported in future clinical practice, I am asking all associated health care professionals (#### employed clinical nurse consultants, clinical nurses, registered nurses and enrolled nurses; and medical practitioners of trial participants) and stage I participants/non-participants to complete the attached questionnaire. It is important that others do not influence your responses. You are under no obligation to complete the questionnaire, however your support would improve the clinical application of the research findings. These findings will be published in my PhD thesis and future journal articles.

The twenty short questions are estimated to take less then eight minutes to complete. Please do not write your name or any other information that may identify yourself. The information contained in this questionnaire is considered confidential. This data will not be used for any other purpose except for this study. All data will be retained for a minimum of seven years to comply with Australian Freedom of Information legislation. This data will be stored in secured compactors at the University of South Australia.

Once you have completed the questionnaire, please return the questionnaire using the attached reply paid envelope by **Monday 14th April 2004**.

Please contact Matthew Leach on [redacted] if you have any questions relating to this study. Any concerns relating to the conduct of this study can be addressed to the Ethics Officer of the University of SA Human Research Ethics Committee, Ms Vicki Allen, on 8302 3118. Thank-you for your interest and support.

School of Nursing & Midwifery
University of South Australia: City East
North Terrace Adelaide SA 5000
Tel: 8302 1020
Mob: 0402 782 374

Appendix 27

Stage IV consent form

STAGE IV CONSENT FORM

Project Title: **Stage IV feasibility study**

Researcher's name: **Mr Matthew Leach**

Supervisor names: **Professor Jan Pincombe & Dr Gigi Foster**

- I have received information about this research project.
- I understand the purpose of the research project and my involvement in it.
- I understand that I may withdraw from the research project at any stage.
- I understand that while information gained during the study may be published, I will not be identified and my personal results will remain confidential.

Name of participant.....

Signed ..... **Date** .....

I have provided information about the research to the research participant and believe that he/she understands what is involved.

Researcher's signature..... **Date** .....

Appendix 28

Additional stage IV results

Table 28.1: Correlations between client attitude and use of venotonic agents, and attitude and use of HCSE (n=50).

	Venotonics are suitable for VLU treatment	Have used venotonics for VLU	Would consider venotonics for future VLU
HCSE is safe	p<0.001, T=0.599	p=0.007, T=0.428	p<0.001, T=0.620
HCSE is effective	p<0.001, T=0.778	p=0.002, T=0.406	p<0.001, T=0.650
HCSE should be incorporated into mainstream medicine	p<0.001, T=0.724	p=0.071, T=0.247	p<0.001, T=0.642
Currently use HCSE for VLU	p=0.001, T=0.466	p=0.001, T=0.399	p<0.001, T=0.646
HCSE is a suitable VLU treatment	p<0.001, T=0.799	p=0.065, T=0.247	p<0.001, T=0.737
Would consider using HCSE for VLU based on current information	p<0.001, T=0.792	p=0.004, T=0.417	p<0.001, T=0.828
Would consider using HCSE for VLU based on positive trial results	p<0.001, T=0.719	p=0.075, T=0.321	p<0.001, T=0.690

Table 28.2: Correlations between nurse attitude on the use of venotonics and nurse attitude and use of HCSE (n=39).

	Venotonics are suitable for VLU treatment	Currently recommend venotonics for patients with VLU	Would consider recommending venotonics in future for VLU
HCSE is safe	p<0.001, T=0.662	p<0.001, T=0.433	p=0.001, T=0.456
HCSE is effective	p<0.001, T=0.662	p=0.002, T=0.396	p<0.001, T=0.577
HCSE should be incorporated into mainstream medicine	p<0.001, T=0.713	p=0.007, T=0.350	p<0.001, T=0.613
Currently recommend HCSE for VLU	p<0.001, T=0.613	p=0.002, T=0.463	p<0.001, T=0.518
HCSE is a suitable VLU treatment	p<0.001, T=0.630	p=0.021, T=0.311	p<0.001, T=0.538
Consider recommending HCSE for VLU based on current information	p<0.001, T=0.724	p<0.001, T=0.6	p<0.001, T=0.699
Consider recommending HCSE for VLU based on positive trial results	p<0.001, T=0.664	p<0.001, T=0.570	p<0.001, T=0.534

APPENDIX 29

PUBLICATIONS

Aesculus hippocastanum

Matthew Leach RN BN(Hons) ND
20 Marrington Circuit, Morphett Vale SA 5162
Email soulmate@picknowl.com.au or
leamj003@students.unisa.edu.au

Aesculus hippocastanum, also known as horsechestnut, Spanish chestnut, buckeye and conqueror tree, is a tree from the Hippocastanaceae family. Most parts of horsechestnut are utilised medicinally, however the part receiving the most attention is the seeds of horsechestnut. Contained within these seeds is the main constituent aescin, which is believed to be responsible for significant venotonic activity, including anti-inflammatory, anti-exudative, anti-enzymatic, anti-edema and antioxidant effects. Multiple clinical trials of horsechestnut seed extract (HCSE) show significant efficacy in the management of chronic venous insufficiency (CVI) with only mild and transient adverse effects. Consequently, the management of CVI with HCSE has received support from the German commission E monographs.

Key Words: *Aesculus hippocastanum*; horsechestnut; venotonic; HCSE.



Fruit capsule and seed of Aesculus hippocastanum

Aesculus is derived from the Latin *esca*, meaning nutrient, whilst *hippocastanum* comes from the Greek *ippos* and *castanon*, meaning horse and chestnut respectively (Bombardelli 1996). Whilst the integration of the terms nutrient and chestnut are appreciated, the adoption of the word horse is unclear. Some authorities suggest that horsechestnut may have resembled horse eyes, whilst others argue that horsechestnut was administered for the treatment of various equine illnesses (Bombardelli 1996; Krapp 2001).

Horsechestnut is both a tree and a shrub, located in the temperate regions of Asia, Europe and North America (Krapp 2001). The horsechestnut tree can grow up to thirty metres in height. Its bark is grey-brown in colour, and its thick widely spreading branches have wart-like eruptions and horseshoe-like markings. The palmate leaves are dark green with serrated edges, growing up to thirty centimetres in length (Krapp 2001). The white and spotted pink flowers are both clustered and irregularly shaped (Bruneton 1995). The five-centimetre polished nut is ovoid, fleshy and oily (Bruneton 1995), and encapsulated by a spiny, toxic, light-green capsule (Krapp 2001). Each capsule may contain up to four large seeds (Bombardelli 1996).

Most aerial parts of the tree are utilised medicinally, including the bark, leaves and seeds (Lininger 1999). However it is recommended that only the seeds of *Aesculus hippocastanum* be used therapeutically as the extracts of horsechestnut bark, leaves and flowers are not only poorly characterised (Wilkinson 1999), but their efficacy has yet to be demonstrated (Blumenthal 1998).

Horsechestnut has traditionally been administered for its circulatory tonic effects, more particularly, its ability to enhance venous tone and strength (Hoffmann 1996). Phlebitis, haemorrhoids, ecchymosis (Hoffmann 1996), varicose veins (Hey 1996), prevention and treatment of deep vein thrombosis (DVT) and pathological conditions with localised oedema (Bone 1987), have traditionally been treated with the internal administration of horsechestnut, whereas the external application has been limited to the management of varicose ulceration, varicose veins and bruises (Krapp 2001). Despite these indications the German commission E monographs only advocate horsechestnut for the

management of chronic venous insufficiency, or CVI, where leg oedema, pruritis, cramps, heaviness and pain are present (Blumenthal 1998).

Chemistry

The main active constituent of *Aesculus* seed is a collection of triterpenoid saponins known as aescin (Wohlmuth 1999). The true level of aescin in horsechestnut is poorly defined, ranging from 3-13% (Bone 1987) to 24-28% (Wohlmuth 1999). The aescin component is comprised of alpha-aescin and beta-aescin. The ß-aescin component contains over thirty derivatives of the triterpenoids barringtogenol C and protoaescigenin, which are primarily located in the seed cotyledons (Wilkinson 1999). Other constituents of horsechestnut seeds include starch, flavones, amino acids, protein, fatty oil, water, sugars and vitamins (Wohlmuth 1999). Of these constituents, the flavonoids such as the oligomeric proanthocyanidins (Bruneton 1995), are argued to be somewhat responsible for the venotonic effects of horsechestnut.

Pharmacodynamics

Since the mid-nineteenth century the chemical composition of horsechestnut has been investigated, however it was not until the early 1950's when experimental studies on horsechestnut began to truly develop. From these studies horsechestnut has been claimed to possess anti-inflammatory, anti-exudative, anti-enzymatic, anti-edema, anticoagulant, venotonic, antioxidant and hypoglycaemic activity. However many of these experimental studies remain un-substantiated by clinical findings.

Anti-inflammatory activity

The anti-inflammatory effects of different components of the aescin complex of *Aesculus hippocastanum* seeds was examined in vivo using a murine model (Matsuda 1997). Oral aescin Ia, Ib, IIa and IIb (50-200mg/kg) inhibited acetic acid and histamine induced vascular permeability in a dose dependent manner. Other than Ia, all aescins also dose-dependently (50-200 mg/kg) inhibited serotonin induced vascular permeability. In addition all aescins (50-20 mg/kg) inhibited carageenin-induced paw edema and compound 48/80-induced scratching behaviour. The authors concluded that aescins inhibit acute inflammatory activity possibly through anti-histaminic or anti-serotoninergic pathways (Matsuda 1997). However the effect on other chemical mediators needs further examination to elucidate this theory.

Hiai, Yokohama and Oura (1981) examined whether the anti-inflammatory effect of aescin was a result of increased corticosterone secretion using a murine model. A significant increase in adrenocorticotropic hormone (ACTH), corticosterone and glucose levels with a corresponding decrease in insulin levels followed the intraperitoneal administration of ß-aescin (5 mg/kg). This effect was less apparent when administered orally. Hexamethonium partially suppressed aescin induced glucose and corticosterone levels, suggesting that these effects may be the result of adrenalin release. The absence of inhibition with diphenhydramine excluded histamine as an alternative cause of aescin-induced cortisone and glucose levels. Thus the authors concluded that aescin stimulates the anterior pituitary to release ACTH which then acts on the adrenal cortex to synthesise and release corticosterone. However the exact pathway of pituitary stimulation remains poorly elucidated.

Anti-enzymatic activity

In vitro research found the saponin aescin to exert greater inhibition of hyaluronidase than two other plant saponins in a dose dependent manner (50-300 µM concentration). The anti-hyaluronidase activity may result from non-competitive inhibition via a denaturing effect on the protein-binding site. Aescin however did not exert any anti-elastase activity. The authors suggested that the remarkable venotonic activity of aescin may be attributed to an inhibition of other key enzymes such as collagenase and ß-glucoronidase (Facino 1995).

Anti-oxidant activity

In a study examining the active oxygen scavenging activity of 65 plant extracts (Masaki 1995), *Aesculus hippocastanum* (5 µg/ml) was the second most active superoxide anion scavenger, next to witch hazel (*Hamamelis virginiana*). This in vitro activity was more potent than the scavenging ability of both ascorbic acid and alpha-tocopherol. Of all extracts *Aesculus hippocastanum* was of equal strength in scavenging hydroxyl radicals but was less effective than ascorbic acid. *Aesculus hippocastanum* was the third most effective

extract in inhibiting singlet oxygen generation, but was once again less effective than ascorbic acid (Masaki 1995). Although all plant extracts inhibited lipid peroxidation, *Aesculus hippocastanum* possessed the greatest antioxidant activity.

In relation to cell protective activity, *Aesculus hippocastanum* increased fibroblast survival ratio by almost four-fold which was more efficacious than any other extract. Thus *Aesculus hippocastanum* was not only a potent active oxygen scavenger in vitro, but also a powerful cell protective agent (Masaki 1995).

Hypoglycaemic activity

The effects of horsechestnut seed extract (HCSE) saponins on glycaemic control were examined in vivo using a murine model (Yoshikawa 1996). When administered orally the saponin fraction (200 mg/kg) exerted weaker hypoglycaemic activity than that of aescin Ia, Ib, IIa and IIb (100 mg/kg). Since the more complex saponin extract exerted a different degree of effect from the individual aescin components, it cannot yet be determined how other components in HCSE may interact and influence glycaemic control.

Pharmacokinetics

The intestinal absorption of aescin is as low as 10% (Markwardt 1996), although this may be improved by crystal micronisation or salt formation (Bruneton 1995). In spite of this it is unclear whether other components of HCSE may influence the absorption of aescin. Pharmacokinetic studies in a murine model show that oral aescin is absorbed into the bloodstream with a maximum concentration at one hour (Bombardelli 1996). The kidneys excrete 40% of the absorbed aescin (Bombardelli 1996) whilst the bile eliminates the remaining 60% (Markwardt 1996).

Clinical Studies

Ecchymosis

In a randomised placebo controlled double blind trial on 71 volunteers, experimentally induced hematomas were treated with either 2% aescin gel or placebo gel. Reductions in hematoma tenderness were more significant in the aescin gel group than the placebo group (Calabrese 1993). Despite this, a decrease in tenderness may not necessarily reflect an improvement in hematoma resolution. Secondly the addition of lavender and orange oil in the gel may potentially increase the efficacy of the aescin gel over the placebo gel due to a synergistic effect. Thus further investigation on the efficacy of aescin gel is required to elucidate these findings.

Chronic Venous Insufficiency (CVI)

In a double blind randomised placebo controlled crossover trial, twenty-two patients with CVI were administered a single 600 mg dose of HCSE, standardised to 100 mg aescin (Bisler 1986). After three hours, transcapillary filtration decreased by 22% in comparison to a slight increase in the placebo group ($p=0.006$). Although there was a small decline in intravascular volume in the HCSE group, this effect was not statistically significant. The reduction in transcapillary filtration may suggest how HCSE is beneficial in the management of edema and the associated sequelae of symptoms of CVI.

In a parallel double blind randomised placebo controlled trial, forty patients with chronic deep vein incompetence were administered either HCSE (standardised to 75 mg aescin) or a matching placebo twice daily during a six-week period with a one-week run-in period (Diehm 1992). Results showed HCSE to be more effective than placebo in reducing leg volume both before ($p<0.01$) and after ($p<0.01$) edema provocation, thus not only reducing edema but also preventing its re-occurrence. A decrease in ankle and calf circumference, phlebodynamic changes and a decrease in leg heaviness, fatigue, pruritis and paresthesias corroborated these findings. The authors concluded that HCSE is a useful adjunct to compression therapy in the treatment of edema (Diehm 1992).

A systematic review of horsechestnut seed extract, found thirteen double blind randomised controlled trials (RCT) of which eight were placebo controlled and five controlled against reference medications (Pittler 1998). All studies found horsechestnut (standardised to 100-150 mg aescin daily) to be superior to placebo whilst being equally effective to reference medications such as O-(ß-hydroxyethyl) rutosides. The outcome measures of these trials were a reduction in lower leg volume, calf and ankle circumference, pain, pruritis and leg fatigue (Pittler 1998). Only one study found HCSE to be superior to O-(ß-

hydroxyethyl) rutosides. This may have been attributed to a higher aescin dose (75 mg) used in this study over comparative trials (50 mg). Commenting on this systematic review, Bielanski and Piotrowski (1999) emphasise that although HCSE may be an effective treatment for CVI in the short term (less than twelve weeks), future studies need to confirm the long term efficacy and safety of HCSE in CVI.

In relation to any potential long term benefits of HCSE, one RCT found that at six weeks follow up there was no significant difference in mean leg volume when compared to post treatment values (Pittler Ernst 1998).



Large upright flower of Aesculus hippocastanum

Toxicology

The seeds of horsechestnut possess low acute and chronic toxicities (Bone 1987). Whilst the fresh fruit and green pericarp of horsechestnut are toxic, heat destroys the toxin, explaining why the dried seeds of horsechestnut are safe (Ozarko 2001). Pilot toxicology studies show the oral LD_{50} of HCSE in mice, rats, rabbits and dogs to be 990 mg/kg, 2150 mg/kg, 1530 mg/kg and 130 mg/kg respectively (Blumenthal 1998).

Adverse effects

HCSE is a well tolerated herb (Hitzenberger 1989) with few documented adverse effects. The German Commission E monographs cite isolated cases of mild and infrequent pruritis, nausea and gastric complaints as side effects associated with oral HCSE (Blumenthal 1998). The adverse drug reactions (ADR) documented in eight RCT were pruritis, headache, nausea and gastrointestinal tract symptoms in a collective sample of 859. The frequencies of these ADR were between 0.9% and 3%. In three of these studies, ADR frequency to HCSE was not significantly different from placebo in a collective sample of 122 (Pittler 1998).

Contraindications and cautions

The German Commission E monographs sight no contraindications or cautions to the use of horsechestnut, any restriction during lactation or pregnancy, nor any interactions between horsechestnut and other pharmaceuticals (Blumenthal 1998).

Whilst some authorities argue that *Aesculus hippocastanum* is contraindicated in individuals with renal or hepatic disease (Lininger 1999), only the intravenous administration of horsechestnut may cause nephrotoxicity (Bruneton 1995). In support of this Lininger affirms that horsechestnut has no nephrotoxic effect when administered orally.

Actions

In experimental studies *Aesculus hippocastanum* possesses anti-inflammatory, anti-enzymatic, anti-oxidant and hypoglycaemic activity.

In clinical studies horsechestnut possesses anti-exudative and anti-edematous activity.

Medicinal uses

The clinical indications for the oral administration of *Aesculus hippocastanum* are:

- Chronic venous insufficiency where leg edema, pruritis, cramps, heaviness and pain are present.
- Prevention and treatment of deep vein thrombosis (DVT)
- Phlebitis
- Varicose veins
- Chronic venous leg ulceration (currently under investigation).

Dosage and administration

The seeds of *Aesculus hippocastanum* are available in the form of capsules, tablets, ampoules, drops, ointments, gels, lotions and

tinctures (Krapp 2001; Gruenwald 2000). The recommended dosage for horsechestnut seeds is as follows:

- Tablet/Capsule 250-312.5 mg twice daily, corresponding to 100 mg aescin daily (Blumenthal 1998).
- Tincture 0.6-1.1 mL daily of the 1:10 tincture (Gruenwald 2000; Ozarko 2001).
- Infusion 5-10 gm three times daily (Hoffmann 1996).
- Topically 1-2% aescin gel applied to intact skin as required (Gruenwald 2000).

To enhance the venotonic effect, HCSE can be combined with other circulatory stimulants including *Zingiber officinale*, *Capsicum annum*, or *Zanthoxylum americanum*.

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After obtaining his Bachelor of Nursing degree in 1995, Matthew Leach pursued nursing as a career. However after becoming disheartened with the medical model, Matthew completed a Diploma of Applied Science in Naturopathy (1998). Despite his preference toward natural medicine, evidence based practice was lacking. As a result Matthew is pursuing a career in research. After obtaining first class honours in 2000, Matthew is now a PhD candidate at the University of South Australia. Matthew's PhD will examine the wound healing effects of horsechestnut using a randomised control trial.

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...ing randomised ...ons learnt from ... & Venous Leg ... Trial (HAVLUT)

STRACT

The RCT is considered the gold standard for testing a therapeutic intervention. However, the conduct of an RCT is not without numerous obstacles. As illustrated through the recent Horsechestnut and Venous Leg Ulcer Trial (HAVLUT), these barriers can be attributed to randomisation, recruitment, retention, blinding and sampling procedures, and to gate keeping. These obstacles, together with strategies to prevent and overcome them, are detailed throughout this article, and are aimed at ameliorating the future design and conduct of RCTs.

