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Honey and venous leg ulceration: a systematic review & randomised controlled trial

Andrew Jull

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

University of Auckland
2007
Abstract


Systematic review: Method – The Cochrane Controlled Trials Register, AMED and LILACS were searched for controlled trials using honey for any type of patient with an acute or chronic wound. Honey manufacturers and researchers were contacted, citations scrutinised and the internet searched. Data from included studies were combined where studies were sufficiently alike. Findings – 18 trials were included. Honey significantly decreased healing time compared to conventional dressings for partial thickness burns (WMD -4.7 days, 95%CI -5.1 to -4.3), but delayed healing time in comparison to early excision and skin grafting for mixed partial and deep thickness burns (WMD 25 days, 95%CI 17.4 to 32.6). No significant effect was found for minor acute wounds or for honey compared to silver sulfadiazine in partial thickness burns. There were no trials of honey for treating venous leg ulcers.

Randomised controlled trial: Method – The HALT trial was a pragmatic, open label randomised trial. Participants received either a manuka honey-impregnated calcium alginate dressing (n=187) or usual care (n=181) for 12 weeks. Both groups received compression bandaging. The primary outcome was the proportion of participants with healed ulcers at 12 weeks. Secondary outcomes were time to healing, change in ulcer area, incidence of infection, adverse events, health-related quality of life and cost-effectiveness. Findings – 104 participants in the honey-treated (55.6%) group and 90 (49.7%) in the usual care group healed at 12 weeks (absolute increase 5.9%, 95%CI -4.3% to 15.7%, p=0.3). Time to healing was not significantly different between the groups (mean difference -1.8 days, 95%CI -7.7 to 4.1, p=0.5), nor was change in ulcer area (mean difference 0.9cm², 95%CI -1.4cm² to 3.2cm², p=0.4) incidence of infection (absolute decrease 5.0%, 95%CI -3.1% to 13.1%, p=0.2), ulcer recurrence (absolute increase 5.2%, 95%CI -0.4% to 10.7%, p=0.1), or quality of life. The average cost of community-based treatment per
participant was higher in the honey-treated group (NZ$862 versus NZ$795). More adverse events were reported in the honey-treated group (RR 1.3, 95%CI 1.1 to 1.6, p=0.01). More participants reported pain as an adverse event when treated with honey (RR 2.5, 95%CI 1.5 to 4.2, p=0.0001).

**Interpretation:** Systematic review – Honey may be an effective treatment for partial thickness burns in comparison to conventional dressings. Honey does not appear to benefit healing in other acute wounds and may delay healing in mixed and partial thickness burns compared to excision and grafting. *The HALT trial* – Honey-impregnated dressings did not have any significant positive effect on venous ulcer healing and were more expensive than usual care. Participants treated with honey experienced more pain than control participants.

**Keywords:** Honey, wound healing, venous leg ulcer, dressings and bandages, systematic review, randomised controlled trial
It is with pleasure that I would like to acknowledge and thank the many people who have contributed to this thesis –

My supervisors – Professor Anthony Rodgers and Dr Natalie Walker – for encouraging my pursuit of a research career and providing the academic support for my doctoral candidacy; my co-investigators – Professor Peter Molan, Professor Bruce Arroll, Julie Betts, Catherine Hammond, Anita Latta, Susan McAuley, and Dr Jill Waters; the District Health Board and Nurse Maude liaison contacts – Jenni Coles, Jill Dibble, Joan Dodd, Sheree East, Denise Kivell, Sandi Millner, Bronwyn Nicholls; the HALT trial Research Nurses - Sue Callender, Mary Cleland, Trish Johns, Anna Reid, Rachel White; Dr Young Mee Yoon at Comvita New Zealand Ltd and Lucy Sanders at USL Medical.

The Clinical Trials Research Unit staff, who all contributed to my learning in trial design and management – Operations (Sheila Fisher, Mary Cosson, Clarissa Gould-Thorpe, Kathy Bos, Deanne Douglas), Data Management (Amanda Milne, Jo Michie, John Faatui, Terry Holloway), IT (Barry Gray, Jaco Van Rooyen, Simon Pink, Colleen Ng, Alex Bormanns, Donovan Marshall, Clarke Mills), Biostatistics (Derrick Bennett, Mark Jones, Steven Vander Hoorn, Varsha Parag), and my colleagues in the Research Fellow team (Dr Natalie Walker, Dr Cliona Ni Mhurchu, Dr Carlene Lawes, Dr Hayden McRobbie, Dr Ralph Maddison, Dr Chris Bullen), and the casual staff – Sue Hawkins, Faith Mahony and Dr Yogini Ratnasabapathy; I would like to especially thank Varsha Parag, for her diligent assistance during analysis and writing of this thesis; and Dr Paul Brown and Kate Butler from the Centre for Health Services Research and Policy for their assistance with the economic analyses.

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The district nursing staff at the four study centres. The study centres were the Auckland, Counties Manukau and Waikato District Health Boards and the Nurse Maude Association in Christchurch. Each study centre consisted of multiple district nursing bases and the district nurses remain unknown to the candidate. Without these nurses, data essential to the cost-effectiveness and time to event analyses could not have been completed.

The Health Research Council of New Zealand and Comvita New Zealand Limited for funding the HALT trial, and the University of Auckland for offering without the candidate applying, a university PhD scholarship, and for allowing the candidate to delay decision on the scholarship until the results of an application for a Senior Health Research Scholarship were known.

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Lastly this trial could not have been possible without the generosity of the study participants and their whanau. This thesis stands on their shoulders.
Funding & support

The HALT trial was funded by a project grant (reference number 03/087) from the Health Research Council of New Zealand.

Comvita NZ Ltd contributed $50,000 unconditionally towards the operational costs of the trial. Comvita also supplied the manuka-impregnated honey dressing at no cost to the trial.

Wound mapping grids were supplied by USL Medical Ltd at no cost to the trial.

The candidate was supported by a University of Auckland Senior Health Research Scholarship during the completion of the candidacy.

The design, conduct, analyses and interpretation of results were made independent of the trial sponsors.
Contributions of the study investigators

Professor Anthony Rodgers and Dr Natalie Walker were the supervisors for this thesis. Under their supervision, the candidate designed and sought funding for the HALT trial and for his PhD candidacy. The candidate was principally responsible for oversight of all aspects of the trial including recruitment of co-investigators; development of the study protocol; writing the manual of procedures; obtaining ethical approval; negotiating collaboration with the study centres and maintaining liaison with the managers and study personnel at the study centres; participating in the employment of the Research Nurses; monitoring participant recruitment and follow up; overseeing resolution of all data queries; collaborating with the study statistician in writing the statistical analysis plan and undertaking the analyses; collaborating with a health economist in the analysis and interpretation of the economic data; interpreting the results and drafting papers and presentations that have been the outputs of this study.

Varsha Parag prepared reports for the data monitoring and safety committee and liaised with the Chair of the committee; drafted the statistical analysis plan; organised the blinded labelling of a dataset with dummy labels; collaborated on the analysis; prepared a dataset for economic analysis; created graphics in S Plus; obtained peer review on the primary analyses; and contributed to reviews of draft papers and presentations.

Katherine Butler and Dr Paul Brown of the Centre for Health Research and Policy collated the initial information for imputation of costs and the statistical code for the analysis; the candidate obtained more detailed information, rewrote the code and completed the analysis.

Professor Rodgers, Dr Walker and the candidate conceived and designed the systematic review of honey for treatment of wounds. Varsha Parag provided statistical guidance. Dr Walker was the second reviewer, who along with the candidate was responsible for selecting studies that met the inclusion criteria, and reviewed the data extraction. The candidate conducted all the analyses for the review and created the figures.
Publications & conference presentations


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<td>ABI</td>
<td>Ankle Brachial Index</td>
</tr>
<tr>
<td>ADHB</td>
<td>Auckland District Health Board</td>
</tr>
<tr>
<td>AMED</td>
<td>Allied and Complementary Medicine Database</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
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<tr>
<td>BCE</td>
<td>Before Common Era</td>
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<tr>
<td>CCTR</td>
<td>Cochrane Controlled Trials Register</td>
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<tr>
<td>CCT</td>
<td>Clinical Controlled Trial</td>
</tr>
<tr>
<td>CE</td>
<td>Common Era</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>CINAHL</td>
<td>Cumulative Index of Nursing and Allied Health Literature</td>
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<td>CIVIQ</td>
<td>Chronic Venous Insufficiency Questionnaire</td>
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<td>CMDHB</td>
<td>Counties Manukau District Health Board</td>
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<td>CRF</td>
<td>Case Record Form</td>
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<td>CTRU</td>
<td>Clinical Trials Research Unit</td>
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<tr>
<td>CVI</td>
<td>Chronic Venous Insufficiency</td>
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<tr>
<td>CXVUQ</td>
<td>Charing Cross Venous Ulcer Questionnaire</td>
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<td>DHB</td>
<td>District Health Board</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
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<td>DSMC</td>
<td>Data Safety and Monitoring Committee</td>
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<td>EQ-5D</td>
<td>EuroQol 5 Dimension survey</td>
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<td>EQVAS</td>
<td>EuroQol visual analogue scale</td>
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<td>EUSOL</td>
<td>Edinburgh University Solution of Lime</td>
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<td>FLQA</td>
<td>Freiburger Lebensqualitäts Questionnaire Assessment</td>
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<td>GP</td>
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<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>ICER</td>
<td>Incremental Cost Effectiveness Ratio</td>
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<td>Interleukin -1 beta</td>
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<td>LILACS</td>
<td>Latin American and Caribbean Health Science Literature</td>
</tr>
<tr>
<td>IPD</td>
<td>Individual Patient Data</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to Treat</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental Component Summary score of the SF-36</td>
</tr>
<tr>
<td>MPFF</td>
<td>Micronised Purified Flavonoid Fraction</td>
</tr>
<tr>
<td>NHP</td>
<td>Nottingham Health Profile</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical Component Summary score of the SF-36</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral Vascular Disease</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SEPS</td>
<td>Subfascial Endoscopic Perforator Surgery</td>
</tr>
<tr>
<td>SF-12</td>
<td>Short Form-12 item survey</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form-36 item survey</td>
</tr>
<tr>
<td>SSD</td>
<td>Silver Sulfadiazine</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour Necrosis Factor-alpha</td>
</tr>
<tr>
<td>UMF</td>
<td>Unique Manuka Factor</td>
</tr>
<tr>
<td>VCSS</td>
<td>Venous Clinical Severity Score</td>
</tr>
<tr>
<td>VIF</td>
<td>Variance Inflation Factor</td>
</tr>
<tr>
<td>WDHB</td>
<td>Waikato District Health Board</td>
</tr>
<tr>
<td>WMD</td>
<td>Weighted Mean Difference</td>
</tr>
</tbody>
</table>
ZAR

South African Rand
CHAPTER 1

Introduction

"The ulcer heals, always breaks down again ... and so it goes on and on ..."¹
Anonymous

The term ulcer is Middle English from the Old French ulcere for a sore,² and was defined in a late medieval English text as a wound "that took more than two or three months to heal."³ The modern definition is similar; leg ulcers are defined as defects in the dermis below the knee and present for more than four to six weeks.⁴⁵ Typically, leg ulceration is a chronic relapsing and remitting condition associated with impaired circulation. The main causal conditions are venous disease, arterial disease, diabetes or unrelieved pressure over a bony prominence. There are also other rarer causes in the developed world, such as sickle cell anaemia. Venous insufficiency is the most common cause of leg ulceration, accounting for up to 80% of leg ulcers,⁴⁶ and venous ulceration is the focus of this thesis.

Ulcer healing, in other than pressure ulcers, is usually temporary as the underlying disorder can only be palliated, not cured. Many ulcers recur, even if the patient is assiduous in taking preventative actions. Consequently, patients will attempt almost any treatment to obtain healing, but always with the knowledge that ulceration is very likely to return.¹⁰ The therapeutic mainstay of venous ulcer treatment is compression of the lower leg by some form of tight bandaging or hose in order to reduce hydrostatic pressure in the leg. This treatment has been known since the seventeenth century and just a few adjuvant treatments have been found to be effective since that time. However, the lack of evidence has not stopped both patients and health workers advocating a plethora of interventions on the basis of opinion, the personal commendation of others, or their own experience. Faced with such choice, as
well as a lack of high quality evidence, health workers develop strong personal preferences. The cyclical advocacy and rejection of these treatments on an almost daily basis by different professionals can cause patient distrust. This situation is not aided by regulatory agencies that allow the sale of medicated products in the absence of evidence.

Honey is a folk remedy that has aroused professional interest in its use in wound care. Over the last decade, there has been an eight-fold growth in the number of studies, reports, and letters discussing the therapeutic potential of honey for treating wounds. Despite the interest, there has been limited evidence from randomised controlled trials to inform lay and professional groups. Additionally, reviews of honey in wound care have generally been non-systematic narratives that overstated the case for honey, or in the case of the one systematic review of trials, no longer includes all the available evidence and may therefore be out-of-date.

The aim of this thesis was to investigate the effect of honey on wound healing by [1] conducting a systematic review on the effectiveness of honey as a treatment in wound care, and [2] evaluating the effect of manuka honey-impregnated dressings in the treatment of patients with venous ulcers in a randomised controlled trial. The objectives for each chapter were:

- To present a qualitative review (defined as a non-systematic overview) of the literature describing the pathophysiology of venous ulceration, the impacts of leg ulceration on individuals and on health systems, the treatments that have been shown to be effective for venous leg ulcers, and to outline the history of honey in wound care, summarise the animal model evidence and describe the English-language clinical reports of honey’s use in wound treatment (Chapter 2)

- To describe the methods and findings of a systematic review of the effect of honey in wound treatment (Chapter 3)

- To outline the methods used in the HALT trial (Chapter 4)

- To describe the results of the HALT trial (Chapter 5)
- To discuss the key findings from the HALT trial, the strengths and limitations of the trial, the relationship of the trial findings to previous research, as well as the clinical and research implications of the findings (Chapter 6).

- To summarise the findings of the research outlined in this thesis, the clinical implications, and possible directions for future research (Chapter 7).
CHAPTER 2

Literature review

2.1 Introduction
This chapter reviews the literature related to leg ulceration and is organised into three sections. The first section reviews the pathogenesis of venous ulceration and the epidemiology, impact and costs of leg ulceration, including venous ulceration. The second section reviews the current evidence for treatments of venous ulceration, including compression therapy, systemic pharmacological treatments, surgery and topical treatments. The third section reviews the use of honey in wound care, including a historical overview, review of the animal model evidence, and review of reports of case studies and case series of honey in wound treatment. The studies and reports included in this literature review were obtained from searches of the MEDLINE (1966-2006), EMBASE (1980-2006), CINAHL (1982-2006), and AMED (1985-2006) databases, Google Scholar, and the Cochrane Controlled Trials Register. Keywords included "honey", "leg ulcer", "varicose ulcer" and "venous ulcer".

2.2 Pathogenesis of venous ulceration
The venous system in the leg is made up of two networks, the superficial and the deep venous systems. The superficial system is composed of the axial superficial veins (the long and short saphenous veins) and their tributaries, which drain blood from the microcirculatory bed. The deep venous system is composed of the main axial veins between the muscle compartments and the venous sinuses within the calf muscles. The superficial and deep venous systems connect at the sapheno-popliteal and sapheno-femoral junctions, as well as communicating...
through the perforator veins. Perforator veins either connect directly to the main axial veins or link to the veins and venous sinuses within the muscles, thus indirectly draining into the main axial veins.¹⁴ ¹⁵

Bicuspid valves are present in almost all veins and ensure that the flow of venous blood is unidirectional towards the heart.¹⁵ ¹⁶ Valves in the perforator veins also serve to protect the superficial venous system from the high compartmental pressures present in the deep veins during contraction of the calf muscle pump. This muscle pump assists the return of blood against gravity.¹⁷ In a leg with normal venous return, the hydrostatic pressure within the superficial and deep venous systems are both approximately 80 mm Hg when a person is upright at rest.¹⁶ However, during exercise such as walking or plantar flexion of the foot, calf muscle contraction increases pressure within the deep veins, closing the valves in the perforator veins and propelling blood in the deep veins towards the heart.¹⁴ Subsequent muscle relaxation following contraction causes pressure in the deep venous system to fall abruptly to a level lower than that in the perforator veins. This sudden pressure drop to between 0 and 10 mm Hg ensures the valves in the superficial system open to refill the deep venous system.¹⁶ Proper functioning of venous return is dependent on competent valves within the veins to prevent retrograde flow or reflux from the deep to the superficial venous system.¹⁴ ¹⁶

Dysfunction in venous return occurs through [1] incompetent valves in the superficial, perforating or deep veins giving rise to venous reflux, [2] outflow obstructions in the deep veins also giving rise to venous reflux, or [3] calf muscle pump failure because of diseases influencing lower limb mobility. The reflux resulting from valvular incompetency or outflow obstructions leads to sustained increases in venous pressure in the superficial system. This venous hypertension is the hallmark of chronic venous insufficiency (CVI).¹⁸ ²⁰ Clinical manifestations of CVI include:

- Telangiectasia or spider veins
- Varicose veins, ranging in severity from submalleolar venous flare to tortuous dilatations of the axial superficial veins
- Dependent oedema in the lower leg
- Atrophie blanche or smooth white scar tissue
- Hyperpigmentation caused by deposition of red blood cells into the dermis, with subsequent redish-purple to brown discolouration of the tissue

- Eczematous skin changes, such as scaling, flaky skin

- Induration of the lower leg caused by fibrosis of subcutaneous fat, giving the appearance of an inverted bottle in its most severe presentations (so called "champagne legs")

- Leg ulceration on the lower third of the leg, but not excluding presentations on the dorsum of the foot.

The physical association of varicosities with leg ulceration led the seventeenth century surgeon Richard Wiseman to coin the term varicose ulcer, although the term did not enter common use until the nineteenth century. Varicose ulcer continued in use into the twentieth century. However, the term was quickly challenged in the mid-nineteenth century by Gay and Spender who independently recognised that varicose veins and leg ulcers were both signs of underlying disorders of the venous system. They therefore introduced the term venous ulcer.

The microcirculatory cascade from venous hypertension to leg ulceration has not been fully described and understanding of the pathogenesis of venous ulcers is incomplete. Various hypotheses have been proposed to explain experimental observations. These hypotheses include pericapillary fibrin cuff formation presenting a barrier to oxygen diffusion, white cells plugging capillaries causing tissue anoxia, and fibrin cuffs trapping growth factors. More recently, ulcer pathogenesis is thought to be an inflammatory chain brought about by a chronic ischaemia-reperfusion cycle. An inflammatory cascade involving cytokines, oxygen-derived free radicals, and activated polymorphonuclear neutrophils promote the deposition of capillary cuffs trapping growth factors and cell adhesion molecules. These matrix cuffs attract and activate more white cells. The repeated activation of this cascade eventually overwhelms compensatory capacity, with balance tipped in favour of tissue destruction. Although the observed cause of ulceration may in many cases be mechanical, for instance an insect bite, healing is arrested or counteracted by the ischaemic-reperfusion cycle until the underlying venous hypertension is corrected.
2.3 Epidemiology of leg ulceration

Forty-one studies, excluding studies reporting isolated diabetic ulcers, have reported estimates of leg ulcer prevalence in 15, mostly developed, countries (Table 2-1). Prevalence is a measure of whether the disease is present or not at a particular time and is useful in determining burden of disease. Estimates of prevalence varied from 0.39/1000 to 128/1000 population for point prevalence and from 0.79/1000 to 37/1000 for period prevalence (Table 2-2). The prevalence of leg ulceration increased with age, suggesting that as Western populations age, the burden of ulceration will increase. Prevalence in men increased approximately five-fold from age 60 years to 80+ years, while prevalence in women increased six- to ten-fold in the same age range.

Prevalence rates include both recurrent cases and new onset or incident cases. Point prevalence cannot provide information on incidence, except by indirect estimation if the duration of ulceration is also captured. However, period prevalence does provide an opportunity to capture information on disease incidence, although it has rarely been used to do so in studies estimating the burden of leg ulceration. Incidence is a useful measure for comparing the risk of individuals in different populations experiencing the first onset of disease, and can support future planning. Seven studies have reported incidence, but in three of these studies prevalence and incidence have been confused. Of the remaining four studies, one study reported cumulative incidence for ulcers of any aetiology (0.32/1000 per year), and two reported cumulative incidence for venous ulceration (0.22/1000 per year and 3.2/1000 per year). The fourth study reported an incidence rate for venous ulceration (1.2 per 100 person years), which is the equivalent of 0.12 per 1000 person years. Thus, estimated incidence ranged from 0.12/1000 to 3.2/1000 per year for venous ulceration. Incidence in men increased six- to eleven-fold from age 60 years to 80+ years, while incidence in women increased four- to six-fold in the same age range.

The wide variation in estimates of prevalence and incidence is likely to be due to the considerable differences in study methodology, including:

- Differences in the status of the included ulcer cases - 14 studies included both people reporting active and healed ulcers, whereas the remaining studies only included people reporting active ulcers.
<table>
<thead>
<tr>
<th>Study, year (Country)</th>
<th>Age (years)</th>
<th>Foot ulcers</th>
<th>Minimum duration</th>
<th>Ulcer Status</th>
<th>Ulcer type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auckland, 1998 (New Zealand)</td>
<td>All</td>
<td>Yes</td>
<td>6 weeks</td>
<td>Active &amp; healed</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Basle II, 1965 (Switzerland)</td>
<td>25-74</td>
<td>Yes</td>
<td>_</td>
<td>Active &amp; healed</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Basle III, 1971 (Switzerland)</td>
<td>25-74</td>
<td>Yes</td>
<td>_</td>
<td>Active &amp; healed</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Basle III, 1982 (Switzerland)</td>
<td>25-74</td>
<td>Yes</td>
<td>_</td>
<td>Active &amp; healed</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Birmingham, 1998 (England)</td>
<td>_</td>
<td>Yes</td>
<td>6 weeks</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Blekinge, 1998 (Sweden)</td>
<td>All</td>
<td>Yes</td>
<td>_</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Botucatu, no date (Brazil)</td>
<td>15+</td>
<td>Yes</td>
<td>_</td>
<td>Active &amp; healed</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Branda, no date (Sweden)</td>
<td>70+</td>
<td>_</td>
<td>6 weeks</td>
<td>Active &amp; healed</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Britain, 1996 (United Kingdom)</td>
<td>65-95</td>
<td>_</td>
<td>_</td>
<td>Active</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Copenhagen, 1969 (Denmark)</td>
<td>All</td>
<td>_</td>
<td>_</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Dublin, 1984 (Ireland)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>Active</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Dunedin, 1991 (New Zealand)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>Active</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Gothenburg, 1980 (Sweden)</td>
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<td>_</td>
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</tr>
<tr>
<td>Gothenburg, 1989 (Sweden)</td>
<td>_</td>
<td>Yes</td>
<td>_</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Harrow, 1981 (England)</td>
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<td>No</td>
<td>_</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Hong Kong, no date (China)</td>
<td>65+</td>
<td>Yes</td>
<td>_</td>
<td>Active</td>
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</tr>
<tr>
<td>Illawarra, 1995 (Australia)</td>
<td>All</td>
<td>_</td>
<td>_</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Klatov, 1961 (Slovakia)</td>
<td>15+</td>
<td>_</td>
<td>_</td>
<td>Active &amp; healed</td>
<td>Venous ulcer</td>
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<tr>
<td>Limerick, 1998 (Ireland)</td>
<td>All</td>
<td>Yes</td>
<td>_</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
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<td>Lisbon, 2001 (Portugal)</td>
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<td>No</td>
<td>Active</td>
<td>All aetiologies</td>
</tr>
<tr>
<td>Lothian &amp; Forth Valley 1981 (Scotland)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>Active</td>
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<td>Malmo, 1990 (Sweden)</td>
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<td>_</td>
<td>Active</td>
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<td>Malmo/Skaraborg, 1990 (Sweden)</td>
<td>50-89</td>
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<td>6 weeks</td>
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<td>All aetiologies</td>
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<td>Missouri, 1996/1998 (USA)</td>
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<td>_</td>
<td>_</td>
<td>Active</td>
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</table>
Table 1 (continued): Studies on the epidemiology of leg ulceration

<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Age (years)</th>
<th>Foot ulcers</th>
<th>Minimum duration</th>
<th>Ulcer Status</th>
<th>Ulcer type</th>
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<td>Newcastle, 1991 (England)</td>
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<td>Perth, 1989 (Australia)</td>
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<td>Yes</td>
<td>4 weeks</td>
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<td>Skaraborg, 1974/1984 (Sweden)</td>
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<tr>
<td>Skaraborg, 1985 (Sweden)</td>
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<td>Skaraborg, 1988 (Sweden)</td>
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<td>Yes</td>
<td>6 weeks</td>
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<td>Skovde, 1991 (Sweden)</td>
<td>30+</td>
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<td>Stockholm, 1993 (Sweden)</td>
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<tr>
<td>Stockbridge, 1982 (Scotland)</td>
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<td>Sydney, 1961/1988 (Australia)</td>
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<td>Tecumseh, 1957 (USA)</td>
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<td>Tubingen, no date (Germany)</td>
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<td>Wandsworth, 1998 (England)</td>
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<td>45+</td>
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</table>

^ Information supplied by the author
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<thead>
<tr>
<th>Study</th>
<th>Sampling strategy</th>
<th>Health professional based</th>
<th>Incidence (per year)</th>
<th>Point prevalence</th>
<th>Period prevalence</th>
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<td>1.2</td>
</tr>
<tr>
<td>Lisbon, 2001</td>
<td>x</td>
<td></td>
<td></td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Lothian &amp; Forth Valley, 1981</td>
<td>x</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Malmo, 1996</td>
<td>x</td>
<td></td>
<td></td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Malmö/Skaraborg, 1990</td>
<td>x</td>
<td></td>
<td></td>
<td>72.7</td>
<td></td>
</tr>
<tr>
<td>Missouri, 1996/1998</td>
<td>x</td>
<td></td>
<td>0.22</td>
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<tr>
<td>(USA)</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Newcastle, 1991</td>
<td>x</td>
<td></td>
<td></td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Ottawa, 1999</td>
<td>x</td>
<td></td>
<td></td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Perth, 1989</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Skaraborg, 1985</td>
<td>x</td>
<td></td>
<td></td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Skaraborg, 1988</td>
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<td></td>
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<td>3.1</td>
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</tr>
<tr>
<td>Skovde, 1991</td>
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<td></td>
<td></td>
<td>22.3</td>
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<tr>
<td>Stockholm, 1993</td>
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<td></td>
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<td>1.2</td>
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</table>
### Table 2 (continued): Sampling strategies and outcomes in epidemiological studies of leg ulceration

<table>
<thead>
<tr>
<th>Study</th>
<th>Sampling strategy</th>
<th>Incidence (per year)</th>
<th>Point prevalence</th>
<th>Period prevalence</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Population based</td>
<td>Health professional</td>
<td>Stockbridge, 1982</td>
<td>36</td>
</tr>
<tr>
<td>Tecumseh, 1957</td>
<td>x</td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Tubingen, no date</td>
<td>x</td>
<td></td>
<td></td>
<td>26.9</td>
</tr>
<tr>
<td>Wandsworth, 1998</td>
<td>x</td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>West Heidelberg, no date</td>
<td>x</td>
<td></td>
<td></td>
<td>111</td>
</tr>
<tr>
<td>West London, 1986</td>
<td>x</td>
<td></td>
<td></td>
<td>12.7</td>
</tr>
<tr>
<td>West London, 1994</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Australia, 1996</td>
<td>x</td>
<td></td>
<td></td>
<td>55.1</td>
</tr>
<tr>
<td>Westphalia, 2000</td>
<td>x</td>
<td></td>
<td></td>
<td>26.8</td>
</tr>
<tr>
<td>Wigan, 1996</td>
<td>x</td>
<td></td>
<td></td>
<td>19.7</td>
</tr>
</tbody>
</table>

- Differences in the definition of a leg ulcer - 19 studies included people reporting foot ulcers, whereas two studies excluded people reporting foot ulcers, and 20 did not report whether location of the ulcer was part of the case definition.