EY WORDS

omised
rolled trials;
keeping;
omisation;
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uitment

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TRODUCTION

ues relating to participant recruitment frequently compromise the conduct of clinical ls. Researchers need to be aware of these riers in the planning and design of clinical ls, and incorporate measures to overcome se obstacles to maximise efficiency and minse expenditure (Lovato et al. 1997). Even re so, is the need for improved recruitment in trials investigating natural medicine due to the widespread interest and utilisation of these therapies, and the increasing demand from both the public and clinicians for rigorous and systematic evaluation of these therapies (Richardson et al. 1998; Vincent & Furnham 1997). The aim of this article is to highlight the obstacles in conducting a Randomised Controlled Trial (RCT), as illustrated through the recent Horsechestnut & Venous Leg Ulcer Trial (HAVLUT), and to suggest measures to overcome these barriers in the future design and conduct of RCTs.

OVERVIEW OF HAVLUT

The Horsechestnut and Venous Leg Ulcer Trial (HAVLUT) was conducted as a prospective, parallel-group, triple-blind, multi-centre, randomised, placebo-controlled trial. Ethical clearance was obtained through the Human

Research Ethics Committee (HREC) of the University of SA and the community nursing service where the sample was obtained. The primary purpose of HAVLUT was to determine whether the oral administration of Horsechestnut Seed Extract (HCSE) influenced the healing rate of venous leg ulceration (VLU) in patients receiving wound management from a large South Australian community nursing service. Recruitment of participants involved informing community nurses about the trial through the provision of team in-services and resource booklets. Staff were then asked to distribute information sheets to all clients manifesting VLU. Clients wishing to participate in the trial then contacted the chief investigator for screening. If clients were eligible to participate in HAVLUT, medical practitioner consent was sought, after which participants were randomly assigned to the treatment or placebo group, and baseline assessments initiated. Patients self-administered HCSE over a twelve-week period, and comprehensive wound assessments were conducted every four weeks. As will be detailed throughout this article, the conduct of HAVLUT by a single investigator with limited funding and resources was not conducive to the successful implementation of an RCT.

The Randomised Controlled Trial Design

The RCT is considered the gold standard for testing a therapeutic intervention (Eskinazi 1998; Jolley 1999; Knipschild 1993; Richardson 2000) and is usually conducted within the clinical setting (Roberts & Taylor 1999). Prospective data collection, control groups (Friedman et al. 1982) and randomisation (Day 1999; Jadad 1998) characterise the RCT design. The RCT is also the most definitive way of determining whether an intervention produces a postulated effect (Friedman et al. 1982; Grimm 2002; Portney & Watkins 2000) and is '...the mainstay of modern evidence-based medicine' (Jolley 1999, p213). As the ultimate aim of designing an RCT is to control against any source of bias (Lloyd-Parks 2001), and thus attempt to discredit any alternative causal explanation (Polit & Hungler 1999), the clinical trial provides a more sound rationale for a therapeutic intervention (Friedman et al. 1982), yielding less biased data than that of any other design (Jolley 1999; Spilker 1991a). The types of bias that an RCT attempts to control are outlined in table 1.0 (Day 1999; Polit & Hungler 1999; Spilker 1991a).

The RCT however, is not applicable to all interventions. Descriptive quantitative or qualitative studies, and projects where human characteristics such as personality and beliefs cannot be manipulated are not suitable for investigation using an RCT design (Roberts & Taylor 1999). Due to the likelihood of financial constraints, poor compliance and high attrition (Jadad 1998), RCTs are also unsuitable for examining interventions with rare or difficult to measure clinical outcomes (Jadad 1998; Vincent & Furnham 1997) or with effects that

Table 1.0: Types of bias controlled against using RCT designs

Ascertainment bias	Bias introduced by the manner in which data was collected
Information bias	Bias introduced from subject beliefs, values and perceptions
Observer bias	Bias introduced from observer measurements or observations
Selection bias	Bias introduced when selected subjects are not representative of the target population
Volunteer bias	Bias introduced when volunteers or 'early comers' are not representative of the target population

elop over a long period of time (Jadad 98). Furthermore, in comparison to other dy designs, clinical trials are often costly time consuming to conduct (Grimm 2002; dson et al. 2001), and thus often require ernal funding to successfully implement rns & Grove 1993; Lovato et al. 1997; tney & Watkins 2000). Therefore, without ficient time, personnel and funding, the isation of an RCT design would not be ible.

Opponents of the RCT design claim that catrising individuals into a common diagnosis s not account for individual variation and parate patterns of healing (Knipschild 1993; cent & Furnham 1997). Furthermore, standised treatment protocols may not always be vant to the procedures typically utilised in ical practice (Knipschild 1993; Margolin et 1998; Vincent & Furnham 1997). In relation placebo-controlled trials, some claim that etting the placebo effect eliminates the benial psychological effect associated with some tments (Knipschild 1993; Vincent & Furn- 1997). Thus, debate over the dependence n rigid RCT designs to determine the validof an intervention are ongoing and at present do not appear to be converging.

HAVLUT: As recommended by The Alexander se Group (1992), the RCT design is essenfor investigating the efficacy of systemic apy in VLU. The nature of HAVLUT also anded the utilisation of a parallel design to d compromising participant recruitment compliance, as would be anticipated with a sover design. Furthermore, a crossover gn was unsuitable for HAVLUT as similar icipant baseline values could not be fore-; a longer trial duration would have been propriate (Spilker 1991a); and the carry- effects of HCSE remain poorly elucidated. addition, The Alexander House Group 92) advises that crossover designs are propriate in ulcer healing studies as base- data in each arm of the study would be different due to ulcer healing occurring during the first arm.

RANDOMISATION

Randomisation relates to the treatment assignment process, whereby all participants have an equal chance of being allocated to each study group. Therefore, individual factors that may influence the study results, both known and unknown, are balanced between groups (Jadad 1998; Juhl 1982). Randomisation also allows for blinding and thus reduces both selection (Spilker 1991a) and volunteer bias (Jolley 1999; Wood and Haber 1998), thus improving the internal and external validity of the study (Portney & Watkins 2000). However, randomisation cannot guarantee that variables between groups will be balanced (Spilker 1991a). Furthermore, randomisation may also disrespect the patient's right to choice of treatment (Knipschild 1993; Reitemeier 2002). To overcome these latter concerns, the use of partially randomised or patient preference trials have been suggested (Thomas & Fitter 2002), with claims that randomised trials do not differ from well-designed observational studies (Lewith et al. 2002). Nonetheless, whilst randomisation may neglect an individual's right to choice of treatment, the absence of randomisation may cast doubt over the validity of findings, and in turn, delay the release of potential benefits to the community.

HAVLUT: Following patient screening and medical consent, clients enrolled in HAVLUT were randomly assigned to either the HCSE treatment group or the placebo group. Group allocation was determined by the block randomisation method, utilising blocks of four. Each block was randomly chosen by the lottery method and subsequently recorded on a randomisation code log. Block randomisation was utilised over other methods, as it is the most powerful method of randomisation (Spilker 1991a). Almost guaranteeing balance between the size of the two groups, block randomisation

also increases the power of the study (Friedman et al. 1982).

Blinding & placebos

Blinding is a process whereby certain information about data, procedures or interventions is withheld from clinicians, participants or data management staff to minimise bias (Day 1999). The greater the level of blinding, the lower the potential of observer, information or ascertainment bias being introduced (Jadad 1998; Jolley 1999; Juhl 1982; Spilker 1991a). In many situations, blinding is achieved by utilising comparative or placebo techniques.

A placebo is an intervention that replicates the treatment under investigation without exerting any direct physical effect (Roberts & Taylor 1998), although the effects of some placebo techniques remain poorly elucidated. The placebo intervention corrects the psychological effects of treatment when used in conjunction with blinding (Juhl 1982) and controls against major sources of misleading data, including patient or investigator prejudice, or spontaneous changes relating to the disease or condition under investigation (Spilker 1991a). The placebo group also controls against any 'placebo' or 'Hawthorne effect' or other extraneous variables that may be evident during the trial (Roberts & Taylor 1999).

Blinding and placebo controls are however not suitable for all modalities. Whilst ingestive therapies such as pharmaceuticals, herbal medicine, homeopathy and nutrition can be evaluated utilising a placebo-controlled and double-blind design, the efficacy of some therapies such as acupuncture, aromatherapy, counselling, chiropractic, physiotherapy, surgery and tactile modalities prove more difficult to evaluate with double-blinding and placebo controls (Jadad 1998; Margolin et al. 1998; Murphy et al. 1999; Richardson 2000; Vincent & Furnham 1997). Attempts to overcome these obstacles may include adopting an open-label design, although open design studies are found to favour and exaggerate the effect of an intervention (Jadad 1998) and are often contaminated by bias and the placebo effect (Spilker 1984). A single-blind design is another option, with the potential for investigator bias being controlled by utilising objective end-points and third party observers whom are unaware of the treatment group (Grimm 2002).

HAVLUT: As with many drug trials, HAVLUT also utilised a placebo tablet as the control intervention. The utilisation of a matching placebo in HAVLUT allowed triple blinding to occur, so patients, nurses, medical practitioners, investigator and statistician were unaware of the participant's treatment. Nonetheless, it is argued that all parties in a trial may have some idea as to which treatment a participant is on. Therefore, the use of a post-trial questionnaire to test the degree of blinding procedures is essential in quantifying the success of blinding (Spilker 1991a). As statistical analysis of HAVLUT is still in progress, results of the blinding questionnaire are not yet available.

Sample & selection criteria

Admission, selection, inclusion, exclusion or eligibility criteria are interchangeable terms that refer to the minimum requirements needed of subjects to enter a study (Day 1999). Selection criteria should be limited to excluding only those who might be harmed and those who are not likely to benefit or comply with the intervention (Friedman et al. 1982). These criteria can include restrictions on patient, disease or treatment characteristics, environmental factors or the parameters of screening tests (Spilker 1991a).

Exclusion criteria and protocol restraints imposed by clinical trials are claimed by some opponents as being reductionist and artificial (Polit & Hungler 1999; Richardson 2000), whilst lacking generalisability to the target population (Jolley 1999) and to clinical practice (Richardson 2000). Although restrictive selection criteria may obtain a more homogenous

ple (Friedman et al. 1982) and allow for re meaningful interpretations (Juhl 1982; ker 1984), strict exclusion criteria can limit eligibility of many subjects, and thus con- in participant recruitment (Friedman et al. 2; Richardson et al. 1998) and limit the eralisability of findings (Juhl 1982; Spilker 4). Subsequently, the feasibility of a trial be reduced (Lloyd-Parks 2001). Alterna- ly, inclusion criteria that are set too broadly result in a heterogenous sample and thus stion the interpretation or relevance of the lts (Juhl 1982; Spilker 1984). The struggle n developing the right level of selection cri- a simply illustrates the ongoing difficulty in ncing the internal and external validity of ical trials (Wittmann & Walach 2002).

AVLUT: The subject selection criteria for VLUT were based on maximising recruit- t, eliminating confounding variables and ntaining homogeneity. In the onset, subjects ning to enrol in HAVLUT needed to meet teen criteria relating to mental capacity; ulcer classification, size and duration; pler results; and concurrent medications treatments. These criteria were however 'restrictive', resulting in poor participant ual. Subsequently, admission criteria were nded, resulting in significant improvements rticipant recruitment.

CRUITMENT & RETENTION

ruitment and retention of participants ssential for the successful conduct of a clin- trial (Lovato et al. 1997). Nonetheless, archers find recruitment the most arduous ess in a trial and frequently underestimate level of difficulty (McNeely & Clements ; Reitemeier 2002; Vickers 2002). Conse- tly, delays in recruitment and the conduct trial may result in increased costs, time, se of resources, and delays in the release portant information about an intervention d-Parks 2001). Whilst many patients e altruistic and participate in RCTs to contribute to medical knowledge on [illegible] belief that they are receiving [illegible] (Cunny & Miller 1994; Lovato et al. [illegible] et al. 1999), these reasons are not enough to encourage large numbers of individuals to participate in research trials. Problems with participant recruitment are generally attributed to either practitioner or patient factors.

Barriers to patient recruitment and compliance with trial protocol's amongst clinicians may include time constraints; lack of training and support staff; concern for the impact on the clinician–patient relationship; concern for patients; loss of professional autonomy and decision-making power; difficulty with consent procedures; financial burden; lack of incentives and recognition; incompatibility with clinical practice; and lack of interest toward the research question (Benson et al. 1991; Lovato et al. 1997; Ross et al. 1999; Spilker 1991b). Staff may also consider the research as less of a priority than existing work commitments (Hudson et al. 2001) particularly when practitioners are under pressure in the workplace (Emanuel & Warburton 1999). Clinical trials also require strict adherence to inflexible protocols, of which practitioners may need to modify their practice to accommodate to the requirements of a protocol (Reitemeier 2002). Unfortunately, adherence to trial protocols may interfere with practitioners' beliefs, and result in practitioner resistance, protocol violation or subject withdrawal (Burns & Grove 1993; Reitemeier 2002). Consequently, the lack of clinician support may hinder the process and success of a clinical trial.

Barriers to participant accrual and retention in an RCT include concern about additional procedures, appointments, discomfort, risks, inconvenience, time, travel and expenses, preference toward or against a specific treatment; aversion to randomisation; uncertainty of treatment; and concerns about level of information and consent procedures (Cunny & Miller 1994; Lovato et al. 1997; Ross et al. 1999). Patient

[illegible] be influenced by family [illegible] about the trial or intervention [illegible], and work, child care [illegible] constraints (Richardson et al. 1998). [illegible] these measures however can be [illegible] with adequate planning and funding.

When recruitment is unsuccessful, strategies may include re-evaluating the desired sample [illegible] sourcing additional sites; replacing poor recruitment sites; extending the recruitment period; modifying participant selection criteria; and lessening protocol demands (Collins et al. 1980; Spilker 1991a; Tygstrup 1982). It is also argued that utilising multiple overlapping strategies maximises participant recruitment in a clinical trial (Bjornson-Benson et al. 1993; Friedman et al. 1982). The range of strategies that maybe employed include accessing registries or medical records; occupational screening; direct mailing; phone solicitation; radio; television; newspaper; video (Friedman et al. 1982; Lovato et al. 1997); community screenings (Bradford 1987); flyers; presentations; public service announcements; referrals from colleagues or other organizations; or through the investigator's practice or place of employment (Spilker 1991a). Amongst several clinical trials examining the success of different recruitment strategies, the most successful methods employed were direct mass mailing (Borhani et al. 1989; Connett et al. 1993; Hollis et al. 1995; Lewis et al. 1998; Rudick et al. 1993); face-to-face contact (Norton et al. 1994); practitioner referrals (Adams et al. 1997; Silagy et al. 1991); and the media (Bjornson-Benson et al. 1993).

A strong research team is necessary in conducting a successful trial (Hudson et al. 2001), including the support from clinical trial nurses to minimise demand on clinician's time and reduce the possibility of inaccurate or biased information being distributed (Ross et al. 1999). Informing participants about the trial through various media including written, oral and video may be more efficient and also less demanding on clinicians (Lovato et al. 1997; Richardson et al. 1998; Ross et al. 1999). Both a nurse and doctor should be available to explain the consent process, and participants be provided with adequate time to formulate a decision (Ross et al. 1999). Strategies that may decrease barriers relating to employment, child-care and other commitments include providing flexible hours and child-care services, and avoiding travel and parking costs, and where patient expenses are unavoidable, providing participant reimbursement (Lovato et al. 1997; Richardson et al. 1998). In relation to the elderly, subject accrual may also be improved by avoiding the need for transport; comprehensive assessments; excessive reading and writing; and by utilising enlarged print (McNeely & Clements 1994). To encourage clinicians to assist or participate in clinical trials, monetary or educational incentives; acknowledgements; thankyou letters; reminder notices; simple and personalised recruitment material; and an emphasis on patient and community benefits may aid in improving participant recruitment and retention (Vickers 2002). Discussions with clinicians about the design and conduct of the trial, the safety and efficacy of the intervention, and measures to preserve patient rights may also allay clinician anxiety and minimise trial obstruction.

Retention of participants in clinical trials, particularly longitudinal studies, is also another barrier to the successful conduct of a clinical trial. Patient compliance can be compromised due to adverse effects; excessive trial duration; increased pain, stress or demand; poor memory; personal costs; or poor trial orientation or preparation (Spilker 1991b). Retention can be improved by maintaining frequent contact with participants and ensuring participants feel important (Vickers 2002). Other methods to improve patient compliance in RCTs include using videos, pamphlets and clinicians to orientate and inform patients about the intervention and trial; utilising medication charts and

sette boxes; decreasing the number of daily edications or doses required; scheduling specific visit times and ensuring visit duration is ief; increasing visit frequency; and having a cific person for all participant contacts ramer 1991).

HAVLUT: The largest obstacle to the conduct HAVLUT was the difficulty in meeting the sired sample size. Whilst the adoption of a lti-centre design, face-to-face recruitment clinicians, clinic flyers, non-restrictive dress- protocols, and home visitation were aimed maximising recruitment in HAVLUT, the use mass media advertising, honorariums, ruitment personnel, or a continuation pro- ol (Spilker 1991a) was not financially feasi- . By the third month of recruitment, the nple size only reached n=3. Recruitment ategies were subsequently scrutinised to ximise accrual and involved loosening selecn criteria. Furthermore, reminder notices re posted to staff and published in the staff vsletter and client magazine, and additional rmation sheets were distributed to all staff. taff incentive scheme was also introduced. revised recruitment strategies only recruita further two participants. Subsequently, a of all clients receiving wound care at the mmunity nursing service was generated and n nurse approached individually to increase f awareness about HAVLUT; identify barrito client recruitment; identify and resolve f concerns about the trial; and identify ch clients would be suitable to approach for icipation in HAVLUT. The recruitment od was extended another two months. The sed strategy resulted in a further twenty- participants. Still short of the desired samsize, reminder notices were distributed to and the recruitment period extended her month. This latter strategy only resultn one additional participant. Attempts to e additional sites and establish a practitionferral system were also unsuccessful. After iled discussions with the organizations director of nursing and [illegible] approval was eventually obtained [illegible] direct mail-out of information [illegible] clients with VLU. After another [illegible] extension of the recruitment period the direct mail-out resulted in an additional [illegible] participants. Therefore, whilst face to face strategies were deemed the most effective in recruiting study participants in HAVLUT the direct mail-out method arguably bypassed staff gate keeping and ensured all eligible clients were informed of the trial.

GATEKEEPING

The gate keeping of health services by medical practitioners is well documented in the literature (Meslin 2001; Pietroni 1992; Strasser & Harvey 1999), as is the presence of gate keeping in clinical trials (Lovato et al. 1997; Meslin 2001; Vickers 2002). Gate keeping can either assist or hinder participant accrual (Lovato et al. 1997), and may involve a number of individuals.

It is frequently a requirement of many intervention trials to seek approval from the primary medical practitioner prior to participant enrolment (McNeely & Clements 1994). Such approval may be for professional courtesy, for pre-screening purposes, or to safeguard against liability (Meslin 2001). Nonetheless, Meslin (2001) argues that the rationale for researchers seeking permission from clinicians for patient recruitment is unclear. Woog (1993) also contends that gatekeepers, whether they be practitioners or committees, have no responsibility in controlling participant entry into a trial instead, it is the individual who should make that decision through informed consent. Furthermore, if the intent of the research is to benefit individuals, and individuals provide [illegible] informed consent, such an obstruction to research by gate keeping is inappropriate as it compromises communitarianism and [illegible] 2001; Woog 1993). Therefore, clients who are eligible to participate in a trial [illegible]

[illegible] an ethical obligation to provide patients with the opportunity to take part with the intent of benefiting the overall community (Kottenmeier 2002). Hence, prospective participants have the right to make the initial decision to partake in research, and thus, it is unduly paternalistic to cede authority to another person to gain access to a study by gate keeping (Hudson et al. 2001; National Bioethics Advisory Commission 2001).