- Differences in the threshold for duration of time since the wound's onset for defining whether a wound was considered an ulcer or not – one study did not set a minimum threshold, three studies required the wound to have been present for four weeks and seven studies required the wound to have been present for at least six weeks before a wound was considered to be an ulcer. The remaining studies did not report a threshold.

- Differences in the type of prevalence reported - eight studies reported period prevalence (the number of cases present at the start of the study plus the number of cases that develop during the period of the investigation), a measure that combines both prevalence and incidence. The remaining studies reported point prevalence (number of cases present at any given point in time).
- Differences in the ages of populations sampled - 14 studies sampled populations with age restrictions, including seven that used maximum age restrictions. Twelve studies did not have any age restriction, whereas the remaining studies did not report age as an entry criterion.

- Differences in the sampling strategy – 19 studies sampled the general population whereas 22 sampled populations known to, or attending, health services.

- Differences in the types of leg ulcer studied – 29 studies included people with leg ulcers of any aetiology, whereas the remaining studies only included participants with venous ulcers.

Studies that clearly defined cases, used assessors rather than relied on self-report, and attempted to identify leg ulcers cases from all possible sources (including cases who are self-caring and without health professional care) were more likely to have provided reliable population estimates of leg ulcer incidence and prevalence. Only three studies met these criteria (Auckland,5, 71 and Ottawa86). Estimates of leg ulcer prevalence (all ulcer types) ranged from 0.39/1000 to 1.8/1000 population for point prevalence and 0.79/1000 and 1.1/1000 population for period prevalence. Only one of these studies estimated incidence,8 with cumulative incidence reported as 0.32/1000 per year. Two of the studies did not provide estimates of prevalence or incidence by ulcer aetiology. One provided data by ulcer aetiology, but the denominator was limbs rather than persons.4, 5, 71 However, the prevalence of purely venous ulcers could be estimated from this study as approximately 0.58/1000,4 although people with venous ulcers complicated by co-morbidities, such as diabetes or rheumatoid arthritis, were not included in this figure.

Estimates of disease frequency will be imperfect as not every case of a disorder will be located, even over long periods with multiple methods of recruitment. For instance, Hook and colleagues found they under-estimated the point prevalence of Huntington's disease by 25-40%, despite using more than ten different methods of case ascertainment.88 Capture-recapture is a statistical method that allows estimation of the number of unidentified cases,89 and has been used by one study to identify the possible prevalence of leg ulceration when estimates of missed cases are included.47 The Auckland Leg Ulcer Study found a point prevalence of 0.39/1000 population and a period prevalence of 0.79/1000 population for leg ulcers of all aetiologies. Capture-recapture analysis suggested point prevalence increased to
2.5/1000 (95% CI 1.5 to 5.0/1000) population, period prevalence to 5.3/1000 (95% CI 3.6 to 8.4/1000) population, and cumulative incidence to 0.32/1000 (95% CI 0.27 to 0.37/1000) population for all ulcers if missed cases were incorporated into the estimation. This analysis suggests that even methodologically sound population-based investigations of leg ulcer prevalence will only provide the lower bound of actual prevalence, unless missed cases are incorporated into the estimation. This study did not provide separate estimates by ulcer aetiology, and thus the impact of missed cases on venous ulceration is unknown.

2.4 Impact of leg ulceration on quality of life

2.4.1 International data
Leg ulcers have been reported in the qualitative literature as having a considerable impact on many aspects of daily life. Pain, sleep impairment, and reduced mobility have been commonly reported.\(^1\) Work capacity has been restricted and personal finances adversely affected.\(^5\) Some activities, such as shopping and interaction with young children, have been reported as being avoided in order to reduce the risk of injury to legs.\(^8\) Social activity has been found to have been minimised due to negative body image, with loneliness a frequent consequence.\(^9\) Psychologically, leg ulceration has been reported to have been associated with feelings of powerlessness and loss of control, low self-esteem and states of hopelessness.\(^1\) There appeared to be little difference in the findings of those studies that included only participants with venous leg ulcers compared to those that recruited participants with a leg ulcer of any aetiology.

Health-related quality of life (HRQoL) has been studied in cross-sections of people with leg ulcers using two generic instruments, the Nottingham Health Profile (NHP) and the Short Form 36-question Health Survey (SF-36).\(^10\) Three studies have used the six domain NHP to investigate the impact of leg ulceration on HRQoL (Table 3).\(^10\) In the largest study (n=758) of patients being treated for venous ulceration in six community trusts in England, participants were found to have significantly lower levels for energy, sleep and physical mobility, more bodily pain, emotional reactions and social isolation, and lower quality of life globally than age- and sex-matched norms.\(^10\) The differences were more pronounced in younger participants across all domains and in men with respect to pain, sleep and social isolation. Similar findings were reported in a smaller Swedish study (n=125) of patients being treated in a hospital clinic for venous, arterial or mixed venous/arterial leg ulcers.\(^10\) Participants reported lower global quality of life than age- and sex-matched norms.
The impact of ulceration was greater on male participants, particularly with respect to pain, emotional reactions, social isolation and physical mobility. These findings could not be included in Table 3, as the study reported the findings as the percentage difference from the population norms. In a third smaller study (n=79) of patients receiving treatment for venous ulceration in an English community trust, participants were found to have significantly lower levels of energy and physical mobility, and more bodily pain and emotional reactions than population norms for 70-74 year olds.103

Table 3: Domain scores reported in the studies that used the NHP to assess the impact of leg ulceration on HRQoL

<table>
<thead>
<tr>
<th>Domain</th>
<th>Franks, et al. 104</th>
<th>Stevens, et al. 103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>33.7</td>
<td>38.6</td>
</tr>
<tr>
<td>Pain</td>
<td>31.1</td>
<td>32.9</td>
</tr>
<tr>
<td>Emotional reactions</td>
<td>17.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Sleep</td>
<td>26.6</td>
<td>24.2</td>
</tr>
<tr>
<td>Social isolation</td>
<td>13.3</td>
<td>11.9</td>
</tr>
<tr>
<td>Physical mobility</td>
<td>36.4</td>
<td>43.9</td>
</tr>
</tbody>
</table>

Three studies have used the eight domain SF-36 to investigate the impact of leg ulcers on HRQoL (Table 4).105-108 The larger study (n=118) was incorporated within a case identification exercise that encompassed both hospital and community services within an English community trust.108 Participants were found to have significantly lower scores on role limitations due to problems with physical functioning, bodily pain, social functioning and role limitations due to problems with emotional functioning than age- and sex-matched norms. A smaller study (n=21) conducted in patients being treated for venous ulcers in outpatient clinics in the United States of America, found participants had descriptively lower scores for physical functioning, vitality and role limitations due to emotional functioning than the population norms for 65-74 year olds.107 Another small study (n=63) of patients being treated for leg ulcers of any aetiology in an English university hospital clinic found that participants had significantly lower scores across all domains, with the exception of mental health, when compared with the English age equivalent norms for 70-74 year olds.105

Table 4: Domain scores reported in the studies that used the SF-36 to assess the impact of leg ulceration on HRQoL

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>29.6</td>
<td>56.2</td>
<td>29.8</td>
</tr>
<tr>
<td>Role physical</td>
<td>41.5</td>
<td>67.9</td>
<td>51.5</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>53.3</td>
<td>75.5</td>
<td>21.8</td>
</tr>
<tr>
<td>General health</td>
<td>54.9</td>
<td>72.7</td>
<td>46.4</td>
</tr>
<tr>
<td>Vitality</td>
<td>46.3</td>
<td>50.0</td>
<td>44.9</td>
</tr>
<tr>
<td>Social functioning</td>
<td>56.5</td>
<td>83.9</td>
<td>43.1</td>
</tr>
<tr>
<td>Role emotional</td>
<td>57.1</td>
<td>81.0</td>
<td>46.2</td>
</tr>
<tr>
<td>Mental health</td>
<td>65.1</td>
<td>80.0</td>
<td>66.2</td>
</tr>
</tbody>
</table>
The cross-sectional studies confirm the information obtained from qualitative studies that leg ulceration has a significant impact on aspects of HRQoL. However, the studies' estimates of these impacts are subject to considerable limitations. First, none of the studies were population-based studies. Although two studies did try to capture patients in both hospital and community care,\textsuperscript{104,108} it is highly unlikely that all people with the condition being investigated were captured.\textsuperscript{99} Therefore the estimates may be under- or over-estimates. Second, although four studies made age- and sex-matched comparisons to population norms, in one study the method could not be scrutinised,\textsuperscript{102} while in two other studies the comparisons were made to the population norms for age ranges that were approximately similar to the age ranges of the study participants, rather than adjusting for age and sex by direct standardisation and then testing the differences.\textsuperscript{103,105} This point is important because improper comparisons with population norms are likely to influence the estimated differences, which in turn may have a bearing on the significance or otherwise of the difference. Third, one study did not use significance testing when comparing the differences between participant scores and population norms.\textsuperscript{107} Finally, none of the studies used control groups. While adjusting for age and sex differences will deliver a more precise point estimate, the impact of co-morbidities cannot be estimated or adjusted for without comparison with a control group. Some co-morbid conditions, such as congestive heart failure, have been found in greater proportion in patients with venous leg ulcers than in age- and sex-adjusted controls.\textsuperscript{109} Controlling for the impact of these co-morbidities is necessary to avoid confounded estimations of impact on HRQoL.

The performance of several generic instruments has been compared within trials of treatments for venous leg ulceration. In one trial which compared the Short Form McGill Pain Questionnaire, the SF-36, the EuroQol 5D (EQ5D) and the Frenchay Activities Index, the McGill Pain Questionnaire was found to be the most responsive instrument at 3 and 12 months.\textsuperscript{106} The SF-36 and the EQ5D were also responsive to changes at 12 months. In a second trial, the SF-36 was compared to the NHP.\textsuperscript{110} The SF-36 had less floor and ceiling effects\textsuperscript{a} than the NHP, but was also less responsive to changes, with only bodily pain demonstrating significant change from baseline to 12 weeks. In a third trial, the performance of the Short Form 12 question survey (SF-12), the EQ5D and the Hyland questionnaire were compared.\textsuperscript{111} Both the SF-12 and the EQ5D were responsive to changes in ulcer state at three months.

\textsuperscript{a} Floor and ceiling effects are percentage of participants reporting the minimum and maximum values of a dependent variable.
As demonstrated by the differences in responsiveness of the EQ5D over time in two studies above, there is uncertainty as to the longitudinal performance of generic instruments. Disease-specific instruments may be more responsive, a feature that is important in clinical trials. Three disease-specific instruments have been used with patients with venous leg ulcers: the Freiburger LebensQualitäts Questionnaire Assessment (FLQA), the Charing Cross Venous Ulcer Questionnaire (CXVUQ), and the Hyland Questionnaire. Other instruments, such as the VEINES-QOL and the Chronic Venous Insufficiency Questionnaire (CIVIQ), have been used to evaluate the impact of chronic venous insufficiency rather than venous leg ulceration. The FLQA is a self-administered 83-item, seven domain instrument, originally developed in German to assess the impact of venous insufficiency on HRQoL. A modified FLQA with 89 items was only validated in English on patients with leg ulcers in 2005. The Hyland questionnaire is a 34-item instrument that measures quality of life in people with open ulcers, but it is unclear whether the instrument is responsive to changes in healing state. Poor performance in comparison to generic instruments led one trials group to recommend use of generic instruments rather than continued use of the Hyland Questionnaire. The CXVUQ is a 20-item, 4 domain self-administered tool developed specifically to assess the impact of venous ulceration on HRQoL. The CXVUQ was reported to be highly correlated with the SF-36 and appeared to be responsive to change in ulcer state over 6 and 11 weeks. However, apart from the validation dataset, the CXVUQ has only been used by its authors in a clinical trial, and by researchers in Hong Kong to validate a Chinese language version of the tool.

2.4.2 New Zealand data
No studies have investigated the impact of venous leg ulcers on HRQoL, although three New Zealand studies have explored the impact of leg ulceration on HRQoL. These studies reported findings similar to those in the international literature. A qualitative study of nine people in Taranaki who had leg ulcers found ulcers had an impact on almost all aspects of the participants' lives, including routine household chores, bathing, any activity that involved standing, as well as recreational activities, family relationships and work. However, as a qualitative study, the findings are specific to the study sample and should not be considered as being generalisable. A Dunedin study compared 14 cases with leg ulcers and 14 controls and found the cases described significantly more problems with activity, pain, and mobility than the controls. The cases also reported lower levels of self-
esteem and poorer affect than the controls, although they did not differ from the controls in terms of other psychological variables, or in their evaluations of general health. Although controlled and using standard questionnaires, a convenience sampling method was used in this study, the sample was small and controls were matched with the cases on several variables (age, marital status, education and income). Matching has been shown to increase selection bias in case-control studies, where analyses have not been stratified. A population-based study compared the HRQoL of 241 cases with a leg ulcer and 224 controls in Auckland using the SF-36. Cases reported significantly lower scores across all domains after adjustment for age, sex and confounding co-morbidities (Figure 1). The pattern of impact was also similar when compared with the New Zealand population norms, although the impact on mental health was just significant at p<0.05 (Figure 2). This study was limited by modest response rates, but has provided the best estimate of the impact of leg ulceration on HRQoL in New Zealand. The order of effect leg ulceration had on HRQoL was similar to that of diabetes and osteoarthritis.

2.5 The cost of leg ulceration

The costs associated with leg ulceration consist of both direct and indirect costs borne by an individual and their family, a health service, or the community generally. Direct costs are those costs attributable to the provision of a health service, such as diagnostic testing, materials and staff time, and are influenced by the efficacy of the intervention, the required frequency of intervention and the ability of a treatment to prevent recurrence. Indirect costs are the costs of lost opportunities for patients, such as lost time at work, forced early retirement or reduced productivity caused by the disease. The measurement of the economic impact of leg ulceration is dependent on what cost information is captured, which is determined by the economic perspective underpinning the data collect. A cost analysis could be taken from the perspective of a health service, or an element of that service. Such an analysis will only incorporate the direct costs of providing the service, whereas an analysis from a societal perspective will incorporate a broader range of costs including the indirect costs attributable to the condition.

2.5.1 International data

The direct costs of treating venous diseases have been estimated to account for 1.5% to 2.0% of the total health budget in the United Kingdom. However, the study used codes from the International Classification of Diseases (ICD) for varicose
Figure 1: Differences (point estimates and 95% confidence intervals) between cases and controls from the Auckland Leg Ulcer Study for SF-36 mean domain scores, adjusted for age, sex, and confounding co-morbidities. PF = physical functioning; RP = role limitations due to physical problems; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role limitations due to emotional problems; MH = mental health (used with permission, Oxford University Press).

Figure 2: Differences (point estimates and 95% confidence intervals) between cases and New Zealand population norms from the Auckland Leg Ulcer Study for SF-36 mean domain scores, standardised for age and sex. PF = physical functioning; RP = role limitations due to physical problems; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role limitations due to emotional problems; MH = mental health (used with permission, Oxford University Press).
veins of lower extremities, venous insufficiency and postphlebitic syndrome, and phlebitis and thrombophlebitis. This estimate will have underestimated the total cost of treating venous diseases by not incorporating indirect costs, and overestimated the cost of treating venous ulceration, as such ulcers will only be present in a fraction of people with venous insufficiency (as represented by the ICD codes). The percentage of people with venous ulceration in estimates of the prevalence of chronic venous insufficiency is between 7% and 13%. The cost of treating venous diseases in Belgium has also been estimated as accounting for 2.0% to 2.5% of the health spend in 1995 terms. This finding was derived from the proportion of the billing data on venous diseases spent in a compulsory health insurance system and suffers from the same limitations as the estimated spend in the United Kingdom.

The better national estimate of the total cost of leg ulcer management is that of a Swedish study, which collected cost information during a two week period from all primary health care centres, nursing homes, dermatologists, and the in-patient and out-patient units of the regional hospital (Linkoping, Sweden). Both direct and indirect costs of leg ulcer care were estimated. Direct costs represented 79% of the total cost, and constituted 1.5% of the total costs of health services in the region. When the indirect costs were incorporated into the estimate, the national cost was estimated at K2,288 million or UK£197 million in 1994 terms. The study is subject to two limitations. First, the national prevalence was assumed to be the same as observed in the study region (2.4/1000), and this figure is twice that of a Swedish population-based study. Secondly, the estimate assumes that there was no resource consumption during ulcer-free periods and this has not been demonstrated. Additionally, this estimate was for the total cost of leg ulcer care for all aetiologies, and venous ulceration will only account for a portion of this cost. However, given that venous ulcers account for up to 80% of all ulcers, it is likely that the majority of the cost will have been incurred for venous ulcer management. Unfortunately, there have been no national estimates of the direct and indirect cost of venous ulceration to test such an approximation.

The total annual direct cost of treating venous ulceration in the United Kingdom has been estimated from interviews of English patients about treatment over the previous two years. When the costs of materials, district nursing time, in-patient and out-patient visits, general practitioner consultations and prescribing, were combined with estimated prevalence, the total cost of venous ulcer treatment was
reported to be UK£230-400 million in 1990-1991 terms. These findings were limited by the potential for recall bias. The annual direct cost of venous ulcer management per patient has also been stochastically modelled from clinical data to incorporate ulceration, ulcer-free periods and recurrence. The annual cost of treatment in Sweden ranged from 1,332 to 2,585 Euro in 2002 terms, depending on the ulcer size, while the cost in the United Kingdom ranged from 814 to 1,994 Euro. The difference in cost was attributable mainly to the difference in frequency of district nursing visits, which were 2.7 times per week in Sweden compared to 1.5 times in the United Kingdom. This study was subject to three limitations. First, it relied on small panels of experts to build the model of treatment in each country and it is not known how representative the clinical models are. Second, all patients were assumed to progress from incident ulcer through a disease-free period and thence to recurrent ulceration during the one year period. Five year recurrence rates are known to be less than 100% from trials of compression to prevent recurrence, so this assumption is likely to over-estimate one year recurrence. Third, it was assumed there was no resource utilisation during the disease-free period, but it was not known whether this assumption is accurate.

2.5.2 New Zealand data
There is very limited information on the cost of leg ulcer care in New Zealand. A study of five family practices with 6,447 registered patients within the district of Otago between 1991 and 1992 found slightly more than 1% of patients aged 40 or over had a venous leg ulcer. These patients accounted for approximately 2.5% of total health care expenditure for this age group, which was more than twice that of the average patient aged over 40 within the practices. The total health care expenditure was estimated from this study to be approximately $6,800 per patient with venous leg ulcers or $80 million per annum nationally. However, the study included an assumed cost for hospitalisations based on discharge codes for peripheral vascular disease (PVD). PVD is a term more commonly associated with arterial conditions, and thus the study may not accurately reflect the costs of hospitalisation for venous ulceration. In addition, the study estimated district nursing on the basis that half of district nursing expenditure could be attributed just to care of patients with venous leg ulcers. Surveys of time spent in leg ulcer care by district nursing services in England found the nurses spent between 10% and 50% of their time on leg ulcer care. A report by Community Health Services at Auckland Healthcare estimated district nurses spent 25% of their time on all leg ulcer care.
Therefore the study is likely to have overestimated the cost of district nursing time spent in venous ulcer management.

2.6 Treatments for venous leg ulceration

This section discusses the venous leg ulcer treatments for which there is relatively clear evidence derived from controlled trials and identifies the topical agents reported in the literature for leg ulcer management. Where the trials have been combined by the candidate to produce a summary estimate, the meta-analysis was performed using Review Manager version 4.2.8 and the results are reported as relative risk (RR) with 95% confidence intervals (95%CI). A random effects model was used in the presence of statistically significant heterogeneity; otherwise a fixed effects model was used.134

2.6.1 Compression therapy for venous ulcers

Compression therapy is the therapeutic mainstay of treatment for venous leg ulcers. Compression therapy involves the application of external pressure to the lower leg to enhance venous return to the heart and counter the venous hypertension that is implicated in ulceration. Compression can be delivered in a variety of modalities: bandaging, hosiery or intermittent pneumatic compression. Although compression hosiery can be used with active ulceration, bandaging is more commonly used in New Zealand and the patient is then switched to hosiery when the ulcer is healed (pers. comm. Anita Latta, Clinical Coordinator, Leg Ulcer Team, Auckland District Health Board).

External compression of the lower limb has been advocated as a treatment for leg ulcers since at least the seventeenth century, when Richard Wiseman (1622-1676), surgeon to Charles II of England, described the impact of venous dilation and valve competency.21 Wiseman believed that some leg ulcers might be the result of stagnation secondary to venous outflow problems. For palliative management of such ulcers, Wiseman recommended the use of "a good bandage or a laced stocking to repress the humours impacted in the part, by which bandage the lips of the ulcer are disposed to cicatrize ..." 21 The rigid leather stocking Wiseman writes of is the first recorded advocacy in the English language of compression to heal venous ulceration, although the use of laced leather stockings has also been accredited to the Italian anatomist, Fabrizio ab Aquapendente.135 Tight bandaging or laced stockings were noted to improve healing in ulcers associated with varicosities by eighteenth century authors, many of whom acknowledged or were familiar with
Wiseman's work.\textsuperscript{136-138} \textsuperscript{139-141} Rigid systems, similar in concept to Wiseman's laced stocking, were proposed and employed in the nineteenth century. George Critchett advocated using plaster bandages to stay on for weeks at a time,\textsuperscript{142} and Paul Unna used a gelatin zinc-oxide bandage that became known as Unna's boot,\textsuperscript{143} a method that continued in use through to the twentieth century.\textsuperscript{144} However, rigid systems suffered from the disadvantages of being relatively difficult to apply and needed to be left intact for prolonged periods. Bandages and stockings that employed elastic materials were developed so they could be removed on a daily basis. Martin's pure rubber bandage and the Jobst stockings are the antecedents of today's elastic high compression systems.\textsuperscript{145} \textsuperscript{146}

A systematic review of randomised controlled trials of compression therapy found compression to be more effective than no compression at healing venous ulcers.\textsuperscript{147} Combination of the studies was not possible because of the heterogeneity in study design and outcomes, but four of the six trials found differences that were statistically significant and the effect sizes ranged from relative risks (RR) of 1.82 to 3.0 in these trials. The sample sizes in these six trials were small (mean size 45) and two larger trials have been reported since the above review, both finding significant differences in favour of compression.\textsuperscript{149} \textsuperscript{150} However, the reports were available in abstract only and relative risks could not be calculated due to inadequate detail about the denominators. In one trial (n=101), the proportion healed at 13 weeks in the compressed group was 64\% compared to 26\% in the uncompressed group and time to healing was significantly shorter (p<0.001).\textsuperscript{149} In the second trial (n=180), the proportion healed at 12 weeks was 77\% in the compressed group and 31\% in the uncompressed group.\textsuperscript{150}

There are a variety of ways of delivering compression bandaging. For instance, bandages can be single layer or multi-layer, and elastic or inelastic. Thus a single layer bandage might be an elastic (long stretch) or an inelastic (short stretch) bandage. Combined elastic systems can consist of three or four layers of different bandages, each contributing some compression. Each system offers advantages and disadvantages. Single layer systems can be reused after they have been washed, but can rapidly lose compression as the leg volume reduces with removal of oedema from the third space. Elastic multi-layer systems are less prone to this loss of compression, but are single use items and are bulky, which can create difficulties if people need to wear normal footwear. Guidelines do not usually specify what type of compression should be used, leaving the options to be negotiated between practitioners and patients.\textsuperscript{151} \textsuperscript{152} However, the systematic review previously
mentioned found multi-layer compression to be more effective than single layer compression (RR 1.41, 95%CI 1.12 - 1.77) for healing venous ulcers.\textsuperscript{147,148} Recent evidence has suggested that bandaging skills may in part explain this difference. The VenUS I trial found an increase in the likelihood of healing at one year with the multi-layer system (hazard ratio 0.85, 95%CI 0.49 - 1.48).\textsuperscript{153} In this trial the standard system was multi-layer bandaging while the new system was short stretch bandaging. In a second trial there was no significant difference between multi-layer and single layer bandages at 16 weeks.\textsuperscript{154} In this trial the standard bandage was a short stretch system, whilst the new system was four layer bandaging. While VenUS I was the larger trial with longer follow up, the authors did not believe that these methodological differences provided the only explanation for the different results obtained by two otherwise similar trials. They suggested the reserve of bandaging skills may have favoured the regimen already established as the standard treatment in the participating study centres.

What is clear from the systematic review of compression trials is that high compression systems were more effective than low compression systems.\textsuperscript{147,148} However, no significant differences between different types of high compression were found. Adjuvant compression systems have also been used in addition to bandaging. Intermittent compression using a pneumatic device, in addition to compression bandaging, has been investigated in three small trials evaluated in a systematic review.\textsuperscript{155} One trial found an effect in favour of the adjuvant treatment, while the other two trials found no effect. These results do not support the routine use of intermittent compression as an adjuvant to compression bandaging.

\textbf{2.6.2 Pharmacological treatments for venous ulcers}

\textbf{2.6.2.1 Micronised purified flavonoid fraction (MPFF)}

MPFF (marketed as Daflon) is a semi-synthetic flavonoid consisting of 90% diosmin and 10% hesperidin synthesised from a citrus species \textit{Rutaceae aurantiae}.\textsuperscript{156} The action of MPFF in venous ulcer healing is unknown, although it has been suggested that its effect is derived from anti-inflammatory effects, possibly through reduction in leucocyte and endothelial activation.\textsuperscript{157} Three randomised controlled trials that enrolled a total of 395 participants investigated the effect of MPFF as an adjuvant to compression bandaging in venous leg ulceration.\textsuperscript{158-160} Combining the three trials in a meta-analysis (Figure 3), complete healing was about two-thirds more likely to occur when patients were treated with MPFF, in addition to compression compared to placebo (RR 1.69, 95%CI 1.30 to 2.19). Two trials were open label trials, raising
<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
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</thead>
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<tr>
<td>01 MPFF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guilhou</td>
<td>14/53</td>
<td>6/52</td>
<td></td>
<td>10.83</td>
<td>2.29 [0.95, 5.50]</td>
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<tr>
<td>Glinski</td>
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<td>19/69</td>
<td></td>
<td>34.45</td>
<td>1.69 [1.07, 2.67]</td>
</tr>
<tr>
<td>Roztocil</td>
<td>53/82</td>
<td>28/68</td>
<td></td>
<td>54.72</td>
<td>1.57 [1.13, 2.17]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>206</td>
<td>189</td>
<td></td>
<td>100.00</td>
<td>1.69 [1.30, 2.19]</td>
</tr>
<tr>
<td>Total events: 100 (Treatment), 53 (Control)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 0.66, df = 2 (P = 0.72), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.98 (P &lt; 0.0001)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Sulodexide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coccheri</td>
<td>63/121</td>
<td>36/114</td>
<td></td>
<td>58.77</td>
<td>1.65 [1.20, 2.27]</td>
</tr>
<tr>
<td>Kucharzewski</td>
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<td>9/21</td>
<td></td>
<td>14.92</td>
<td>2.33 [1.42, 3.82]</td>
</tr>
<tr>
<td>Scondotto</td>
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<td>15/42</td>
<td></td>
<td>26.31</td>
<td>1.62 [1.01, 2.58]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>196</td>
<td>177</td>
<td></td>
<td>100.00</td>
<td>1.74 [1.38, 2.20]</td>
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<tr>
<td>Total events: 116 (Treatment), 60 (Control)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 1.56, df = 2 (P = 0.46), I² = 0%</td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 4.65 (P &lt; 0.00001)</td>
<td></td>
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</tbody>
</table>

**Figure 3.** Meta-analysis of trials using MPFF or sulodexide as an adjuvant to compression for treatment of venous leg ulcers.
<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
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<td>Schumann</td>
<td>2/12</td>
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<td></td>
<td>3.46</td>
<td>0.67 [0.13, 3.30]</td>
</tr>
<tr>
<td>Colgan</td>
<td>23/38</td>
<td>12/42</td>
<td></td>
<td>15.53</td>
<td>2.12 [1.23, 3.65]</td>
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<tr>
<td>Barbatino</td>
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<td>1/6</td>
<td></td>
<td>2.60</td>
<td>4.00 [0.61, 26.12]</td>
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<tr>
<td>Pizarro</td>
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<td>6/25</td>
<td></td>
<td>9.78</td>
<td>1.91 [0.84, 4.34]</td>
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<tr>
<td>Dale</td>
<td>65/101</td>
<td>52/99</td>
<td></td>
<td>24.54</td>
<td>1.23 [0.97, 1.55]</td>
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<tr>
<td>Falanga</td>
<td>61/86</td>
<td>28/45</td>
<td></td>
<td>23.73</td>
<td>1.14 [0.87, 1.49]</td>
</tr>
<tr>
<td>Belcaro</td>
<td>55/84</td>
<td>24/88</td>
<td></td>
<td>20.36</td>
<td>2.40 [1.65, 3.49]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>351</td>
<td>317</td>
<td></td>
<td>100.00</td>
<td>1.59 [1.15, 2.18]</td>
</tr>
</tbody>
</table>

Total events: 221 (Treatment), 126 (Control)
Test for heterogeneity: $\chi^2 = 17.23$, df = 6 ($P = 0.008$), $I^2 = 65.2%$
Test for overall effect: $Z = 2.85$ ($P = 0.004$)

**Figure 4.** Meta-analysis of trials using pentoxifylline as an adjuvant to compression for treatment of venous leg ulcers.
the possibility of attribution bias. However, the blinded study had a larger treatment effect than the open label studies, although this may have been due to a relatively short follow up period (eight weeks) in comparison to the 6-month follow up periods in the other two trials. A recent systematic review that included data from the above studies plus two unpublished trials found the relative risk increase of complete healing at six months was 32% (95%CI 3 to 70%) better in patients receiving MPFF. The data from the unpublished studies were provided by the drug’s manufacturer, which may raise some doubt about the completeness of the information.

2.6.2.2 Sulodexide

Sulodexide (marketed as Vessel Due F) is a heparinoid consisting of dermatan sulfate and low molecular weight heparin that is derived from porcine intestinal mucosa. The action of sulodexide in venous ulcer healing is unknown, although the drug is considered to have antithrombotic and antiplatelet actions. Three trials have investigated the effect of sulodexide in venous ulceration. Combining the trials in a meta-analysis (Figure 3), complete healing was about three-quarters more likely to occur when patients were treated with a sulodexide in addition to compression compared to placebo 1.74 (95%CI 1.38 to 2.20). However, one of the trials used a pseudo-random method of allocation, although removing this trial from the analyses changed the estimate very little (RR 1.64, 95%CI 1.26 to 2.13).

2.6.2.3 Pentoxifylline

Pentoxifylline (marketed as Trental) is also known as oxpentifylline. It is a methylxanthine derivative and a haemorrheological agent. Its microcirculatory effect in venous ulcer healing is unknown, although among its many effects, pentoxifylline has been shown to inhibit leucocyte adhesion, reduce free radical expression and reduce platelet aggregation. One systematic review of randomised controlled trials investigated the effect of pentoxifylline on healing in chronic leg ulcers and healing rates favoured the drug (RR 1.49, 95%CI 1.11 to 2.01). This was also the case when the drug was used in addition to compression (RR 1.30, 95%CI 1.10 to 1.54). Three more trials have been identified since the systematic review was published. In one of these trials it is not clear whether it is a 12-month follow-up from the 6-month study, or whether different participants were recruited into a 6-month and a 12-month trial. Therefore only the 6-month report was considered here. When the two new trials that used compression as a background treatment are included in the previously published
meta-analysis (Figure 4), participants receiving pentoxifylline in addition to compression were 60% more likely to heal than those receiving placebo (RR 1.59, 95% CI 1.15 to 2.18). However, two independent sources have suggested the existence of an unpublished negative trial (pers. comm., Professor Mike Stacey, Dr Gianni Belcaro), although attempts to locate this trial have not been successful. Such a trial may temper these findings.

2.6.2.4 Other treatments

Findings for other systemic drug treatments for venous ulceration have either been equivocal or have been too small to deliver clear estimates of treatment effects. These drugs include: aspirin, \textsuperscript{177} \textsuperscript{178} granulocyte-macrophage colony-stimulating factor, \textsuperscript{179} hydroxyethyl-rutosides, \textsuperscript{180} \textsuperscript{181} mesoglycan, \textsuperscript{182} prostaglandin E\textsubscript{1}, \textsuperscript{183} stanozolol, \textsuperscript{184} \textsuperscript{185} thromboxane A\textsubscript{2} inhibitors, \textsuperscript{186} and zinc sulphate. \textsuperscript{187} Similarly, topical growth factors and drugs have not lived up to their early promise. These treatments include: keratinocyte growth factor-2, \textsuperscript{188} platelet-derived growth factor, \textsuperscript{189} human growth hormone, \textsuperscript{190} epidermal growth factor, \textsuperscript{191} and tissue plasminogen activator. \textsuperscript{192} Other treatments for which there is a limited evidence base include: hydrogen peroxide cream, \textsuperscript{193} laser, \textsuperscript{194} electromagnetic therapy, \textsuperscript{195} larval (maggots) therapy, \textsuperscript{196} skin grafting, \textsuperscript{197} and ultrasound. \textsuperscript{198}

2.6.3 Surgical treatment for venous ulcer healing

Surgery to correct superficial venous incompetence has been thought to have the potential to improve the rate of ulcer healing, but the trial findings conflict. \textsuperscript{199} Three longer trials found no significant difference in healing rates between surgery with compression and compression alone, \textsuperscript{119} \textsuperscript{200-203} while another smaller trial did find a difference. \textsuperscript{204} The differences may reflect the different designs, the different surgical procedures and the role of bias. Thus whether surgery assists in healing venous ulcers remains unresolved. A fifth surgical trial was stopped early after recruiting only 75 of the planned 1000 participants following publication by Barwell, \textit{et al.} \textsuperscript{201} No results from this study have been published. \textsuperscript{205} The smallest trial (n=44) compared minimally invasive surgical ablation to compression. \textsuperscript{204} Participants allocated to surgery also received compression bandaging until surgery. Participants allocated to compression received short stretch compression until the ulcer healed and then the participant was switched to elastic stockings delivering 20-30 mm Hg pressure at the ankle. Participants were followed for three years to evaluate recurrence rates. The median time to healing respectively
was 31 days and 63 days (p<0.005) and there were fewer recurrences in the surgical group than the compression group (2 versus 9, RR 0.25, 95% CI 0.07 to 0.92). A quality assessment was not possible for this study as the trial methods were not outlined in the report, although it does appear that follow up was complete and intention-to-treat analysis was used. The small sample size raises the possibility of random error being responsible for the findings. In addition, participants in the compression group did not receive optimal levels of compression for preventing recurrence, but used grade 2 stockings. However, there was no statistically significant difference between grade 2 and grade 3 stockings in a trial with five year follow up, although there was a difference at three years.

A larger trial (n=76) compared surgery for venous ulcers plus four-layer compression (n=37) to four-layer compression alone (n=39). Healing rates at six months were 68% in the surgery group compared to 64% in the compression group (p=0.8), with median healing time being 83 days in the surgery group compared to 98 days in the compression group (p=0.4). The trial did not describe randomisation, but used allocation concealment (sealed envelope), had complete follow up and probably used intention-to-treat analysis. Additionally, participants received high compression bandaging. A mix of surgical procedures was used (superficial ligation, with stripping or sequential avulsion, and phlebotomies; and perforator surgery, with either ligation or subfascial endoscopic perforator surgery – SEPS). This variation in procedures would mimic real world practice, but raises the pragmatic question of whether particular procedures are more effective. The lack of a sample size calculation also raised the possibility the findings could be explained by type II error.

The largest trial (n=341) compared surgery and four-layer high compression bandages (n=156) to four-layer high compression bandages alone (n=185) and also found no difference in healing rates between the groups. The 24-week rate of healing was 65% in both groups (p=0.9). This trial used random assignment (computer generated) with adequate allocation concealment (sequentially numbered sealed envelopes), and intention-to-treat analysis. A mix of simple surgical procedures was used (superficial ligation, with stripping or avulsion), but with 25% of participants not receiving complete superficial ablation because of their anaesthetic risk. This variation in procedures would mimic real world practice, but as with the previously described trial raises the question of whether particular procedures are more effective. This trial was part of a larger trial (n=500) to observe whether surgery had any impact on 12-month ulcer recurrence rates and the trial was
powered for this outcome. Arguably, the 24-week healing outcome is either a secondary outcome or a subgroup analysis, and as the trial was not powered for either, there is the possibility the findings could be a type II error. The trial did find that 12-month recurrence rates were significantly lower in the surgery group than the non-surgery group (Hazard Ratio -2.8, 95%CI -1.8 to -4.3), suggesting downstream savings in leg ulcer treatment if the finding was stable over a longer period.

A fourth trial (n=170) also compared surgery plus compression to compression alone.\textsuperscript{202} \textsuperscript{203} Compression was standardised – participants received short stretch compression bandaging until healed and then switched to compression stockings (grade 2 or 3 depending on the presence of deep vein incompetence). The trial used random assignment (computer generated) with adequate allocation concealment (independent randomisation service), and intention-to-treat analysis. This trial used a mixture of superficial ablative techniques, with SEPS for perforator surgery, and ulcer-free time as the primary outcome. Healing and recurrence rates were secondary endpoints, with ulcer-free time the primary endpoint. Mean follow up time was 29 months in the surgical group and 26 months in the compression group. Total ulcer-free time was 72\% in the surgery group and 53\% in the non-surgery group (p=0.1). There was a non-significant increase in healing rates favouring the surgery group (83\% versus 73\%, p=0.2), but no difference in recurrence rates (22\% versus 23\%, p value not reported). However, this trial randomised legs rather than participants and may be subject to unit of analysis errors as a consequence.

The effect of surgery remains unclear and the methodological differences between the trials meant that combination in a meta-analysis was not feasible. However, on the basis of the current evidence and in spite of the caveats on the quality of the studies, it would seem reasonable to assume surgery does not confer any additional benefit in terms of rates of ulcer healing. Unfortunately, the effect of surgery on recurrence rates cannot be similarly resolved. Although the largest trial found recurrence rates were reduced with surgery,\textsuperscript{201} the follow up was only over a 12-month period and another reasonably sized trial with approximately 2 years of follow up found no difference in recurrence rates.\textsuperscript{203} Without further reports over the course of longer follow up from Barwell, et al.,\textsuperscript{208} the issue will remain unresolved and more trials will be required.
2.6.4 Other pharmacological treatments for venous ulcers

The long list of salves, powders and ungualts used for leg ulcer care in the Eighteenth Century led a surgeon of the time to depict their advocacy as a "farrago of empiricism", meaning a hotchpotch of ignorant and unscientific practice. Modern practices seem to differ little in this respect. Three English studies have reported large numbers of products in use. One study recorded 90 different topical agents used in 108 different ways on 357 patients, while the second found 59 different topical agents were being used in addition to 36 different dressings on patients with leg ulcers in a prospective audit. A retrospective audit found 516 different products and agents had been used by 86 district nurses. Similarly large numbers of products and agents for the treatment of leg ulcers have been reported in other countries. A Swedish study found 51 dressing products were being used on 294 patients with foot and leg ulcers, while a New Zealand study found 136 different topical and systemic products were used on 205 participants with leg ulcers.

Many topical treatments are used to enhance ulcer debridement, reduce pain, for antisepsis or to enhance healing. Examples reported in the modern literature include: acetic acid, activated charcoal, aluminium salts, chlorhexidine, chloramidine, dextranomer, EUSOL (Edinburgh University Solution of Lime), EMLA cream, hydrogen peroxide, iodophors (cadexomer iodine, povidone-iodine), potassium permanganate, silver-based products (silver releasing dressings, silver nitrate and silver sulfadiazine), sucralfate, sugar, tea tree oil, and zinc oxide, as well as pharmaceutical agents such as allopurinol, dimethylsulfoxide (DMSO), hyaluronic acid, iloprost, phenytoin, copper peptides, sulphydryl-containing agents (DL-cysteine, DL-methionine-methyl sulphonium chloride) and streptokinase-streptodornase. A recent addition to this list is honey.

2.7 Honey

Honey is a viscous, supersaturated sugar solution derived from nectar gathered and modified in vivo by the honeybee. It is usually the honey of Apis mellifera that is commercially exploited in wound care, although honey from other bee species such as the Africanised Apis mellifera and the stingless bees (Melliponinae) in Brazil have been investigated. Honey consists of approximately 40% fructose, 30% glucose and 5% sucrose, in addition to approximately 20% water. It has a low water
activity (12-14%), is acid (pH ranging between 3.2 and 4.5), and contains a large number of substances, such as amino acids, vitamins, minerals and phytochemicals.\(^{256,257}\) Over the past two decades, there has been a surge of interest in honey as a wound treatment, with a more than twenty-fold increase in citations in MEDLINE, EMBASE and CINAHL from 1980-1984 to 2000-2004.

Honey has been found to have antibacterial properties and is claimed to stimulate rapid healing.\(^{253,258}\) Honey’s antibacterial properties are attributed to the combined effects of its osmolarity, acidity, and hydrogen peroxide content. The antibacterial effect of honey was first recognised in 1882 and it was initially thought to be due to honey’s sugar content, which dessicates bacteria when the honey is undiluted.\(^{256,259}\) However, osmotic removal of water does not explain all the antibacterial activity of honey, as the effect is retained when the sugar is dialysed out of honey.\(^{260}\) Honey’s acidity was also thought to provide an explanation of honey’s antibacterial activity. The acidity is due to honey’s organic acid content, especially gluconic acid, although the actual acids may vary depending on the floral variety of the honey.\(^{253,256}\) Glucose oxidase secreted by bees catalyses glucose to gluconic acid, which is thought to be sufficiently acidic to have an inhibitory effect on bacteria growth.\(^{259}\) Another product of the glucose oxidase reaction is hydrogen peroxide. This is the antibacterial substance which was previously called “inhibine” prior to its identification as hydrogen peroxide.\(^{261}\) In addition, some honeys still retain their antibacterial activity despite the addition of catalases to remove peroxide-based activity. Honey derived from the New Zealand manuka tree (\textit{Leptospermum scoparium}), is one such honey that has been found to have this non-peroxide activity.\(^{258}\) A phytochemical substance, yet to be characterised but currently termed Unique Manuka Factor (UMF), is the substance thought to be responsible for the non-peroxide bacteriocidal properties of New Zealand manuka honey. Similar activity has also been observed in honey from another \textit{Leptospermum} species, the Australian jelly bush tree (\textit{Leptospermum polygalifolium}).\(^{256}\)

The claims with respect to honeys stimulating rapid healing are largely derived from clinical observation in humans and animals, with limited histological investigation. Clinically, honey is thought to have reduced inflammation, oedema and exudate levels, although these observations have not been obtained from blinded studies or accurately quantified.\(^{258}\) Histological evidence of early reparative changes, in the form of granulation tissue and epithelisation, have been observed in honey-treated patients with superficial burns when compared with patients treated with silver sulfadizine (SSD).\(^{262}\) Similar changes have been observed in honey-treated pigs
with standard burns, when compared with pigs treated with SSD. Increased granulation tissue, keratinisation of wounds and thicker basal cell and epidermal layers have been found in honey-treated animals with surgically created wounds in comparison to placebo-treated animals with similar wounds. Biochemical investigations of honey's possible effects are relatively recent, and early cell-line evidence suggests honey may promote the secretion of pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α). These cytokines are integral to the tissue deposition-degradation cycle so important to wound healing.

2.7.1 Historical uses of honey in wound care

Although interest in honey as a wound treatment is resurgent, honey has been employed in wound care since ancient times. Honey is frequently mentioned in early pharmacopoeia. Dioscorides (40-80 CE), a pharmacopoeist from lesser Armenia, compiled the medicinal properties of more than 1000 natural products in de materia medicis, and often mentioned honey as a vehicle for carrying therapeutic agents. However, Dioscorides paid relatively little attention to wounds, and honey was not noted as an agent for wound care in its own right. Hippocrates (460-377 BCE) is frequently cited as having employed honey in wound care, but it was simply one of the many ingredients in the multitude of unguents described in his texts.

The first sustained and deliberate advocacy of honey as a wound treatment was advanced by Egyptian healers, although the rationale was not identified. The anonymous author in the Edwin Smith Papyrus, a treatise focusing on surgical and wound practices thought to have been written between 2600-2200 BCE, recommended a honey-grease salve in 22 of the cases described in the papyrus. This salve consisted of one part honey to two parts grease (which could consist of any fat from vegetable oil to snake grease) and was applied to wounds after suturing, although not to infected wounds. Another Egyptian text, the London Medical Papyrus written around 1325 BCE, recommended a dressing made of honey and a plant called 'djaret' for 'white spots' associated with burns. Egyptian advocacy of honey probably needs to be considered in its cultural context. The royal title for upper Egypt incorporated the expression "belonging to the bee", and honey was the most popular of Egyptian remedies, being part of more than 50% of the 900 known remedies.

Honey was used in other early medical traditions. A honey and clarified butter dressing for burns was referred to in the Sushruta Samhita, an Ayurvedic surgical
text written in circa 600 BCE, and honey mixed with badger oil is mentioned in an early Chinese text. The Roman physicians Celsus and Galen recommended honey in the first and second centuries CE. Galen's recommendation was carried forward by the Muslim physician Ali Ibn Al-Husain al Sina (Avicenna, 980-1037 CE), who translated Galen's work into the *Canon Medicina*. The *Canon Medicina* was considered the foremost medical text in Northern Europe and the Mediterranean region until the seventeenth century.

Early renaissance surgeons also used honey in wound care. An anonymous manuscript written in 1392 includes honey in lists of constituents for unguents to cleanse wounds, absorb exudates and treat slow healing wounds (endearingly termed "wicked wounds"). Rose honey was also advocated for "mundification" (wound debridement) by Giovanni de Vigo, a Genoan surgeon during the fifteen century. Another anonymous text, bound with a second manuscript dated 1446, also included honey as a constituent to assist with wound debridement. Authorship of the previously unknown manuscript had been tentatively ascribed to Thomas Morstede, a London surgeon circa 1350-1400 CE. However, it is now thought to have been written by John Bradmore, surgeon to Henry IV. Bradmore was renowned for removing an arrowhead from the battlefield injury suffered by Prince Harry (later Henry V) at the Battle of Shrewsbury. Before surgery could proceed, Bradmore used innovative wound spreaders of his own design to gradually open the facial wound over several days to provide access to the arrowhead. The spreaders were wrapped in honey-soaked lint to cleanse the wound before surgery. More recently, Russian soldiers were said to have used honey to prevent wound infections and to accelerate healing during World War One.

### 2.7.2 Honey and wound healing in the animal model

Sixteen controlled animal studies across five different animal models (n=475) have investigated the effect of topical honey on wound healing. Details from a Brazilian study were extracted from the English language abstract. Eight studies were excluded because they did not evaluate honey's effect on healing, were duplicate reports, or did not include a control. Apart from one study, all other studies found honey accelerated wound healing in comparison to control treatments (Table 5). The studies only used animals with acute wounds. Acute wounds in humans differ physiologically from chronic wounds, and there is no reason for this not to be the case in animal models. The lack of studies investigating the effect of honey in induced chronic wounds represents a clear gap in the animal evidence. An additional concern is that the animal studies did not
report the design elements necessary to assess the quality of the studies. Only seven (44%) studies reported that random assignment was employed either in allocation of animals or wounds to treatment. However, the method of randomisation was not reported in these seven studies and allocation always resulted in equal numbers in groups, a situation that would be unusual with such small groups unless block randomisation was used. Additionally only one report stated whether or not observers were blind to treatment allocation. Both random allocation and blinding are known to influence the estimates of treatment effects in human studies, but animal studies frequently do not report either randomisation or blinding. A systematic review of highly cited animal studies that were translated into human research found that only 20% of the 76 included studies reported blinding and less than 15% reported randomisation. Other reviews of specific treatments such as low level laser for wound healing, nimodipine for cerebral ischaemia and albumin for fluid resuscitation have also noted the poor methodological quality of animal model reports. If the purpose of animal experimentation is to provide evidence of safety and efficacy in order to evaluate whether human experimentation is justified, assessment of experiments’ internal validity is required. Poorly reported studies do not deliver the information on which to base such decisions, as the sources of bias cannot be assessed. With respect to honey, questions must be asked about the necessity of continued animal experimentation in a treatment that has already been used safely in humans for centuries.

2.7.3 Honey and wound healing in humans

There have been 40 case reports of honey being used on a wide variety of wounds in 875 patients (Table 6). The wound types include: abdominal wound disruptions following burns, decubitis ulcers, diabetic ulcers, diaper dermatitis (nappy rash), epidermolysis bullosa, Fournier’s gangrene, hidradenitis suppurativa, hydroxyurea-induced leg ulcers, infected skin grafts, mixed leg ulcers, post-operative wound infections, surgical wounds, skin graft donor sites, and skin tears. In addition, there have been short reports of honey being employed on a mix of wound aetiologies in paediatric and adult populations and letters of support where the correspondent reported their own use of honey, but all without detail. The majority of reports either did not observe or did not report adverse events. Where adverse events were reported, these were confined to localised side effects. Transient pain following application of the honey was noted in eight of the case reports, and continuous pain in two reports. Pain did not seem to be associated with any particular wound type.