Accessing participants for clinical trials can be obstructed not only by practitioners, but also by significant others acting as gatekeepers (Hudson et al. 2001). These gatekeepers may include ethics committees, club presidents, chief executive officers or family members (McNeely & Clements 1994). Due to strict protocols, randomisation and the need for informed consent, approval by an institutional ethics committee is essential (Jolley 1999). Nonetheless, ethics committees can adopt the role of gatekeeper (Hudson et al. 2001) and create significant obstacles to subject enrolment. Consequently, participant recruitment may be constrained and the research process prolonged, ultimately delaying the release of results to the community (Gurwitz et al. 2001; Meslin 2001). Furthermore, delays in recruitment may also increase costs and decrease staff and participant enthusiasm (Richardson et al. 1998).

Methods to reduce gate keeping involve building rapport and trusting relationships with gatekeepers and other members of the organization (Lovato et al. 1997; McNeely & Clements 1994); providing individuals with adequate information (Hudson et al. 2001); and informing clinicians that clients may directly benefit from the intervention, and that they would be contributing to improvements in health care (Hudson et al. 2001). Nonetheless, the most effective strategy to encumber gate keeping is to avoid utilising on-site clinical staff to recruit participants (Hudson et al. 2001).

HAVLUT: Gate keeping was a major obstacle throughout all stages of HAVLUT. Initially, the ethics committee were dubious about utilising a herbal medicine in the management of VLU. Murphy et al. (1999) highlight that institutional ethics committees can be barriers to the implementation of an RCT involving a natural modality, due to the lack of evidence supporting the efficacy and safety of many natural therapies, and the difficulty in understanding the natural therapeutic rationale through a biomedical mind. The ethics committee also requested that consent be sought from treating physicians prior to participant enrolment. The need for medical consent adversely affected patient accrual in HAVLUT, with several practitioners refusing to give consent for patients due to unjustified beliefs about Horsechestnut, natural medicine and conventional wound management. In addition to medical practitioners, nursing staff were also gate keeping, with many nurses only approaching clients they deemed suitable under their 'own' selection criteria. The participating organization also prolonged recruitment and hindered participant accrual by initially delaying the utilisation of a direct mail-out method to patients. Therefore, despite avoiding clinician involvement in recruitment, and adequately informing clinicians about the trial and intervention, gate keeping still occurred (Hudson et al. 2001).

Conclusion

The dilemma facing practitioners and researchers alike, is that without sufficient clinical evidence to support the efficacy of new therapies, practitioners are reluctant to incorporate these therapies into practice (Eskinazi 1998). However, without practitioner and institutional support, researchers may find it difficult to investigate new therapies in the clinical setting. Whilst the RCT may provide the most convincing evidence of the efficacy of an intervention, many obstacles prohibit the successful conduct of an RCT, and thus compromise the validity of findings. Consequently, practitioners

continue to be reluctant to pursue the new rapy without further supportive evidence. vever, unless adequate discourse on the bar- s to conducting RCTs and strategies to rcome these obstacles are highlighted in the rature, neophyte trialists are destined to ounter similar difficulties to HAVLUT, par- larly if researching in the fields of nursing natural medicine.

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The clinical feasibility of natural medicine, venotonic therapy and horsechestnut seed extract in the treatment of venous leg ulceration: a descriptive survey

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KEYWORDS
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Summary *Background*: The primary treatment of choice for venous leg ulceration (VLU) is compression therapy, however serious clinical issues demand the development of new treatments. An extract believed to promote VLU healing is Horsechestnut Seed Extract (HCSE).

Methods: The clinical feasibility of HCSE in VLU was explored in a two-stage design. The second stage presented here, was a descriptive survey exploring current opinion and utilisation of natural therapies, venotonics and HCSE in VLU. A questionnaire mailed to 122 district nurses, 73 medical practitioners (MPs) and 53 clients with VLU resulted in a response rate of 32, 31.5 and 81 per cent, respectively.

Results: Natural therapy and HCSE use for VLU was minimal in all groups. Half of all groups supported venotonics, with a similar proportion of nurses and clients utilising venotonics in practice. MPs were however less likely to utilise venotonics for VLU.

Conclusion: Whilst clinicians indicate that clinical evidence may influence the utilisation of HCSE in clinical practice, the evidence currently does not exist. Positive findings from well-designed trials may ameliorate the integration of natural medicine into mainstream practice.
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Introduction

In the past 20 years, the popularity of natural medicine has increased.[1–6] As presented elsewhere,[7] reasons for the surge of interest in natural medicine reflect a need to improve upon existing health care options.

An area where natural therapy use is becoming more prevalent is in dermatology.[8] Following homeopathy, a systematic review found herbal medicine to be the most frequently used therapy for skin conditions and the most favoured internationally.[8] Also identified, was a positive association between complementary therapy use and an increase in dermatological disease duration and severity.[8–11] Venous leg ulceration is one such common and largely neglected[12] chronic dermatological condition.

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Venous leg ulceration (VLU) afflicts approximately 0.6 per cent of the western population,[13] amounting to $654 million, 600 million pounds and $1 billion annually in Australia, the United Kingdom[14] and the United States,[15] respectively. Other than financial implications, individuals with VLU frequently experience depression, anxiety, social isolation, sleeplessness, impaired mobility and reduced working capacity.[16–18] At present, the treatment of VLU remains diverse, with various topical and surgical treatments available. Whilst the primary treatment of choice for VLU is compression therapy,[15,19,20] the paucity of clinical evidence[21] and the reporting of discomfort,[22] poor patient compliance[23–25] and serious complications with compression therapy[26] demand more convenient, safer and efficacious treatments for VLU be developed. An area where potential treatments may be uncovered is the field of natural medicine.

A therapy that may assist in the healing of VLU is Horsechestnut Seed Extract (HCSE), a venotonic herb with established safety and efficacy in the treatment of chronic venous insufficiency (CVI).[27] As HCSE may attenuate the pathogenesis of CVI, and CVI is the precursor of VLU,[12,23,28] it is argued that HCSE may hasten wound healing and reduce ulcer recurrence. Furthermore, the anti-oedema,[25,29,30] anti-inflammatory,[25,29,31] anti-exudative[32–35] and astringent[31] properties of HCSE are claimed to further support VLU healing. Nonetheless, the efficacy of oral HCSE in the management of VLU has not been explored, explaining why the feasibility of HCSE as a treatment for VLU was recently investigated. The first stage (stage I) of the two-stage study was a triple-blind, randomised, placebo-controlled trial of 42 participants with active VLU, treated through a large South Australian district nursing service. The 12-week trial examined whether the oral administration of HCSE was associated with an improvement in the rate of completely healed VLU when compared to placebo at week 12. Whilst the stage I findings may provide support for a systemic approach to the treatment of VLU, it remains poorly elucidated whether practitioners and clients would utilise venotonic agents or HCSE in the management of venous ulceration. As a result, the second stage (stage II) emerged, exploring client, district nurse (DN) and medical practitioner (MP) opinion and use of natural medicine, venotonic therapy and HCSE. The primary purpose of stage II therefore was to determine whether the integration of these treatments into mainstream medicine would be feasible after stage I was completed. The design, results and interpretation of the stage II findings are presented below.

Study design

Stage II was a small local non-experimental study, utilising a descriptive survey methodology. The aims of stage II were to:

- explore DN, MP and client opinion and use of natural medicine, venotonic therapy and HCSE,
- determine whether DNs and MPs would recommend natural medicine, venotonic therapy and HCSE to clients with VLU, and
- identify which factors constrain the utilisation of natural medicine, venotonic therapy and HCSE in clinical practice.

Research questions

To address the aforementioned research aims, the following questions were investigated:

1. Do DNs, MPs and clients believe natural medicine and HCSE are safe and effective?
2. Do DNs, MPs and clients believe venotonic therapy and HCSE are suitable treatment options for the management of VLU?
3. Do clients, DNs and MPs currently utilise natural medicine, venotonic therapy or HCSE for VLU?
4. Do clients, DNs and MPs plan to utilise natural medicine, venotonic therapy or HCSE for VLU in future?

Setting and sample

Nurses, MPs and clients registered in stage I were selected for stage II through convenience sampling. To participate in stage II, individuals had to be residents of metropolitan Adelaide (South Australia); possess prior knowledge of HCSE and stage I; and be mentally competent to complete the questionnaire. In addition to being directly informed of the stage I trial, practitioners required clinical exposure to VLU, whilst clients had to demonstrate a previous history of VLU. As a result, 122 district nurses, 73 medical practitioners, and 54 clients with VLU who registered their interest in stage I were invited to participate.

Instrumentation

Despite a comprehensive search of MEDLINE, CINAHL and AMED between the years 1960 and 2002, no single instrument adequately addressed all the aims of stage II. A 20-item pencil and paper self-administered questionnaire was therefore designed and developed to support the aims of the current study. The stage II questionnaire

demonstrated a high degree of validity and internal consistency, with a Cronbach's alpha of 0.96, and face and content validity confirmed by six experts in wound care, district nursing, natural medicine and allopathic medicine.

Procedures/data collection

Stage II commenced following the completion of stage I in April 2003. Preliminary notification of clients was implemented during the clients final stage I wound assessment. Nursing staff were informed about stage II through posted flyers, and MPs informed through facsimiled notices. Client and practitioner questionnaires and reply-paid envelopes were dispatched by mail to all participants during early April 2003. Two weeks after questionnaire dispatch, non-responders were identified by questionnaire coding, and subsequently dispatched the first round of follow-up letters. Two weeks after the first follow-up, a second round of follow-up letters were distributed to non-respondents. The stage II study was terminated 3 weeks after follow-up.

Ethical considerations

To ensure the rights and welfare of participants in stage II were protected, the study was reviewed and approved by both the Human Research Ethics Committee (HREC) of RDNS, and the HREC of the University of South Australia.

Planned statistical analysis

Following the final receipt of questionnaires in May 2003, participant responses were coded and entered onto SPSS (version 11.0) for data cleaning and analysis. Measures of central tendency and variability were utilised for descriptive data; content analysis utilised for open-ended questions; and relationships between ordinal-level variables calculated using the Kendall's Tau correlation coefficient (Tau).

Results

Demographics of sample

The overall response rate for clients, DNs and MPs was 81 (43/53), 32 (39/122) and 31.5 (23/73) per cent, respectively. Demographic characteristics of clients, DNs and MPs are presented in Tables 1–3.

Table 1 Demographics of clients ($n = 43$).

		Number (%)
Age	50–59 years	3 (7.0)
	60–69 years	5 (11.6)
	70–79 years	17 (39.5)
	80 + years	13 (30.2)
	Missing	5 (11.6)
Gender	Male	26 (60.5)
	Female	17 (39.5)
Participated in stage I	Yes	29 (67.4)
	No	14 (32.6)

Client utilisation and attitude toward natural therapies

Whilst the majority of clients believed massage (22/53) and nutrient supplementation (21/53) were safe, clients with VLU were generally uncertain about the safety and efficacy of most natural therapies, particularly the efficacy of aromatherapy (34/53) and homeopathy (35/53). Clients were also undecided whether natural modalities should be incorporated into mainstream medicine, with a particular hesitancy toward aromatherapy (32/53) and homeopathy (32/53).

The majority of clients had never utilised natural therapies for the treatment of VLU (Table 4), although more than a third of clients demonstrated an interest to pursue massage, herbal medicine and nutrient supplementation in future. Reasons why clients utilised and avoided the use of natural therapies both currently and in the future are highlighted in Tables 5 and 6. A moderate positive correlation between current use and participation in stage I was evident ($P = 0.015$, Tau $= 0.412$).

Client utilisation and attitude toward venotonic agents

Almost half of clients believed venotonic agents were a suitable treatment for VLU (43 per cent), with 52 per cent of clients utilising venotonic agents daily for the management of VLU. Whilst almost half (25/53) of clients had never utilised venotonic therapy, half considered the utilisation of venotonic agents in future. Reasons for clients utilising and avoiding venotonics both currently and in the future are illustrated in Tables 7 and 8.

A moderate negative correlation between client age and attitude toward venotonic agents was

Table 2 Demographics of medical practitioners ($n = 23$).

		Number	%
Age	30–39 years	7	30.4
	40–49 years	7	30.4
	50–59 years	6	26.1
	Missing	3	13.0
Gender	Male	20	87.0
	Female	3	13.0
Type of practitioner	GP	21	91.3
	Dermatologist	2	8.7
Medical experience (years)	7–8 years	1	4.3
	9–10 years	3	13.0
	11 years and over	16	69.6
	Missing	3	13.0
Frequency of treating VLU	Infrequently	5	21.7
	Monthly	5	21.7
	Weekly	9	39.1
	Daily	2	8.7
	Missing	2	8.7
Exposure to participant in stage I	Yes	16	69.6
	Unsure	2	8.7
	No	5	21.7

evident ($P = 0.031$, Tau $= -0.370$). Similarly, the current use of venotonic agents ($P = 0.051$, Tau $= -0.285$) and the intention to utilise these agents in future ($P = 0.048$, Tau $= -0.319$) was negatively associated with client age, but strongly associated with participation in stage I ($P = 0.042$, Tau $= 0.602$). Clients demonstrating a positive attitude toward venotonic agents were also more likely to be supportive of the safety ($P = 0.028$, Tau $= 0.329$) and efficacy ($P = 0.027$, Tau $= 0.379$) of herbal medicine, and to utilise herbal medicine for the future treatment of VLU ($P = 0.04$, Tau $= 0.395$).

Client utilisation and attitude toward HCSE

The majority of clients with VLU do not utilise HCSE (34/53), with less than one in five clients (19 per cent) utilising HCSE on a daily basis, and 2.4 per cent on an infrequent basis. Notwithstanding, client's attitudes toward HCSE were generally positive (Table 9). Almost half of clients considered utilising HCSE based on current information, and half considered using HCSE if future findings were positive. Factors influencing client opinion about the suitability of HCSE treatment, and reasons for clients using and avoiding HCSE for VLU are highlighted in Tables 10–12.

A positive attitude toward herbal medicine ($P < 0.02$, Tau < 0.379) and the frequent use of herbal medicine ($P = 0.045$, Tau $= 0.298$) were both correlated with a positive attitude toward HCSE. Client use and opinion of HCSE were also significantly associated with current ($P < 0.05$, Tau > 0.332) and future use ($P = 0.0001$, Tau > 0.620) of venotonics, and belief that venotonics are a suitable treatment for VLU ($P < 0.02$, Tau > 0.378).

Medical practitioner utilisation and attitude toward natural therapies

MPs were generally supportive of the safety of natural therapies, particularly toward meditation and relaxation (22/23), massage (20/23) and acupuncture (15/23). However, the majority of MPs were uncertain about the safety of herbal medicine (17/23) and homeopathy (10/23). MPs also believed meditation/relaxation (17/23), massage (14/23) and acupuncture (11/23) were efficacious, although the majority of practitioners believed aromatherapy (13/23) and homeopathy

Table 3 Demographics of nurses ($n = 39$).

		Number	%
Age	20–29 years	6	15.4
	30–39 years	10	25.6
	40–49 years	12	30.8
	50–59 years	10	25.6
	Missing	1	2.6
Gender	Female	36	92.3
	Male	2	5.1
	Missing	1	2.6
Type of practitioner	RN	22	56.4
	CN	12	30.8
	EN	3	7.7
	CNC	1	2.6
	Missing	1	2.6
Nursing experience (years)	5–6 years	2	5.1
	7–8 years	5	12.8
	9–10 years	3	7.7
	11 years and over	28	71.8
	Missing	1	2.6
Frequency of treating VLU	Daily	24	61.5
	Weekly	14	35.9
	Missing	1	2.6
Exposure to participant in stage I	Yes	23	59.0
	No	15	38.5
	Missing	1	2.6

Table 4 Clients level of natural therapy use for the management of VLU ($n = 43$).

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Vitamin/mineral supps	11 (26.2)	0	0	0	31 (73.8)
Herbal medicine	9 (21.4)	2 (4.8)	0	4 (9.5)	27 (64.3)
Meditation/relaxation	6 (14.3)	2 (4.8)	0	2 (4.8)	32 (76.2)
Massage	2 (4.8)	3 (7.1)	1 (2.4)	1 (2.4)	35 (83.3)
Homeopathy	2 (4.8)	0	0	1 (2.4)	39 (92.9)
Acupuncture/pressure	1 (2.4)	0	0	1 (2.4)	40 (95.2)
Touch/spiritual healing	1 (2.4)	2 (4.8)	0	1 (2.4)	38 (90.5)
Aromatherapy	0	0	0	0	42 (100)
Mean response	4.0	1.1	0.1	1.1	35.5

(11/23) were ineffective. MPs did not support the integration of natural therapies into mainstream medicine, particularly those therapies they believed were ineffective. Likewise, those therapies believed to be safe and effective were supported by MPs as modalities to be incorporated into mainstream medicine.

More than two-thirds of MPs never recommended natural therapies to patients with VLU, although one in five recommended massage and nutrient supplementation on a frequent basis (Table 13). Whilst the majority of MPs demonstrated no intent to utilise any natural therapy in future, almost half of practitioners agreed they would utilise massage and nutrient supplementation in the future management of VLU. Reasons for recommending and avoiding natural therapies both currently and in the future are listed in Tables 5 and 6. A moderate positive correlation between MP intent to recommend natural therapies in future, and frequent

Table 5 Reasons why clients and practitioners use and avoid natural therapies (NT) in the treatment of VLU.

	Clients ($n=43$)	DN ($n=39$)	MP ($n=23$)
Why NT are used for treating VLU, *n* (%)			
Recommended by health professional	4 (9.5)	—	—
Recommended for stage I	2 (4.8)	—	—
To improve circulation	2 (4.8)	1 (2.6)	1 (4.3)
To promote wound healing	—	5 (12.8)	3 (13)
Why NT are not used for treating VLU, *n* (%)			
Lack of opportunity	5 (11.9)	—	—
Lack of evidence or efficacy	3 (7.1)	4 (10.3)	8 (34.8)
District nurse provides care	2 (4.8)	—	—
Unfamiliar with therapies	2 (4.8)	—	—
Lack of knowledge or information	—	10 (25.6)	—

DN = district nurses; MP = medical practitioners; (—) = no response.

Table 6 Reasons why clients and practitioners may use and avoid natural therapies (NT) in the future treatment of VLU.

	Clients ($n=43$)	DN ($n=39$)	MP ($n=23$)
Why NT may be used for VLU in future, *n* (%)			
Improves wound healing	4 (9.5)	—	—
To improve circulation	3 (7.1)	—	—
No adverse effects	2 (4.8)	—	—
Experience or familiarity with therapies	—	2 (5.1)	—
Why NT may not be used for VLU in future, *n* (%)			
Lack of evidence or efficacy	6 (14.3)	2 (5.1)	6 (26.1)
Unfamiliarity with therapies	1 (2.4)	—	1 (4.3)
Too expensive	—	1 (2.6)	1 (4.3)
Lack of knowledge	—	9 (23.1)	—

DN = district nurses; MP = medical practitioners; (—) = no response.

exposure to patients with VLU was present ($P=0.027$, Tau = 0.319).

Medical practitioner attitude and recommendation of venotonic agents

More than half of MPs believed venotonic agents were a suitable treatment for VLU (12/23), with 8/23 uncertain, and 3/23 believing venotonics were unsuitable. The majority of MPs had never prescribed venotonics as a treatment for VLU (13/23), although 35 per cent of MPs recommended venotonics on an infrequent basis and 9 per cent monthly. Likewise, over a third of practitioners (35 per cent) planned to recommend venotonics to patients with VLU in future. Factors motivating the current and future use of venotonic therapy are detailed in Tables 7 and 8.

MP attitude toward venotonic agents was positively correlated with practitioner recommendation of nutrient supplementation ($P=0.041$, Tau = 0.327) and acupuncture ($P=0.017$, Tau = 0.396); and MP intent to recommend massage ($P=0.008$, Tau = 0.438) and herbal medicine ($P=0.017$, Tau = 0.407) to patients with VLU in future. MPs considering venotonic agents for the future treatment of VLU were positively correlated with the opinion that HCSE should be incorporated into mainstream medicine ($P=0.046$, Tau = 0.371) and HCSE is a suitable treatment for VLU ($P=0.044$, Tau = 0.376).

Medical practitioner attitude and recommendation of HCSE

More than half of MPs believed HCSE was safe, although most were uncertain about the efficacy of

Table 7 Reasons why clients and practitioners use or avoid venotonic agents for the treatment of VLU

	Clients ($n = 43$)	DN ($n = 39$)	MP ($n = 23$)
Why venotonics are being used for VLU, *n* (%)			
Addresses underlying cause	—	2 (5.1)	—
Previous success with venotonics	—	1 (2.6)	—
Adds to the benefit of support bandages	—	—	1 (4.3)
Why venotonics are not being used for VLU, *n* (%)			
Lack of personal experience	—	6 (15.4)	—
Limited knowledge	—	9 (23.1)	3 (13.0)
Lack of efficacy	—	—	3 (13.0)

DN = district nurses; MP = medical practitioners; (—) = no response.

Table 8 Reasons why clients and practitioners may use and avoid venotonic agents in the treatment of VLU in future.

	Clients ($n = 43$)	DN ($n = 39$)	MP ($n = 23$)
Why venotonics may be used for VLU in future, *n* (%)			
Due to previous success	8 (19.0)	—	1 (4.3)
Some hope of cure	3 (7.1)	—	—
If recommended by district nurse or MP	2 (4.8)	—	—
With further evidence and information	—	9 (23.1)	1 (4.3)
To improve wound healing time	—	2 (5.1)	—
Why venotonics may not be used for VLU in future, *n* (%)			
Adverse effects	2 (4.8)	—	—
Lack of evidence	1 (2.4)	3 (7.7)	4 (17.4)
Unfamiliarity with treatment	1 (2.4)	3 (7.7)	2 (8.7)
Lack of information	—	2 (5.1)	—

DN = district nurses; MP = medical practitioners; (—) = no response.

HCSE for the management of CVI (Table 9). Almost two thirds of practitioners were uncertain about the suitability of HCSE as a treatment for VLU and whether HCSE should be incorporated into mainstream medicine. The majority of MPs (91 per cent) had never recommended HCSE for the treatment of VLU, although more than two thirds considered recommending HCSE in future if supported in clinical trials. Factors influencing MP use of HCSE and opinion about the suitability of HCSE in VLU are highlighted in Tables 10–12.

Nurse attitude and recommendation of natural therapies

Nurses were very positive about natural therapies, with more than three quarters of nurses believing massage, nutrient supplementation and meditation were safe and efficacious, and should be incorporated into mainstream medicine. However, over half of staff were uncertain about the safety and efficacy of homeopathy and herbal medicine, and thus were uncertain about the integration of these therapies into mainstream medicine.

Nurses were not likely to recommend natural therapies to patients with VLU, with only a third of nurses recommending massage and nutrient supplementation on a frequent basis (Table 14). Nonetheless, more than half of nurses demonstrated intent to utilise nutrient supplementation (90 per cent), massage (67 per cent) and meditation (56 per cent) in future. Reasons for recommending and avoiding natural therapies for VLU both currently and in the future are highlighted in Tables 5 and 6.

Nurse attitude and recommendation of venotonic agents

Half of nurses believed venotonics were a suitable treatment for VLU (51 per cent) with 49 per cent uncertain. Almost half of nurses never utilised

venotonic agents for the treatment of VLU (49 per cent), although over a third recommended these therapies on an infrequent basis (39 per cent). In terms of future use, 49 per cent of nurses considered recommending venotonics to patients with VLU in future, with 44 per cent uncertain. Factors motivating the current and future use of venotonic therapy are detailed in Tables 7 and 8. Increased exposure to participants in stage I was moderately associated with a more positive attitude toward venotonic agents ($P=0.001$, Tau = 0.442), and the recommendation of these agents both currently ($P<0.0001$, Tau = 0.493) and in the future ($P=0.004$, Tau = 0.409).

Nurse attitude and recommendation of HCSE

Two thirds of nurses believed HCSE was a safe treatment (66.7 per cent), although half were uncertain about the efficacy and suitability of HCSE, and the integration of HCSE into mainstream medicine (Table 9). Almost half of nurses (49 per cent) had recommended HCSE treatment to patients with VLU, with the majority of nurses considering the recommendation of HCSE in future if findings from clinical trials were positive. Factors motivating the current and future use of HCSE, and nurse opinion about the suitability of HCSE in VLU are detailed in Tables 10–12.

Older nurses were found to be less positive toward HCSE ($P=0.01$, Tau = −0.332) whilst nurses exposed to stage I participants reported a more positive attitude ($P<0.0001$, Tau = 0.505). Nurses demonstrating a positive attitude toward HCSE and supporting the use of HCSE both currently and in the future were most likely to support the suitability of venotonic therapy ($P<0.0001$) and to recommended venotonic agents both currently ($P<0.02$) and in the future ($P<0.001$).

Discussion

Demographics of sample

Despite previous studies indicating VLU is more prevalent amongst females,[36] stage II clients with a history of VLU were predominantly male. The small sample size and potential for sampling bias almost certainly explains the conflicting demographic profile of participants. The profile of practitioners however were consistent with that reported in state workforce surveys.[37,38]

Client use and attitude toward natural therapies

Very few clients with VLU utilise natural therapies for leg ulceration, most likely due to uncertainty over the safety and efficacy of these modalities. Client use of natural therapies may be further constrained by lack of opportunity, evidence, familiarity and practitioner opinion. Nonetheless, a client's intent to utilise natural therapies in future maybe steered by a need to actively maintain self-health and wellbeing.[3,11,39] Indeed, further research is needed to verify these claims of autonomy.

Medical practitioners use and attitude toward natural therapies

A key factor contributing to the lack of MP support for natural medicine and the low level of current and future recommendation of natural treatments to clients with VLU is a lack of supportive evidence. Opinions about lack of evidence replicate findings from previous studies,[4,40] and are justified based on a recent review of natural therapies in wound care.[41] Notwithstanding, other constraints of natural therapy use amongst MPs including prejudice cannot be excluded. Hence, qualitative research is needed to further explore both the impeding and influential factors of natural therapy use amongst MPs.

Nurse use and attitude toward natural therapies

Despite a generally positive attitude toward natural medicine, very few nurses recommended natural modalities on a frequent basis, other than massage and nutrient supplementation. The lack of clinical evidence[41] and a paucity of knowledge are legitimate reasons for avoiding any modality, and indicate education and additional clinical evidence to support natural treatments may improve the level of natural therapy use amongst nurses.

Client utilisation and attitude toward venotonic agents

Half of clients with VLU were supportive of venotonic therapy despite being based upon unfounded claims of previous success. Some clients may in effect be utilising venotonic treatments without sufficient clinical evidence to support its use. Indeed, clients with VLU may see venotonic therapy as a promising new treatment to treat a chronic debilitating condition. Naturally, further investigation of a client's motivation to choose venotonic therapy and other treatments may

Table 9 Client and practitioner opinion of HCSE.

	CLIENTS			NURSES			MPs		
	A (%)	U (%)	D (%)	A (%)	U (%)	D (%)	A (%)	U (%)	D (%)
HCSE is safe	25 (59.5)	15 (35.7)	2 (4.8)	26 (66.7)	13 (33.4)	0 —	12 (52.2)	10 (43.5)	1 (4.3)
HCSE is effective for CVI	18 (42.9)	22 (52.4)	2 (4.8)	19 (48.8)	19 (48.8)	1 (2.6)	5 (21.7)	17 (73.9)	1 (4.3)
HCSE should be incorporated into MM	18 (42.9)	22 (52.4)	2 (4.8)	18 (46.2)	20 (51.3)	1 (2.6)	7 (30.4)	14 (60.9)	2 (8.7)
HCSE is suitable for VLU	18 (42.8)	22 (52.4)	2 (4.8)	18 (46.2)	20 (51.3)	1 (2.6)	7 (30.4)	14 (60.9)	2 (8.6)
Consider using/recommending HCSE based on current information	20 (47.6)	19 (45.2)	3 (7.2)	19 (48.7)	17 (43.6)	3 (7.7)	6 (26.1)	13 (56.5)	4 (17.4)
Consider using/recommending HCSE based on positive research findings	21 (50)	18 (42.9)	3 (7.2)	31 (79.5)	8 (20.5)	0 —	16 (69.5)	6 (26.0)	1 (4.3)
Mean responses	20	19.7	2.4	21.8	16.2	1.0	8.8	12.3	1.9

A = agree; U = unsure; D = disagree; MP = medical Practitioner; MM = mainstream medicine.

Table 10 Reasons why clients and practitioners believe HCSE is a suitable or unsuitable treatment for VLU.

	Clients ($n = 43$)	DN ($n = 39$)	MP ($n = 23$)
Why HCSE is a suitable treatment for VLU, *n* (%)			
Due to previous success	4 (9.5)	3 (7.7)	1 (4.3)
Controls leg oedema/pain	4 (9.5)	—	—
Promotes wound healing	2 (4.8)	1 (2.6)	—
Improves venous circulation	1 (2.4)	1 (2.6)	—
Supported by clinical evidence	—	1 (2.6)	1 (4.3)
Why HCSE is not a suitable treatment for VLU, *n* (%)			
Lack of evidence or efficacy	3 (7.1)	1 (2.6)	1 (4.3)
Lack of information	—	—	3 (13.0)

DN = district nurses; MP = medical practitioners; (—) = no response.

enable clinicians to better meet client needs, and may best originate from qualitative methods such as in-depth interviews and focus groups.

Medical practitioner utilisation and attitude toward venotonic agents

Although over half of MPs supported venotonic therapy, very few utilised or planned to recommend the therapy to clients in future. Conflicting opinions about the level of clinical evidence of venotonic therapy suggests some MPs are not practising evidence-based medicine. Whilst opinions about the lack of evidence may be legitimate, they may also be a reflection of MP prejudice against alternative treatments. Hence, it is uncertain whether an increase in clinical evidence would correspond with a rise

Table 11 Reasons why clients and practitioners do and do not use HCSE for the treatment of VLU.

	Clients ($n = 43$)	DN ($n = 39$)	MP ($n = 23$)
Why HCSE is currently used for VLU, *n* (%)			
Due to previous success	5 (11.9)	—	1 (4.3)
To promote ulcer healing	3 (7.1)	3 (7.7)	—
To reduce pain and oedema	2 (4.8)	—	—
Current evidence suggestive of a benefit	—	1 (2.6)	1 (4.3)
Why HCSE is not currently used for VLU, *n* (%)			
Uncertainty over efficacy	2 (4.8)	—	2 (8.7)
Unfamiliar with HCSE treatment	1 (2.4)	—	1 (4.3)
Lack of information	—	2 (5.1)	2 (8.7)

DN = district nurses; MP = medical practitioners; (—) = no response.

Table 12 Reasons why clients and practitioners would and would not consider HCSE treatment for future VLU.

	Clients ($n = 43$)	DN ($n = 39$)	MP ($n = 23$)
Why HCSE may be utilised in future, *n* (%)			
Due to previous success	6 (14.3)	1 (2.6)	1 (4.3)
To promote wound healing	3 (7.1)	—	—
If there is clear evidence	2 (4.8)	3 (7.7)	2 (8.7)
Existing treatments are ineffective	2 (4.8)	—	—
To benefit clients	1 (2.4)	2 (5.1)	—
If approved by nurse or GP	1 (2.4)	2 (5.1)	—
Worth a try	—	2 (5.1)	2 (8.7)
Why HCSE may not be utilised in future, *n* (%)			
If advised against by GP	2 (4.8)	—	—
Adverse effects	2 (4.8)	—	—
Lack of information	—	2 (5.1)	2 (8.7)
Lack of evidence	—	—	1 (4.3)

DN = district nurses; MP = medical practitioners; (—) = no response.

Table 13 The frequency of medical practitioner recommendation of natural therapies to patients with VLU ($n = 23$).

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Massage	4 (17.4)	3 (13.0)	1 (4.3)	5 (21.7)	10 (43.5)
Meditation/relaxation	1 (4.3)	1 (4.3)	2 (8.7)	2 (8.7)	17 (73.9)
Vitamin/mineral supps	0	3 (13.0)	3 (13.0)	9 (39.1)	8 (34.8)
Acupuncture/pressure	0	1 (4.3)	1 (4.3)	3 (13.0)	18 (78.3)
Herbal medicine	0	0	4 (17.4)	2 (8.7)	17 (73.9)
Aromatherapy	0	0	1 (4.3)	0	22 (95.7)
Homeopathy	0	0	0	2 (8.7)	21 (91.3)
Touch/spiritual healing	0	0	0	0	23 (100)
Mean response	0.6	1.0	1.5	2.9	17.0

in the future use of venotonic therapy for VLU.

Nurse utilisation and attitude toward venotonic agents

More than half of nurses support venotonic therapy in the management of VLU, and correspondingly, more than half of nurses recommend venotonic agents to clients. Despite the trend toward evidence-based practice, many nurses are engaging in treatment that is not supported by clinical evidence. Whilst the stage I trial may have influenced many nurses to utilise venotonic therapy, other factors swaying the use of alternative treatments in wound care need to be explored.

Table 14 The frequency of nurse recommendation of natural therapies to patients with VLU ($n = 39$).

	Daily (%)	Weekly (%)	Monthly (%)	Infrequently (%)	Never (%)
Vitamin/mineral supps	4 (10.3)	12 (30.8)	11 (28.2)	9 (23.1)	3 (7.7)
Aromatherapy	2 (5.1)	2 (5.1)	3 (7.7)	7 (17.9)	25 (64.1)
Meditation/relaxation	2 (5.1)	3 (7.7)	7 (17.9)	9 (23.1)	18 (46.2)
Herbal medicine	1 (2.6)	3 (7.7)	5 (12.8)	11 (28.2)	19 (48.8)
Massage	1 (2.6)	1 (2.6)	15 (38.5)	8 (20.5)	14 (35.9)
Acupuncture/pressure	1 (2.6)	1 (2.6)	1 (2.6)	6 (15.4)	30 (76.9)
Touch/spiritual healing	1 (2.6)	0	2 (5.1)	6 (15.4)	30 (76.9)
Homeopathy	1 (2.6)	0	1 (2.6)	4 (10.3)	33 (84.6)
Mean response	1.6	2.8	5.6	7.5	21.5

Such research may identify whether existing wound care products are meeting client and practitioner needs in order to improve the development of future wound treatments.

Client utilization and attitude toward HCSE

Claims of minimal venotonic use in western countries[42] were supported in stage II, with very few clients utilising HCSE, and the majority of clients first finding out about the extract through stage I. Anecdotal evidence of wound healing with HCSE, and the use and support of venotonic therapy and herbal medicine all influenced client use of the extract. Nonetheless, inconclusive stage I findings, gate keeping and lack of information arise as major constraints of current and future HCSE use amongst clients.

Medical practitioner utilization and attitude toward HCSE

Due to a lack of information and clinical evidence, MP attitude toward HCSE was generally irresolute, and HCSE use was consequently minimal. Whilst further evidence may improve MP utilisation of HCSE, medical prejudice may continue to constrain its use. Thus, further research is needed to identify which barriers hinder MP use of HCSE. By addressing these obstacles, clients with VLU may potentially be exposed to a larger range of treatment options.

Nurse utilization and attitude toward HCSE

Nurse's attitudes toward HCSE were generally more positive than MP attitudes, although the majority of nurses remained uncertain. Consequently, the utilisation of HCSE both currently and in the future is likely to be minimal. Other than a paucity of evidence and information, unfamiliarity with HCSE and the potential for organisational and MP gate keeping may further constrain nurse utilisation of the extract.

Quality and limitations of study

Stage II was the first study to explore the utilisation of venotonic therapy amongst practitioners, and clients with VLU. Stage II was also one of few studies to investigate natural therapy use amongst practitioners and clients with an instrument demonstrating a high degree of internal consistency and established face and content validity. Notwithstanding, the generalisability of the findings was limited by a poor practitioner response rate, a small convenience sample, and the potential for refusal, sampling and response set bias. Therefore, these findings are likely to only apply to DNs, MPs and clients in metropolitan Adelaide. Future research may address these limitations by reducing survey length and the number of open questions,[43] counterbalancing question responses,[44] and utilising randomised sampling techniques.[45]

Conclusion

Nurses were most supportive and subsequently more likely to utilise natural therapies for the treatment of VLU than clients and MPs. Nonetheless, the future use of natural modalities amongst practitioners is expected to decrease whilst client use is likely to rise. Although a lack of knowledge and evidence may influence the decline in practitioner use, attempts to improve wound healing and maintain self-health may motivate clients to turn to natural modalities. Venotonic therapy received greater support than natural medicine from all groups, however MPs were once again less likely to utilise venotonic therapy. Clients and practitioners were also supportive about the safety of HCSE, although uncertain about the efficacy, suitability and integration of HCSE into mainstream medicine. Subsequently, less than half of nurses, and very few clients and MPs reported HCSE use. Notwithstanding, positive stage

I findings may improve client and practitioner use of HCSE in future. Thus, stage II affirms that findings supporting the clinical efficacy of HCSE in the treatment of VLU may facilitate the incorporation of the extract into clinical practice. Nonetheless, even if stage I findings were statistically significant, the integration of HCSE into mainstream wound management maybe further constrained by medical and organizational gate keeping. Whilst findings pertaining to stage II clients may reciprocate that of the wider community, the poor response rate and sample size of clinicians suggests further research is required to verify whether stage II findings apply to other practitioners.

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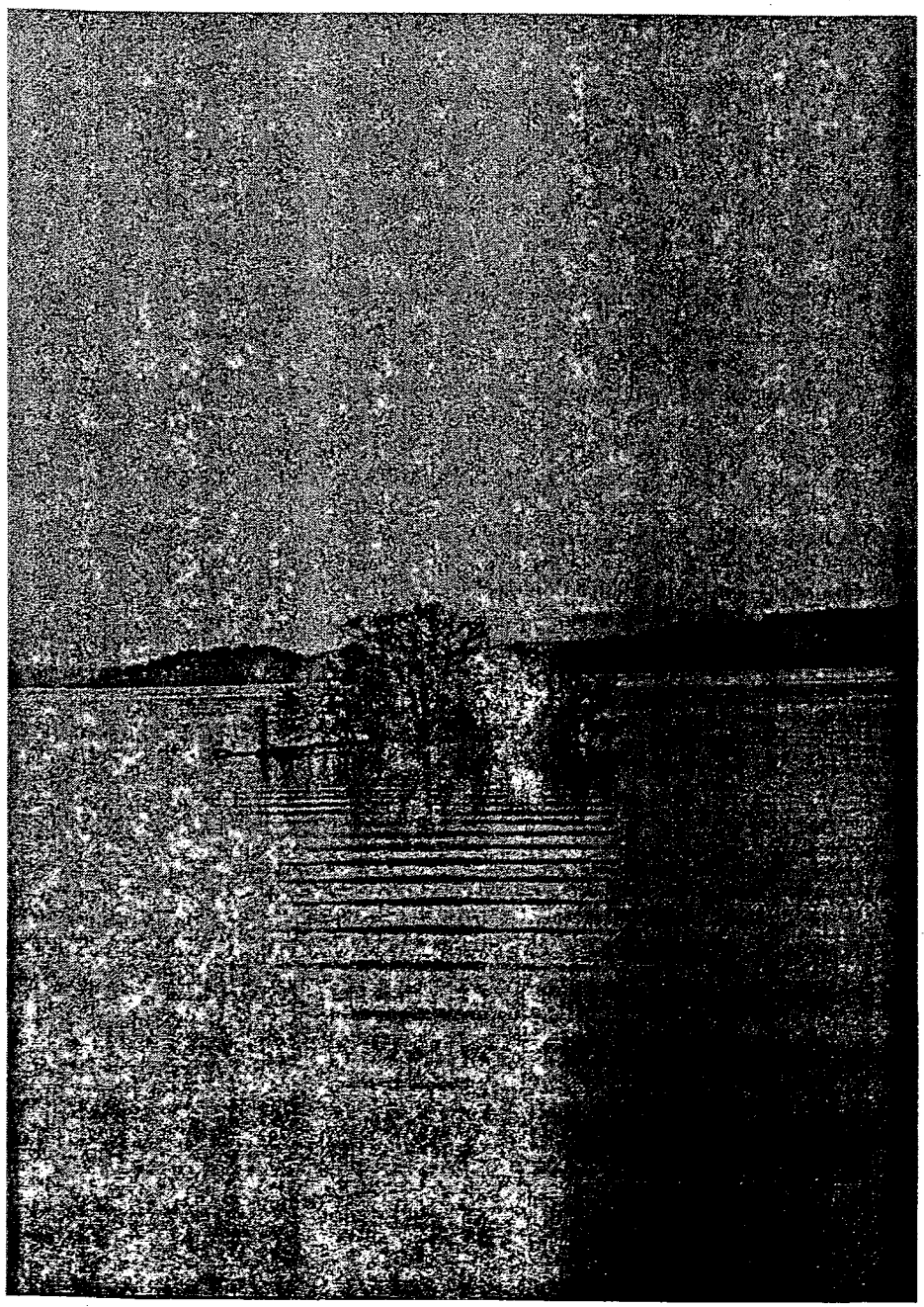

(Photo: D. Rankin-Box).