<table>
<thead>
<tr>
<th>Study</th>
<th>Wound type</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Kennany, et al., 2003</td>
<td>Acute -</td>
<td>Sixteen rabbits, randomly assigned to four equal groups; two incisions</td>
<td>Wounds in groups 1 and 2 remained unhealed; wounds in honey-treated animals healed by day seven compared to day 10 in the myrtle-treated group. Histological examination showed epithelium thinner in honey-treated wounds compared to wounds treated with Myrtle. Comment:</td>
</tr>
<tr>
<td></td>
<td>Incisional</td>
<td>made on the back of each animal and inoculated with <em>S. aureus</em> (10^10</td>
<td>Method of randomisation not reported, blinded not reported, no formal statistical testing of differences in wound healing, histology reported qualitatively.</td>
</tr>
<tr>
<td></td>
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<td>bacterial cells). Group 1 animals treated with normal saline; group 2</td>
<td></td>
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<td></td>
<td></td>
<td>animals not treated; group 3 animals treated with twice daily topical</td>
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<td></td>
<td></td>
<td>honey (5%); group 4 animals treated with topical extract of *Myrtus</td>
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<tr>
<td></td>
<td></td>
<td><em>communis</em> (Myrtle). Wounds in groups 3 and 4 covered with sterile</td>
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<tr>
<td></td>
<td></td>
<td>gauze and bandaged.</td>
<td></td>
</tr>
<tr>
<td>Al-Waelli, 2004</td>
<td>Acute -</td>
<td>Forty-eight Swiss mice, assigned to 2 equal groups, and each group</td>
<td>Time to healing was 2 days in control animals, 4 days in honey-treated animals, 9 days in gentamicin-treated animals and 12 days in control animals. <strong>Comment:</strong> Method of assignment not reported, blinded not reported, no formal statistical testing of differences in wound healing.</td>
</tr>
<tr>
<td></td>
<td>Incisional</td>
<td>subdivided into 4 equal subgroups; 15mm incision made in dorsum of</td>
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<tr>
<td></td>
<td></td>
<td>each animal. Control animals in groups 1A and 2A, the incision was</td>
<td></td>
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<td></td>
<td></td>
<td>sutured; groups 1B-1D were inoculated with <em>S. hemolyticus</em> and 2B-2D</td>
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<td></td>
<td></td>
<td>were inoculated with Klebsiella. Groups 1C and 2C were treated with</td>
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<td></td>
<td></td>
<td>topical honey 4 times daily; groups 1D and 2D were treated with topical</td>
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<tr>
<td></td>
<td></td>
<td>gentamicin 4 times daily.</td>
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</tr>
<tr>
<td>Bergman, et al., 1983</td>
<td>Acute -</td>
<td>Twenty-four Hb/lmg mice assigned to 2 equal groups; area 100 mm^2</td>
<td>Area of the wound was 55.1 (± 2.1) mm^2 at day 9 in the honey treated animals compared to 105.6 (± 2.8) mm^2 in the control animals. Rate of epithelialisation was significantly greater in the honey-treated animals than the control animals (p&lt;0.001) as was the thickness of granulation tissue (p&lt;0.001). No wounds showed signs of infection. <strong>Comment:</strong> Method of assignment not reported, blinded not reported.</td>
</tr>
<tr>
<td></td>
<td>Excisional</td>
<td>excised from neck of each animal. Group 1 wounds dressed twice daily</td>
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<tr>
<td></td>
<td></td>
<td>with topical honey; group 2 wounds dressed twice daily with 0.9% saline.</td>
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<tr>
<td></td>
<td></td>
<td>Four animals in each group euthanased at days 3, 6 and 9.</td>
<td></td>
</tr>
<tr>
<td>El-Banby, et al., 1989</td>
<td>Acute -</td>
<td>Sixty albino rats, assigned to six equal groups; 10mm incision created</td>
<td>At day 3 mean wound length was 4 (± 0.33) mm in group 1, 5 (± 0.26) mm in group 2, 8 (± 0.26) mm in group 3. By day 9, all group 1 wounds were healed; mean wound length was 2 (± 0.21) mm in group 2, and 2 (± 0.21) mm in group 3. <strong>Comment:</strong> Method of assignment not reported, blinded not reported, no formal statistical testing of differences in wound healing.</td>
</tr>
<tr>
<td></td>
<td>Incisional</td>
<td>on the back of each animal. Group 1 wounds dressed with topical floral</td>
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<tr>
<td></td>
<td></td>
<td>honey, group 2 wounds treated with topical non-floral honey (sugar-fed</td>
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<tr>
<td></td>
<td></td>
<td>bees), group 3 wounds treated with topical 0.9% saline. Groups 4-6</td>
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<tr>
<td></td>
<td></td>
<td>treated orally.</td>
<td></td>
</tr>
<tr>
<td>Fei, et al., 2003</td>
<td>Acute -</td>
<td>Thirty albino rats assigned to two equal groups; partial thickness</td>
<td>At day 5 moderate numbers of fibroblasts and new epidermal layers found in honey-treated animals in comparison to no epidermal layers and few fibroblasts in control animals. By day 10, epidermal layer complete in group 2 animals, but no epidermal regeneration in control animals. No significant difference in tensile strength between groups (p&gt;0.05). <strong>Comment:</strong> Method of assignment not reported, blinded not reported.</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>burn created on left and right sides. Group 1 animals covered with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>burn</td>
<td>dressing, group 2 animals treated with manuka honey daily.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Wound type</td>
<td>Methods</td>
<td>Results</td>
</tr>
<tr>
<td>------------------------</td>
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<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ghaderi &amp; Afshar, 2004</td>
<td>Acute - Incisional</td>
<td>Twelve mice randomly assigned to two equal groups; 2mm full-thickness wound created on back of each animal. Group 1 animals treated daily with applications of Ummia honey, group 2 animals dressed with sterile gauze. Outcomes assessed by 3 blinded assessors.</td>
<td>At day 4, mean distance between the two wound edges was 0.4 (±0.03) mm in group 1 and 0.2 (±0.06) mm in group 2. At day 7 mean distance between the two wound edges was 0.3 (±0.04) mm in group 1 and 2 (±0.03) mm in group 2. Increased formation of granulation tissue, density and activation of fibroblasts, thickness of basal membrane and less inflammation observed in histology assessments. Comment: Method of randomisation not reported, histological assessment blinded, no formal statistical testing of differences in wound healing.</td>
</tr>
<tr>
<td>Gupta, et al., 1992</td>
<td>Acute - Incisional</td>
<td>Nine buffalo calves, randomly assigned to three equal groups; ten 8 cm² areas inoculated with S. aureus (10⁶ bacterial cells), five each side of the vertebral column. Full thickness wounds created in each area 48 hours after inoculation. Group 1 animals treated with ampicillin ointment; group 2 animals treated with honey; group 3 animals treated with mixture of 2.5% ampicillin in natural honey. Half of wounds on each animal served as control. Control wounds were irrigated with 0.9% saline.</td>
<td>Granulation tissue appeared after day 4-5 in honey treated group. All honey-treated wounds were completely healed by day 26. Wounds remained unhealed in ampicillin and honey-ampicillin treated groups. Comment: Method of randomisation not reported, blinded not reported, no formal statistical testing of differences in wound healing.</td>
</tr>
<tr>
<td>Miri, et al., 2005</td>
<td>Acute - Standard burn</td>
<td>Sixty Indian pigs randomly assigned to 3 equal groups; 8.5cm² area burn created on right groin of each animal using standard method (exposure to boiling water steam for 10 seconds) and inoculated with Pseudomonas aeruginosa. After 4-6 hours, group 1 animals had burns dressed with unprocessed honey, group 2 animals with acetate mafenide 8.5% and group 3 animals with silver sulfadiazine 1%. Dressings were changed daily.</td>
<td>Six animals in the honey group died as opposed to 9 in group 2 and 8 in group 3 animals (p=0.6). Average wound size in survivors at day 30 was 3cm² in the honey group as opposed to 6.59cm² in group and 6cm² in group (p&lt;0.001). Comment: Method of randomisation unclear (possible lottery), blinded not reported.</td>
</tr>
<tr>
<td>Oladejo, et al., 2003</td>
<td>Acute - Incisional</td>
<td>Thirty Wistar rats randomly assigned to three equal groups; full-thickness 4 cm² wound created on right flank. Wounds packed with gauze soaked in allocated dressing agent, covered with second layer of gauze and secured. Dressings changed every five days until completely healed. Group 1 animals treated with soaked gauze, group 2 animals treated with extraction of Ageratum conyzoides and group 3 animals treated with 0.9% saline.</td>
<td>Mean wound contraction at day 10 significantly greater in the honey-treated animals (4.42cm² p&lt;0.001) and Ageratum-treated animals (4.02cm² p&lt;0.001) than the control animals (3.06cm²). Comment: Method of randomisation not reported, blinded not reported.</td>
</tr>
<tr>
<td>Oryan &amp; Zaker, 1998</td>
<td>Acute - Incisional</td>
<td>Forty New Zealand white rabbits randomly assigned to four equal groups; 3cm full-thickness incision made on left thigh of each animal, bluntly dissected for subcutaneous tissue, skin flaps approximated and sutured. Five animals in each group were treated with 5ml topical honey. Control animals received no treatment.</td>
<td>At day 2, lesions in control animals were larger and more swollen than treated animals. At day 14 the treated animals had complete skin repair, whereas control animals had scab and some epithelialisation. At day 21 there was no difference between treated and control animals. Ultimate and yield of the treated lesions was significantly greater than the untreated lesions (p&lt;0.05 and p&lt;0.02). Comment: Method of randomisation not reported, blinded not reported.</td>
</tr>
</tbody>
</table>
### Table 5 (Continued): Animal studies on honey and wound healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Wound type</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osman, et al., 2003[297]</td>
<td>Acute-Excisional</td>
<td>Thirty albino rats assigned to three equal groups; 60 mm² full thickness wound created on each dorsum. Group 1 animals treated daily with topical honey on right dorsal wound and silver sulfadiazine (SSD) on left dorsal wound; group 2 animals treated twice daily with honey compound (constituents not specified) on right dorsal wound and SSD on left dorsal wounds; group 3 animals treated twice daily with honey on right dorsal wounds and honey compound on left dorsal wounds.</td>
<td>Wound healing lasted 9±2 days in group 1 and group 2 honey/honey compound treated animals. Healing period was equal at 8±3 days in group 3 animals. Wound healing lasted 12±2 days in group 1 and group 2 animals treated with SSD. Comment: Method of assignment not reported, blinding not reported, no formal statistical testing of differences in wound healing.</td>
</tr>
<tr>
<td>Osuagwu, et al., 2004[297]</td>
<td>Acute-Excisional</td>
<td>Twenty Wistar rats assigned to two equal groups; 4 cm² wound created on each animal's back. Group 1 animals were treated with topical honey and group 2 animals with 0.9% saline. The wounds were dressed with gauze, and secured.</td>
<td>Wound dimensions at day were significantly smaller in honey treated animals compared to controls (1.15cm² vs 2.38cm², p&lt;0.05) Percentage wound contraction by day 10 was significantly greater in honey-treated animals than controls (79.2% vs 53.5%, p&lt;0.05) Comment: Method of assignment not reported, blinding not reported.</td>
</tr>
<tr>
<td>Postmes, et al., 1993[349]</td>
<td>Acute-Standard burn</td>
<td>Three Yorkshire pigs; 12 49 cm² burns created by standard method, six on each flank of the pigs. One pig (120) was treated with daily applications of 1% SSD cream or lime honey (inhibine score 15), a second pig (64) was treated honey alone and the third pig (137) was treated with daily applications of lime honey or a sugar paste. The sugar paste consisted of 40% glucose, 40% fructose, 10% saccharose and 10% water, with an osmolality similar to that of honey.</td>
<td></td>
</tr>
<tr>
<td>Rahal, et al., 2003[294]</td>
<td>Acute-Excisional</td>
<td>Sixty Wistar female rats assigned to three equal groups; 3 cm² wound produced on left lateral thoracic region on each animal; Group 1 animals treated with once daily with propolis; group 2 animals once daily with honey and group 3 animals treated once daily with 0.9% saline. Five animals in each group were euthanased at days 3, 7, 14 and 21.</td>
<td>100% epithelialisation was attained by day 21 in both the honey-treated and sugar-treated pigs (64 and 137). Honey-treated wounds were 100% closed between day 21-28 in pig 120, compared to between day 28-35 for the SSD-treated wounds. Comment: Method of assignment not reported, blinding not reported.</td>
</tr>
<tr>
<td>Sudhakar Rao, et al., 2003[296]</td>
<td>Acute-Incisional</td>
<td>Nine albino rats randomly assigned to 3 equal groups; wound 1.5 cm long created on back of each animal. Group 1 animals treated with tumeric paste daily for two weeks, group 2 animals treated with honey once daily for two weeks and group 3 animals were left untreated.</td>
<td>There were no significant differences in healing rates (p&gt;0.05). Histological examination showed less inflammatory response in propolis and honey-treated groups and faster re-epithelialisation in the propolis treated group. Comment: Method of assignment not reported, blinding not reported, histology reported qualitatively.</td>
</tr>
<tr>
<td>Suguna, et al., 1993[295]</td>
<td>Acute-Excisional</td>
<td>Twenty-four male albino rats assigned to four groups; a full thickness 4 cm² wound was created on the back of each animal. Group 1 animals were left untreated; group 2 animals were treated with 1ml topical honey; group 3 animals were treated with 1ml oral honey and group 4 animals were treated with 1ml intraperitoneal honey</td>
<td>Honey exhibited maximum wound healing followed by tumeric, in comparison to the control animals. Comment: Method of randomisation not reported, blinding not reported, histology reported qualitatively. At day 4, mean wound contraction was 35% in group 1 compared to 50%, 55% and 60% in groups 2, 3 and 4 (p&lt;0.001). At day 16, mean wound contraction was 80% in group 1 compared to 92%, 95% and 97% in groups 2, 3 and 4 (p value not reported). Honey-treated animals had increased tensile strength compared to controls (p&lt;0.05). Comment: Method of randomisation not reported, blinding not reported.</td>
</tr>
</tbody>
</table>
A burn-like skin reaction was also noted in one report.\textsuperscript{338} Skin maceration and excoriation was observed in two reports involving venous leg ulcers,\textsuperscript{252 350} and candidal or yeast infections in two reports, one involving patients with dehisced vulvectomies,\textsuperscript{329} and the second involving venous leg ulcers.\textsuperscript{341}

There have been seven case reports of honey being used on 41 patients with venous leg ulcers.\textsuperscript{252 350-355} Five of the reports were single case studies, including one report on a patient already included within an earlier case series.\textsuperscript{355} This case study was not considered in the following review. Overall, the case reports indicated honey was associated with wound healing and decreased pain and odour. In the two studies that reported adverse effects, they were limited to pain, either transient or continuous pain following dressing changes, and excoriation and/or maceration of the surrounding skin.\textsuperscript{324 350}

In two of the four single case reports, the patients had bilateral leg ulcers and the contralateral leg was used as a control.\textsuperscript{351 352} In one of these studies the patient was treated with unprocessed honey on one leg, with the dressing changed daily for one month.\textsuperscript{351} The other leg was treated with bovine fibrinolysin (Elase R) for six days and then with an alginate dressing for the remainder of the month. Initial wound healing was reported as being more rapid on the honey-treated leg, but after one month both legs were “healing well”. Time to healing was not reported. In the second of the studies using the contralateral leg as a control, the ulcers were infected with haemolytic streptococci, Proteus spp and anaerobes.\textsuperscript{352} Medihoney, a commercially available honey consisting of a mix of Australian and New Zealand Leptospermum honey, was applied once daily for ten days to one leg. The dressing regimen for the other leg was not identified, but was described as an ‘appropriate non-honey dressing’. After ten days the honey-treated leg was considered to have improved symptomatically, with reduced odour and a cleaner wound bed than in the opposing leg.

In the remaining two single case reports the ulcers were treated with honey obtained from the Leptospermum species.\textsuperscript{350 353} In one of the reports, the patient had had venous ulcers of 16 months duration that had been resistant to 12 weeks of treatment with reduced compression.\textsuperscript{353} The patient was referred to a specialist clinic, where she was treated twice-weekly with Medihoney and compression. The
Table 6: Case reports of honey on wounds (any aetiology)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Wound type</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adesunkanmi &amp; Oyelami, 1994</td>
<td>13</td>
<td>Burns</td>
<td>Natural honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Ahmed, et al., 2003</td>
<td>60</td>
<td>Chronic wounds, Surgical wounds, Traumatic lesions</td>
<td>HoneySoft (honey impregnated in ethyl vinyl dressing)</td>
<td>Pain after application (n=1)</td>
</tr>
<tr>
<td>Alcarez &amp; Kelly, 2002</td>
<td>1</td>
<td>Infected venous leg ulcers</td>
<td>Irradiated manuka honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Al-Waili, 2005</td>
<td>12</td>
<td>Diaper dermatitis (mild to severe erythema with ulceration)</td>
<td>Honey, olive oil and beeswax in 1:1:1 v/v equivalent to (Wv) honey 50%, olive oil 29% and beeswax 21%</td>
<td>None reported</td>
</tr>
<tr>
<td>Armon, 1980</td>
<td>2</td>
<td>Decubitus ulcer</td>
<td>Pure honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Attipou, et al., 1998</td>
<td>79</td>
<td>Necrotising fasciitis, Burns, Tropical leg ulcers, Diabetic leg ulcers, Post-operative wound infections</td>
<td>Honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Cooper, et al. (2001)</td>
<td>1</td>
<td>Hidradenitis suppurativa</td>
<td>Irradiated manuka honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Cavanagh, et al., 1970</td>
<td>12</td>
<td>Wound breakdown following radical vulvectomy</td>
<td>Commercially available honey</td>
<td>Candidal infection noted (n=3) near edges of wound.</td>
</tr>
<tr>
<td>Dumronglet, 1983</td>
<td>20</td>
<td>Chronic wounds</td>
<td>Pure honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Dunford, et al., 2000</td>
<td>1</td>
<td>Infected skin graft wounds secondary to meningitis</td>
<td>Irradiated manuka honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Dunford, et al., 2000</td>
<td>2</td>
<td>Chronic wounds</td>
<td>Manuka honey</td>
<td>Pain after application (n=1)</td>
</tr>
<tr>
<td>Dunford, 2001</td>
<td>1</td>
<td>Infected abdominal wound following lymph node biopsy</td>
<td>Manuka honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Dunford &amp; Hanano, 2004</td>
<td>40</td>
<td>Venous leg ulcers</td>
<td>Manuka honey (Medihoney)</td>
<td>Pain on application (n=14 – transient pain (n=6), continuous pain (n=8)), maceration and excoriation (n=2)</td>
</tr>
<tr>
<td>Dunford, 2005</td>
<td>1</td>
<td>Venous leg ulcer with associated calcinosis cutis</td>
<td>Manuka honey (Medihoney)</td>
<td>None reported</td>
</tr>
<tr>
<td>Eddy &amp; Gideonsen, 2005</td>
<td>1</td>
<td>Diabetic foot ulcer</td>
<td>“Ordinary” honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Efem, 1988</td>
<td>59</td>
<td>Fournier’s gangrene, Burns, Various ulcers, Cancrum oris, Decubiti</td>
<td>Fresh unprocessed honey</td>
<td>None observed</td>
</tr>
<tr>
<td>Efem, 1993</td>
<td>20</td>
<td>Fournier’s gangrene</td>
<td>Unprocessed honey (including honey soaked gauze for packing)</td>
<td>None observed</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Wound type</td>
<td>Intervention</td>
<td>Adverse events</td>
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<tr>
<td>Farouk, et al., 1988 227</td>
<td>11</td>
<td>Diabetic wounds, Chronic ulcers, Abscesses, Infected surgical scar</td>
<td>Sudanese honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Gethin &amp; Cowman, 2005 325</td>
<td>8</td>
<td>Diabetic ulcer, non-healing surgical excision, burn, animal bite, rheumatoid ulcer, venous ulcer, mixed aetiology ulcer</td>
<td>Manuka honey</td>
<td>Pain after application (n=2)</td>
</tr>
<tr>
<td>Gurdal, et al., 2003 320</td>
<td>6</td>
<td>Fournier's gangrene</td>
<td>Pure unprocessed honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Harris, 1994 351</td>
<td>1</td>
<td>Venous ulcer</td>
<td>Unprocessed honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Hejase, et al., 1996 318</td>
<td>38</td>
<td>Fournier's gangrene</td>
<td>Unprocessed honey dressings</td>
<td>None reported</td>
</tr>
<tr>
<td>Hon, 2005 317</td>
<td>1</td>
<td>Epidermolysis bullosa</td>
<td>Manuka honey (Activon honey-impregnated tulle gauze)</td>
<td>Hypergranulation</td>
</tr>
<tr>
<td>Hutton, 1966 313</td>
<td>3</td>
<td>Decubiti</td>
<td>Comb honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Kingsley, 2001 341</td>
<td>2</td>
<td>Venous ulcer, infected biopsy wound</td>
<td>Manuka honey</td>
<td>Yeast infection (n=1)</td>
</tr>
<tr>
<td>Misirlioglu, et al., 2003 332</td>
<td>87</td>
<td>Skin graft donor sites</td>
<td>Unprocessed honey impregnated in gauze</td>
<td>None reported</td>
</tr>
<tr>
<td>Natarajan, et al., 2001 322</td>
<td>1</td>
<td>Hydroxurea-induced leg ulcer</td>
<td>Manuka honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Ndayisaba, et al., 1993 332</td>
<td>40</td>
<td>Surgical wounds, traumatic lesions, infected wounds, trophic wounds, burns</td>
<td>Honey</td>
<td>Burn-like reaction to honey (n=1)</td>
</tr>
<tr>
<td>Phuapradit &amp; Saropala, 1992 333</td>
<td>150</td>
<td>Abdominal wound dehiscence following Caesarean section</td>
<td>Unboiled commercial honey</td>
<td>None observed</td>
</tr>
<tr>
<td>Remmen, et al., 2005 337</td>
<td>1</td>
<td>Excision of melanoma, including axillary node clearance</td>
<td>Honey and gauze dressing</td>
<td>None observed</td>
</tr>
<tr>
<td>Robson, 2002 335</td>
<td>1</td>
<td>Venous leg ulcer</td>
<td>Manuka honey</td>
<td>None observed</td>
</tr>
<tr>
<td>Robson, 2004 326</td>
<td>2</td>
<td>Venous leg ulcer, Arterial leg ulcer</td>
<td>Manuka honey (Medihoney)</td>
<td>None observed</td>
</tr>
<tr>
<td>Schumacher, 2004 334</td>
<td>6</td>
<td>Split skin grafting of venous leg ulcer</td>
<td>Honey</td>
<td>None observed</td>
</tr>
<tr>
<td>Simon, et al., 2006 343</td>
<td>14</td>
<td>Dehisced surgical wounds, infected wounds and tumours, infected portal and central catheter sites, abscess</td>
<td>Manuka honey (Medihoney)</td>
<td>Local pain (n=1)</td>
</tr>
<tr>
<td>Stephen-Haynes, 2004 342</td>
<td>20</td>
<td>Mixed aetiology leg ulcers, venous leg ulcers, ischaemic leg ulcers, burns, traumatic wounds, decubiti</td>
<td>Manuka honey (Activon honey-impregnated tulle gauze)</td>
<td>Pain after application (n=4)</td>
</tr>
</tbody>
</table>
Table 6 (Continued): Case reports of honey on wounds (any aetiology)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Wound type</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandeputte, 2003</td>
<td>89</td>
<td>Skin tears, burns, venous ulcers, pressure ulcers, mixed wounds</td>
<td>L-Mesitran (mix of honey, lanolin, sunflower oil, cod liver oil, marigold extract, aloe vera, zinc oxide and vitamins C and E)</td>
<td>Pain after application – transient (n=12), continuous (n=4)</td>
</tr>
<tr>
<td>Van der Weyden, 2003</td>
<td>2</td>
<td>Decubitus ulcer</td>
<td>ApiNate (manuka honey impregnated calcium alginate dressing)</td>
<td>None reported</td>
</tr>
<tr>
<td>Van der Weyden, 2005</td>
<td>1</td>
<td>Venous leg ulcer</td>
<td>ApiNate (honey impregnated calcium alginate dressing)</td>
<td>Excoriated skin secondary to maceration</td>
</tr>
<tr>
<td>Vardi, et al., 1998</td>
<td>9</td>
<td>Post-operative wound infections in neonates</td>
<td>Commercial unprocessed unpasteurised, non-irradiated honey</td>
<td>None reported</td>
</tr>
<tr>
<td>Wood, et al., 1997</td>
<td>10</td>
<td>Venous ulcers, neuropathic ulcers, traumatic lesion, arterial ulcer</td>
<td>Manuka honey</td>
<td>Pain after application (n=3)</td>
</tr>
<tr>
<td>Yang, 1944</td>
<td>50</td>
<td>Chilblains, chilblain ulcers, ordinary ulcers, other small wounds</td>
<td>Salve of 80% honey and 20% Vaseline or lard</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Two case series reports have been published on honey for leg ulcer treatment. The largest series reported on 40 patients with venous ulcers that had not healed after at least 12 weeks of compression. The patients received Medihoney with each change of compression bandaging for a total of twelve weeks. Fourteen patients (35%) reported pain after dressing change; six reported the pain was transient, while eight reported continuous pain after the dressing was applied. Two patients also experienced maceration and excoriation of the wound margins, due to increased exudate. Thirteen patients withdrew from treatment (32%), with six giving pain as the reason, and two giving ulcer deterioration as the rationale. Seven ulcers were reported as having healed at the end of the treatment period and the authors considered significant improvements had occurred in a further 20 ulcers. The second case series reported on six patients who had had venous leg ulcers of
greater than 12 months duration that had failed to respond to conventional treatments, including compression.\textsuperscript{354} The participants had split-thickness skin grafting followed by honey dressings. The mean time to healing was 22 days, with no graft revision required. No ill-effects were observed and participants remained complication free with no recurrence of ulceration for the average of 19-months post-discharge follow-up.

2.8 Summary

Venous ulceration is a chronic remitting relapsing condition with age-related increases in incidence and prevalence. Quality of life is adversely affected and estimates of the cost of leg ulcer treatment suggest that national expenditure is likely to be substantial. Effective treatments for venous leg ulcers that are available in New Zealand consist of compression therapy and pentoxifylline. Honey has had a long history of use in wound care and there has been renewed interest in its use for wounds over the last 20 years. While the animal model evidence generally supports the hypothesis that honey improves wound healing, inadequate randomisation and lack of blinding may have produced bias and the acute wound models used in the animal studies are not necessarily generalisable to chronic wounds. Case reports on honey's use with patients across a variety of acute and chronic wounds appear to support honey having a beneficial effect in wound care. However, these reports do not offer reliable evidence on which to base decisions about the efficacy or effectiveness of honey in the treatment of wounds. A systematic review of randomised controlled trials of honey in wound care was indicated.
CHAPTER 3

Systematic review of honey for wound treatment

3.1 Introduction
Randomised controlled trials are the most reliable method for establishing treatment effects.\textsuperscript{359} A systematic review published in 2001 found seven trials of honey in wound care, six of which were in patients with moderate burns.\textsuperscript{13} The review could not conclude whether honey conferred extra benefit in wound healing, largely because the poor quality of the reports precluded a confident determination. Communication with the authors of the review revealed there were no plans to update the review (pers. comm. RA Moore), and in the five years since the systematic review had been completed at least one further trial had been published.\textsuperscript{360} In addition, two other trials not identified by the review’s search strategy were located by the candidate.\textsuperscript{361, 362} Therefore, it was considered appropriate to undertake a systematic review of the literature to provide an updated summary of the effect of honey on wound healing.

3.2 Aims and objectives
The aim of this review was to assess whether the use of honey confers any benefit in wound healing. The primary objectives were to determine whether honey

- Increases the rate of healing in acute wounds (burns, lacerations and other traumatic wounds)
• Increases the rate of healing in chronic wounds (venous ulcers, arterial ulcers, diabetic ulcers, pressure ulcers, infected surgical wounds).

3.3 Methods
This review was conducted in accord with a protocol published in the Cochrane Library. The methods employed in this review follow the policies of the Cochrane Wound Review Group and the guidelines outlined in the Cochrane Handbook.

3.3.1 Inclusion criteria
3.3.1.1 Types of studies
Randomised controlled trials (RCTs) or clinical controlled trials (CCTs) were included. A CCT was any trial that used a non-random allocation strategy, such as alternate days, date of birth, or hospital number. There was no language restriction and both published and unpublished studies were sought.

3.3.1.2 Types of participants
Participants of any age had to have had an acute or chronic wound for the trial to be included. Acute and chronic wounds are terms in regular use in clinical practice, yet definition of these terms has received little attention. Any definition needs to be flexible enough to allow categorisation of seemingly similar wounds (e.g. surgical wounds with tissue loss healing by secondary intention and infected surgical wounds that have dehisced) to retain its utility. This review employed the definition proposed by Lazarus, et al. (1994), who suggested acute wounds proceed through to healing "in an orderly and timely reparative process". Orderliness refers to the healing sequence of inflammation, angiogenesis, matrix deposition, wound contraction, epithelialisation, and scar remodeling. Timeliness is subjective, but refers to a healing time that could be reasonably expected. A chronic wound is a wound where the orderly biological progression to healing has been disrupted and healing is delayed. For the purposes of this review an acute wound was considered to be any of the following: burns, lacerations or other skin injuries resulting from minor trauma, and minor surgical wounds healing by primary or secondary intention. Chronic wounds were considered to be the following: skin ulcers of any type and infected wounds healing by secondary intention.
3.3.1.3 **Types of intervention**

At least one group of participants had to have received topically applied honey to an acute or chronic wound for the trial to be included. The honey could be applied in any form, by any means, either alone or in combination with other dressings.

3.3.1.4 **Types of outcome measures**

An outcome in the included studies had to have been proportion of participants with completely healed wounds or time to wound healing.

3.3.2 **Search strategy for identification of studies**

Trials were identified using the following methods:

- An electronic search of the Cochrane Collaboration's Controlled Clinical Trials Register (CCTR) and the trials register of the Cochrane Collaboration Wound Review Group. The Wound Review Group's register includes references that have not yet been assessed as clinical trials and included in the CCTR. It is derived from comprehensive and regular searches of 19 databases, hand searches of electronic journals and conference proceedings, and contacts with manufacturers and experts in the field. The search strategy for the registers is listed below:

1. SKIN ULCER :MESH
2. FOOT ULCER :MESH
3. LEG ULCER :MESH
4. VARICOSE ULCER :MESH
5. VENOUS ULCER :MESH
6. DIABETIC FOOT :MESH
7. WOUND HEALING :MESH
8. DECUBITUS ULCER :MESH
9. (leg near ulcer*)
10. ((foot near ulcer*) or (feet near ulcer*))
11. (skin near ulcer*)
12. (varicose near ulcer*)
13. (venous near ulcer*)
14. (stasis near ulcer*)
15. (diabetic near ulcer*)
16. (diabetic next foot)
17. (arterial near ulcer*)
18. (varicose near wound*)
19. (arterial near wound*)
20. (diabetic near wound*)
21. (bed near sore*)
22. (pressure near sore*)
23. (decubitus near ulcer*)
24. (pressure near ulcer*)
Electronic searches of the AMED (Allied and Complementary Medicine) and LILACS (Latin American and Caribbean Health Science Literature) databases using the keyword "honey", and Google Scholar using the keywords "honey" and "trial"

- Contact with manufacturers of honey products for wound care, namely, Comvita New Zealand Ltd and MediHoney Australia Pty Ltd

- Contact with researchers involved in the use of honey in wound care, namely Professor Peter Molan, Director of the Honey Research Unit at the University of Waikato and the authors of included trials

- Scrutinising citations within all the obtained studies and reviews of honey for wound care.

**3.3.3 Study selection**

Searches of the Wounds Group trials register were performed by Ali Baba Akbari Sari at the editorial base and forwarded as text files that were imported into EndNote (version 7) for review by the candidate (AJ) and the second reviewer, Dr Natalie Walker (NW). Searches of AMED, LILACS and Google Scholar were conducted by the candidate, who also approached manufacturers and honey researchers for information about any additional studies. All references were entered into an EndNote library. AJ and NW independently reviewed the titles, descriptors, or abstracts in the library to identify all potentially relevant trials. Full text copies of all
relevant trials, or trials that might be relevant to the review, were obtained for review by both reviewers. The citations from these studies were scrutinised and any previously unidentified studies were obtained. The two reviewers independently selected the trials using the inclusion criteria. Disagreements were resolved by discussion.

3.3.4 Collection of data from the included trials

Data were extracted from studies meeting the inclusion criteria by one reviewer (AJ) and recorded on a standardised form (Appendix 2). The extracted data were independently reviewed for accuracy by the second reviewer (NW) and disagreements resolved by discussion. If the data from the trial report were inadequate or ambiguous, additional information was sought from the authors.

3.3.5 Data synthesis

Where studies were sufficiently alike in terms of population and comparison interventions, results from the studies were combined. Data synthesis was carried out using Review Manager Version 4.2.8, with weighted mean differences and 95% confidence intervals reported for continuous outcomes. Statistical heterogeneity was tested by comparing Cochran’s Q statistic and the Chi-squared distribution. Heterogeneity was assumed with p values of less than 10%. In addition, the I² statistic was used to determine the percentage of variation due to heterogeneity rather than chance, and any sources of heterogeneity were explored. Where significant statistical heterogeneity was present, a random effects model was used when combining studies. Risk ratios and 95% confidence intervals for adverse events were calculated in Excel Version 11 using a standard method. It was assumed that one event equaled one participant for this analysis. A funnel plot was used to assess for the presence of publication bias. The mean difference and the standard error for each trial were used to calculate this plot.