A Critical Review of Natural Therapies in Wound Management

– Matthew J. Leach, RN, BN(Hons), ND

The use of natural medicine by both the general population and the nursing profession is increasing. Also referred to as unconventional, alternative, and complementary, these therapies often are derived from natural sources and facilitate improvements in health and well being by supporting innate healing processes of the body. Although the application of natural therapies in wound management is still in its infancy, several — honey, larval therapy, aromatherapy, herbal medicine, homeopathy, nutrition, and mind-body-spirit techniques — are demonstrating potential benefit in the management of acute and chronic wounds. Existing evidence of safety and effectiveness is predominantly based on the results of in vivo studies; confirmation from well-designed clinical trials is deficient. Consequently, clinical research is needed to examine these therapies to address the escalating incidence of chronic wounds in a climate of increasing healthcare costs.

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The use of natural medicine by both the general population and the nursing profession is increasing worldwide,[1-7] particularly in the treatment of dermatological conditions.[8] A systematic review of seven surveys on complementary therapy use in dermatology found the lifetime prevalence of clients utilizing alternative therapies ranged from 35% to 69%.[8] Degrees of dermatological improvement with natural therapies varied, with the majority reporting no change to some improvement.[10] Homeopathy was the most used approach, followed by herbal medicine, which internationally was the most favored.[8] A positive association between the duration and severity of dermatological disease and an increase in the use of complementary medicine also was identified.[8-10] Because leg ulceration is one such chronic and largely neglected condition,[11] individuals with chronic wounds are, therefore, likely experimenting with natural therapies.

As the elderly population increases, the incidence of acute and chronic wounds also will escalate; with increasing healthcare costs, demand on an already burdened healthcare system will grow. Therefore, emerging wound care treatments should not only accelerate the rate of healing, but also prevent wound recurrence. Using topical agents for the management of wounds is more often than not the sole form of treatment by many practitioners. However, treating the wound bed and not the underlying cause arguably results in delays in wound healing

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while increasing the potential for complications. Therefore, in addition to addressing the underlying etiology of wounds, an effective wound treatment should endeavor to promote normal immunity; increase tissue perfusion; promote wound healing; decrease edema; alleviate pain; and debride slough, necrotic tissue, and debris.[12]

The treatment options available for managing wounds are diverse and contentious, ranging from topical agents, compression therapy, pharmaceuticals, and surgery to natural therapies and nutritional intervention. Likewise, the myriad of ancillary measures such as weight reduction, smoking cessation, exercises, lymphatic drainage, physical therapy,[13] skin care, and positioning[14,15] add to the complexity of wound management. Many natural therapies are currently utilized in wound management, including iodine, sugar, plant extracts, magnetic therapy, acupuncture, and massage.[16] However, only therapies demonstrating some degree of evidence of their positive effect on wound healing will be discussed in this article. These treatments include larval therapy, honey, aromatherapy, herbal medicine, homeopathy, nutrition, and mind-body-spirit techniques. The goal here is to explore the evidence base of several topical and systemically administered natural therapies in wound care and to highlight the role of emerging treatments and the need for further research into alternative approaches to wound management.

Larval Therapy

Larvae from various fly species produce hemolymph and alimentary secretions,[17] allantoin, calcium carbonate, and ammonium ions.[18,19] These substances are purported to promote wound healing by enzymatically debriding necrotic tissue; decreasing microbial levels; increasing wound pH; promoting granulation[18,19]; and stimulating human fibroblast activity.[17]

A preliminary *in vitro* study[20] on the secretions of larvae from *Lucilia sericata* demonstrated marked antimicrobial activity against cultured *Staphylococcus aureus* and *Streptococcus* A and B, and partial activity against *Pseudomonas spp.* and methicillin-resistant *S. aureus* (MRSA). Although these properties may be beneficial in treating and preventing wound infection, clinical trials are required to verify claims regarding antimicrobial action. Despite the paucity of clinical studies investigating the antimicrobial activity of larval therapy, claims of clinical wound healing activity are emerging.

Studies. A 72-year-old man with bilateral plantar ulcers of unknown etiology demonstrated no improvement in wound healing after 12 months of conventional treatment.[19] His left foot wound, which measured 3.3 cm x 2.5 cm, was treated with larval therapy. After 13 weeks, the wound reduced to a 4-mm eschar. By comparison, the smaller right foot ulcer, which measured 2.4 cm x 1.8 cm over the same period of time, demonstrated no improvement with normal saline dressings. A similar case study of a 74- year-old man with a circumferential necrotic venous ulcer that was unresponsive to frequent surgical debridement achieved complete debridement within 3 weeks of larval therapy.[21] In another case, a 56- year-old man with a 4-cm unclassified chronic leg ulcer demonstrated complete healing within 4 weeks after two applications of larval therapy, followed by hydrocolloid dressings and topical phenoxy ethanol.[22] Nonetheless, these case studies are anecdotal and must be considered cautiously.

In a small retrospective study[22] of outpatients, larval therapy was used as a treatment for nonhealing wounds of varying etiologies. Of the 21 wounds studied, 52% were completely healed after an average of 4 weeks of treatment, with an additional 33% healed by 6 months. Larval therapy also decreased the need for surgical resection or amputation by more than 62%. However, possible contamination from sample, observer, placebo, and recall bias limits the generalizability of these findings.

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KEY POINTS

- Slowly but surely, evidence about the potential effects of so-called "non-traditional" medicine and nutrition on wound healing is emerging.
- Although much remains unknown, existing evidence and the risk-benefit ratio of general patient support measures such as providing optimal nutrition and addressing patient stress suggest that these strategies should be implemented in clinical practice.

In a prospective randomized controlled trial (RCT),[23] where the clinical efficacy and cost effectiveness of larval debridement was compared to hydrogel in 12 patients with sloughy venous leg ulcers, 33% of ulcers receiving hydrogel were debrided within a month; whereas, all ulcers in the larval group desloughed after two applications. In addition, the cost of larval therapy treatment was slightly more than 78 £ ($125 USD) for six patients, compared to 136 £ ($218 USD) for the six patients receiving hydrogel. However, while significant differences were evident between the two treatments, confounding by sample, observer, and placebo bias cannot be excluded.

Honey

The use of honey as a wound dressing has re-emerged in recent times.[24] A growing number of studies suggests the wound healing activity of honey may be attributed to antibacterial, debriding, anti-inflammatory, immunostimulant, and antioxidant properties or through the stimulation of granulation and epithelialization.[24] Many of these properties have been supported in recent clinical trials.

Studies. In a study of 59 patients with wounds of varying etiologies that were unresponsive to conventional treatment and then received daily treatment with unprocessed honey,[25] all wounds (excluding a Buruli ulcer) yielded no growth of organisms after the first week of treatment. Furthermore, wound odor, periwound edema, slough, and necrotic tissue decreased while granulation and epithelialization rapidly increased. Despite these results, the validity of these findings is questionable due to the absence of blinding and controls.

In a prospective RCT,[26] 104 patients with burns that covered between 5% and 40% percent of the body were treated topically with either honey or silver sulfadiazine (SSD). Within 7 days, swab cultures demonstrated no growth in 91% percent of patients treated with honey, compared to 7% of those using SSD. Evidence of granulation with honey occurred after a mean of 7.4 days, much earlier than the 13.4 days demonstrated with SSD. Time to total wound healing was also more rapid in the honey group (P <0.0001), with 63% of wounds healed by 10 days, compared to 6% with SSD. Patients in the honey group also demonstrated fewer cases of hypergranulation, post-burn contracture, scar hypertrophy, and pain.[26]

Similarly, honey demonstrated a faster rate of healing (P <0.001) and a lower incidence of infection and inflammation when compared to SSD in another RCT of 50 partial-thickness burns.[27] Likewise, burns treated with honey-impregnated gauze also healed significantly faster than those treated with polyurethane film (P <0.001, n = 92).[28] Although these aforementioned trials were well designed, the absence of blinding creates the question of potential placebo and observer bias contamination.

Herbs

Herbs possess multiple properties that are potentially conducive to wound healing, including the ability to serve as an astringent, demulcent, antimicrobial, antifungal, and immunostimulant, as well as their nutritive and vulnerary activity.[29,30] Numerous herbs demonstrate these aforementioned properties (see Table 1),[30-37] but the wound healing activity of the majority of these herbs has not been validated in clinical trials.

Aloe — *Aloe vera.* Aloe has been used both internally and externally for healing burns, skin injuries, abrasions, frostbite, and ulcerations.[38] Aloe's ability to stimulate fibroblast and connective tissue formation and the presence of zinc and vitamins C and E support wound healing. Additional properties conducive to healing include anaesthetic, antipruritic, moisturizing, anti-inflammatory, and demulcent activity.[35,38] Aloe also demonstrates antibacterial and antifungal activity similar to that exhibited by SSD.[38]

Studies. Topical and subcutaneous administration of acemannan from *Aloe vera* was tested in young and old, normal weight and obese rats with surgical biopsy wounds.[39] Treated wounds in young rats healed 4 days faster than control wounds. Acemannan-treated wounds in normal weight older rats healed 5 days earlier than controls, with treated wounds in older obese rats healing 3 days earlier than controls. These findings suggest that the acemannan from *Aloe vera* may foster wound healing in acute wounds in the young, elderly, normal weight, and obese by promoting macrophage activity or by potentiating the activity of wound growth factors.[39]

TABLE 1
HERBS WITH REPORTED EFFECTS ON WOUND HEALING

Aloe	Antifungal; demulcent; hemostatic; vulnerary
Calendula	Anti-inflammatory; antifungal; antimicrobial; astringent; vulnerary
Chickweed	Astringent; demulcent; vulnerary
Comfrey	Astringent; cytophylactic; demulcent; hemostatic; vulnerary
Echinacea	Antibacterial; anti-inflammatory; immunostimulant; vulnerary
Elderflower	Anti-inflammatory; vulnerary
Fenugreek	Anti-inflammatory; antimicrobial; demulcent
Ginseng	Immunostimulant; anti-inflammatory
Golden seal	Antimicrobial; astringent; hemostatic; vulnerary
Gotu kola	Vulnerary
Greater plantain	Astringent; demulcent; hemostatic; vulnerary
Horsetail	Anti-inflammatory; astringent; hemostatic; vulnerary
Marshmallow	Demulcent; vulnerary
Mullein	Astringent; anti-inflammatory; demulcent; vulnerary
Slippery elm	Astringent, demulcent; nutritive; vulnerary
St. John's Wort	Analgesic; anti-inflammatory; antiseptic; astringent; vulnerary
Yarrow	Astringent; antiseptic

In a study[40] where the effect of oral and topical *Aloe vera* on biopsy wounds in mice was explored over an 8-week period, *Aloe vera* significantly decreased wound diameter in both orally and topically treated mice compared to controls ($P < 0.05$ and $P < 0.001$, respectively). Treated wounds also demonstrated greater vascularity and healthier granulation tissue.

The results of treating Stage II, III, and IV pressure ulcers with either *Aloe vera* hydrogel or conventional saline-soaked gauze dressings were assessed in 30 patients.[41] No significant difference in the number of healed wounds or mean duration of healing between the two treatment groups was noted. Nonetheless, these results must be considered with caution due to the small sample and the absence of blinding. In contrast, results of clinical studies with acute wounds are more robust. Partial-thickness burns treated with *Aloe vera* gel healed more rapidly than wounds treated with Vaseline (Tyco Health Care/Kendall, Mansfield, Mass.), healing after an average of 11.9 days compared to 18.2 days, respectively ($P < 0.002$).[42] On histological examination, *Aloe vera* gel produced rapid organization of fibrovascular and collagen tissue and more rapid growth of squamous epithelium. These histological effects were not demonstrated with Vaseline gauze. Although placing both treatments adjacent to each other on the same wound may have resulted in cross-contamination, the histological findings dispute any such effect. However, sampling bias from a convenience sample of 27 patients may exist.

In a small clinical study[43] involving 18 patients who had undergone facial dermabrasion, the efficacy of stabilized *Aloe vera* gel polyethylene oxide dressing was compared to a standard polyethylene oxide dressing, each applied to half of the face. Within the first 24 to 48 hours, the aloe-treated side demonstrated intense vasoconstriction and edema reduction compared to controls. By 72 to 96 hours, crusting and exudation were less evident with the aloe treatment, and by day 5 to day 6, 90% re-epithelialization was evident with the aloe gel compared to less than 50% with controls. The aloe gel dressing reduced wound healing time by approximately 3 days. However, the presence of observer and sample bias in this open-label design and confounding from the chilled aloe dressing casts doubt over the validity of these findings.

Calendula — ***Calendula officinalis***. For centuries, calendula has been used in the treatment of wounds,[44] possibly due to its anti-inflammatory, antimicrobial, antifungal, immunostimulant, styptic, and granulatory properties.[30-33,35,38] However, most recent findings suggest the vulnerary activity of calendula is attributed to an increase in angiogenesis,[44] collagen, nucleoprotein, and glycoprotein metabolism.[45,46]

Studies. The efficacy of an ointment containing 4% *C. officinalis* and 1% allantoin on ellipsoid cutaneous excisions was examined in a controlled study in 72 Wistar rats.[46] The combination of calendula and allantoin produced greater phagocytic activity, macrophage differentiation, granulation, and epithelialization than the use of either allantoin or base

ointment. Furthermore, the combination of calendula and allantoin in a previous study also demonstrated greater changes in wound surface area than the singular use of calendula.[46]

In another controlled murine study[47] that explored the wound healing effect of a 1:10 alcoholic extract of *C. officinalis*, paravertebral incisions treated with topical calendula demonstrated significantly greater wound breaking strength than controls ($P < 0.01$) after 10 days of treatment. In full-thickness excised wounds, the period to complete epithelialization with topical calendula also was significantly less than control wounds ($P < 0.001$). These results suggest topical calendula may facilitate collagen maturation and epithelialization.

In a double blind RCT[48] on 18 patients with trophic ulceration, 10% calendula ointment was compared to topical neomycin and placebo paraffin ointment. Topical calendula prevented secondary infection and demonstrated a 40% reduction in wound diameter and volume within 4 weeks. However, the comparative effects of neomycin and placebo ointment on wound healing were not detailed.

Comfrey - *Symphytum officinale.* Comfrey possesses vulnerary, demulcent, astringent, and cell proliferative properties that are beneficial in controlling bleeding, accelerating wound healing, and discouraging abnormal scar formation.[33,35] These properties have been attributed to allantoin,[29,32,38] although the activity of mucilage, protein, zinc, cyanocobalamin, glycine, and proline cannot be excluded.[49,50] Nonetheless, controversy surrounds the possible hepatotoxicity of topical applications of comfrey onto open wounds.[32,38]

Study. The wound healing activity of topical comfrey in cutaneous excisions was compared to saline using a murine model.[49] Comfrey significantly increased wound fibroblast levels by days 7, 11, and 14, with a corresponding increase in the number of collagen fibers by day 14. An initial increase in angiogenesis was also evident by day 7. Orally administered comfrey also produced a weak analgesic effect. Although stages of wound healing were not compromised with topical comfrey in rats, clinical studies are required to verify these claims in humans.

Echinacea — *Echinacea purpurea.* Echinacea has been used for centuries as an immunostimulant, although it also shows promise as an anti-inflammatory, antibacterial, lymphatic, and vulnerary agent.[51]

Studies. The efficacy of *E. purpurea* on the healing of surgical skin flaps was compared to normal saline and pentoxifylline using a murine model.[52] Echinacea promoted greater flap perfusion ($P < 0.01$) and a lesser degree of skin flap necrosis when compared to controls. Although these findings are yet to be confirmed clinically, surgical incisions in guinea pigs treated with an ointment containing *Echinacea spp.* also were found to produce a greater rate of healing than controls ($P < 0.05$).[53]

German chamomile — *Matricaria recutita.* German chamomile is indicated in slow-healing wounds[38] and possesses anti-inflammatory, analgesic, diuretic, vulnerary, immunostimulant, antifungal, and antimicrobial properties.[30,35,38,50] Although azulene is the constituent most likely responsible for the vulnerary activity of chamomile,[32] the presence of vitamin C,[54] flavonoids, and amino acids[50] also may affect wound healing.

Study. The wound healing effect of a blend of calendula, chamomile, linden, cornflower, hypericum, and hydrocortisone was compared to 0.5 % hydrocortisone cream in five subjects, each with a series of three surgically induced abrasions.[54] Wounds treated with the herbal blend healed an average of 16% faster than controls, while hydrocortisone-treated wounds healed only 3% faster than controls. However, the generalizability of these findings is limited by the small sample size and the absence of participant details.

Gotu kola — *Centella asiatica.* The herb Gotu kola produces diuretic, dermatological, vulnerary, venotonic, and peripheral vasodilator effects[55] and may be useful in the treatment of vascular wounds.

Studies. Centella asiatica used as a healing agent was examined in rats with full-thickness dermal excisions.[56] Compared to controls, topical and oral *C. asiatica* significantly increased wound cellular proliferation, collagen synthesis, epithelialization, wound contraction, collagen maturation, and cross-linking. Likewise, surgical wounds on guinea pigs treated topically with a *C. asiatica* and essential oil formulation demonstrated accelerated wound healing, eschar

TABLE 2
ESSENTIAL OILS WITH REPORTED EFFECTS ON WOUND HEALING

Bergamot	Analgesic; antimicrobial; cicatrisant; deodorant; vulnerary
Chamomile	Analgesic; anti-inflammatory; antineuralgic; bactericidal; cicatrisant; vulnerary
Eucalyptus	Analgesic; antifungal; antibacterial; anti-inflammatory; antineuralgic; astringent; cicatrisant; deodorant; vulnerary
Frankincense	Anti-inflammatory; antiseptic; astringent; cicatrisant; cytophylactic; immunostimulant; vulnerary
Geranium	Analgesic; antibacterial; anti-inflammatory; astringent; cicatrisant; cytophylactic; deodorant; hemostatic; immunostimulant; vulnerary
Lavender	Analgesic; bactericidal; cicatrisant; cytophylactic; deodorant; vulnerary
Myrrh	Anti-inflammatory; antifungal; antimicrobial; astringent; cicatrisant; fungicidal; vulnerary
Rosemary	Analgesic; antiseptic; astringent
Tea tree	Bactericidal; cicatrisant; fungicidal; immunostimulant
Thyme	Bactericidal; cicatrisant
Yarrow	Anti-inflammatory; astringent; cicatrisant; hemostatic

formation, and an increased number and size of keratohyaline granules when compared to controls.[57] Both studies concluded that *C. asiatica* influenced all phases of wound healing.

In an open-label trial,[57] the healing and antimicrobial activity of *C. asiatica* and essential oil formulation also was explored in 20 patients with various chronic, surgical, and traumatic wounds. In the wounds studied, topical treatment resulted in 64% of wounds healing in a mean period of 6 weeks, with 16% of wounds demonstrating some degree of improvement. Treatment also decreased microbial growth and wound infection in 75% of patients with contaminated wounds. These findings suggest that *C. asiatica* may promote wound healing in various acute and chronic wounds, but the addition of essential oils and the potential contamination with placebo, observer, and sample bias casts doubt over the validity of these results.

St. John's Wort — *Hypericum perforatum.* Hypericum has received significant attention in recent times as an effective treatment for depression; however, the role of hypericum in wound management is starting to emerge. In addition to vulnerary activity, hypericum also displays anti-inflammatory, antimicrobial, astringent, granulatory, and analgesic properties.[30,32,33,35,58]

Study. The wheat germ oil extracts of *H. perforatum* and *C. arvensis* were compared to wheat germ oil in 24 patients with post-caesarean incisional wounds.[59] Treatment twice daily with the plant extract-impregnated gauze resulted in a 38% decrease in wound surface area (cm^2) by 16 days, compared to a 16% reduction in the control group. However, the large treatment effect is ambiguous without some level of significance. Furthermore, despite the homogenized sample and standardized treatment, the selection, randomization, and blinding procedures were not elucidated; thus, the external validity of these findings is in question.

Aromatherapy

Essential oils from various parts of plants possess numerous properties — ie, antiseptic, anti-inflammatory, analgesic, astringent, cicatrisant, cytophylactic, deodorant, fungicidal, hemostatic, immunostimulant and vulnerary activity — that may accelerate wound healing (see Table 2).[60-63] Unlike other agents, the concomitant effects of essential oils also may reduce psychological stress, subsequently improving immunity, enhancing the healing activity of the individual, and shortening the duration of convalescence.[64] However, a paucity of clinical evidence supports the safety and efficacy of essential oils in wound care.[65-67] This lack of evidence may be attributed to difficulties in achieving double-blind conditions with essential oils.[68] Another concern with aromatherapy research is the inconsistent application of these oils. Ranging from neat[69] and diluted applications[67] to the use of oil-impregnated dressings,[67] these incompatible techniques may limit the external validity of pooled findings.

Lavender — *Lavandula officinalis.* Lavender essential oil demonstrates analgesic, anti-inflammatory, antiseptic, bactericidal, deodorant, cytophylactic, cicatrisant, immunostimulant, and vulnerary properties.[60,61,63,69] Lavender is believed to be beneficial in

ınd care by inhibiting tis-
destruction and promot-
the synthesis of new tis-
.[69] Isolated reports of indi-
uals with unclassified
onic leg ulcers suggest
ender and tea tree oil
ıance wound healing,[69]
ıough anecdotal evidence
poor measure of validity.
Study. In a small RCT[67], the
ınd healing effect of an
ential oil blend was com-
ed to conventional wound
e in four patients with
onic wounds of varying eti-
gy. Of the four wounds
ated with the chamomile
l lavender essential oil, three
aled by 77, 79, and 176 days. In the control group,
y one of two wounds healed by 182 days.
hough this study is the first to explore the safety
l efficacy of essential oils in the healing of chronic
man wounds, the small and unequal group size,
terogenous wound types and treatments, different
atment settings, and absence of blinding casts
ubt over the validity of these findings.

utrition

Adequate nutritional intake is essential for opti-
l wound healing,[70-72] as poor nutritional status
y contribute to delayed wound closure and
creased wound tensile strength.[71] Nutrients
quired for wound healing are listed in Table 3.[36,73]
me authors claim that sufficient levels of nutrients
y not reach lower limb wounds when lower limb
rfusion is compromised, particularly in the
lerly,[72,74] setting up the argument that topical appli-
ions of nutrients should be used to ensure that
trients reach the wound and surrounding tissue.
me topical mineral dressings already in use are
lcium alginate, iodine, and zinc-paste dressings.[72,74]
Vitamin A. Vitamin A promotes phagocytosis,
tibody production, intercellular adhesion,[36] epithe-
l cell differentiation,[73] and collagen synthesis.[70] In a
uble-blind RCT[75] of 40 patients post-photorefrac-
e keratectomy, the effect of high dose vitamin A

TABLE 3
NUTRIENTS THAT CONTRIBUTE TO WOUND HEALING

Arginine
Copper
Glycine
Leucine
Lysine
Proline
Silicon
Threonine
Vitamin A
Vitamin B_5
Vitamin C
Vitamin E
Zinc

(25,000 IU retinol palmitate) and vitamin E (230 mg alpha-tocopherol nicotinamide) on re-epithelialization was examined. Vitamin supplementation significantly decreased re-epithelialization time when compared to controls ($P = 0.029$), with 65% of treated eyes re-epithelializing within 3 days, compared to 30% of controls. However, whether these wound healing effects extend to chronic wounds is unclear.

Vitamin B_5. Pantothenic acid supports wound healing by promoting fibroblast proliferation and antibody production.[36] In a prospective, double blind RCT[76] of 40 patients undergoing successive tattoo resection, the efficacy of ascorbic acid (vitamin C) and pantothenic acid (vitamin B_5) in wound healing was examined. One week before resection, patients were administered either 1 g ascorbic acid and 200 mg pantothenic acid or placebo for 21 days. Although no direct measures of wound healing were discussed, supplementation significantly decreased the postoperative decline in vitamin C and B_5 levels and increased the mobilization of trace elements when compared to controls. Supplementation also increased scar fibroblast proliferation, although this effect was not statistically significant. Greater healing properties may have been demonstrated with higher therapeutic doses of ascorbic acid and pantothenic acid.

Vitamin C. In addition to its antioxidant, angiogenesis, and immunomodulating effects,[36,70,71] vitamin C also promotes wound healing by facilitating the hydroxylation of proline and lysine to form procollagen.[73] However, scant research has been conducted on the wound healing ability of vitamin C.

Studies. The efficacy of ascorbic acid in the treatment of 20 patients with pressure sores of unspecified locations were evaluated in a prospective, double blind controlled trial.[77] The daily administration of 1 g ascorbic acid more than doubled leucocyte ascorbic-acid levels

and resulted in an 84% reduction in ulcer size by 4 weeks, compared to 42% in controls ($P < 0.005$). Furthermore, twice as many ulcers completely healed in the treatment group (n = 6) compared to controls (n = 3). However, in a similarly designed clinical trial,[78] 500 mg ascorbic acid was no more effective than 10 mg ascorbic acid in promoting pressure sore healing. Differences in dosage and the utilization of an active control may have misconstrued findings.

Vitamin E. Vitamin E is another potential wound healing nutrient that demonstrates antioxidant, anti-inflammatory, and immunostimulant activity.[36] In addition, vitamin E also promotes angiogenesis and reduces scarring.[79]

Study. In a controlled study[80] in albino rats, the healing ability of alpha-tocopherol (vitamin E) in experimental gingival wounds was explored. Rats receiving oral alpha-tocopherol demonstrated greater epithelialization and less inflammation and suppuration than controls, possibly attributed to an increase in immune function. However, levels of significance were not detailed; hence, true differences between groups remain unclear.

Zinc. Zinc is also required for wound healing,[36] playing an essential role in protein and collagen synthesis and degradation.[73] However, in a review of studies to date, the efficacy of oral zinc supplementation in wound healing remains inconsistent and inconclusive.[81] On the other hand, topical zinc may be beneficial.

Study. In a small double blind RCT[74] of 37 patients, 83% of arterial and venous wounds treated with zinc-impregnated gauze improved, compared to 42% treated with plain gauze. Furthermore, by 12 weeks, 61% of zinc-treated wounds were completely healed, compared to 21% in the control group. Although the sample size was small, the trial was well designed and suggests topical zinc dressings may be conducive to wound healing.

Homeopathy

Homeopathy is a system of medicine that uses serial dilutions of plant, mineral, or organic matter to stimulate curative mechanisms in order to restore equilibrium.[82] Because of its antiseptic, vulnerary, and analgesic properties and its ability to prevent scarring, homeopathic hypericum was reportedly used by soldiers during World War I for gunshot wounds.[83] More recently, homeopathic calendula has been used postoperatively in humans and canines[83]; however, a paucity of clinical evidence exists to support the use of homeopathic calendula.

Studies. In a controlled *in vivo* study[47] using a murine model, orally administered 1 C homeopathic *H. perforatum* demonstrated a significant increase in wound-breaking strength of acute incised wounds ($P < 0.001$) and a significant decrease in epithelialization time in acute excised wounds ($P < 0.001$). Furthermore, as a measure of healing in dead-space wounds, hypericum also increased the breaking strength of cotton-pellet granulomas ($P < 0.001$).

The treatment of traumatic ear wounds with orally administered homeopathic silica was compared to saline using a murine model.[84] Mice treated with 10^{-10}, 10^{-60}, and 10^{-400} homeopathic dilution of silica over 4 to 20 days demonstrated a greater rate of healing and significantly smaller wounds ($P < 0.05$-0.001) than saline-treated mice. Healing was also more significant at the higher silica dilutions. Although these findings are promising, they are yet to be confirmed clinically.

Mind-Body-Spirit Therapy

To date, the conventional management of wounds is primarily focused on topical applications; thus, the wound is addressed from a purely physiological viewpoint. However, because humans are psychosocial and spiritual beings, non-physical influences on wound healing cannot be excluded. Wientjes[85] argues that negative thought patterns, attitudes, and behaviors (eg, feelings of guilt, anger, depression, anxiety, fear, and poor self-worth) might contribute to delays in wound healing. Not surprisingly, these aforementioned emotions are typical manifestations of individuals with chronic leg ulceration[3,86]; therefore, mind-body-spirit techniques (MBST) such as positive affirmations, guided imagery, relaxation, energy healing, hypnosis, conscious breathing, and prayer may address the psycho-emotional impediments that delay wound healing.[85,87]

Studies. Several studies have demonstrated that stress can contribute to delays in wound healing. Among 26 patients recently relocated to a nursing home, significantly higher serum cortisol levels were

reported in patients who developed pressure ulcerations ($P < 0.02$).[88] Compared to controls, stress also significantly delayed the healing of punch biopsy wounds in mice,[89] dental students,[90] and caregivers of relatives with Alzheimer's disease.[91] Delayed healing of chronic wounds also was demonstrated in subjects with higher anxiety and depression scores.[92]

An intervention study[93] involving 24 patients post-cholecystectomy demonstrated that listening to an audiotape that employed guided imagery and relaxation techniques significantly reduced the level of patient anxiety, urinary cortisol, and wound erythema compared to controls receiving quiet time. Although MBST may address the stress and negative emotions that contribute to delays in wound healing, a paucity of evidence exists to associate MBST with hastened wound closure.

In a series of five double-blind RCTs,[94] the efficacy of therapeutic touch (TT), or "laying of the hands," on the re-epithelialization rate of deltoid biopsy wounds was examined. While two studies demonstrated TT significantly accelerated wound healing compared to control interventions ($P < 0.001$ and $P < 0.041$), the remaining studies demonstrated either no treatment effect or a positive control effect. Wirth, Richardson, and Eidelman[94] claim the negative findings in the three latter studies may have been attributed to variations in subject populations and treatment environments, as well as to possible transference and cancellation effects. Further research using similar protocols to the two positive studies are required to identify whether TT supports wound healing.

Conclusion

Despite the diversity of options, the efficacy of existing wound care treatments fails to be supported by substantial evidence from randomized controlled trials.[95] The paucity of evidence also applies to natural therapies. The majority of studies investigating natural therapies for wound management are frequently contaminated by placebo, sample, observer, and selection bias through the absence of randomization, blinding, adequate controls, and sufficient sample size. The generalizability of findings is also limited by wide variations in the preparation and application of treatments and the paucity of standardization, particularly with plant extracts. As demonstrated in the horsechestnut and venous leg trial (HAVLUT),[96] a randomized controlled trial investigating the clinical efficacy of horsechestnut seed extract (HCSE) in the treatment of venous leg ulceration, some of these aforementioned shortfalls may be explained by a lack of funding and support or by the presence of gatekeeping.

According to Gilchrist,[12] many natural therapies reflect the ideal dressing as they demonstrate immunomodulating, anti-edema, analgesic, and debriding activity. However, evidence to support the wound healing activity of the majority of these therapies is insufficient. Clinical evidence of wound healing activity is particularly lacking among herbs, essential oils, MBST, and the majority of nutrients. Notwithstanding, honey and *Aloe vera* demonstrate some degree of clinical efficacy in the treatment of acute wounds, as does larval therapy in chronic wounds. Although many natural therapies are supported *in vivo*, the investigation of these therapies within a randomized, controlled design, together with the application of standardized treatment protocols, are now needed. These studies will determine whether natural therapies have a role in the future management of acute and chronic wounds and the treatment of wound infection. - OWM

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Public, nurse and medical practitioner attitude and practice of natural medicine

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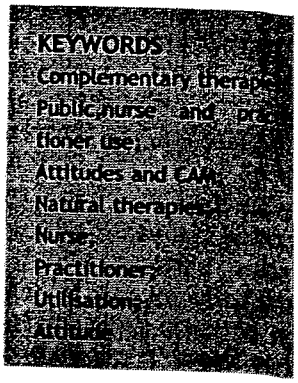

Summary In the past 20 years, the popularity of natural medicine has increased, with nurses and medical practitioners being amongst several groups of clinicians expressing a widespread interest in natural therapies. It is argued that the degree of natural therapy use and the attitudes of these practitioners toward natural medicine may not only influence patient exposure to these therapies, but also have some bearing on the future use of natural medicine. Hence, in a critical review of recent studies, the utilisation of natural therapies and the attitudes of nurses, medical practitioners and the public toward natural medicine are explored.
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Introduction

In the past 20 years, the popularity of natural medicine and natural therapies has increased,[1–4] with popularity extending globally.[5] Reasons for a surge of interest in natural medicine vary. Public opinion suggests individuals are moving toward natural therapies due to dissatisfaction with orthodox medicine[4,6] and to actively maintain one's own health and wellbeing.[7–9] Nurses however believe natural therapies not only support health and healing,[10] but augment nursing practice.[11,12] In contrast, medical practitioners believe natural therapies are complementary to conventional treatment[13] and are useful when conventional techniques are ineffective.[14] Therefore, the shift toward natural therapies may reflect a need to improve upon existing health care options. Notwithstanding, disparate legal, political, historical and medical positions between countries may also explain variations in the levels of interest and types of therapies utilised across the globe.[4,15]

The trend toward natural medicine is strongly influenced by conventional health care practitioners. Whilst patients may question nurses about various natural therapies, the nurses response can greatly influence the decision made by the patient.[16] Responses from other clinicians may also significantly manipulate a patient's choice. Therefore, ascertaining nurse and medical practitioner opinion on natural therapies may determine how patients are informed and ultimately how they are exposed to these aforementioned therapies.

Public use of natural therapies

Exploring the level of natural therapy use among individuals throughout the western world has received significant attention, with claims that use is increasing worldwide.[5] However, whilst many studies have identified the level of natural therapy use in isolated populations, variations in study geography, demographics and methodology

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challenge whether a global increase in natural therapy use is actually evident.

In a survey of over 3000 South Australians, 48 per cent of participants reported the use of at least one natural medicine, with the majority utilising vitamin supplements (38 per cent) and herbal medicine (10 per cent).[17] The utilisation of natural medicines amongst South Australians over 15 years of age equated to an annual expenditure of $51 million, and $621 million nationally. In the same year, the annual expenditure of pharmaceutical medications only reached $360 million nationally. Whilst the majority of natural medicine users were young, well exercised and optimistic, a Perth study found clients seeking advice on natural therapies to be professional females over the age of 35.[18]

A population-based survey of 5010 English adults revealed over 28 per cent of participant's utilised natural therapies and medicines during the 12 months preceding the survey, and nearly half had utilised natural therapies in a lifetime.[19] The annual out-of-pocket expenditure for six natural therapies was estimated at 450 million pounds, similar to Australia's estimated costing.

A population survey involving 1000 Japanese adults reported a comparatively higher proportion of natural therapy use than Western countries.[15] Seventy-six per cent of participants had utilised a complementary therapy during the 12 months preceding the survey, compared to 66 per cent of residents who had used orthodox medicine. The most prevalent complementary therapies used were nutritional and tonic drinks, dietary supplements and health-related appliances. In contrast to Australian findings,[17] the out-of-pocket expenditure for complementary medicine was half that for orthodox medicine, with complementary and orthodox medicine costing each respondent 19,080 Yen and 38,360 Yen, respectively.[15] Nonetheless, with only 1000 of 4292 residents responding to the survey and the high likelihood of recall bias, the generalisability of these findings is limited.

In the United States, the degree of alternative therapy utilisation amongst a random sample of 1539 in 1990 and 2055 in 1997 were compared.[20] In 1990, nearly 34 per cent of Americans reported the use of an alternative therapy, which increased significantly to more than 42 per cent in 1997 ($p<0.001$). The therapies experiencing the greatest rise in popularity were herbal medicine, massage and nutrient supplementation. Consistent with other studies[9,17–19,21–24] alternative therapy use was most frequent amongst tertiary-educated, higher income earning, female Caucasians within the age range of 35–49 years. Whilst the level of natural therapy use reported by Eisenberg et al.[20] is similar to that reported in Australia[17] and England,[19] Eisenberg et al.[20] findings may be misrepresented. Other than a disparity in sample demographics, the exclusion of non-English speakers, those without telephones, the utilisation of monetary incentives in the 1997 study and a high likelihood of recall bias, suggests Eisenberg et al.[20] results must be considered cautiously.

In another trend study involving North East Scotland residents, changes in the use of, and attitude toward complementary medicine were compared from 1993 ($n=341$) to 1999 ($n=432$).[24] Over the 6-year period, complementary therapy use increased from 29 to 41 per cent, with a statistically significant increase in the use of aromatherapy, acupuncture and reflexology ($p<0.001$). These results reciprocate the trend occurring in the US,[20] however given a response rate of only 54 per cent and the use of different sampling frames, further research is needed to substantiate these findings.

In a survey of 567 medical centre outpatients, 85 per cent of participants reported the use of one or more complementary therapies, particularly diet, manual healing and mind and body control techniques.[25] Despite such a high percentage of users, many patients believed they were inadequately informed about complementary therapies. The higher rate of complementary therapy use reported by Boutin et al.[25] conflicts with previous study findings, and maybe indicative of geographical indifference, sampling bias or poorly established instrument validity.

A sample of 416 randomly selected Ontario residents revealed 37 per cent were users of at least one holistic therapy, with chiropractic, massage and herbal medicine predominating.[26] These findings compare favourably to those reported in the US[20] and amongst 85 medical inpatients at a major Canadian teaching hospital.[27] Forty-four per cent of Ontario residents intended to utilise a holistic therapy in the future, with less than 20 per cent opposing the future utilisation of any holistic therapy. As in Eisenberg et al.[20] study, Lewis et al.[26] findings may also be confounded by recall and selection bias.

A large study involving 16 institutions over 15 US cities found 67 per cent of 6852 randomly selected pre-operative patients utilised complementary therapies.[28] Of these therapies, nutritional supplements and herbal medicine prevailed. Complementary therapy use was predominant amongst college-educated Caucasian females undergoing obstetrical/gynaecological or neurological procedures. However, in conflict with others studies,

users of complementary therapies were most likely to be over the age of 40 years. Whilst these findings may be isolated to pre-operative patients, reasons for the disparity in user characteristics remain unclear.

The use of natural medicine amongst specific patient populations has also been explored[23,28,29,30–36] with a higher level of natural therapy use evident amongst more chronic conditions, which may reflect the inability of orthodox medicine to adequately treat these chronic conditions.[9]

Worldwide statistics affirm that at least a half of individuals in the industrial world are utilising natural medicine. There is also a clear tendency toward the use of ingestive therapies such as nutrient supplementation and herbal medicine, and manual therapies such as massage and chiropractic. Although minimal data are available, an increasing trend in natural therapy utilisation is evident in the United States and Scotland, which is likely to extend globally.