3.4 Description of studies

Forty-three potentially eligible citations were found, 22 from searching the Cochrane Wound Group’s trial register and 21 from additional searches of LILACS, AMED, Google Scholar, reviewing citations, and contact with manufacturers and other researchers in the field (Figure 5). Twenty-three studies were determined to be ineligible for inclusion in the review, and two reports could not be obtained despite repeated attempts by interloan librarians to contact the relevant universities in Central America. It was not clear from the abstracts whether these studies...
would have met the inclusion criteria. From scrutiny of the citations and abstracts, ten studies were found not to meet the inclusion criteria, and thus the full papers were not obtained. The studies were not obtained because they: were ongoing studies (n=5), were not controlled trials (n=1), did not employ honey as an intervention (n=3) or did not employ honey on wounds (n=1). The full reports of 31 studies were obtained for further review. Thirteen of the studies did not meet the inclusion criteria for the reasons outlined in Table 7.

Figure 5: Identification and selection of studies

Table 7: Studies obtained and excluded

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Waili, 2003</td>
<td>Population did not have an acute or chronic wound</td>
</tr>
<tr>
<td>Al Waili, 2004</td>
<td>Not an RCT or CCT</td>
</tr>
<tr>
<td>Bangroo, et al., 2005</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Biswal, et al., 2003</td>
<td>Population did not have an acute or chronic wound</td>
</tr>
<tr>
<td>Chokotho &amp; van Hassett, 2005</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Gad, et al., 1988</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Johnson, et al., 2005</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Misirlioglu, et al., 2003</td>
<td>Not an RCT or CCT</td>
</tr>
<tr>
<td>Memon, et al., 2005</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Nagane, et al., 2004</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Quadri &amp; Huraib, 1999</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Subrahmanyan, et al., 2003</td>
<td>No relevant outcome information</td>
</tr>
<tr>
<td>Tostes, 1994</td>
<td>Not an RCT or CCT</td>
</tr>
</tbody>
</table>
Eighteen trials met the inclusion criteria as at October 2006 (Table 8). Additional data were obtained from studies through contact with the investigators (pers. comm., Ronald Ingle, Akin Okeniyi, O. Oluwatosin, Caroline McIntosh and M. Subrahmanyam). Twelve trials recruited participants with acute wounds, nine with burns,379 380 262 360 362 381-384 two with minor surgical excisions,385 386 and one with minor trauma.387 Five trials recruited participants with chronic wounds, one with infected surgical wounds,388 one with decubiti,389 one with leg ulcers,248 one with pyomyositic abscesses,390 and one with men suffering Fourier’s gangrene.391 One trial recruited participants with either acute wounds (burns) or ulcers of any aetiology (diabetic, decubitus, venous or traumatic).392 Eleven trials were conducted by the same investigator.379 380 262 360 362 381-384 392 391 One trial recruited children,390 and three trials recruited adults only.387 386 391 The remaining trials did not specify an age range,385 386 or recruited both children and adults. Four trials were conducted in outpatient clinics.385-387 390 The remaining trials were conducted in hospital settings. Monofloral honey (aloe, jarrah, jambhul or jamun, or manuka) was the intervention in five trials,360 385-387 391 and the floral type of honey was not specified in the remaining trials.

3.5 Methodological assessment of included studies

The methodological quality of the included studies was evaluated using the determinants of trial quality recommended by the Cochrane Collaboration’s Wound Review Group. These determinants are allocation concealment, loss to follow up, intention-to-treat analysis, blinded outcome assessment, and baseline comparability (Table 9). In addition, the Wound Review Group recommends assessing whether the required sample size was estimated a priori.

3.5.1 Randomisation and allocation concealment

Seventeen trials were described as randomised controlled trials, but only three trials reported how their allocation sequence was generated.387 385 386 One trial was not described as a randomised controlled trial.248 Further information from the author revealed that allocation was by alternate days (pers. comm., O. Oluwatosin).

Authors were approached for additional information about the generation of the allocation sequence. Information was supplied by one author for 11 trials. The method of randomisation was described as “by the chit method” (pers. comm., M. Subrahmanyam),262 360 362 379-384 391 392 but it is not known what this method involved. Allocation concealment was reported in two studies,385 386 and in both instances
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Country</th>
<th>Participants</th>
<th>Wound type</th>
<th>Honey (frequency)</th>
<th>Comparison (frequency)</th>
<th>Setting</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Wail, et al., 1999 368</td>
<td>50</td>
<td>United Arab Emirates</td>
<td>Women with infected caesarean and hysterectomy wounds</td>
<td>Chronic</td>
<td>Yemeni honey (twice daily)</td>
<td>70% ethanol, saline or povidine iodine washes, gauze (twice daily)</td>
<td>Hospital</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td>Ingle, et al., 2006 347</td>
<td>87</td>
<td>South Africa</td>
<td>Men with shallow wounds and abrasions</td>
<td>Acute</td>
<td>Monofloral aloe honey (daily)</td>
<td>Hydrogel (daily)</td>
<td>Outpatient clinic</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td>McIntosh, 2006 398</td>
<td>100</td>
<td>England</td>
<td>Patients undergoing partial or total toenail removal with matrix phenolisation</td>
<td>Acute</td>
<td>Manuka honey-impregnated calcium alginate dressings (twice weekly)</td>
<td>Paraffin gauze (twice weekly)</td>
<td>Outpatient clinic</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td>Marshall, 2005 363</td>
<td>44</td>
<td>England</td>
<td>Patients undergoing partial or total toenail removal with matrix phenolisation</td>
<td>Acute</td>
<td>Jarrah honey (daily)</td>
<td>Iodine dressing (daily)</td>
<td>Outpatient clinic</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td>Okenyli, et al., 2005 360</td>
<td>32</td>
<td>Nigeria</td>
<td>Children with pyomyositis abscesses</td>
<td>Chronic</td>
<td>Undiluted honey (twice daily)</td>
<td>EUSOL soaked gauze (twice daily)</td>
<td>Hospital</td>
<td>Mean hospital stay</td>
</tr>
<tr>
<td>Oluwatosin, et al., 2000 260</td>
<td>38</td>
<td>Nigeria</td>
<td>Patients with chronic leg ulcers (posttraumatic or post infective)</td>
<td>Chronic</td>
<td>Unprocessed undiluted honey (daily)</td>
<td>Honey/phenytoin mixture (200mg phenytoin/ml honey) or phenytoin alone (200mg/ml sodium chloride) (daily)</td>
<td>Outpatient clinic</td>
<td>Mean % change in ulcer area at four weeks</td>
</tr>
<tr>
<td>Subrahmanyam, 1991 379</td>
<td>104</td>
<td>India</td>
<td>Patients with superficial thermal burns &lt; 40% of TBSA</td>
<td>Acute</td>
<td>Unprocessed undiluted honey (daily)</td>
<td>Silver sulfadizine-impregnated gauze (daily)</td>
<td>Hospital</td>
<td>Time to event</td>
</tr>
<tr>
<td>Subrahmanyam, 1993a 383</td>
<td>92</td>
<td>India</td>
<td>Patients with partial thickness burns &lt; 40% of TBSA</td>
<td>Acute</td>
<td>Unprocessed undiluted honey impregnated gauze (alternate days)</td>
<td>Polyurethane film (at day 8 unless evidence of infection, excessive exudate or leakage)</td>
<td>Hospital</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td>Subrahmanyam, 1993b 362</td>
<td>100</td>
<td>India</td>
<td>Patients with burns or ulcers (including diabetic, traumatic, decubiti and venous ulcers)</td>
<td>Acute (50) and chronic (50)</td>
<td>Unprocessed undiluted honey (daily)</td>
<td>Silver sulfadizine-impregnated gauze (daily)</td>
<td>Hospital</td>
<td>Time to event</td>
</tr>
</tbody>
</table>

TBSA = Total Body Surface Area  
EUSOL = Edinburgh Solution of Lime
Table 8 (continued): Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Country</th>
<th>Participants</th>
<th>Wound type</th>
<th>Honey (frequency)</th>
<th>Comparison (frequency)</th>
<th>Setting</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subrahmanyam, 1994</td>
<td>64</td>
<td>India</td>
<td>Patients with partial thickness burns &lt; 40% of</td>
<td>Acute</td>
<td>Unprocessed undiluted honey</td>
<td>Amniotic membrane (intact until day 8, then alternate days)</td>
<td>Hospital</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBSA</td>
<td></td>
<td>impregnated gauze</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam, 1996a</td>
<td>900</td>
<td>India</td>
<td>Patients with partial thickness burns &lt; 40% of</td>
<td>Acute</td>
<td>Unprocessed undiluted honey</td>
<td>Conventional dressings, either soframycin (90), vaseline gauze (90), polyurethane film (90) or sterile linen (90) (alternate days)</td>
<td>Hospital</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBSA</td>
<td></td>
<td>(alternate days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam, 1996b</td>
<td>100</td>
<td>India</td>
<td>Patients with partial thickness burns &lt; 40% of</td>
<td>Acute</td>
<td>Unprocessed undiluted honey</td>
<td>Boiled potato peel dressings (alternate days)</td>
<td>Hospital</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBSA</td>
<td></td>
<td>(alternate days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam, 1996c</td>
<td>84</td>
<td>India</td>
<td>Patients with partial thickness burns &lt; 40% of</td>
<td>Acute</td>
<td>Honey</td>
<td>Honey with added vitamin C (300mg), vitamin E (400mg) and polyethylene glycol 4000 (1unit 25% solution/100ml) (at day 2, then alternate days)</td>
<td>Hospital</td>
<td>Mean time to healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBSA</td>
<td></td>
<td>(at day 2, then alternate days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam, 1998</td>
<td>50</td>
<td>India</td>
<td>Patients with superficial thermal burns &lt; 40% of</td>
<td>Acute</td>
<td>Unprocessed undiluted honey</td>
<td>Silver sulfadiazine impregnated gauze (daily)</td>
<td>Hospital</td>
<td>Time to event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBSA</td>
<td></td>
<td>(alternate days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam, 1999</td>
<td>50</td>
<td>India</td>
<td>Patients with mixed (partial and full) thickness</td>
<td>Acute</td>
<td>Unprocessed honey</td>
<td>Tangential excision and skin grafting</td>
<td>Hospital</td>
<td>Mean hospital stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>burns &lt; 30% TBSA</td>
<td></td>
<td>(alternate days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam, 2001</td>
<td>100</td>
<td>India</td>
<td>Patients with burns &lt; 40% of TBSA</td>
<td>Acute</td>
<td>Unprocessed undiluted unifloral jamhul honey</td>
<td>Silver sulfadiazine impregnated gauze (alternate days)</td>
<td>Hospital</td>
<td>Mean time to healing Time to event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(alternate days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam, 2004</td>
<td>30</td>
<td>India</td>
<td>Men with Fournier's gangrene</td>
<td>Acute</td>
<td>Unprocessed undiluted unifloral jamhul honey</td>
<td>EUSOL soaked gauze (daily)</td>
<td>Hospital</td>
<td>Mean hospital stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>impregnated gauze</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(daily)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weheida, et al., 1991</td>
<td>40</td>
<td>Egypt</td>
<td>Patients with uninfected pressure ulcers</td>
<td>Chronic</td>
<td>Honey</td>
<td>Saline soaked gauze (daily)</td>
<td>Hospital</td>
<td>Proportion healed Mean time to healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(daily)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TBSA = Total Body Surface Area  EUSOL = Edinburgh Solution of Lime
Table 9: Assessment of studies methodological quality as reported in the publication.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Randomised (method)</th>
<th>Allocation concealed</th>
<th>Loss to follow-up</th>
<th>ITT analysis</th>
<th>Assessor blinding</th>
<th>Baseline equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Waili, et al., 1999 368</td>
<td>50</td>
<td>Described as RCT (NR)</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Ingle, et al., 2006 342</td>
<td>87</td>
<td>Yes (random permuted blocks)</td>
<td>NR</td>
<td>5</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>McIntosh, 2006 366</td>
<td>100</td>
<td>Yes (random tables)</td>
<td>Yes (telephone)</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Marshall, 2005 365</td>
<td>51</td>
<td>Yes (random tables)</td>
<td>Yes (telephone)</td>
<td>7</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Okeniyi, et al., 2000 346</td>
<td>32</td>
<td>Described as RCT (NR)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Oluwatosin, et al., 2000 346</td>
<td>38</td>
<td>No (alternate days)</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<td>Subrahmanyam, 1991 375</td>
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<td>NR</td>
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<tr>
<td>Subrahmanyam, 1994 391</td>
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<tr>
<td>Subrahmanyam, 1996b 342</td>
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<td>Described as RCT (NR)</td>
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<td>NR</td>
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<tr>
<td>Subrahmanyam, 1996c 383</td>
<td>84</td>
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<tr>
<td>Subrahmanyam, 1998 362</td>
<td>50</td>
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<td>NR</td>
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<tr>
<td>Subrahmanyam, 1999 394</td>
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<td>NR</td>
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<td>NR</td>
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<td>Subrahmanyam, 2001 360</td>
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<td>Described as RCT (NR)</td>
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<td>NR</td>
<td>Yes</td>
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<tr>
<td>Subrahmanyam, 2004 391</td>
<td>30</td>
<td>Described as RCT (NR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<tr>
<td>Weheida, et al., 1991 349</td>
<td>40</td>
<td>Described as RCT (NR)</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
</tr>
</tbody>
</table>

ITT = Intention-to-treat  
NR = Not reported

Allocation concealment (central telephone) was considered adequate. Additional information was supplied on 11 trials, where the method of allocation concealment was described as "sequential numbered envelopes" (pers. comm., M. Subrahmanyam).262 360 362 379-384 391 392 It is not known whether the envelopes were sealed and/or opaque. A unit of analysis error was possible in two studies as the
unit of allocation may have been by wound rather than by participant. This method of allocation could lead to a single participant contributing data from more than one wound. However, in one trial, the mean hospital stay for each group was also presented, suggesting that participants with more than one wound were allocated to the same treatment. In the other trial, the allocation strategy was alternate days. The individual wounds could only have been allocated to different treatments if participants presented on different days for each wound. The mean age of participants was reported by group so it is assumed in this review that multiple wounds on a single participant were allocated to the same treatment.

3.5.2 Loss to follow up
Loss to follow-up was reported by 13 studies. Loss ranged from 6-16% in three studies, with no loss in ten studies.

3.5.3 Intention-to-treat analysis
Intention-to-treat analysis was defined in this review as analysis that included all participants regardless of whether they received the treatment, completed treatment or were found not to meet entry criteria after randomisation. Only one study reported using intention-to-treat (ITT) analysis, but participants were excluded after randomisation, thus failing to meet the criteria for ITT analysis. Participants in another trial by the same trialist were also excluded after randomisation. These participants were excluded from the analysis because they were lost to follow up, withdrew or were non-compliant with treatment or required further surgery. Participants in another trial were excluded after randomisation, either because they were found not to have met the entry criteria, withdrew or crossed over treatment. In the remaining trials, it is unknown whether intention-to-treat analysis was employed, or how participants who were lost to follow up, non-compliant or withdrew were managed in the analysis.

3.5.4 Follow up and blinding
The majority of trials reported either mean time to complete healing, and/or time to event. In all of these trials, follow up appears to have been until complete healing. Mean hospital stay was reported in three trials. Hospital stay was taken as a proxy for wound healing, although this proxy will probably be inaccurate because wound healing is unlikely to be the only factor in a discharge decision. Proportion healed and mean percentage change in ulcer area was reported in one trial, and mean time to healing and proportion healed in
another. The duration of follow up in the two trials was four weeks and until complete healing respectively.

Five studies used assessor blinding. The remaining studies did not report whether blinding was employed. Additional information about blinding was sought from authors of these trials. Information was supplied by one author on 11 trials, who confirmed the outcome assessor was blinded to participant allocation.

3.5.5 Baseline comparability of prognostic factors

The majority of studies reported baseline data, although the reported data were limited in many cases. Additional information was sought from authors. Information was supplied by one author for 11 trials. Baseline equivalence appeared to be present in these 11 studies, but was not reported in six studies. Two studies did not have equivalent groups, and in each instance this imbalance appeared to favour the comparison treatment, potentially influencing the results.

3.5.6 Sample size calculation

Only two trials reported an a priori sample size calculation. In one of these trials, the difference the study was powered to detect was not reported, although the effect was stated to be "clinically significant".

3.6 Results

A total of 18 trials including 2,015 participants were included in this review. The trials were generally small (median sample size was 64, range 32-900). There was very clear clinical and methodological heterogeneity in the included trials. For instance, although 14 trials reported the same outcome (mean time to healing), there were 11 different comparison treatments. Therefore it was not appropriate to combine the trials in a meta-analysis to produce a summary statistic for honey overall, or even subgroup summary statistics (acute, chronic, mixed wounds). A summary forest plot (without summary statistics) is shown overleaf to illustrate the heterogeneity (Figure 6).

3.6.1 Acute wounds

3.6.1.1 Minor acute wounds

Three trials (n=213) recruited participants with minor acute wounds. In two
<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Treatment Mean (SD)</th>
<th>N</th>
<th>Control Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Minor acute wounds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingle</td>
<td>40</td>
<td>16.50 (8.40)</td>
<td>42</td>
<td>16.90 (11.30)</td>
<td>0.49 (0.34) [-4.70, 3.90]</td>
<td>49.49</td>
<td>-0.40 [-4.70, 3.90]</td>
</tr>
<tr>
<td>Marshall</td>
<td>23</td>
<td>33.40 (15.70)</td>
<td>21</td>
<td>25.30 (8.70)</td>
<td>29.30 (8.10) [0.68, 15.52]</td>
<td>29.30</td>
<td>8.10 [0.68, 15.52]</td>
</tr>
<tr>
<td>McIntosh</td>
<td>47</td>
<td>40.30 (18.21)</td>
<td>40</td>
<td>39.98 (25.42)</td>
<td>21.21 (0.32) [-9.12, 9.76]</td>
<td>21.21</td>
<td>0.32 [-9.12, 9.76]</td>
</tr>
<tr>
<td><strong>02 Burns</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam 1991</td>
<td>52</td>
<td>9.40 (2.30)</td>
<td>52</td>
<td>17.20 (3.20)</td>
<td>-7.80 (1.87) [-8.87, -6.73]</td>
<td>13.21</td>
<td>-7.80 [-8.87, -6.73]</td>
</tr>
<tr>
<td>Subrahmanyam 1993a</td>
<td>46</td>
<td>10.80 (3.90)</td>
<td>46</td>
<td>15.30 (3.00)</td>
<td>-4.50 (1.92) [-5.92, -3.08]</td>
<td>12.89</td>
<td>-4.50 [-5.92, -3.08]</td>
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<tr>
<td>Subrahmanyam 1994</td>
<td>40</td>
<td>9.40 (2.52)</td>
<td>24</td>
<td>7.50 (6.66)</td>
<td>1.90 (0.68) [0.59, 4.68]</td>
<td>11.16</td>
<td>1.90 [0.59, 4.68]</td>
</tr>
<tr>
<td>Subrahmanyam 1996a</td>
<td>450</td>
<td>8.80 (2.10)</td>
<td>450</td>
<td>13.50 (4.10)</td>
<td>-4.70 (5.31) [-5.13, -4.27]</td>
<td>13.57</td>
<td>-4.70 [-5.13, -4.27]</td>
</tr>
<tr>
<td>Subrahmanyam 1996c</td>
<td>42</td>
<td>8.30 (2.40)</td>
<td>42</td>
<td>6.40 (3.61)</td>
<td>1.90 (3.21) [0.59, 3.21]</td>
<td>13.00</td>
<td>1.90 [0.59, 3.21]</td>
</tr>
<tr>
<td>Subrahmanyam 1998</td>
<td>25</td>
<td>4.92 (3.61)</td>
<td>25</td>
<td>8.22 (8.31)</td>
<td>-3.30 (6.85) [0.25]</td>
<td>10.00</td>
<td>-3.30 [0.25]</td>
</tr>
<tr>
<td>Subrahmanyam 2001</td>
<td>50</td>
<td>15.40 (3.20)</td>
<td>50</td>
<td>17.20 (4.30)</td>
<td>-1.80 (3.29) [-3.29, -0.31]</td>
<td>12.83</td>
<td>-1.80 [-3.29, -0.31]</td>
</tr>
<tr>
<td><strong>03 Mixed acute &amp; chronic wounds</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam 1993b</td>
<td>50</td>
<td>9.50 (6.20)</td>
<td>50</td>
<td>22.50 (5.20)</td>
<td>-13.00 (15.24) [-15.24, -10.76]</td>
<td>100.00</td>
<td>-13.00 [-15.24, -10.76]</td>
</tr>
<tr>
<td><strong>04 Chronic wounds</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Weheida</td>
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<td>20</td>
<td>9.93 (0.27)</td>
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<td>1.73 [-2.37, -1.09]</td>
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<td>Al-Walli</td>
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<td>22.00 (7.30)</td>
<td>-11.30 (14.37) [-14.37, -6.23]</td>
<td>44.28</td>
<td>-11.30 [-14.37, -6.23]</td>
</tr>
</tbody>
</table>

Figure 6: Summary of trials of honey versus control comparisons, with mean days to healing as the outcome.
Figure 7: Meta-analysis of trials of honey in minor acute wounds, with mean days to healing as the outcome.

Figure 8: Meta-analysis of trials of honey versus conventional dressings in treatment of burns, with mean days to healing as the outcome.
<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Treatment Mean (SD)</th>
<th>N</th>
<th>Control Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subrahmanyam 1991</td>
<td>52</td>
<td>9.40 (2.30)</td>
<td>52</td>
<td>17.20 (3.20)</td>
<td>-8.80 [-8.87, -6.73]</td>
<td>35.48</td>
<td>-8.80 [-8.87, -6.73]</td>
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<td>25</td>
<td>8.22 (8.33)</td>
<td>-3.30 [-6.85, 0.25]</td>
<td>29.68</td>
<td>-3.30 [-6.85, 0.25]</td>
</tr>
<tr>
<td>Subrahmanyam 2001</td>
<td>50</td>
<td>15.40 (3.20)</td>
<td>50</td>
<td>17.20 (4.30)</td>
<td>-1.80 [-3.29, -0.31]</td>
<td>34.85</td>
<td>-1.80 [-3.29, -0.31]</td>
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<td>Total (95% CI)</td>
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<td></td>
<td>127</td>
<td></td>
<td>100.00 [-8.94, 0.19]</td>
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<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 42.95$, df = 2 ($P < 0.00001$), $I^2 = 95.3\%$

Test for overall effect: $Z = 1.88$ ($P = 0.06$)

**Figure 9**: Meta-analysis of trials of honey versus silver sulfadiazine in treatment of burns with mean days to healing as the outcome.
trials, the wounds were surgical wounds created following partial or total toenail avulsions, with the control group treated with paraffin gauze in one trial and an iodophor dressing in the second trial. The remaining trial recruited mine workers with lacerations or shallow abrasions and control participants were treated with a hydrogel. Combination was undertaken using a fixed effects model (Figure 7). There was no statistically significant difference between treatments for mean days to healing (weighted mean difference (WMD) 1.6 days, 95%CI -1.9 to 5.0 days, p=0.4). Moderate heterogeneity was present ($I^2=48\%$), although this was not statistically significant.

3.6.1.2 Burns
Two trials (n=154) recruited participants with superficial thickness burns, and five trials (n=1,240) recruited participants with partial thickness burns. Two trials (n=200) recruited participants with mixed partial and full thickness burns. There were six comparison treatments in the trials that reported mean days to healing. These interventions were grouped under the categories conventional dressings, silver sulfadiazine and unconventional dressings for this review.

Honey versus conventional dressings or treatment
Three trials (n=1,042) compared honey with conventional treatments. However, one of the trials did not report information on healing rates. Therefore it was only possible to combine the results from the two trials (n=992) that compared honey to conventional dressings. Both these trials recruited participants with partial thickness burns. In one trial (n=92) the comparison was a polyurethane film dressing and in the other trial (n=900) the control participants were treated with either a polyurethane film (n=90), vaseline-impregnated gauze (n=90), sterile linen dressings (n=90), or a soframycin dressing (n=90). Mean days to healing were reported but not the standard deviations, although this information was provided by the author (pers. comm., M. Subrahmanyan). The WMD was -4.7 days (95%CI -5.1 to -4.3 days, p<0.0001) in favour of honey (Figure 8).

The remaining trial (n=50) recruited participants with partial and full thickness burns and compared honey dressings and late excision and skin grafting to early tangential excision and skin grafting. Mean duration of hospital stay favoured early excision and skin grafting (mean difference 25.0 days, 95%CI 17.4 to 32.6 days, p<0.0001). Graft take (99% versus 74%) also favoured early excision and skin
grafting, as did the number of participants with grafts rated as good to excellent on functional and cosmetic appearance (92% versus 55%).

**Honey versus silver sulfadiazine**

Three trials (n=254) compared honey to silver sulfadiazine. Two of the trials recruited participants with superficial burns, while the other trial did not report on the depth of the burns in recruited participants. One trial reported mean time to healing and time to event data, and the other two trials provided time to event data only. Time to event data in the two trials was reported using different schedules e.g. reporting complete healing at days 7, 14 and 21 compared to reporting complete healing at days 10, 15 and 20. Mean time to healing was provided by the author (pers. comm., M. Subrahmanyam) and this was used as the outcome (Figure 9). The weighted mean difference between the trials was not significant (WMD -4.4 days, 95%CI -8.9 to 0.2, p=0.06). A random effects model was used as there was significant statistical heterogeneity (p<0.1, I²=95%) despite the apparent clinical and methodological similarities. Heterogeneity was contributed by one trial, but it was not possible to determine what it was about this trial that contributed the heterogeneity.

**Honey versus unconventional dressings**

Three trials (n=248) by the same investigator compared honey to unconventional dressings or materials. The interventions were too dissimilar to combine in a meta-analysis. Therefore the trials are summarised here in a narrative review.

One trial (n=100) recruited participants with partial thickness burns and compared honey to treatment with boiled potato peel dressings. Mean days to healing was reported, but without the standard deviations. This information was supplied by the author (pers. comm., M. Subrahmanyam). The findings favoured the honey. Mean time to healing was 10.4 days in the honey-treated group and 16.2 days in the comparison group (mean difference -5.8 days, 95%CI -6.7 to -4.9 days).

The remaining two trials both recruited participants with partial thickness burns. One trial (n=64) compared honey-impregnated gauze to treatment with amniotic membranes. Mean days to healing was reported, although without the standard deviations. This information was supplied by the author (pers. comm., M. Subrahmanyam). Mean time to healing was 9.4 days in the honey-treated group and 7.5 days in the comparison group, with a non-significant mean difference of 1.9 days.
Participant allocation was uneven in this trial at approximately 2:1 in favour of the honey-treated group (40 versus 24 participants allocated to honey or comparison, respectively). No rationale was provided for this imbalance. The remaining trial (n=84) compared honey to treatment with honey-plus. The honey-plus consisted of unprocessed undiluted honey with added vitamins C and E, and polyethylene glycol. Mean days to healing was reported, but without the standard deviations. This information was supplied by the author (pers. comm., M. Subrahmanayam). Mean time to healing was 8.3 days in the honey-treated group and 6.4 days in the comparison group, with a significant mean difference of 1.9 days (95%CI 0.6 to 3.2 days) in favour of the control treatment.