Nurses' use of natural therapies

Nurses are amongst several groups of practitioners that are expressing a widespread interest toward natural therapies. Practising these therapies either in conjunction with nursing practice, or solely as natural therapists,[37] nurses are in a unique position to introduce these therapies to a large number of individuals in the community. Furthermore, the integration of complementary medicine into the public health care system is claimed to address nursing labour shortages by resolving nurse disillusionment with existing health care services.[38]

A survey conducted by the Australian Nursing Journal (ANJ) identified amongst 356 randomised readers of ANJ, that 81 per cent were utilising natural therapies.[3] Amongst these therapies, massage, counselling and aromatherapy prevailed. Similarly, amongst 393 readers of 'Nursing Times', over half of readers reported utilising natural therapies in the workplace, with massage and aromatherapy also predominant.[39] Whilst the majority of Nursing Times participants received training for the therapies they practiced, the level of training was not explored. Furthermore, the representativeness of the sample in both studies was unclear due to the paucity of study details.

Rankin-Box[40] surveyed 178 members of the Royal College of Nursing Complementary Therapy Forum (RCNCTF), exploring the degree of natural therapy utilisation and training amongst members. The majority of nurses practised massage, aromatherapy and reflexology with over 94 per cent reporting one or more qualifications in natural therapies, predominantly at certificate and diploma level. However, considering the poor response rate (9.3 per cent) and the source of the sample, sampling bias was highly probable. Therefore, these findings should be considered with caution. Nevertheless, these results were supported by a recent Australian study.

Leach[11] investigated the utilisation, training and attitudes toward natural therapies amongst nurses in a South Australian community setting. Fifty-six nurses, giving a response rate over 87 per cent, demonstrated a positive attitude toward natural therapies. Half of nurses utilised natural therapies infrequently, predominantly practising massage, nutrition and relaxation. Contrary to the findings of Rankin-Box,[40] less than two-thirds of staff reported training in natural therapies at a level often not exceeding 1 day. The inadequate level of training was reflected by a poor natural therapy knowledge base, a finding reciprocated amongst Israeli family practitioners.[41] However, the external validity of Leach's[11] findings is somewhat limited by the small sample size.

Hayes and Cox[42] surveyed 45 critical care units throughout London, and found that over half of units used natural therapies, with only 7 per cent providing therapies routinely. The modalities that predominated were massage and aromatherapy. However, responses for each unit were solicited from a single staff member, hence the accuracy of responses remains questionable. Furthermore, the level of natural therapy utilisation and training in critical care units is likely to be underestimated.

Four hundred and sixty-seven Ohio registered nurses were surveyed to ascertain both their personal and clinical utilisation of natural therapies.[43] Similarities were evident between those therapies utilised for both personal and clinical use, with a preference toward diet, prayer and visualisation. However, nurses were twice as likely to utilise natural therapies on themselves than on clients. Reasons for the differences in the level of natural therapy use were however not examined. Whilst King et al.[43] were amongst the first researchers to utilise random sampling in a large population of nurses in a variety of fields, a response rate of only 17 per cent casts doubt over the generalisability of these findings.

Amongst 202 Connecticut Nurse Practitioners surveyed, over a third had practiced natural therapies within their workplace, particularly meditation and imagery. Almost two-thirds of nurses reported to be slightly knowledgeable about natural therapies.[44] However, measurement of

knowledge by means of subjective self-assessment is arguably a poor indicator of knowledge, and questions the validity of such responses. Furthermore, the level of natural therapy education amongst practitioners was unclear.

Previous studies suggest nurses are implementing natural therapies within their workplace, with a particular preference toward massage and aromatherapy. However, definitions of these therapies may vary between nurses, particularly the difference between therapeutic massage and 'back rub'. Furthermore, studies examining natural therapy utilisation amongst nurses to date are not of high quality, often flawed methodologically by sampling bias or poorly established instrument validity and reliability.[11] Further research is warranted to identify international trends of natural therapy utilisation amongst nurses, utilising well-validated instruments, multiple settings and randomised sampling.

Medical practitioner's use of natural therapies

At present, the extent to which patients are exposed to natural modalities is partially dependent on the level of medical practitioner use of these therapies and the degree of referrals made to natural therapists. Correspondingly, as gatekeepers of medical services[45] and key stakeholders in legislative change, medical practitioners will continue to influence the future of natural medicine.

Throughout the United Kingdom, general practitioner use of natural therapies ranges from 13 to 32 per cent[2,46–48] with acupuncture, homeopathy and chiropractic/osteopathy the most predominant. Referrals to natural therapists ranges between 25 and 76 per cent, with therapies referred being similar to those practiced.[2,46–49] Of concern however, is that of the UK physicians practicing natural therapies, only 13–38 per cent had obtained any specific natural therapy training.[2,48,49] Current studies on medical practitioner use in the UK remain inconsistent, which may be indicative of geographical indifference, or due to undesirable response rates[2,46,48] and questionable tool validity and reliability.[2,46,47]

Amongst 300 medical and nursing staff employed by a large Wisconsin medical centre, over a third of providers utilised herbal medicine and over half had used nutritional supplements for their patients.[50] Referral of clients for biofeedback and chiropractic care was reported by more than half of providers, with a similar number of practitioners also indicating a future desire to utilise natural therapies. Comparisons between provider responses demonstrated a significant difference in personal use, referrals and future use of natural therapies, with a more positive and diverse response reported amongst female providers and nursing staff. These findings were reciprocated in a study of 373 university faculty staff and students.[51]

In another United States (US) survey, the utilisation of complementary therapies amongst 85 physicians at a major medical centre was explored.[25] Many physicians believed they were not adequately informed about complementary therapies, and consequently very few practiced complementary medicine. Whilst less than a quarter of physicians prescribed no more than nutritional supplements to their patients, over a third of physicians recommended the use of nutritional supplements, relaxation and massage. Nonetheless, with only a third of physicians responding to the survey, the external validity of these findings is questionable.

Amongst 370 randomly selected Auckland GPs, over 30 per cent had practiced some form of alternative therapy, with acupuncture being the most prevalent.[13] In contrast to the UK, over 78 per cent of Auckland GPs had received formal training for one or more alternative therapies. Notwithstanding, the level of training was unclear. Whilst 67 per cent of GPs responded to the survey, ambiguity of the term alternative therapies amongst GPs may have contributed to discrepancies in Marshall et al.[13] findings. The issue of ambiguity in natural therapy terminology has also been observed elsewhere.[52]

In an Australian survey, 282 Perth GPs were surveyed about their use of natural therapies.[18] Thirty-eight percent of Perth GPs reported practising a natural therapy, with the majority also utilising acupuncture. A finding reciprocated by Marshall et al.[12] and amongst 488 randomly selected GPs in Victoria, Australia.[53] Nearly half of GPs had obtained postgraduate natural therapy training, with 63 per cent indicating a desire to pursue training in future. The majority of Perth GPs had also referred their patients to a complementary therapist within the last 9 months. Whilst findings may have been subject to recall bias, a response rate of 75 per cent, randomised sampling and survey piloting indicates greater generalisability and validity to that of previous studies on the practice of natural medicine.

A survey of 192 Canadian GPs revealed 16 per cent were practicing alternative medicine, particularly acupuncture and hypnosis, with 20 per cent of GPs reporting varying levels of alternative

medicine training.[14] A finding reciprocated amongst 146 randomly selected Quebec GPs.[54] Canadian GPs more likely to practice alternative medicine were young, male, viewed alternative medicine positively, had received training in alternative medicine, and worked in a solo practice. Whilst Verhoef and Sutherland[14] are among a few to assess the utilisation of alternative medicine with a validated tool, a response rate of 50 per cent was less than desirable.

Studies exploring natural therapy use amongst medical practitioners are frequently compromised by poor response rates and undemonstrable tool validity and reliability. These flaws are reflected by significant variation in the levels of natural therapy practice reported world wide, ranging from thirteen to fifty percent throughout Australia, New Zealand, the US and UK, up to 95 per cent in Germany.[55] In addition, the characteristics of practitioners utilising natural therapies also remains inconsistent. Naturally, geographical and political indifference is likely to be a contributing factor. The predominant use of acupuncture amongst practitioners however was reciprocated globally. Physician referrals to natural therapists also varied, ranging from 25 to 75 per cent. The poor level of training and knowledge of clinicians practising natural therapies[45] may be reflected by the lack of training requirements to practice complementary medicine.[56] This is of concern, as many individuals approach medical practitioners to make an informed choice about natural therapies.[45] As adequate training is needed to implement a natural therapy both safely and competently,[57] patients are at potential risk of being either poorly informed or injured as a result of poor natural therapy training. Further research is needed to examine the competency of medical practitioners engaging in natural medicine.

Public attitude toward natural therapies

Studies to date have mainly concentrated on identifying the level of natural therapy use by the public, and have largely ignored the attitudes of individuals toward natural medicine.[9] In one study however, Klepser et al.[58] identified that users of herbal medicines were more likely to have a positive perception of the safety and efficacy of herbs, and were less positive of the safety of prescription medicines. The efficacy of natural medicine has also been supported by half of respondents in other studies,[15,24,29,32] although comparisons to non-users were not explored. Nonetheless, the safety and efficacy of any treatment is best supported from scientific evidence and not anecdotal accounts.

A survey of 199 patients attending one of 17 Canadian orthodox and complementary clinics examined the different health beliefs and motivations of users and non-users of natural medicine.[9] Regular users of complementary medicine possessed greater health-awareness behaviours, were likely to be dissatisfied with orthodox medical practitioners and manifested a greater number of health problems than users of conventional medicine. Dissatisfaction with allopathic medicine amongst users of natural therapies is also reported elsewhere.[22] An impetus for over 40 per cent of individuals turning to natural medicine was the failure of orthodox medicine to adequately treat their health problems. However, only half of patients responded to the questionnaire and thus the generalisability of these findings is limited.

Whether the attitudes of users of natural therapies and natural medicine compare differently to non-users remains poorly elucidated, and suggests further research is needed to explore the attitudes of the public toward natural medicine.

Nurses' attitude toward natural therapies

Nurses are an integral component of the health care system, providing a diverse range of services to a wide spectrum of the community. With such a high degree of exposure to individuals in the community, nurses are at the forefront of informing individuals both about their health and their health care options. These options not only include the spectrum of conventional treatments, but also the range of natural therapies that may support the health and wellbeing of the individual. Therefore, the attitudes of nurses toward natural medicine may reflect the level of individual exposure to natural therapies both in the present and in the future.

In a telephone survey of 20 female nurses, the majority of nurses believed that patients were inadequately informed about natural therapies as a direct result of poorly prepared health care professionals.[16] Participants believed patients were more likely to discuss natural therapies with nurses rather than medical practitioners, suggesting that an open dialogue by all health care professionals is needed. However, the degree of subjective responses from participants casts doubt over the validity of these findings.

Salmenpara et al.[59] reported a less positive attitude toward natural therapies from 92 Finish oncology nurses. The majority of nurses believed natural therapies were neither safe nor beneficial, involved unknown risk factors, and were offered by quacks for financial gain. Nonetheless, opinions toward natural therapies were significantly more positive ($p<0.005$) amongst nurses who were utilising natural therapies. However, the generally negative opinion in this study does not corroborate with other studies, and may suggest geographical or methodological indifference.

In contrast to previous findings,[59] a more positive attitude toward natural therapies was reported amongst 467 Ohio registered nurses.[43] In a series of attitudinal statements, similar to those utilised in other studies[2,5] the majority of nurses viewed natural therapies favourably and supported the integration of these therapies into mainstream medicine. Nevertheless, an undesirable response rate hindered the generalisability of results.

Leach[11] also identified a positive attitude toward natural therapies amongst 56 South Australian district nurses. The majority of nurses agreed that natural therapies were safe, effective, and result in a positive patient outcome. Over half of respondents believed nurses should have a basic knowledge of natural therapies, and these therapies could and should be utilised within nursing practice. Nurses with a positive attitude toward natural therapies also demonstrated a greater natural therapy knowledge base. Although not explored by Leach, a more positive attitude toward complementary therapies has been associated with higher levels of natural therapy training,[51] suggesting knowledge and training are closely correlated with a favourable stance on natural medicine.

A generally positive attitude toward natural therapies is evident amongst nurses. However, inadequate sample size, narrow sectors of health care and a paucity of international findings limit the generalisability of existing studies.

Medical practitioners' attitude toward natural therapies

Several studies to date have explored the attitudes of medical practitioners toward natural medicine. As in nursing, many individuals may approach physicians for information on natural therapies, and thus the opinion and attitude of the practitioner may influence how individuals are informed and consequently engage in these therapies.

In a survey of 249 Auckland GPs, 38 per cent demonstrated a positive attitude toward alternative medicine, indicating the therapies were safe, effective and complementary to orthodox medicine.[13] Thirty-three per cent of GPs indicated a negative attitude toward alternative medicine, believing natural therapies were unscientific or ineffective. In relation to usefulness, GPs indicated that acupuncture was most useful, with the majority of therapies being regarded as useless. However, with only six therapies being examined, the list was neither comprehensive nor complete.

Hall and Giles-Corti[18] explored the attitudes of 282 Perth GPs toward 10 complementary therapies. Two-thirds of GPs believed acupuncture, meditation, massage and hypnosis were of some or great benefit to patients. The majority of GPs however did not support the efficacy of homeopathy, aromatherapy and herbal medicine.

Amongst 293 Netherlands GPs, the majority did not believe in the efficacy of many alternative therapies, particularly herbal medicine and nutritional supplementation.[60] Nonetheless, over half of GPs believed acupuncture, yoga and manual therapy were efficacious for various medical conditions. Whilst the validity and reliability of the tool were not detailed, the response rate of 74 per cent was representative of Netherlands GPs.

The attitudes of 87 GPs, 81 hospital doctors and 230 medical students toward alternative medicine were compared in a Southwest Thames survey.[47] Medical students were found to be the least informed about the principles of alternative medicine but demonstrated the most positive attitude. However, unlike other studies, Perkin et al.[47] explored practitioner attitudes toward systems of alternative medicine and not single therapies, arguably demanding a greater depth of knowledge from respondents and thus influencing the overall findings.

Attitudes toward natural medicine amongst 131 Liverpool GPs[48] and 2748 UK physicians[2] were also generally positive, although actual scores were not detailed.[2] Attitudes were more positive amongst female and younger physicians, and in those specialising in palliative medicine. Conversely, negative attitudes predominated amongst specialists in dermatology. The majority of physicians believed natural therapies should be subject to further scientific testing before orthodox physicians could accept these therapies.[2]

Attitudes toward natural therapies were explored in a mailed questionnaire to all physicians practising in a County Medical Centre.[61] Almost 60 per cent of physicians claimed natural therapies result in a positive treatment outcome. However, whilst patients were most likely to initiate

discussion relating to the benefits of natural therapies, physicians most frequently initiated discussions on the harmful effects of natural therapies. Hence, suggesting a reluctance of medical practitioners to initiate an open dialogue on natural therapies with their patients. The utilisation of a single centre with a close affiliation to the office of alternative medicine, and a response rate of only 40 per cent, suggests these results be considered cautiously.

In a Tasmanian study involving 289 GPs, responses to a series of attitudinal statements on complementary therapies were examined.[5] GPs with a positive attitude were younger, practiced in smaller clinics, and had patients whom endorsed the therapies. These GPs believed complementary therapies were advantageous and effective. Conversely, GPs possessing negative attitudes against complementary therapies were older, and believed the therapies had harmful adverse effects and an ineffective palliative rate. With a response rate of 62 per cent and a Cronbach's alpha of 0.84, these findings should be considered more valid and reliable than previous studies. Nonetheless, the percentage of GPs who viewed natural therapies both positively and negatively were not detailed, thus it is difficult to compare findings to similarly designed studies.

Canadian GPs were also generally positive toward alternative therapies, although only 50 per cent of 192 GPs responded to the survey.[14] GPs believed alternative medicine was a useful supplement to orthodox medicine, and that orthodox medicine could benefit from the concepts and methods of alternative medicine. Chiropractic, hypnosis and acupuncture were perceived as being the most useful therapies, with over a quarter of GPs believing that they possess considerable knowledge of these aforementioned modalities. Furthermore, over half of GPs referred their patients to alternative practitioners due to a lack of response from conventional treatment, a finding similar to that reported amongst 146 Quebec GPs.[54]

Studies on the attitudes of medical practitioners toward natural medicine reflect a generally positive position throughout the western world. Practitioners were particularly more optimistic of the efficacy of acupuncture and manipulative therapies and not surprisingly, were more likely to utilise and refer patients to these aforementioned modalities.

Conclusion

Natural medicine has demonstrated a surge of interest in the past decade, particularly amongst individuals and health care practitioners of western countries. Whilst the public have demonstrated a predominant interest toward herbal medicine and nutrition, practitioners have not. Instead, nurses are more likely to practice massage and aromatherapy, with medical practitioners engaging predominantly in acupuncture. A generally positive attitude toward natural medicine is evident amongst health care practitioners and the public, which maybe an indicator of growing acceptance of these therapies amongst industrialised countries. However, sampling bias and questionable instrument validity and reliability frequently confound current studies. With further research, the benefits of natural therapies should '...encourage nurses and other health care professionals to recommend and use many of these therapies in the care of chronic conditions',[1] and thus increase the treatment options available to these individuals. Therefore, allowing individuals to construct informed choices about their care.

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Making sense of the venous leg ulcer debate: a literature review

Venous leg ulcers cause patients much distress. Treating them is expensive, with many hidden costs. As understanding of the causes and development of this condition improves, debate over the best treatments or treatment combinations is growing

chronic venous leg ulceration; chronic venous insufficiency; venous hypertension; compression

The generation of new information on the epidemiology, pathophysiology and implications of venous leg ulceration has improved practitioners' understanding and stimulated the development of new treatments. This paper aims to provide practitioners with a greater understanding of venous leg ulceration, and highlights the lack of consensus in the literature and the need for further research.

Epidemiology

The estimated prevalence of active leg ulceration in the western world varies from 0.11 to 0.63%,[1-4] escalating to 1% when active and healed ulcers are combined.[5,6] Others have argued that the prevalence is closer to 2% as studies have excluded individuals who manage their own wounds, who account for 21–38% of people.[3,4,7]

Chronic ulceration is associated with cyclic episodes of remission and recurrence,[2,8-10] with the latter estimated at 67%,[11] 76%[12] or 80–90%.[5]

Chronicity estimates also vary:

- 50–75% for up to nine months[1,11]
- 50–72% for up to one year[3,13,14]
- 13–29% for over two years.[1,11]

Gender

The onset of ulceration in males and females aged under 30 is comparable. However, after 30, the male-to-female ratio shifts to 1:2[4,13] and widens further after the age of 80 to 1:7.[11] While these differences in sex distribution may be explained by hormonal[15,16] or pregnancy-associated changes,[11] geographical or methodological factors cannot be excluded as a recent Australian study reported a male-to-female ratio of only 1:1.19.[1]

Age

As the elderly population continues to increase, so will the incidence of leg ulceration.[1,17] The proportion of people with leg ulcers is:

- Under 60: less than 1%
- 61–70: 2.6%
- Over 80: 15%.[1]

Financial implications

Costs associated with ulcer management are substantial.[18,19] In France and the UK they are estimated at 1.1% and 1.3% of the health-care budget respectively,[1] and in Australia cost between $AU553.8 and $AU654.5 million annually, or $AU27,493 per wound.[20]

Outpatient management and hospitalisation costs are also significant.[21] Four months of treatment in the USA cost an estimated $US2500 per outpatient.[18] In Australia, private hospital costs average $AU8734 per admission for a mean stay of 23.9 days.[22]

Community nursing services and ongoing preventive care to reduce recurrence also incur costs,[10] as do transport, time lost from work and the potential need for care in a nursing or residential facility.[23] Phillips et al. found finances were compromised in 68% of cases, with 30% reporting an annual out-of-pocket expense between $US100 and $US1000.[24]

Despite these findings, the economic implications of leg ulceration remain indeterminate.