3.6.2 Mixed acute and chronic wounds

One trial (n=100) recruited participants with burns or leg ulcers. The severity of the burns was not described. The number of participants with traumatic ulcers, decubiti, diabetic ulcers, venous ulcers or trophic ulcers was twenty, fourteen, eight, six and two respectively. The comparison treatment was silver sulfadiazine. Information on mean time to healing was provided by the author (pers. comm., M. Subrahmanayam). The mean difference was -13.0 days (95%CI -15.2 to -10.8 days) in favour of honey.

3.6.3 Chronic Wounds

Five trials (n=190) recruited participants with chronic wounds. One recruited men with Fournier's gangrene, one recruited children with pyomyostatic abscesses, one recruited adults with leg ulcers, one recruited women with infected post-caesarean or hysterectomy wounds, and one trial recruited adults with uninfected pressure ulcers. Two trials reported mean time to healing, two mean hospital stay (but one without standard deviations), and one mean change in ulcer area (but without standard deviations). The comparison treatments were EUSOL-soaked gauze, saline soaked gauze, antiseptic washes (70% ethanol and povidine iodine), and a honey/phenytoin mix or phenytoin powder. Two of the trials may have been subject to unit of analysis errors (see Section 3.5.1 Randomisation and allocation concealment). Given this clinical and methodological heterogeneity, it was not possible to combine the studies and they are summarised here in a narrative review.
3.6.3.1 Fournier's gangrene

One trial (n=30) of men with Fournier's gangrene randomly allocated participants to treatment with unifloral (jamun) honey-soaked gauze dressings or EUSOL-soaked gauze dressings. Fournier's gangrene is an infection of the scrotum that can also involve the perineum and abdominal wall. No information was presented on wound healing. One participant died in the honey-treated group and two participants died in the EUSOL-treated group. Skin grafting was required in nine participants in each group. Mean hospital stay favoured the honey-treated group (28 versus 32 days, p<0.01).

3.6.3.2 Pyomyositis abscesses

One trial (n=32) of children with pyomyositis abscesses randomly allocated participants to either honey- or EUSOL-soaked gauze packing. Abscesses were surgically drained and left to close by secondary intention. Participants were all treated with a course of penicillins and an aminoglycoside. This trial may have been subject to a unit of analysis error, as there were more wounds than participants, and healing was presented by wound. The proportion of wounds healed at day 21 was greater in the honey-treated group than in the EUSOL-treated group (86.9 versus 55.0%, p<0.05). Mean hospital stay also favoured the participants with honey-treated wounds (16.1 versus 18.6 days, p<0.02).

3.6.3.3 Leg ulcers

One trial (n=38) allocated participants with post-traumatic or post-infective leg ulcers to either of three treatments: honey, a honey/phenytoin mix or topical phenytoin alone. Allocation was by alternate days (pers. comm., O. Oluwatosin) and 50 ulcers were treated. This trial may have been subject to a unit of analysis error, as there were more wounds than participants, and healing was reported by mean change in total ulcer area. The standard deviation for the data was not reported. Potential participants with diabetes, sickle cell disease, venous disease, or malignancy were excluded. Participants were treated for four weeks. Mean ulcer area at baseline favoured the phenytoin-only group (42.0 versus 43.9 versus 18.7 cm² for honey, honey/phenytoin mix, and phenytoin respectively). Four ulcers in the phenytoin-terated group had healed by four weeks and none in the other groups. However, mean percentage reduction in ulcer size was not significantly different between the three groups at four weeks (27.0 versus 25.9 versus 35.5% respectively, p=0.9).
3.6.3.4 Infected post-operative wounds

One trial (n=50) randomly allocated participants with infected Caesarean or hysterectomy wounds to twice daily applications of honey or antiseptic washes of 70% ethanol and povidine-iodine.388 There was very limited information on baseline equivalence and no indication of the duration of treatment or length of follow up. Mean time to healing favoured the honey-treated group (10.7 versus 22.0 days, p<0.05), as did mean hospital stay (9.4 versus 19.9 days, p<0.05).

3.6.3.5 Pressure ulcers

One trial (n=40) randomly allocated participants with uninfected grade I or grade II pressure ulcers greater than 2 cm in diameter to daily applications of honey or saline-soaked gauze dressings.389 There was very limited information on baseline equivalence and no indication of the duration of treatment or length of follow up. Mean time to healing favoured the honey-treated group (8.2 days versus 9.9 days, p<0.001).

3.6.4 Adverse events

Three trials did not report adverse events,248 389 390 and three trials reported no events occurred.382 385 386 The remaining trials may have limited reporting of events to specific events, rather than encouraging reports of any event. A total of 70 events were reported in the honey-treated groups and 188 events in the comparison groups, giving a crude risk ratio of 0.4 (95%CI 0.3 to 0.5) in favour of honey. The frequency of specific events is reported in Table 10.

| Table 10: Adverse events reported by included trials |
|---------------------------------|--------|--------|
| Adverse event                   | Honey  | Comparison |
| Local irritation (itching, burning, pain) | 17     | 14      |
| Wound dehiscence & resuturing   | 4      | 18      |
| Hypergranulation                | 9      | 22      |
| Contractures                    | 10     | 19      |
| Minor & hypertrophic scarring   | 28     | 101     |
| Skin grafting                   | 9      | 13      |
| Death                           | 4      | 3       |

3.6.5 Publication bias

The 14 trials providing data on time to healing enabled the creation of a funnel plot to explore whether publication bias might be present (Figure 10). The funnel plot indicated a lack of studies around the base of the funnel, with no studies at all on the positive side of the base. It is notable that the studies conducted by one researcher have standard deviations for mean days to healing that are remarkably similar, no matter what the sample size.262 360 362 378-384 391 392 These studies are all tightly
grouped at the top of the triangle, whereas other studies with similar sample sizes are more scattered towards the base.385-387

Figure 10: Funnel plot of 14 trials reporting mean time to healing.

3.7 Discussion

The 18 trials included in this review were generally of poor methodological quality. Few studies reported on randomisation, allocation concealment, or blinded outcome assessment. Poor quality reporting of methods is associated with over-estimation of treatment effects when compared with studies that have detailed reporting of methods.305 395 The small sample sizes also mean the chance of detecting an event rate close to the true event rate is considerably decreased.396 In addition, the number of reports from one investigator where the standard deviation appears to be unrelated to study size, combined with the heterogeneity of the many comparison interventions suggested the necessity for caution when interpreting the data from many of the included studies.

The key finding of this review is that honey dressings might only be effective in treating mild to moderate partial thickness burns in comparison to conventional dressings, such as impregnated gauze, saline soaks, or polyurethane film dressings. However, mixed thickness burns (partial and deep thickness burns) appear unlikely to benefit from honey dressings and treatment should focus on preparation of the
burn for early grafting. Although this finding is based on a small trial, which reported hospital length of stay rather than healing time, the treatment effect clearly favoured the comparison treatment. The evidence does not support the routine use of honey in acute wounds such as abrasions and lacerations, or on minor uncomplicated wounds left to heal by secondary intention following surgery. Further trials of honey may be justified in these types of wounds as the possibility of a modest effect in favour of honey cannot be ruled out.

The evidence for honey's use in the treatment of burns in comparison to other treatments is more uncertain. While amniotic membrane dressings performed better than honey dressings in one trial, honey dressings performed better than boiled potato dressings in another trial. Both trials were small and of uncertain quality and thus these results should only be used to inform future research efforts. The effect of honey compared to silver sulfadiazine in treating partial thickness burns has not been established, although the trend is towards favouring honey. However, a trend towards honey may be as a consequence of inappropriate use of the comparison treatment. Although silver sulfadiazine is recommended for use on thermal burns until healing,397 trials indicate that use of silver sulfadiazine until healing impedes healing times in comparison to inactive treatments, such as hydrocolloid dressings and silicone-impregnated dressings.398 It is in recognition of this evidence that the New Zealand Guideline for the Management of Burns and Scalds in Primary Care recommends that silver sulfadiazine only be used for approximately three days in the treatment of deep partial thickness burns, but not in superficial partial thickness burns.399

The effect of honey in the treatment of chronic wounds cannot be established based on current evidence. All trials were small and thus subject to random effects. Three trials also used antiseptic comparators that are thought to impede wound healing,399 and the remaining trial had a base line imbalance in favour of the comparison, which may have biased the outcome.248 There is a complete lack of trial evidence with which to guide best clinical practice in the management of patients with venous leg ulcers.

The reporting of adverse events was poor in most studies, and non-existent in a few studies. This makes accurate assessment of the risk of adverse events associated with honey dressings difficult. Two trials reported treatment withdrawals, but without specifying the reasons for withdrawal beyond non-compliance with treatment.385 386
In both these trials, the author stated there were no adverse events, but given that adherence with a treatment regimen is likely to be strongly correlated with the treatment itself, it is possible that adverse events were missed in the two trials. In the trials recruiting participants with burns, information on the types of adverse events appears to have been pre-specified, as these studies originate from the same author and several studies reported zero events across both groups for particular adverse events e.g. allergy and renal failure. Thus it is possible that adverse events have been under-reported.

The funnel plot indicated there are few trials with large standard errors, which is unusual given that most studies had small sample sizes and tended to be published by one author. Although a funnel plot is not a definitive test, it provides a visual cue as to the possibility of publication bias where there is not an inverted funnel of results around the summary statistic. Publication bias appears likely to be present in this review as there were no positive and few negative studies scattered around the base of the funnel. However, it should be noted that four studies could not be included in this assessment as they did not report mean time to healing.

The findings of this systematic review advance those of the previous review in the area. That review only found seven trials in comparison to the 18 trials included in this review. The poor quality of the reports and the fact that six of the seven trials were conducted by the same sole researcher meant the authors of the previous review were unable to make any recommendations. The better quality of recent reports and the provision of additional information by authors have facilitated meta-analyses in this systematic review that were not possible in the previous review. However, the candidate agrees that full confidence in all the trials is not yet possible. Hence, the key findings are couched in caution as are this review's conclusions.

Future trials can avoid the problems of the trials included in this systematic review by ensuring the trials are large enough to avoid type II error and detect clinically relevant differences. In addition, trials should use true randomisation strategies, adequately conceal allocation to the point of randomisation, use blinded outcome assessors where possible, or ensure outcome assessment is verified, make every effort to follow up all participants and use the intention-to-treat principle to guide the primary analysis, where the outcomes are dichotomised. To ensure that the above elements of trial quality are adequately reported, triallists should report in a manner consistent with the Consolidated Statement on Reporting of Trials.
In order to assist future efforts to synthesise all the trial evidence, publication of trials should be considered a duty to the participants. However, researchers should also register their trials in registries that meet the World Health Organisation criteria and keep their contact details updated to ensure evidence reviews are complete even where trials remain unpublished.\textsuperscript{402}

3.8 Summary

In this review there is the strong possibility that publication bias is present. In addition, the included trial reports were generally of poor quality. However, based on current evidence, honey may be an effective treatment for partial thickness burns, but only in comparison to conventional dressing materials, such as paraffin gauze and polyurethane film dressings. Honey does not appear to benefit healing in other acute wounds, such as lacerations. Using honey in mixed partial and full thickness burns may delay recovery. No clear recommendations can be made with respect to the treatment of chronic wounds with honey. No trials were identified that investigated the effect of honey on the healing of venous leg ulcers.
CHAPTER 4

The HALT trial

4.1 Introduction

The Auckland Leg Ulcer Study (ALUS), conducted at the Clinical Trials Research Unit (CTRU) from 1997 to 1998, established a network of health workers and researchers interested in leg ulcer research. At the same time the Honey Research Unit at the University of Waikato in Hamilton, New Zealand, was involved in the development of honey-based products for use in wound care. The groups combined to submit a project grant application for the Honey as Adjuvant Leg ulcer Therapy (HALT) trial to the Health Research Council of New Zealand in the 2001 and 2002 grant rounds. In addition, ApiMed Medical Honey Ltd agreed to support the proposed trial by providing product and an unconditional contribution towards operating costs. This agreement was maintained when ApiMed was acquired by Comvita New Zealand Ltd. The candidate was notified in May 2003 that the project grant application had been successful in the 2002 grant round and planning for the HALT trial commenced. This chapter outlines the materials and methods used in the HALT trial, a multicentre, open label, parallel group, randomised controlled trial designed to evaluate the effectiveness of a honey-impregnated calcium alginate dressing in venous and mixed venous/arterial leg ulcers.

4.2 Study hypothesis

The primary hypothesis was that among people with venous and mixed venous/arterial ulcers, the addition of a honey-impregnated dressing to compression bandaging would increase the proportion of people with healed ulcers at 12 weeks.
4.3 Methods of the HALT trial

4.3.1 Study participants

4.3.1.1 Case definition

Only people with venous or mixed venous/arterial leg ulcers were recruited into the HALT trial. Since there was no widely agreed-upon definition of a leg ulcer, a leg ulcer was considered to be any break in the skin on the leg (below the knee), which had been present for six weeks or more. This definition was previously used in ALUS.132 Where the participant was known to have had previous venous leg ulcers, the temporal criterion within the case definition was relaxed.

A participant was considered to have a purely venous leg ulcer where there was no other causative aetiology, the ulcer appeared clinically venous (moist, shallow, irregular shape, presence of haemosiderian pigmentation, venous eczema, ankle oedema, and/or lipodermatosclerosis), and the study participant had an ankle-brachial pressure index (ABI) of greater than 0.8.151 An ABI < 0.8 indicates that there is a high probability that arterial insufficiency is present (positive predictive value = 95% in a general practice population).403 All study centres used non-directional Doppler ultrasound with 8MHz probes to obtain ABI after the method by Vowden, et al.404 A participant was considered to have a mixed venous/arterial leg ulcer with venous insufficiency as the primary causative aetiology where there was no other causative aetiology, the ulcer appeared clinically venous (moist, shallow, irregular shape, presence of haemosiderian pigmentation, venous eczema, ankle oedema, and/or lipodermatosclerosis), and the study participant had an ABI ≥ than 0.7.405

4.3.1.2 Eligibility

The HALT trial was a pragmatic trial designed to reflect the community-based leg management provided by district nursing services. Patients over the age of 18 years were eligible for inclusion if they satisfied all the following criteria:

- The patient met the case definition for venous leg ulceration or mixed venous/arterial leg ulceration, as determined by the district nurse and the HALT trial Research Nurse

- The patient was being treated with or able to be treated with compression bandaging at one of the study centres
The patient, in the view of the district nurse or HALT trial Research Nurse, was capable of providing informed consent.

A Doppler-determined ABI > 0.7 had been obtained on the leg with the reference ulcer within the previous three months.

The patient resided in one of the study regions.

Patients were excluded if they met any of the following criteria:

- The patient had a diagnosis of diabetes, rheumatoid arthritis or significant peripheral arterial disease.
- The patient had a known allergy to either honey or calcium alginate.
- The patient was already using honey as a treatment for their leg ulcer.

4.3.1.3 Study region & participant recruitment

This trial was conducted in four District Health Board areas in New Zealand: Auckland, Counties Manukau (South Auckland), Waikato and Canterbury. Recruitment began the week ending May 14, 2004, in three District Health Boards (Auckland, Counties Manukau and Canterbury) and the week ending July 2, 2004, in the Waikato District Health Board. Recruitment ended on July 29, 2005, in the Auckland centre, September 2, 2005, in the Canterbury centre, and September 16, 2005, in the Counties Manukau and Waikato centres.

4.3.1.4 Baseline screening

A summary of screening, recruitment and data collection is outlined in Table 11. In each District Health Board the district nurses involved in leg ulcer care identified potential participants, provided them with a participant information sheet (Appendix 8), obtained written consent to pass on the person's contact details (Appendix 8), and having obtained consent, notified the HALT trial Research Nurse. The Research Nurse assigned each person a registration number from a consecutive sequence, and registered them as a potential participant in the HALT trial. The Research Nurse contacted each potential participant, collected information on age and sex, verified that they did not meet the exclusion criteria, and arranged a baseline assessment to
Table 11: Summary of study visits and procedures completed at each visit.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Telephone</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Telephone</th>
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<tr>
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<td>Week -1</td>
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<td>Weeks 1-11</td>
<td>Week 12</td>
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<td>Case Record Form</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
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<td>X</td>
<td></td>
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<tr>
<td>District Nurse</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Eligibility criteria</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Consent</td>
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<tr>
<td>Demographic data</td>
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<tr>
<td>Ulcer width/length</td>
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<td></td>
</tr>
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<td>Clinical examination</td>
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<td></td>
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<tr>
<td>Clinical history</td>
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<td>Ankle Brachial Index</td>
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<td>Venous disease severity</td>
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<td>Ulcer tracing</td>
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<td>Digital photography</td>
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<td></td>
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<tr>
<td>Quality of life measures</td>
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<td></td>
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<tr>
<td>Ulcer healing</td>
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<td></td>
</tr>
<tr>
<td>Medications</td>
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<tr>
<td>Adverse events</td>
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<tr>
<td>Dressing count</td>
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<td>Type of compression</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Additional dressings</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Visits to other professionals</td>
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<td></td>
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<tr>
<td>Signs of infection</td>
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<tr>
<td>Ulcer recurrence</td>
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</tr>
<tr>
<td>Study treatment</td>
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<td></td>
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</tr>
<tr>
<td>Manuka honey dressing</td>
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</tr>
<tr>
<td>Usual care</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* 13% were collected by the candidate.

interview them, at a time and place convenient to the potential participant (Appendix 9: Form A). The baseline assessment took place either in the potential participant’s home or during a clinic visit. At the baseline interview, prior to randomisation and assessment, the Research Nurse confirmed that the potential participant met the inclusion criteria, provided further explanations about the HALT trial and obtained written informed consent if the person decided to participate in the trial.

4.3.1.5 Baseline assessment

Demographic information was collected at the baseline assessment (Appendix 9: Form B). Ethnicity data followed the format of the 2001 New Zealand Census. Ethnicity was determined by the participant, who chose as many of the options as they wished. In addition, information was collected on:

- History of ulceration
- Presence of infection, using the classical clinical signs and symptoms (erythema, pain, local oedema, purulent exudate)

- Venous disease severity, using the Venous Clinical Severity score, a 10-item inventory to produce a score out of 30. Scores ≥ 8 have a sensitivity and specificity of 70% and 96% in consecutive patients presenting to a vascular clinic for detecting severe venous disease (American Venous Forum CEAP Class 5 and 6 disease).

- Current wound management strategy, namely the dressing choice if allocated to usual care, and the system of compression bandaging chosen

- Relevant medical history

- Current smoking status

- Current alcohol use

- Degree of mobility.

Three quality of life instruments (Appendix 9: Participant Questionnaire) were also completed at this time, the reference ulcer photographed and a wound tracing obtained (refer to section 4.3.4.2.2 Change in ulcer area for more details of methods used).

### 4.3.2 Randomisation

Consented participants were randomly assigned to the study or control treatment by a central telephone randomisation service provided by a commercial telephone service (First Contact) via an 0800 freephone number. The allocation sequence was stratified by study centre and the Margolis index, using a range of block sizes generated by (and known only to) the study statistician (Varsha Parag). The Margolis index is a validated prognostic index for venous ulcer healing with 24 weeks of compression therapy. The index assigns a score of 0-2 based on the absence (score 0) or presence of one (score 1) or both prognostic factors (score 2). The prognostic factors are:

- Reference ulcer size > 5 cm²
- Reference ulcer present for more than six months.

Where more than one leg ulcer was present the largest ulcer was to be used as the reference ulcer and all ulcers were treated with the allocated treatment.

4.3.3 Interventions
All participants received compression bandaging in the first instance as a standard background therapy to ensure that any observed effect was related only to the treatment being evaluated. The range of compression bandaging reflected that normally available to district nursing services, with the choice of system determined by the participant's and/or the district nurse's preference. Where compression bandaging could not be sustained, the participant continued with the allocated treatment.

4.3.3.1 Manuka honey-impregnated dressing
The treatment group received manuka honey dressings for 12 weeks. The dressings were packaged to meet the labelling requirements specified in the Medicines Act 1981 (s30) and the Medicines Regulations 1984 (s12-14, s24) and marked “For clinical trial use only”. The manuka honey was impregnated in a standard calcium alginate dressing for ease of use. The manuka honey dressing was prepared as a single batch from Unique Manuka Factor (UMF) 12+ honey for Comvita NZ Ltd, packaged in single-use packs, gamma-irradiated for sterilization, and stored by Comvita NZ Ltd for transfer as requested by the study centres. The UMF rating refers to the level of non-peroxide antibacterial activity equivalent on a weight per volume activity of phenol. The batch was verified as having non-peroxide antibacterial activity equivalent to 15% phenol by an independent laboratory and assessed by Comvita NZ Ltd's laboratory as being compliant for maximum pesticide residue and heavy metal levels. Twenty manuka-honey impregnated dressings were left with each participant in a kit box containing case record forms (CRFs) for the district nurse to complete and a guideline for using the honey dressings. The guideline was written by an associate investigator (Julie Betts) with extensive experience in wound care and the use of manuka honey dressings (Appendix 7).

4.3.3.2 Usual care
The usual care group received the dressings deemed appropriate by the district nurse at the time of each visit for 12 weeks. The dressing choices reflected the
normal range of choices available to district nursing services at each study centre (Table 12).

### Table 12: Dressings available to district nurses by generic category and trade name

<table>
<thead>
<tr>
<th>Category</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium alginate</td>
<td>Algisite, Kaltostat, Seasorb</td>
</tr>
<tr>
<td>Hydrofibre</td>
<td>AQUACEL, SEASORB</td>
</tr>
<tr>
<td>Hydrocolloid</td>
<td>COMFEE, COMBIDERM, Duoderm</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>Curafili, Solosite</td>
</tr>
<tr>
<td>Iodophor impregnated</td>
<td>Iodosorb, Infadine</td>
</tr>
<tr>
<td>Polyurethane foam</td>
<td>Allevyn, Polymax, HydroSorb</td>
</tr>
<tr>
<td>Silver impregnated</td>
<td>Acticoat, Aquacel AG, Avance</td>
</tr>
<tr>
<td>Non-adherent</td>
<td>Adaptive, Cuticel, Tricotex, paraffin gauze</td>
</tr>
<tr>
<td>Absorbent</td>
<td>Gauze, combine, Exudry, Melolin</td>
</tr>
</tbody>
</table>

#### 4.3.4 Outcome measures

Study participants were followed up for six months, with data collected at 12 weeks and six months post-randomisation. The Research Nurse at each study centre conducted all the 12-week assessments. The majority (87%) of the six month assessments were completed by the same Research Nurses, with the remaining six month assessments being completed by the candidate. Information on the progress of the ulcer and concurrent treatment was collected at each visit by the district nurse caring for the participant (Appendix 9: Form C). At 12 weeks following randomisation, information was collected by the Research Nurses on ulcer healing (Appendix 9: Form D), quality of life, and concurrent treatments. The reference ulcer or site of the reference ulcer was photographed at this time, and a wound tracing obtained if the ulcer was unhealed.

**4.3.4.1 Primary outcome measure**

The primary outcome was the proportion of participants with a healed leg ulcer as determined by the Research Nurse at 12 weeks after randomisation. Healing was defined as complete epithelialisation of the ulcer with no scab. A digital photograph of the ulcer or site of the healed ulcer from the 12-week assessment of each participant was obtained to compare levels of agreement between the Research Nurses and a blinded reviewer and to conduct a sensitivity analysis using the healing state as determined by the blinded reviewer.

**4.3.4.2 Secondary outcome measures**

**4.3.4.2.1 Time to healing**

The healing state of the reference ulcer was recorded by the district nurses each time they attended the participant. The actual date of healing was not recorded, but
rather the date of the first district nursing visit where the ulcer was determined by the district nurse to meet the operational definition for healing.

4.3.4.2.2 Change in ulcer area
The size of the reference ulcer at baseline and at 12-weeks was measured after the method proposed by Soloman and colleagues. Measurement of a two-dimensional plane, such as a photograph of an ulcer, will underestimate the three dimensional surface area of the ulcer because of the curvature of the leg. An acetate ring of known area was placed over the ulcer and a photograph taken (Figure 11). The difference between the measured area of the acetate ring and the known area of the circle facilitated calculation of a correction for the curvature of the leg. Digital photographs of the reference ulcer for each participant at baseline and at the 12-week assessment for each participant were measured twice by a nurse blinded to treatment allocation. The average of the two measures was used to calculate change in ulcer size. Circumferential tracings of the ulcer using a wound mapping grid were also obtained at baseline and follow-up to provide substitute measures should the ulcer photograph be unusable.

Figure 11: Example of digital photograph of a leg ulcer with the acetate ring to allow for correction of curvature

4.3.4.2.3 Incidence of infection
The accurate identification of wound infection is a difficult clinical issue. The classical signs of infection (erythema, pain, oedema, and purulent exudate) may be disguised by the common features of venous ulceration. For example, trophic skin changes may make erythema difficult to distinguish, pain is commonly experienced by people with venous ulcers, and purulent exudate can be diluted by the volume of exudate generated by compression bandaging, especially in the early stages of treatment. Additional criteria have been proposed and are used in clinical practice, but these have only been evaluated on groups that excluded leg
ulcers or on mixed groups without differentiating between aetiologies. For the purpose of the HALT trial, and in the absence of a widely accepted definition, a participant's leg ulcer was defined as infected if the ulcer was clinically assessed as being infected or a wound swab was obtained, and the participant was treated with antibiotics for ulcer infection. Episodes of infection were considered independent if the treatment with antibiotics was followed by an absence of the signs and symptoms of infection for a period of greater than seven days following completion of the course of antibiotics.

4.3.4.2.4 Health-related quality of life
Each person's perception of his or her general health was assessed using the standard version of the Short Form 36 version 1 (SF-36), the Charing Cross Venous Ulcer Questionnaire (CXVUQ) and the EuroQol 5D (EQ-5D). The SF-36 is the most widely used generic health-related quality life instrument in the world, and is considered a valid and reliable instrument, including when used with older adults. It has been used for the two New Zealand Health Surveys (1996 and 2002), as well as with a variety of New Zealand patients, and leg ulcer patients. The SF-36 measures perceived health across eight domains using a 1-100 scale: physical function, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Higher scores reflect better perceived health, with 100 being the best possible score for a domain. However, the SF-36v1 may not be responsive to changes in ulcer state (healed versus unhealed) at three months. Therefore a disease-specific instrument, the CXVUQ was also used.

The CXVUQ measures four dimensions: social function, domestic activities, emotional status and cosmesis (concern for appearance) using a 0-100 scale. Higher scores reflect greater affliction with 100 being the worst possible score for a domain. The CXVUQ has good reliability, correlates well with the SF-36, and appears responsive to changes over time. However, the CXVUQ does not have widespread acceptance, having only been used by its creators and to validate a Chinese language version in Hong Kong. Review of the questionnaire revealed that in two questions, the coding of the responses was the reverse of what it should be and thus would deliver higher scores in those with a healed ulcer. This finding appears to have been due to a translocation error on the part of the journal. Approaches to the authors of the CXVUQ remained unanswered. However, the authors of the Hong Kong study had independently come to the same
conclusion and the same solution (pers. comm. Professor David Thompson, Nethersole School of Nursing, Chinese University of Hong Kong).

The EQ-5D is also a generic quality of life instrument in common use,\textsuperscript{415} and can be used to generate a single index of health status for use in economic analyses.\textsuperscript{424-425} It is considered a valid and reliable instrument,\textsuperscript{426-428} with discriminant properties over time.\textsuperscript{111} It has previously been used with leg ulcer patients\textsuperscript{153, 429-430} and in a variety of New Zealand populations.\textsuperscript{431-435} The EQ-5D measures five domains: mobility, self-care, ability to undertake usual activities, pain, anxiety and depression. In addition, respondents rate their own health status using a visual analogue scale (EQVAS) of 0-100. Responses to the five questions locate participants in one of 243 health states. The utility of each health state has been valued in the range from zero (equivalent to dead) to one (equivalent to excellent health) in northern European countries with very similar results.\textsuperscript{424} Ratings from the EQVAS can also be used as a measure of differences between individuals or groups.\textsuperscript{424}

4.3.4.2.5 Adverse events
All adverse events that participants experienced were recorded throughout the trial by the district nurses attending to their patients, or by the Research Nurse in the course of the 12-week assessment (Appendix 9: Form X). An adverse event was defined as any untoward clinical occurrence and could therefore be any unfavourable sign, symptom, or disease temporally associated with use of the interventions, whether or not related to the products used. All adverse events were categorised by a medical coder (Terry Holloway) who was blind to treatment allocation. If the adverse event was thought to be related or possibly related to the treatment, this was recorded on the CRF by the nurse completing the form.

4.3.4.2.6 Cost-effectiveness
The purpose of a cost-effectiveness analysis is to assess whether a new therapy is an efficient use of resources in the usual clinical environment.\textsuperscript{436} Such an assessment compares alternatives in terms of both costs and consequences, therefore taking into account differences in costs and treatment effects. The aim of the cost-effectiveness analysis was to calculate the marginal cost of the addition of a manuka honey dressing to compression therapy compared with usual care for venous ulceration. The outcome of the analysis was the incremental cost of leg ulcer healing over the 12 week treatment period, taking the DHB perspective. The prices and costs were in New Zealand dollars (2005) and the information collected for this perspective included:
• The type and number of compression bandages used

• The type and number of dressings used

• The number and duration of district nursing visits

• The antibiotics prescribed for leg ulcer treatment

• General practitioner and other community consultations for leg ulcer treatment (self-reported)

• Outpatient consultations for leg ulcer treatment (self-reported)

• Hospitalisation for leg ulcer treatment (self-reported). Duration of hospitalisation was obtained from the participant's discharge summary

4.3.4.2.7 Ulcer recurrence
Participants were contacted by telephone six months after randomisation by either the Research Nurse or the candidate. The leg with the reference ulcer was identified and participants were asked to report whether a new ulcer had occurred on that leg after the 12-week assessment. Participants that had healed at the 12-week assessment and reported a new ulcer at six months after randomisation were deemed to have had a recurrent ulcer.

4.3.5 Sample size calculation
A sample size of 360 people (180 in each group) was calculated as necessary to detect a 30% relative increase (RR 1.30) in the proportion of participants with completely healed leg ulcers in the intervention group at 12 weeks with 90% power and an alpha of 5%. The relative increase equated to an absolute increase in healed ulcers from 55% to 71% at 12 weeks, a benefit that had been suggested by the controlled trials in burns patients available at the time the study was being developed.262 379 382 A recruitment rate of 45% was assumed for the HALT trial and was based on information provided by three of the four study centres:

• In 2001 the Auckland Leg Ulcer Team (with a patient catchment of 338,000) treated on average 19 new patients per month or 228 patients per year with compression (pers. comm. Anita Latta)
- The Health Waikato District Nursing Service received approximately 370 requests each year for Doppler assessment of patients with leg ulcers (pers. comm. Julie Betts)

- In 1999 South Auckland Home Healthcare assessed 111 leg ulcer patients with Doppler ultrasound over a nine month period (pers. comm. Susan McAuley). Annualising this figure suggested approximately 140 leg patients would have been assessed over a 12-month period. It was thought this was an underestimate of current figures (pers. comm. Bronwen Nicholls).

The Nurse Maude Association assured the candidate that they would be able to provide up to 100 participants, despite not being able to provide data in support of this assertion. Based on these figures it was estimated that it would take 12 months to recruit approximately 100 people from each of the four centres. A 10% dropout rate was incorporated into the sample size, so the target recruitment was 400 participants.

4.3.6 Statistical analyses

All statistical analyses were specified a priori in a statistical analysis plan (Appendix 5) collaboratively prepared by the candidate, the study statistician (Ms Varsha Parag), the Manager of the Biostatistics Team at CTRU (Mr Stephen Vander Hoorn) and Professor Anthony Rodgers, the candidate’s supervisor. Cost-effectiveness analyses were also specified a priori and incorporated into the statistical analysis plan. The proposed analyses were collaboratively prepared by the candidate, Dr Paul Brown, and Ms Kate Butler, Health Systems Section, School of Population Health, University of Auckland.

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc. Cary NC) and SPLUS. All statistical tests were two-tailed and a 5% significance level maintained throughout the analyses. No adjustments for multiplicity were planned for the secondary endpoints or adverse events. Summaries of continuous variables were presented as means and standard deviations for normally distributed data or medians and inter-quartiles for skewed data. Categorical variables were presented as frequencies and percentages. Continuous variables were compared with Student’s t-tests where data was normally distributed, or Mann-Whitney tests where the data was non-normal. Categorical data were tested with the Chi-squared test or Fisher’s Exact test as appropriate. The study statistician and the candidate
conducted all analyses. Analyses were conducted blind to treatment allocation; a data set with dummy treatment variables was prepared by a second non-study statistician (Ray Buey Lin) within CTRU. The primary analyses were peer reviewed by the same non-study statistician.

4.3.6.1 Analysis of primary outcome

The primary analysis was conducted using the intention-to-treat principle. Participants lost to follow-up were deemed treatment failures. The unadjusted absolute increase in the proportion of participants with healed venous leg ulcer at 12 weeks between the treatment groups and the number needed to treat (NNT) were calculated. Unadjusted odds ratios (ORs) and relative risk (RR) were calculated. Adjusted analyses were conducted using logistic regression. Covariates found to be significant were retained in the model. The ORs obtained from the logistic regression were converted to an absolute risk difference and NNT. Use of the ORs was necessary when comparing unadjusted and adjusted analyses, although ORs can overestimate RR, particularly when the comparison group event rate is greater than 30%. The likelihood ratio Chi-squared test of the unadjusted and adjusted logistic regression models was used to assess whether the covariates in the adjusted model significantly improved the goodness of fit of the model.

The digital photographs of the reference ulcer or ulcer site were reviewed as healed, probably healed, probably not healed, or not healed by a medical practitioner (Dr Yogini Ratnasabapathy) blind to the treatment allocation of the participant. To obtain levels of agreement on the healing state of the reference ulcer as observed by the Research Nurses and the blinded reviewer, the reviewer's determination was dichotomised into healed/not healed. Agreement was obtained from a 2 x 2 table with a kappa statistic and 95% confidence interval calculated.

Three sensitivity analyses were planned a priori. First, to test whether the level of agreement between the Research Nurses and the blinded verification had an impact on the outcome, healing state identified by the blinded reviewer was used in a sensitivity analysis. Second, to test the assumption that participants lost to follow-up were treatment failures the last healing state reported by the district nurse was carried forward in a sensitivity analysis. Third, to test the effect of participant withdrawals from treatment, cross-over between treatment groups and loss to follow up, participants with these major protocol violations were excluded in a sensitivity analysis.
4.3.6.2 Analysis of secondary outcomes

4.3.6.2.1 Time to healing
Time to healing was analysed using Kaplan-Meier curves and the log rank test. As the log rank test is a hypothesis test, it provides no direct estimate of the difference between the groups. Therefore, Cox proportional hazards regression analysis was used to assess time-to-event data, taking into account the effect of known covariates and the varying times since randomisation to produce a hazard ratio (HR). Prior to inclusion in the model, the assumption of proportionality for each covariate was reviewed using formal testing and visual assessment of scaled Schoenfeld residuals plots. Proportionality was assumed if the p-values in formal testing were greater than 5% and the plotted Schoenfeld residuals did not vary significantly from a straight line. Covariates were only entered into the model if the assumption of proportionality was valid.

4.3.6.2.2 Change in ulcer area
Analyses were conducted using linear regression. The assumptions of linearity, homogeneity of variance and normality of errors were tested prior to analysis. Factors included in the adjusted model were assessed for multi-collinearity to determine variance inflation factors. Multi-collinearity arises when two or more independent variables in a regression model are highly correlated. The consequent interdependence can result in unstable parameter estimates in the model. A threshold of 10 for the variance inflation factor (VIF) was set a priori as indicative of multi-collinearity. Whilst a VIF < 10 does not preclude significant multi-collinearity, only values approaching 10 would have been subject to closer scrutiny. The likelihood ratio Chi-squared test of the unadjusted and adjusted models was used to assess whether the covariates in the adjusted model significantly improved the goodness of fit of the model.

4.3.6.2.3 Incidence of infection
The incidence of leg ulcer infection between the treatment groups during the 12 week study period was compared using the Chi-squared test. The number of episodes of infection per participant was compared using Fisher’s Exact test because of too few numbers in some cells to use the Chi-squared test.

4.3.6.2.4 Health-related quality of life
Participants that did not complete quality of life questionnaires were excluded from the analysis. Reasons for non-completion were recorded where appropriate. SF-36 and CXVUQ data were initially analysed by comparing crude mean scores at follow
up. Where there are differences between groups at baseline, statistical significance between treatment groups could be influenced by the correlation between baseline and follow up scores.\textsuperscript{446} Therefore, ANCOVA was used to adjust for baseline differences and avoid the potentially confounding effects of both high and low correlation between baseline and follow up scores. The reversed coding found in the CXVUQ (discussed in section 4.3.4.2.4 Health-related quality of life) was corrected prior to this analysis.

4.3.6.2.5 Adverse events
Adverse events were summarised in a frequency table, excluding infection, by local and systemic events. The relative risk (RR, 95%CI) of reporting one or more adverse events in each category was calculated, as well as the RR of reporting one or more adverse events overall.

4.3.6.2.6 Cost-effectiveness
Average costs per participant within each treatment group were calculated. The incremental cost effectiveness ratio (ICER) was calculated using the standard method \( (\Delta C_t - C_s) / \Delta E_t - E_s \) where \( C = \text{cost, } E = \text{effect, } t = \text{new treatment and } s = \text{standard treatment} \), to produce a ratio of the marginal cost of using honey over the difference between the proportions healed in each group.\textsuperscript{447} Confidence intervals for the ICER were estimated using the bias corrected and accelerated method of non-parametric bootstrapping.\textsuperscript{448} Bootstrapping are data-driven simulation methods for estimating precision where the sampling distribution of the estimate is unknown and conventional methods are likely to prove unreliable.\textsuperscript{449}

The base case analysis was an intention-to-treat analysis. All participants were included in the denominator and participants lost to follow up were treated as treatment failures at 12 weeks. Costs incurred by participants lost to follow up were included up to the last contact with the district nurses. The retail costs of bandages and dressings were used in the primary analysis to ensure that the costs did not reflect the different volume-based pricing the study centres might have negotiated with their suppliers (see Appendix 1, Tables 1, 2 and 3). In some instances where the retail cost of dressings could not be obtained, the price paid by the district health board (DHB), or the average of the prices paid by each DHB was increased by 13%. This figure was the average difference between prices paid by the DHBs and the retail price across a range of dressings where the values of both were known.
As the time horizon for treatment was shorter than one year, costs were not discounted. The costs of the drugs used in treating participants' leg ulcers were obtained from the New Zealand Pharmaceutical Schedule (April 2006)\textsuperscript{450} and thus do not include retail mark up, dispensing cost or goods and services tax. The daily cost of drug treatment was calculated from the full price if the product was fully subsidised, or from the subsidy if part-funded (see Appendix 1, Table 4). The cost of consultations with health workers was obtained from the appropriate employment agreements (see Appendix 1, Table 5). The hourly rate was obtained by dividing the annual salary by 2080 (the equivalent 52 weeks multiplied by 40 hours). However, medical officers and medical specialists work more than a 40 hour week. For these groups a full-time equivalent was assumed to be 1.2 and the hourly rate was obtained by dividing the annual salary by 2496 (1.2 multiplied by 2080). The ratio of direct care to indirect care time per patient contact was obtained from the 2005 report \textit{Unit Costs of Health and Social Care}, a British resource to support economic analyses.\textsuperscript{451} Where information on particular professional groups was not available within this report, the ratio was imputed from similar groups.

The duration of patient contact for district nurses was obtained from the CRF for each visit. The average duration of district nurse consults for participants in the usual care group was used to impute the duration of a community orthotist's consult. The duration of nurse practitioner consults was imputed from the average duration of general practitioner (GP) consultations obtained from the study of the cost-effectiveness of green prescriptions for exercise in New Zealand.\textsuperscript{452} Nurse practitioner consults have been reported on average as about twice that of GPs.\textsuperscript{453} In the absence of any New Zealand information on the average duration of an outpatient consultation, consultation with a junior doctor (registrar) was assumed to be the same duration as a nurse practitioner consultation. Outpatient consults with medical or surgical specialists were assumed to be the same duration as that of a GP.\textsuperscript{452} The average duration of practice nurse consults was obtained from the study of the cost-effectiveness of green prescriptions for exercise in New Zealand.\textsuperscript{452} This value was also used for laboratory nurse consults.

The income model for GPs differs from that of the other health workers consulted by trial participants. GPs can receive either a salary or fee-for-service. A fee-for-service model involves revenue streams from both government subsidy and patient co-payment. The Royal New Zealand College of General Practitioners has reported on the annual average income of GPs, but this figure inevitably includes both subsidy and co-payment. As the cost analysis used a health services perspective, the cost of
a GP consultation was taken as the government subsidy to Primary Healthcare Organisations for patients 65 years and over, for the year July 2004 to July 2005. The per diem hospital cost was the cost charged by the Auckland DHB for international patients in 2002, inflated by 6.7%. This inflation adjustment was calculated for the period of the first quarter 2003 to the fourth quarter of 2005, as calculated using the Reserve Bank of New Zealand's online inflation calculator (http://www.rbnz.govt.nz/statistics/0135595.html). The cost of testing of wound swabs incorporated the cost of the wound swab and the cost of a microbiological culture and sensitivity test, as provided by the Auckland DHB's laboratories.

Uncertainty in the findings was explored using sensitivity analyses. It was anticipated that the price of dressings that different DHBs can obtain through negotiating supply contracts could be a cost driver. To test this scenario, the supply prices were used to explore the sensitivity of the cost analyses to DHB pricing. These prices were supplied by three DHBs on the understanding that this information was commercially sensitive and would not be released, except in aggregate. Therefore the prices paid by each of the DHBs are not specified in this thesis. The price of the honey dressing was not varied in this analysis as the product is not currently available within hospitals and thus a contract price was not available. Other costs were examined to determine the potential effect of any other cost driver. The cost of hospitalisation was considered a cost driver. This cost was excluded from the analysis in order to explore the sensitivity of hospitalisation costs on the cost analyses.

4.3.6.2.7 Ulcer recurrence
The number of participants with a recurrent ulcer six months after randomisation was compared using the Chi-squared test.

4.3.7 Study organisation
The candidate was the principal investigator, who conducted the trial from the CTRU at the School of Population Health, University of Auckland. The candidate also acted as Study Manager and was assisted by a Steering Committee to provide strategic oversight, a Study Management Committee to provide operational support, a Data Monitoring and Safety Committee, and a Study Monitor. Members of these committees are listed in the HALT trial protocol (Appendix 4). A district nurse at each of the four study centres was seconded 0.5 FTE from the employing organisation (Auckland DHB, Counties Manukau DHB, Waikato DHB, Nurse Maude Association) to the HALT trial as a Research Nurse. The employing organisation
received a per participant payment to cover the salary and operating expenses for the Research Nurse.

4.3.8 Data management

The design and management of the databases was undertaken by the data management and information technology teams at the CTRU. The databases were constructed in Oracle 8i and migrated to Oracle 10g whilst the trial was underway. Database entry was via an html interface for internet data entry. The Research Nurses at each study centre entered the data from the CRFs. The case record files for each participant were kept in a locked filing cabinet at each site whilst the study was underway. On study closure, the case record files were transferred to the CTRU for secure storage.

Validation rules for each form were specified by the candidate in association with a senior data manager. The validation rules specified range checks to help with early identification of inaccuracies. Where a value fell outside the range check, was missing or unclear, a query was raised requiring the Research Nurse to confirm the value as correct, or re-enter the correct value. Each query confirmed as correct by the Research Nurse was scrutinised by the candidate. The candidate sought explanations from the Research Nurses for the values or accepted the entries where appropriate.

A medical coder, who was blind to the treatment allocation of the participants, classified information such as living arrangements, concurrent treatments, and medications. ICD-10-AM guidelines were used to code medical conditions and adverse events.\textsuperscript{455} Study specific codes, where necessary, were developed by the coder in association with the candidate.

4.3.9 Consultation with Maori

The CTRU Maori Research Advisory Committee reviewed the funding applications made to the Health Research Council of New Zealand in 2000 and 2001. The committee consisted of Professor Colin Mantell (Chair), Brian Emory, Dianne Moss, Elizabeth Mitchelson and Dr Jonathon Koea, and provided advice on:

- How to ensure that Maori tikanga was recognised and respected throughout the research process


- How to ensure that Maori received the maximum benefit from the research
- How to ensure that Maori had access to information for their own health development.

In addition, Mata Forbes (Coordinator, Maori Health Services, Auckland DHB), Rose Smith (Kaumatua Kaunihera, Iwi Affiliations Raukawa, Waikato), Annette Finlay (Te Kai Hapai Tikanga Maori, Te Komiti Whakarite, Christchurch) and the Maori Research Review Committee (Auckland DHB) reviewed and provided advice on the ethics application, participant information sheet and consent form.

4.3.10 Ethical & management approval

Multicentre ethical review was sought from the Auckland Regional Ethics Committee X (AKX/03/09/232), the Waikato Ethics Committee (WAI/03/09/062) and the Canterbury Ethics Committee (CTR/03/09/145), with the Auckland Ethics Committee X being the lead committee. Upon receiving notice of ethical approval pending management approval from the participating organisations, approval was sought and obtained from each of the three DHBs (Auckland, Counties Manukau and Waikato) and the Nurse Maude Association in Christchurch, using each organisation's research approval process. Management approvals from each organisation were forwarded to the Auckland Ethics Committee to obtain ethical approval to recruit participants. Ethical approval for the HALT trial was granted on the 9th December 2003 (Appendix 3). Subsequent to this approval, further approval was obtained from the Chairperson for:

- Field testing of digital photography on patients under the care of the Auckland Leg Ulcer Team (18 December 2003)
- Administrative amendments to the study protocol (2 June 2004)
- Administrative amendments to the study protocol (24 January 2005).

Following national restructuring of the ethics committees, responsibility for ethical supervision transferred from the Auckland Ethics Committees to the Multi-region Ethics Committee in Wellington on 19 April 2005.
4.3.11 Data safety & monitoring

The purpose of data safety and monitoring is to "protect the safety of trial participants, the credibility of the study and the validity of the study results". Ellenberg and colleagues suggest four criteria to assist in determining whether a Data Safety and Monitoring Committee (DSMC) is necessary (Table 13). If two or more criteria are met, they suggest a DSMC is necessary. If no criteria are met, then a DSMC would not normally be considered necessary. The HALT trial only met the first criteria, but it was thought necessary at least to have independent review of safety information (adverse event reports). Therefore a DSMC was deemed necessary. Members of the DSMC are listed in the trial protocol (Appendix 4).

Table 13: Criteria for determining whether a DSMC is necessary

| Criteria | 1 | Is the trial intended to provide definitive information about the effectiveness and/or safety of a medical intervention? |
| 2 | Are there prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity? |
| 3 | Is the trial evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications? |
| 4 | Would it be ethically important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not fully addressed? |

Using the decision model proposed by Ellenberg and colleagues (Table 14), an internal DSMC was constituted. The DSMC established their terms of reference and met twice during the course of the trial.

Table 14: Criteria for determining whether to establish an independent or internal DSMC

<table>
<thead>
<tr>
<th>Setting 1</th>
<th>Setting 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (Phase 2b, 3, 4)</td>
<td>RCT (Any phase)</td>
</tr>
<tr>
<td>RCT (Phase 1, 2a)</td>
<td>Non-randomised</td>
</tr>
<tr>
<td>Non-randomised trials</td>
<td></td>
</tr>
<tr>
<td>Imperatives</td>
<td>Ethical</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>YES</td>
<td>Likely</td>
</tr>
<tr>
<td>Maybe</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

* Setting 1 includes: life-threatening diseases; diseases causing serious irreversible morbidity; novel treatments for life-threatening diseases with potentially significant adverse events; vulnerable populations

b Setting 2 includes all trials not included in setting 1

Each study centre was audited on four occasions by the Study Monitor. The Monitor followed a standard operating procedure. The visits were scheduled after the first five participants were enrolled, when 25 participants were enrolled, when 50 participants enrolled and at each study centre close out. The role of the monitor was to:
- Verify the existence of all enrolled participants by confirming the participant details against district nursing service admission records

- Audit study centre compliance with the ethical duty to obtain informed consent, and ensure all written consents were properly documented

- Compare all electronic data entry against the paper case record forms for the first five participants enrolled at each centre and thereafter a random sample of 10 records from the remaining records at second and third visits.

- Provide an opportunity for the Research Nurses and site investigators at each study centre to give and receive feedback on the conduct of the HALT trial.

Reports of the audits were provided to the candidate and the study centre, and the Study Monitor counselled the Research Nurses at each site on the adjustments required to ensure compliance with the study protocol.

4.2.12 Trial Registration

The HALT trial was prospectively registered with the Current Controlled Trials Ltd's web-based public domain trials register on 23 March 2004. The trial was assigned an International Standardised Randomised Controlled Trial Number (ISRCTN06161544), with details available at www.controlled-trials.com. Further information was subsequently provided in 2005 to meet the International Committee of Medical Journal Editors' (ICMJE) requirements for trials registration.\(^{402}\)
CHAPTER 5

Results from the HALT trial

5.1 Participant recruitment & retention

Three hundred and ninety-two patients were notified to the HALT Trial Research Nurses, contacted, and registered (Figure 12). It is not known how many patients with leg ulcers were screened by the district nurses as possible participants to be approached by the Research Nurses. Three hundred and sixty-eight participants were randomised, with a third coming from each of the South Auckland and Christchurch study centres (Table 15).

Table 15: Number of participants randomised at each study centre by treatment group (percentage of group)

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Honey (n=187)</th>
<th>Usual care (n=181)</th>
<th>Total (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auckland</td>
<td>27 (14)</td>
<td>25 (14)</td>
<td>52 (14)</td>
</tr>
<tr>
<td>South Auckland</td>
<td>62 (33)</td>
<td>60 (33)</td>
<td>122 (33)</td>
</tr>
<tr>
<td>Waikato</td>
<td>41 (22)</td>
<td>41 (23)</td>
<td>82 (22)</td>
</tr>
<tr>
<td>Christchurch</td>
<td>57 (30)</td>
<td>55 (30)</td>
<td>112 (30)</td>
</tr>
</tbody>
</table>

The 24 people notified to the trial but not randomised either did not consent (13), did not have a venous ulcer (2), had an ABI < 0.7 (1), had diabetes or rheumatoid arthritis (5), could not tolerate compression bandaging (1) or were already using honey (2). These people were on average slightly older (69.2 years, SD 19.0 years) than the trial participants (67.5 years, SD 17.3 years), but this difference was not significant (p=0.7). Those people not randomised were also more likely to be female than the randomised participants (62.5% versus 51.1%), but again this difference was not significant (p=0.3).
Figure 12: Flow of participants in the HALT trial
Thirty one participants (8%) withdrew from treatment in the honey group, and were treated with the normal range of dressings available to the district nurses in the study centre. The rationale for participant withdrawal is listed in Table 16. Five participants (9.6%) in the Auckland centre withdrew, 13 (10.7%) in the South Auckland centre, two (2.4%) in the Waikato centre and 11 (9.8%) in the Christchurch centre. No participants in the usual care group crossed over to use honey.

<table>
<thead>
<tr>
<th>Rationale</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health professional’s advice</td>
<td>7</td>
</tr>
<tr>
<td>Participant’s choice</td>
<td>3</td>
</tr>
<tr>
<td>Ulcer infection</td>
<td>7</td>
</tr>
<tr>
<td>Ulcer pain</td>
<td>4</td>
</tr>
<tr>
<td>Ulcer bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Deterioration of ulcer or surrounding skin</td>
<td>1</td>
</tr>
</tbody>
</table>

Three hundred and sixty-two (98.4%) participants were followed up at 12 weeks. Six participants were lost to follow up, all in the usual care group. Two participants died (both for reasons unrelated to treatment), three participants moved out of the area (one to Samoa, one to England, and one within New Zealand, but could not be traced) and one participant could not be contacted. All participants who withdrew from treatment with honey were followed up at 12 weeks.

### 5.2 Baseline characteristics

The participants' baseline characteristics are summarised in Table 17. Overall the mean age of participants was 67.5 years (SD 17.3) and 51% were female. Mean ulcer area was 6.9cm$^2$ (SD 14.7) and mean duration of the reference ulcer at trial entry was 43 weeks (SD 99). Mean ABI was 1.1 (SD 0.2) and mean venous clinical severity score (VCSS) was 14.6 (SD 3.8). Overall the baseline characteristics were well-balanced, although there were clear differences between the groups for mean ulcer area, mean ulcer duration and mobility. Mean ulcer area was greater in the usual care group, but this difference was solely attributable to one participant in the honey-treated group who had an ulcer of 280cm$^2$. Mean ulcer area was 6.4cm$^2$ in both groups when this participant was removed (for the sake of comparison only). The mean duration of ulcer was longer in the honey-treated group. The difference between the groups for mean ulcer duration was largely attributable to two participants, one with a reference ulcer that had been present for 15 years and the other with a reference ulcer that had been present for more than 19 years. Mean ulcer duration was approximately 39 weeks in both groups when these outlying participants were excluded (for the sake of comparison only).
Table 17: Baseline demography and clinical characteristics of participants by treatment group (number and percentage of treatment group unless otherwise indicated)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Honey (n=187)</th>
<th>Usual care (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>66.9 (17.5)</td>
<td>68.3 (17.1)</td>
</tr>
<tr>
<td>Female</td>
<td>96 (51)</td>
<td>92 (51)</td>
</tr>
<tr>
<td>Currently smokes</td>
<td>37 (20)</td>
<td>32 (18)</td>
</tr>
<tr>
<td>Currently drinks alcohol</td>
<td>66 (35)</td>
<td>59 (33)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>146 (76)</td>
<td>137 (76)</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>23 (12)</td>
<td>30 (17)</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>16 (9)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mean ABI (SD)</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.2)</td>
</tr>
<tr>
<td>ABI ≥ 0.8</td>
<td>184 (98.4)</td>
<td>175 (96.7)</td>
</tr>
<tr>
<td>ABI 0.7 - 0.79</td>
<td>2 (1.1)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Mean ulcer area cm² (SD)</td>
<td>7.4 (18.2)</td>
<td>6.4 (9.8)</td>
</tr>
<tr>
<td>Mean ulcer duration, weeks (SD)</td>
<td>38.7 (76.3)</td>
<td>47.9 (118.1)</td>
</tr>
<tr>
<td>Venous Clinical Severity Score (SD)</td>
<td>14.3 (3.8)</td>
<td>15.0 (3.9)</td>
</tr>
<tr>
<td>Margolis Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (ulcer size ≤ 5cm² and ≤ 6 months)</td>
<td>85 (45)</td>
<td>84 (46)</td>
</tr>
<tr>
<td>1 (ulcer size &gt; 5cm² or &gt; 6 months)</td>
<td>69 (37)</td>
<td>68 (38)</td>
</tr>
<tr>
<td>2 (ulcer size &gt; 5cm² and &gt; 6 months)</td>
<td>33 (18)</td>
<td>29 (16)</td>
</tr>
<tr>
<td>Compression system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short stretch</td>
<td>2 (1)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Long stretch</td>
<td>5 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Three layer</td>
<td>74 (40)</td>
<td>65 (36)</td>
</tr>
<tr>
<td>Four layer</td>
<td>106 (57)</td>
<td>106 (59)</td>
</tr>
<tr>
<td>Medications with potential to influence healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentoxifyline</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>53 (28)</td>
<td>60 (33)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>7 (4)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Zinc</td>
<td>2 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>40 (21)</td>
<td>30 (17)</td>
</tr>
<tr>
<td>Lower limb joint replacement</td>
<td>26 (14)</td>
<td>26 (14)</td>
</tr>
<tr>
<td>Leg fracture</td>
<td>33 (18)</td>
<td>41 (23)</td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easily without aids</td>
<td>11 (1)</td>
<td>85 (47)</td>
</tr>
<tr>
<td>Slowly without aids</td>
<td>26 (14)</td>
<td>28 (15)</td>
</tr>
<tr>
<td>With stick or walker</td>
<td>48 (26)</td>
<td>67 (37)</td>
</tr>
<tr>
<td>Independent in wheelchair</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dependent</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>SF-36 Summary Component score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Component Score (SD)</td>
<td>36.7 (10.1)</td>
<td>34.0 (9.8)</td>
</tr>
<tr>
<td>Mental Component Score (SD)</td>
<td>48.7 (11.8)</td>
<td>50.5 (12.4)</td>
</tr>
</tbody>
</table>

SD = Standard deviation

5.3 Primary outcome

Although the point estimate favoured the honey-treated group, there was no significant difference between the treatment groups for healing at 12 weeks. One hundred and four participants (55.6%) in the honey group and 90 participants (49.7%) in the usual care group healed at 12 weeks, giving a 5.9% (95% CI -4.3 to 15.7%, p=0.3) absolute increase in healing at 12 weeks. The number needed to treat was 17 (95% CI NNT[B] 6 to 8 to NNT[H] 23). The RR of healing was 1.12 (95% CI 0.9 to 1.4), with an unadjusted OR of 1.3 (95% CI 0.8 to 1.9).