Psychosocial implications

Ulceration is often associated with a myriad of physiological and psychosocial implications. People under 65 report a greater impact on quality of life,[25] so not surprisingly complete healing improves most quality-of-life parameters, particularly pain, sleep, mobility, emotion and energy.[25]

In Phillips et al.'s study of the psychosocial implications of ulceration, most participants — despite having severe medical problems — viewed it as their most significant condition:[24]

- Fifty-seven per cent believed it had severely affected their mobility
- All, particularly the younger participants, reported job loss, time lost from work and financial constraints
- Over half required up to eight hours a week for ulcer treatment
- Sixty-eight per cent reported negative emotions, including fear, depression, anger, anxiety, social isolation and negative self-image.

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Table 1. Leg ulcer classifications[8,9,14,16,30-34]

Venous	Pressure	Haematological
Arterial	Diabetic	Rheumatoid
Mixed arterial and venous	Neoplastic	Infective
Traumatic	Metabolic	Immunological
Lymphatic	Neuropathic	Cryopathic

In Callam et al.'s study of the psychosocial implications of venous ulceration, 21% reported a moderate to severe limitation of working capacity, with 5% reporting unemployment as a direct result of ulceration.[26] Leisure activities were moderately to severely limited in 42% of cases. Over 10% directly attributed their limited mobility to their leg ulcer. Conversely, Baker and Stacey reported that 16% had limited mobility, with 45% housebound.[1] While both studies had similar methodologies, the variations in findings may be attributed to demographic or geographical differences.[12]

Franks et al. investigated the relationship between healing and quality of life.[27] A significant reduction in hostility, cognition, depression and anxiety was identified following 12 weeks of treatment, along with a reduction in pain and worry, and less interference with daily and social activities.[27] Although an improvement in leg ulcer healing appears to be associated with an improvement in quality of life, the lack of control groups threatens the internal validity of these findings.

Charles et al.'s phenomenological study explored the physical and psychosocial effects of ulceration.[28] Physical concerns related to pain, sleeplessness and impaired mobility. Psychologically, feelings of hopelessness, helplessness and lack of control were identified, along with loneliness, social isolation, diminished human interaction and altered working capacity. Hofman et al. also found that pain was the worst feature of venous ulceration.[29]

Whether different aetiologies have different psychosocial implications remains unclear. Further insight into the psychosocial sequelae of each ulcer type, therefore, may predict which classes of ulceration are more likely to have a greater impact on quality of life.

Aetiology

Leg ulcers are often classified by the predominant aetiology (Table 1).[8,9,14,16,30-34] Venous classification is most prevalent in the west,[7,9,10] although the percentage remains inconclusive. Several authors have claimed that 80–90% of leg ulcers are of venous aetiology,[9,34] although others have suggested 46–79%.[3,4,12-14,35]

Pathophysiology

Chronic venous insufficiency, a precursor of venous leg ulceration,[10,44,36-38] is the insufficient return of lower limb venous blood,[39] manifested by pathological changes in the skin and subcutaneous tissue.[5,40]

Chronic venous insufficiency is thought to originate from macrovascular injury, such as thrombotic damage, congenital predilection,[41] deep vein thrombosis (DVT),[9,12,42,43] varicose veins[34] or external leg trauma.[44] Indeed, patients with venous leg ulcers often have a history of DVT, phlebitis, varicose veins or surgery.[9,30]

Following venous injury and subsequent valvular incompetence, venous reflux develops,[41,45] leading to ambulatory venous hypertension.[7,10,30,46,47] The increased venous pressure causes capillary filtration to rise, leading to interstitial oedema[41] and consequent integumentary changes in the lower leg, including ulceration.[42]

While the progression from venous hypertension to leg ulceration is unclear,[16,36,48] several theories have attempted to shed light on the process.

Trophic skin changes associated with venous leg ulceration may be secondary to capillary and endothelial cell dysfunction arising from increased endothelial permeability, leucocyte adherence and transendothelial migration.[41]

The fibrin cuff theory

This theory suggests that venous hypertension leads to capillary distension, resulting in endothelial pore dilation and fibrinogen leakage.[49] The fibrinogen then polymerises into fibrin and, aided by impaired fibrinolysis from increased levels of tumour necrosis factor (TNF-α), pericapillary fibrin cuffs develop.[49,50]

These fibrin cuffs inhibit oxygen and nutrient transport,[38] resulting in tissue hypoxia, malnutrition, induration, lipodermatosclerosis and ulceration.[41] Additionally, extracellular matrix proteins in these fibrin cuffs act as potent chemoattractants for leucocytes and platelets, which in the skin of patients with chronic venous insufficiency contributes to chronic inflammation.[48]

The presence of pericapillary fibrin in a small sample of patients with venous ulcers[50] partially supports the fibrin cuff theory.

Less detailed theories suggest that lymphatic microangiopathy and capillary network abnormalities may also be responsible for the development of leg ulceration.[51]

Nitric oxide theory

The nitric oxide (NO) theory claims that chronic venous insufficiency leads to a reduction in endothelial fluid shear stress, or sliding forces over the vessel wall, so less NO is released and more leucocyte-endothelial binding proteins are expressed.[41] ▶

7 Lopez, A., Phillips, T. Venous ulcers. Wounds 1998; 10: 5, 149-157.

8 Goldstone, J. Veins and lymphatics, In: Way, L (ed). Current Surgical Diagnosis and Treatment. Appleton and Lange, 1994.

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13 Nelzen, O., Bergqvist, D., Lindhagen, A. Leg ulcer etiology — a cross sectional population study. J Vasc Surg 1991; 14: 4, 557-564.

14 Salaman, R.A., Harding, K.G. The aetiology and healing rates of chronic leg ulcers. J Wound Care 1995; 4: 7, 320-323.

15 Bergan, J. Varicose veins: chronic venous insufficiency. In: Moore, W. (ed.). Vascular Surgery: A comprehensive review (4th edn). WB Saunders, 1993.

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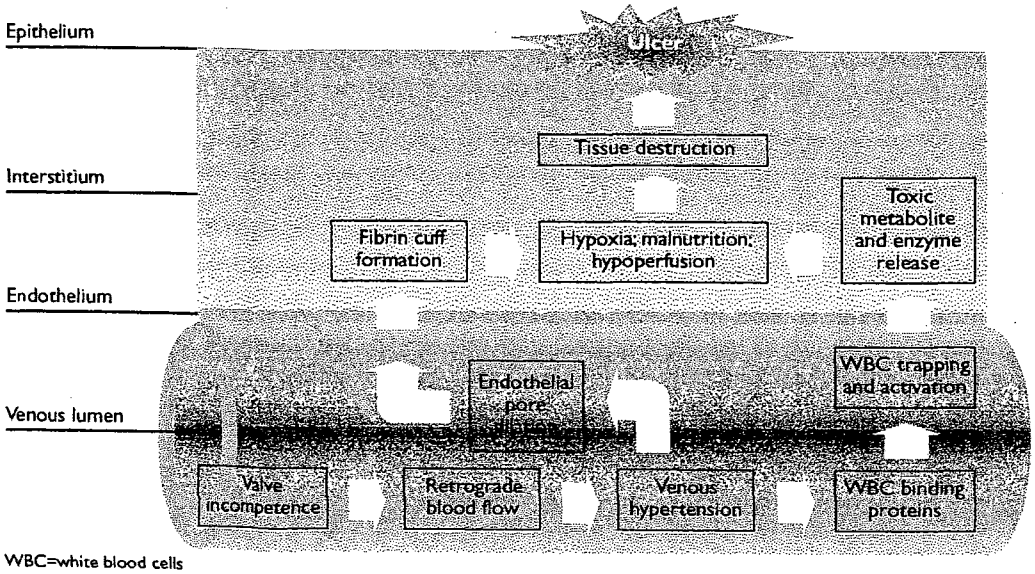
17 Falanga, V. Commentary — advances in wound care: are we there yet? Wounds 2000; 12: 3, 51-52.

18 Falanga, V. Venous ulceration. J Dermatol Surg Oncol 1993; 19: 8, 764-771.

Fig 1. White blood cell trapping hypothesis



WBC=white blood cells

As a result, leucocytes become 'trapped' within the venous endothelium, partially obstructing the capillary lumen and reducing tissue perfusion.[38,41] Moreover, increased tissue resistance leads to a deficit in tissue oxygen and nutrients,[52] as has been observed in the legs of patients with chronic venous insufficiency.[53]

White blood cell trapping hypothesis

Extending on from the NO theory and as illustrated in Fig 1, the white blood cell trapping hypothesis claims that, once entrapped, white blood cells are activated and release toxic metabolites, TNF-α and proteolytic enzymes. Consequently, vascular destruction occurs, permeability is increased, fibrinogen leakage takes place and pericapillary fibrin-cuffs develop.[38,50,54]

Increased neutrophil degranulation during experimental venous hypertension in healthy volunteers supports this hypothesis,[55] as does the presence of accumulated leucocytes[38] and toxic oxygen metabolites[56] in the dependent legs of patients with chronic venous insufficiency.

Clinical features

Diagnosis is often based on appearance, location and concomitant manifestations. Typically located in the gaiter area of the lower leg,[30,34,37] venous leg ulcers are:

- Shallow[18,30,43]
- Irregularly shaped[9,34]
- Well defined[47]
- Covered with slough[57]
- Bordered by erythemic, weeping and scaling skin.[7]

Moreover, there are:

- Large amounts of serous exudate[30,34,47]
- Lower limb heaviness, aching and discomfort
- Lipodermatosclerosis
- Pruritis
- Atrophy blanche
- Oedema
- Ochre pigmentation[7,9,34,57]
- Telangiectatic veins[47]
- Strong, palpable foot pulses
- Distended veins.[30]

Pain is also a frequent manifestation of ulceration,[31,44,58] typically exacerbated when standing and ameliorated following leg elevation.[30,47]

While some have warned of the inappropriateness of basing the categorisation and treatment of venous leg ulcers on their location,[58,59] Brunk argued that venous ulcers do not develop on the plantar surface of the foot or above the knee.[60]

Furthermore, by eliminating arterial and neuropathic disease, the likelihood of a leg ulcer being of venous aetiology rises to 93%.[59]

Treatment

The treatment options for venous leg ulceration are diverse and contentious, ranging from topical agents, compression therapy, pharmaceuticals and surgery, to natural therapies and nutritional intervention.

Likewise, the myriad of ancillary measures such as weight reduction, smoking cessation, walking, lymphatic drainage, physical therapy,[47] calf exercises, skin care and leg elevation[7,61] add to the complexity of management.

19 Stacey, M.C., Jopp-McKay, A.G., Rashid, P. et al. The influence of dressings on venous ulcer healing — a randomised trial. Eur J Endovasc Surg 1997; 13: 2, 174-179.

20 Santamaria, N., Austin, D., Clayton, L.A. multi-site clinical evaluation trial of the Alfred/Medseed Wound Imaging System prototype. Primary Intention 2002; 10: 3, 120-125.

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22 Grindlay, A., MacLellan, D. Inpatient management of leg ulcers: a costly option? Primary Intention 1997; 5:1, 24-26.

23 Bosanquet, N., Franks, P. Venous disease: the new international challenge. Phlebology 1996; 11: 1, 6-9.

24 Phillips, T., Stanton, B., Provan, A., Lew, R. A study of the impact of leg ulcers on quality of life: financial, social, and psychologic implications. J Am Acad Dermatol 1994; 31: 1, 49-53.

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26 Callam, M.J., Harper, D.R., Dale, J.J., Ruckley, C.V. Chronic leg ulceration: socio-economic aspects. Scott Med J 1988; 33: 6, 358-360.

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29 Hofman, D., Ryan, T.J., Arnold, F. et al. Pain in venous leg ulcers. J Wound Care 1997; 6: 5, 222-224.

30 Collier, M. Leg ulceration: a review of causes and treatment. Nurs Stand 1996; 10: 31, 49-51.

31 Baker, S.R., Stacey, M.C., Singh, G. et al. Aetiology of chronic leg ulcers. Eur J Vasc Surg 1992; 6: 3, 245-251.

Table 2. Therapeutic claims of compression therapy[7,47,62,63]

Reduces	Improves
• Lipodermatosclerosis	• Calf muscle pump function
• Oedema	• Local capillary clearance
• Venous reflux	• Venous ejection volume
• Venous hypertension	• Oedema fluid resorption
• Venous dermatitis	• Transcutaneous pO_2
• Superficial vein capacity and pressure	• Deep vein blood flow velocity
	• Venous refilling time
	• Plasminogen activator and prostacyclin release

32 Hunter, J. Diseases of the skin. In: Edwards, C., Bouchier, I., Haslett, C., Chilvers, E. Davidson's Principles and Practice of Medicine (17th edn). Churchill Livingstone, 1996.

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34 Goldstein, D., Vogel, K., Mureebe, L., Kerstein, M. Differential diagnosis: assessment of the lower extremity ulcer — is it arterial, venous, neuropathic? Wounds 1998; 10: 4, 125-131.

35 Scriven, J.M., Hartshorne, T., Bell, P.R. et al. Single-visit venous ulcer assessment clinic: the first year. Br J Surg 1997; 84: 3, 334-336.

36 Callam, M.J., Harper, D.R., Dale, J.J., Ruckley, C.V. Arterial disease in chronic leg ulceration: an underestimated hazard? Lothian and Forth Valley leg ulcer study. BMJ 1987; 294: 6577, 929-931.

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38 Thomas, P.R., Nash, G.B., Dormandy, J. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. BMJ 1988; 296: 6638, 1693-1695.

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However, substantial evidence from controlled trials on the efficacy of these treatments is lacking,[9] although leg elevation and compression therapy prevail as the primary treatment.[9,16,18,36,44]

Compression therapy

Use of long-term graduated compression therapy, even after healing, is claimed to prevent recurrence by addressing the underlying aetiology.[22] Other therapeutic claims of compression therapy are outlined in Table 2.[7,47,62,63]

Although compression is advocated by several authorities,[7,47,64,65] its efficacy has been supported in very few clinical trials.[66] In fact, most trials are of poor quality and flawed by inadequate sample size[67] and the absence of randomisation, heterogeneity, consistent bandaging techniques,[62] standardised treatments and adequate controls. Furthermore, it also remains uncertain whether compression or the primary dressing is responsible for wound healing.[68]

Notwithstanding these reservations, a systematic review of 24 randomised controlled trials suggested that compression, particularly multilayer bandaging, produces higher venous ulcer healing rates than non-compression.[67]

Compression stockings are palliative not curative,[63,66] so need to be worn continually to maintain the effect of treatment.[8,47,64,66] However, patient concordance with compression therapy is poor[37,63,69,70] and is associated with a lower healing and higher recurrence rate.[71]

There are also some potentially serious complications,[10,63] with 147 cases of compression-induced injury reported in one study, necessitating seven cases of arterial reconstruction and 12 amputations.[72] However, without support from other studies, the true extent of compression-induced injury remains poorly elucidated.

Surgery

Surgical intervention is another option, including:

- Venous valve reconstruction and transplantation
- Varicose and communicating vein excision
- Skin grafting
- Sclerotherapy
- Ligation.

However, skin grafting does not address the underlying aetiology.[22,47]

Ablative techniques such as venous sclerotherapy and ligation are also controversial, with a recurrence rate of 21–100%.[15]

Recurrence also occurs in 41% of patients within three years of post-subfascial perforator ligation,[73] in contrast to 16% of patients receiving compression over 2.5 years.[74]

Topical therapy

Other than compression therapy, topical dressings are more often than not considered the primary treatment, although many argue that no dressing has yet been proven to enhance healing.[19,40] Thus, the efficacy of topical agents remains debatable. Treatment should aim to address the underlying aetiology,[8,47] otherwise recurrence and chronicity are likely to persist.[8,47]

Systemic management

An alternative approach to treatment is systemic management with orally administered phlebotonic or venotonic agents.

Venotonic agents, such as horse chestnut seed extract (HCSE), and the semisynthetic agents flavonoids diosmin and 0-β,-hydroxyethyl)-rutosides (HR) (Paroven, Novartis) possess anti-exudative and oedema-protective properties.[52] They are widely prescribed in Germany, France and most of southern Europe,[75] but rarely in the UK,[75] USA or Australia, causing Diehm to suggest that patients are being denied a safe and effective treatment alternative.[52]

The effects of phlebotonic agents such as aescin, HR and Daflon (Servier) persist after cessation of treatment.[76] They reduce inflammation, neutrophil migration, venous damage and growth factor release by attenuating the drop in adenosine triphosphate in the hypoxic venous endothelium.[76] It is the sequence of events following adenosine triphosphate reduction that allegedly perpetuates venous insufficiency.

There is insufficient evidence to suggest that any phlebotonic agent is superior or inferior to compression therapy. However, as both treatments have different modes of action, combining the two may produce a more beneficial effect for patients with venous leg ulcers.[52,76]

Studies have supported this claim, indicating that the rate of healing is superior when venotonic agents are combined with compression therapy as opposed to compression therapy alone.[77,78] Nonetheless, it is still unclear whether venotonic therapy produces permanent results. ▶

Conclusion

While existing theories remain fragmented and incomplete, and so do not comprehensively elucidate the pathogenesis of venous leg ulceration, the cascade of tissue destruction appears to originate from an episode of macrovascular injury.

Future management should therefore focus on the early stages of venous hypertension in order to cut short the process leading to tissue destruction and ulceration.

At present, compression therapy is the cornerstone of venous ulcer treatment in Australia, the USA and the UK, and claims to prevent recurrence by reducing venous hypertension. However, the efficacy of compression therapy remains debatable, as does that of skin grafting, venous surgery and topical dressings.

As is already the case in Europe,[76] integrating systemic venous agents into the management of venous leg ulceration may provide a more complete solution to this problem. Clearly, well-designed clinical trials need to investigate this treatment combination further. ■

Box 1. Summary of the main points

This literature review summarises recent theories on the causes and progression of venous leg ulceration, and outlines opinions of how it should be treated

It discusses the fibrin cuff theory, which suggests that venous hypertension leads to capillary distension, resulting in endothelial pore dilation and fibrinogen leakage. It also looks at the nitric oxide (NO) theory, which claims that chronic venous insufficiency leads to a reduction in endothelial fluid shear stress, causing a diminution in NO release and a rise in the expression of leucocyte-endothelial binding proteins

Treatments range from topical agents, compression therapy, drugs, surgery and nutritional and natural therapies. Compression therapy is the cornerstone of treatment in Australia, the USA and the UK, despite lack of proof on its efficacy. Other countries in Europe integrate systemic agents into management

Well-designed clinical trials are needed to examine the efficacy of current treatments in a bid to find new and improved ways of treating these ulcers, possibly by combining more than one method of treatment

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43 Young, H. Peripheral vascular disease: 2. Venous disorders of the lower limb. Br J Occup Ther 1989; 52: 4, 130-132.

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50 Claudy, A., Mirshahi, M., Soria, C., Soria, J. Detection of undegraded fibrin and tumor necrosis factor-α in venous leg ulcers. J Am Acad Derm 1991; 25: 4, 623-627.

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59 Vowden, K., Goulding, V., Vowden, P. Hand-held Doppler assessment for peripheral arterial disease. J Wound Care 1996; 5: 3, 125-128.

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61 Odetunde, Z. The treatment of venous leg ulcers. Physiotherapy 1989; 75: 2, 125-126.

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70 Diehm, C., Vollbrecht, D., Amendt, K., Comberg, H. Medical edema protection: clinical benefit in patients with chronic deep vein incompetence. VASA 1992; 21: 2, 188-192.

71 Erickson, C., Lanza, D., Karp, D. et al. Healing of venous ulcers in an ambulatory care program: the roles of chronic venous insufficiency and patient compliance. J Vasc Surg 1995; 22: 5, 629-636.

72 Callam, M., Ruckley, C., Dale, J., Harper, D. Hazards of compression treatment of the leg: an estimate from Scottish surgeons. BMJ 1987; 295: 6610, 1382.

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