The findings did not alter appreciably in the adjusted analysis. Age, sex, ethnicity, study centre, the Margolis index, baseline ulcer area, baseline ulcer duration, baseline VCSS, and mobility were considered as covariates in the initial model. Age,
sex, ethnicity and mobility were non-significant. Study centre, the Margolis index, baseline ulcer area, and baseline VCSS were statistically significant covariates. Prior to inclusion into the final model, correlations between the statistically significant co-variates were checked. As expected, the Margolis index was highly correlated with both baseline ulcer area (Spearman Rho=0.6, p<0.0001) and baseline ulcer duration (Spearman Rho=0.8, p<0.0001). Baseline VCSS was also moderately correlated to the Margolis index (Spearman Rho=0.4, p<0.0001), as it collected information on ulcer size and duration (as well as other information). Therefore, only the stratification factors (study centre and Margolis index) were retained in the final model. The final adjusted model (OR 1.4, 95%CI 0.9 to 2.2) significantly improved the goodness of fit (p<0.0001) in comparison to the unadjusted results. The adjusted model resulted in a 28% change in the beta co-efficient. The adjusted absolute increase in healing at 12 weeks was non-significant at 8.1% (95% CI -3.1 to 18.6%), giving a number needed to treat of 12 (95% CI NNT[B] 6 to ∞ to NNT[H] 33).

5.3.1 Sensitivity analyses
The findings of the sensitivity analyses are tabulated along with the results of the unadjusted and adjusted primary outcome analysis in Table 18.

<table>
<thead>
<tr>
<th>Table 18: Results of the primary outcome analysis and sensitivity analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Primary analysis – unadjusted</td>
</tr>
<tr>
<td>Primary analysis – adjusted</td>
</tr>
<tr>
<td>Sensitivity analysis - blinded review</td>
</tr>
<tr>
<td>Sensitivity analysis – loss to follow up</td>
</tr>
<tr>
<td>Sensitivity analysis – per protocol</td>
</tr>
</tbody>
</table>

5.3.1.1 Agreement between Research Nurses & blinded review
Agreement between the Research Nurses and the blinded reviewer on the healing state of the reference ulcer was 85% (Figure 13). The kappa for agreement over chance was strong (0.7, 95%CI 0.6 to 0.8). Although, overall the analysis was robust to this sensitivity analysis, when the healing state as determined by blinded review was used in place of that determined by the Research Nurses in an adjusted analysis, the result moved towards the null (OR 1.0 95%CI 0.7 to 1.6), giving a non-significant absolute increase in 12-week healing of 0.5% (95%CI -10.6 to 11.3%).

5.3.1.2 Loss to follow up
The analysis was robust to carrying forward the last value for healing reported by the district nurses for the six participants in the usual care group who were lost to
follow-up. Four participants were reported as being healed and two unhealed after their last district nursing contact. When these values were used in place of the default value (not healing) in an adjusted analysis, the size of effect was reduced with little effect on precision (OR 1.3, 95%CI 0.8 to 2.0), giving a non-significant absolute increase in 12-week healing of 5.6% (95%CI -5.7 to 16.1%).

5.3.1.3 Per protocol analysis

The analysis was robust to a sensitivity analysis in which participants who withdrew from treatment with honey (n=31) and those lost to follow up (n=6) were excluded from the analysis. When these participants were excluded in an adjusted analysis, the estimate was not changed appreciably (OR 1.5, 95%CI 0.9 to 2.4), giving a non-significant absolute increase in 12-week healing of 9.8% (95%CI -2.0 to 20.3%).

5.4 Secondary outcomes

5.4.1 Time to healing

The mean number of days to healing was 63.5 days in the honey-treated group and 65.3 days in the usual care group (Figure 14, mean difference -1.8 days, 95%CI -7.7 to 4.1 days, p=0.5, Hazard Ratio 1.1, 95%CI 0.8 to 1.5, p=0.5). Covariates entered into the adjusted model were study centre and Margolis index. The covariates did not breach the assumption of proportionality as identified by p values in Table 19.
and Schoenfeld plots. The HR for time to healing did not change in the adjusted model (HR 1.2, 95% CI 0.9 to 1.6, p=0.2).

Table 19: P values testing the assumption of proportionality for Cox regression

<table>
<thead>
<tr>
<th>Covariate</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study centre 1 (Christchurch) *</td>
<td>0.1</td>
</tr>
<tr>
<td>Study centre 2 (South Auckland) *</td>
<td>0.2</td>
</tr>
<tr>
<td>Study centre 3 (Waikato) *</td>
<td>0.8</td>
</tr>
<tr>
<td>Prognostic index level 1 (Score 0)**</td>
<td>0.2</td>
</tr>
<tr>
<td>Prognostic index level 2 (Score 1)**</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Reference value Auckland
** Reference value prognostic index level 3 (Score 2)

Figure 14: Kaplan-Meier survival plot for time to healing, by treatment group

5.4.2 Change in ulcer area

There was no significant difference between the treatment groups for change in ulcer area from baseline. Change in ulcer area was approximately normally distributed with long tails at either end. Mean baseline ulcer area was 7.4 cm² in the honey-treated group and 6.4 cm² in the usual care group. The unadjusted mean difference from baseline ulcer area was 3.7 cm² in the honey-treated group and 2.8 cm² in the usual care group, giving an unadjusted between-group mean difference of 0.9 cm² (95% CI -1.4 to 3.2 cm², p=0.4).
In the adjusted analysis, age, sex, ethnicity, mobility and the stratification factors were considered as co-variates for inclusion in the model. Baseline imbalances in ulcer size and duration were not included as covariates as the mean change from baseline area precluded the necessity of adjustment for size, and duration was highly correlated with the Margolis index (see Section 5.3 Primary outcome). The only statistically significant co-variate was the Margolis index, but study centre was forced into the model for the sake of congruence with the other adjusted analyses. Neither of the included co-variates had a VIF of greater than 1.1 and thus multicollinearity was assumed to be insignificant (Table 20). The findings did not alter when the result was adjusted (0.9 cm², 95%CI -1.4 to 3.2 cm², p=0.5). Although there appeared to be no difference between the adjusted and unadjusted results, the final model significantly improved the goodness of fit (p<0.0001) with a 4% change in the beta co-efficient in comparison to the unadjusted results. The lack of apparent difference in the two models was due to rounding.

Table 20: Variance inflation factors for covariates in adjusted analysis for change in ulcer area

<table>
<thead>
<tr>
<th>Covariate</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study centre</td>
<td>1.0</td>
</tr>
<tr>
<td>Prognostic index</td>
<td>1.0</td>
</tr>
</tbody>
</table>

5.4.3 Incidence of Infection

Thirty-two participants (17%) in the honey-treated group and 40 participants (22%) in the usual care group had episodes of infection. The difference between groups was not significant (absolute decrease 5.0%, 95%CI -3.1 to 13.1%, p=0.2). The 72 participants were treated for 86 episodes of leg ulcer infection. Sixty participants had a single episode of infection, ten participants had two episodes and two participants had three episodes of infection. There was no difference between the groups for numbers of episodes (Table 21).

Table 21: Number of episodes of ulcer infection, by treatment group

<table>
<thead>
<tr>
<th>Number of episodes</th>
<th>Honey (%) N=187</th>
<th>Usual care (%) N=181</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>155 (83)</td>
<td>141 (78)</td>
<td>296 (80)</td>
</tr>
<tr>
<td>1</td>
<td>28 (15)</td>
<td>32 (16)</td>
<td>60 (16)</td>
</tr>
<tr>
<td>2</td>
<td>3 (2)</td>
<td>7 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>3</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

* Fisher's Exact test, p=0.5

Wound swabs were obtained for 60 episodes of infection. Multiple species were present in 24 episodes. The majority of identified species were staphylococci, streptococci or pseudomonas (Table 22).
Table 22: Infective agents identified in participants with episode of infection that had a wound swab reported

<table>
<thead>
<tr>
<th>Species</th>
<th>Honey (%)</th>
<th>Usual care (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>21 (46)</td>
<td>23 (52)</td>
<td>44 (49)</td>
</tr>
<tr>
<td>Streptococci</td>
<td>3 (7)</td>
<td>10 (23)</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>7 (15)</td>
<td>7 (16)</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Mixed</td>
<td>5 (11)</td>
<td>2 (5)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>E. coli</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>2 (4)</td>
<td></td>
<td>2 (2)</td>
</tr>
<tr>
<td>Candida</td>
<td>4 (9)</td>
<td></td>
<td>4 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

5.4.4 Health-related quality of life

One hundred and eighty-six participants (99%) in the honey-treated group and 174 participants (96%) in the usual care group completed the HRQoL instruments at follow up, giving an overall response rate of 98%. The one non-responder in the honey-treated group did not return the form, while one participant in the usual care group was too unwell to complete the form, and six were lost to follow up. There was a small but significant difference between the groups in the crude SF-36 domain scores for physical functioning favouring the honey-treated group. There were no other significant differences on the SF-36. There remained a significant difference between the groups for physical functioning after adjustment for baseline imbalance, but the differences were not significant for any other domain or the component summary scores (Table 23).

Table 23: Adjusted mean SF-36 domain scores, by treatment group

<table>
<thead>
<tr>
<th>SF-36 Domain</th>
<th>Honey</th>
<th>Usual care</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>56.4</td>
<td>53.8</td>
<td>4.6 (95% CI 0.5 - 8.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Role physical</td>
<td>53.9</td>
<td>48.2</td>
<td>5.7 (95% CI -2.7 - 14.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>65.0</td>
<td>63.2</td>
<td>1.8 (95% CI -4.2 - 6.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>General health</td>
<td>69.3</td>
<td>66.9</td>
<td>2.4 (95% CI -1.0 - 5.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Vitality</td>
<td>60.8</td>
<td>58.0</td>
<td>2.8 (95% CI -0.7 - 6.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Social functioning</td>
<td>74.6</td>
<td>73.3</td>
<td>1.3 (95% CI -3.7 - 6.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Role emotional</td>
<td>78.3</td>
<td>74.0</td>
<td>4.3 (95% CI -3.2 - 11.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Mental health</td>
<td>79.3</td>
<td>78.5</td>
<td>0.8 (95% CI -2.0 - 3.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>PCS</td>
<td>39.0</td>
<td>37.9</td>
<td>1.1 (95% CI -0.8 - 3.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>MCS</td>
<td>51.1</td>
<td>50.4</td>
<td>0.7 (95% CI -1.1 - 2.4)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Higher scores indicate better outcomes

There was no significant difference between the groups in the CXVUQ domain scores in the unadjusted scores. After adjustment for baseline imbalance, differences between the groups remained non-significant on all domains (Table 24).
Table 24: Adjusted mean CXVUQ domain scores, by treatment group

<table>
<thead>
<tr>
<th>CXVUQ Domain</th>
<th>Honey</th>
<th>Usual care</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social functioning</td>
<td>30.3</td>
<td>31.9</td>
<td>-1.7 (95%CI -4.5 - 1.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Domestic activities</td>
<td>28.8</td>
<td>29.0</td>
<td>-0.2 (95%CI -3.1 - 2.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Cosmesis</td>
<td>36.0</td>
<td>38.2</td>
<td>-2.2 (95%CI -5.4 - 1.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Emotional status</td>
<td>39.9</td>
<td>42.5</td>
<td>-2.6 (95%CI -5.5 - 1.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Overall</td>
<td>33.5</td>
<td>35.1</td>
<td>-1.6 (95%CI -4.2 - 0.9)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Lower scores indicate better outcomes

There was no significant difference between the groups for health state measured by the EQVAS (75.1 versus 73.5). The mean difference between the groups was 1.6 (95%CI -1.5 to 4.7, p=0.3). Similarly, there was no significant difference in utility scores between the two groups (0.70 versus 0.72, mean difference 0.01, 95%CI -0.04 to 0.05, p=0.8) or for differences in the proportions between the two groups reporting no problems, some problems or otherwise on the five descriptive domains (Table 25).

Table 25: EQ-5D descriptive domain scores, by treatment group

<table>
<thead>
<tr>
<th>EQ-5D Domain</th>
<th>N</th>
<th>Honey</th>
<th>%</th>
<th>Usual care</th>
<th>%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility No problems</td>
<td>98</td>
<td>52.4</td>
<td>78</td>
<td>44.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility Some problems</td>
<td>88</td>
<td>47.1</td>
<td>96</td>
<td>55.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility Confined to bed</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self care No problems</td>
<td>154</td>
<td>82.4</td>
<td>135</td>
<td>77.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self care Some problems</td>
<td>30</td>
<td>16.0</td>
<td>38</td>
<td>21.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self care Unable to</td>
<td>3</td>
<td>1.6</td>
<td>1</td>
<td>0.1</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Usual activities No problems</td>
<td>90</td>
<td>48.1</td>
<td>79</td>
<td>45.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual activities Some problems</td>
<td>87</td>
<td>46.5</td>
<td>83</td>
<td>47.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual activities Unable to</td>
<td>10</td>
<td>5.4</td>
<td>12</td>
<td>6.9</td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Pain/discomfort None</td>
<td>91</td>
<td>48.7</td>
<td>71</td>
<td>40.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/discomfort Moderate</td>
<td>87</td>
<td>46.5</td>
<td>92</td>
<td>62.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/discomfort Extreme</td>
<td>9</td>
<td>4.8</td>
<td>11</td>
<td>6.9</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Anxiety/depression None</td>
<td>139</td>
<td>74.3</td>
<td>136</td>
<td>78.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety/depression Moderate</td>
<td>46</td>
<td>24.6</td>
<td>36</td>
<td>20.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety/depression Extreme</td>
<td>2</td>
<td>1.1</td>
<td>2</td>
<td>1.2</td>
<td></td>
<td>0.7</td>
</tr>
</tbody>
</table>

* Fisher's Exact test

5.4.5 Adverse events

One or more adverse events were reported by 111 participants (55%) in the honey-treated group and 84 participants (46%) in the usual care group. The overall RR of adverse event was 1.3 (95%CI 1.1 to 1.6, p<0.01) in favour of the usual care group (Table 26). The excess in reports of pain in the honey-treated group were the only statistically significant difference between the groups.
Table 26: Number of participants reporting one or more adverse events in each category, by treatment group (excluding infection)

<table>
<thead>
<tr>
<th>Event type</th>
<th>Honey</th>
<th>Usual care</th>
<th>RR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>47</td>
<td>18</td>
<td>2.5 (1.5 to 4.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
<td>3</td>
<td>1.0 (0.2 to 4.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>8</td>
<td>8</td>
<td>1.0 (0.4 to 2.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>Deterioration of ulcer **</td>
<td>19</td>
<td>9</td>
<td>2.0 (1.0 to 4.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Erythema</td>
<td>6</td>
<td>4</td>
<td>1.5 (0.4 to 5.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Oedema</td>
<td>4</td>
<td>1</td>
<td>3.9 (0.4 to 34)</td>
<td>0.2</td>
</tr>
<tr>
<td>Increased exudate</td>
<td>5</td>
<td>1</td>
<td>4.8 (0.6 to 41)</td>
<td>0.1</td>
</tr>
<tr>
<td>Deterioration of surrounding skin</td>
<td>5</td>
<td>3</td>
<td>1.6 (0.4 to 6.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>New ulceration</td>
<td>16</td>
<td>15</td>
<td>1.0 (0.5 to 2.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>3</td>
<td>1.9 (0.5 to 7.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4</td>
<td>3</td>
<td>1.3 (0.3 to 5.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>2</td>
<td>1.0 (0.1 to 6.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Neurological</td>
<td>4</td>
<td>1</td>
<td>3.8 (0.4 to 34.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>2</td>
<td>1.9 (0.4 to 10)</td>
<td>0.4</td>
</tr>
<tr>
<td>Injury</td>
<td>10</td>
<td>9</td>
<td>1.1 (0.5 to 2.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>13</td>
<td>9</td>
<td>1.4 (0.6 to 3.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6</td>
<td>3</td>
<td>1.9 (0.5 to 7.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>7</td>
<td>0.4 (0.1 to 1.8)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

5.4.6 Cost-effectiveness

The resources consumed by each group are reported in the appendices (Appendix 1, Table 6). A summary of results for the base case and the sensitivity tests is reported in Table 27. The district nursing cost was the main overall cost, accounting for more than 85% of the costs of treatment in each treatment group. There were no differences between the groups for the frequency of district nursing visits. The mean number of district nursing visits was 12.4 (SD 8.9) in the honey group and 12.1 (SD 7.4) in the usual care group (p=0.8). In all analyses, the average cost of treatment was greater with honey than usual care group, when the district nursing and other community costs were considered. However, the total average cost of treatment varied depending on whether hospitalisation costs were included.

Table 27: Summary of total average costs and ICER for each cost analysis by treatment group (New Zealand dollars)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Total average cost</th>
<th>Healed at 12 weeks</th>
<th>Total average cost</th>
<th>Healed at 12 weeks</th>
<th>ICER (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case analysis</td>
<td>$917.00</td>
<td>55.6%</td>
<td>$972.68</td>
<td>49.7%</td>
<td>-$9.45 (-$39.63 to $16.07)</td>
</tr>
<tr>
<td>Sensitivity analysis – contract-based costs</td>
<td>$816.02</td>
<td>55.6%</td>
<td>$8853.74</td>
<td>49.7%</td>
<td>-$6.39 (-$40.71 to $15.29)</td>
</tr>
<tr>
<td>Sensitivity analysis – excluding hospitalisation costs</td>
<td>$877.90</td>
<td>55.6%</td>
<td>$811.12</td>
<td>49.7%</td>
<td>$11.34 ($-2.24 to $26.25)</td>
</tr>
</tbody>
</table>
5.4.6.1 Base case analysis

When all treatment costs were incorporated into the base case analysis, honey was less expensive than usual care (Table 28), due to the higher average hospital costs in the usual care group. The average cost of treatment per participant with honey was $917.00 compared with $972.68 for usual care. The ICER was -$9.45 (95% CI -$39.63 to $16.07) favouring honey. The ICER means that there would be savings of $9.45 (95% CI -$39.63 to $16.07) per healed patient, if all patients were treated with honey-impregnated dressings compared with all patients being treated with usual care.

Table 28: Base case of average health service costs per participant, by treatment group and outcome (New Zealand dollars)

<table>
<thead>
<tr>
<th>Item</th>
<th>Honey healed</th>
<th>Honey not healed</th>
<th>Total honey</th>
<th>Usual care healed</th>
<th>Usual care not healed</th>
<th>Total usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>104</td>
<td>83</td>
<td>187</td>
<td>90</td>
<td>91</td>
<td>181</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>$0.93</td>
<td>$3.58</td>
<td>$2.11</td>
<td>$1.03</td>
<td>$4.91</td>
<td>$2.98</td>
</tr>
<tr>
<td><strong>District Nursing</strong></td>
<td>$581.15</td>
<td>$124.79</td>
<td>$662.39</td>
<td>$513.19</td>
<td>$1072.88</td>
<td>$794.58</td>
</tr>
<tr>
<td><strong>Nursing</strong></td>
<td>$224.78</td>
<td>$517.68</td>
<td>$354.78</td>
<td>$212.44</td>
<td>$434.38</td>
<td>$324.02</td>
</tr>
<tr>
<td><strong>Dressings</strong></td>
<td>$92.16</td>
<td>$161.19</td>
<td>$147.21</td>
<td>$36.39</td>
<td>$148.28</td>
<td>$94.28</td>
</tr>
<tr>
<td><strong>Bandages</strong></td>
<td>$259.39</td>
<td>$460.70</td>
<td>$348.74</td>
<td>$258.28</td>
<td>$471.37</td>
<td>$365.41</td>
</tr>
<tr>
<td><strong>Swab</strong></td>
<td>$4.61</td>
<td>$20.23</td>
<td>$11.66</td>
<td>$2.78</td>
<td>$18.65</td>
<td>$10.88</td>
</tr>
<tr>
<td><strong>Outpatient Consult</strong> *</td>
<td>$2.47</td>
<td>$7.46</td>
<td>$4.68</td>
<td>$2.36</td>
<td>$5.83</td>
<td>$4.10</td>
</tr>
<tr>
<td><strong>Community Care</strong> **</td>
<td>$4.08</td>
<td>$14.55</td>
<td>$8.72</td>
<td>$2.38</td>
<td>$16.45</td>
<td>$9.45</td>
</tr>
<tr>
<td><strong>Hospitalisation</strong></td>
<td>$56.24</td>
<td>$17.62</td>
<td>$39.09</td>
<td>$16.25</td>
<td>$305.28</td>
<td>$161.56</td>
</tr>
<tr>
<td><strong>Total average cost</strong></td>
<td>$644.86</td>
<td>$1258.00</td>
<td>$917.00</td>
<td>$535.20</td>
<td>$1405.35</td>
<td>$972.68</td>
</tr>
</tbody>
</table>

* Visits to any outpatient hospital clinic
** Visits to community-based health worker e.g. GP, practice nurse, etc.

5.4.6.2 Sensitivity analysis – contract-based costs

Within the district nursing cost, dressings and bandages accounted for between 55% and 60% of the cost of district nursing care in each treatment group. District nursing costs can be influenced by the supply contracts each health service negotiates with product manufacturers and distributors. To test whether the results were sensitive to such a scenario, the retail costs were substituted for the costs each health service paid for dressing and bandaging products (Table 29). The result showed that the district nursing cost still remained the main overall cost driver, although the dressings and bandages accounted for between 50% and 55% of the overall district nursing cost in each treatment group. In this scenario, honey remained a less expensive treatment, but with a reduced cost-effectiveness ratio. The weighted costs of honey treatment were $816.02 compared with $853.74 for usual care, giving an ICER of -$6.39 (95% CI -$40.71 to $15.29), favouring honey. The ICER means that there would be savings of $6.39 (95% CI -$40.71 to $15.29) per healed patient, if all patients were treated with honey-impregnated dressings compared to all patients being treated with usual care.
Table 29: Sensitivity of average health service costs to using contract prices paid by health services, by treatment group and outcome (New Zealand dollars)

<table>
<thead>
<tr>
<th>Item</th>
<th>Honey healed</th>
<th>Honey not healed</th>
<th>Total honey</th>
<th>Usual care healed</th>
<th>Usual care not healed</th>
<th>Total usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>104</td>
<td>83</td>
<td>187</td>
<td>90</td>
<td>91</td>
<td>181</td>
</tr>
<tr>
<td>Drug</td>
<td>$0.93</td>
<td>$3.58</td>
<td>$2.11</td>
<td>$1.03</td>
<td>$4.91</td>
<td>$2.98</td>
</tr>
<tr>
<td>District Nursing</td>
<td>$581.15</td>
<td>$124.79</td>
<td>$862.39</td>
<td>$513.19</td>
<td>$1072.88</td>
<td>$794.58</td>
</tr>
<tr>
<td>Nursing</td>
<td>$224.78</td>
<td>$517.68</td>
<td>$354.78</td>
<td>$212.44</td>
<td>$434.38</td>
<td>$324.02</td>
</tr>
<tr>
<td>Dressings</td>
<td>$90.20</td>
<td>$190.02</td>
<td>$139.50</td>
<td>$28.23</td>
<td>$112.89</td>
<td>$70.79</td>
</tr>
<tr>
<td>Bandages</td>
<td>$188.42</td>
<td>$341.75</td>
<td>$256.48</td>
<td>$192.12</td>
<td>$346.95</td>
<td>$269.97</td>
</tr>
<tr>
<td>Swab</td>
<td>$4.81</td>
<td>$20.23</td>
<td>$11.66</td>
<td>$2.78</td>
<td>$18.85</td>
<td>$10.86</td>
</tr>
<tr>
<td>Outpatient Consult*</td>
<td>$2.47</td>
<td>$7.46</td>
<td>$4.68</td>
<td>$2.36</td>
<td>$5.83</td>
<td>$4.10</td>
</tr>
<tr>
<td>Community Care **</td>
<td>$4.08</td>
<td>$14.55</td>
<td>$8.72</td>
<td>$2.38</td>
<td>$16.45</td>
<td>$9.45</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>$56.24</td>
<td>$17.62</td>
<td>$30.09</td>
<td>$16.25</td>
<td>$305.28</td>
<td>$161.56</td>
</tr>
<tr>
<td>Total average cost</td>
<td>$571.92</td>
<td>$1121.89</td>
<td>$816.02</td>
<td>$457.59</td>
<td>$1245.54</td>
<td>$853.74</td>
</tr>
</tbody>
</table>

* Visits to any outpatient hospital clinic  
** Visits to community-based health worker e.g. general practitioner, practice nurse, etc

5.4.6.3 Sensitivity analysis – excluding hospitalisation costs

The main driver of the cost difference between groups was hospital utilisation. Three participants reported they were hospitalised for leg ulcer-related treatment for a total of ten days in the honey-treated group, while six participants reported they were hospitalised for leg ulcer-related for a total of 40 days in the usual care group. The mean hospital utilisation was 0.05 days in the honey-treated group versus 0.22 days in the usual care group (mean difference 0.17 days, 95%CI -0.38 to 0.04 days, p=0.1). As hospitalisation rates are likely to vary between different areas depending on different health practices (and the differences between the two groups was likely to be due to random variation), it was necessary to determine whether the ICER was sensitive to the exclusion of hospital utilisation (Table 30). The findings were sensitive to this scenario, with the ICER being reversed to $11.34 (95%CI -$2.24 to $26.25) in favour of usual care, suggesting that for it would cost $11.34 more (95%CI -$2.24 to $26.25) per healed patient, if all patients were treated with honey-impregnated dressings compared with all patients being treated with usual care.

Table 30: Sensitivity of average health service costs to exclusion of hospital costs, by treatment group and outcome (New Zealand dollars)

<table>
<thead>
<tr>
<th>Item</th>
<th>Honey healed</th>
<th>Honey not healed</th>
<th>Total honey</th>
<th>Usual care healed</th>
<th>Usual care not healed</th>
<th>Total usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>104</td>
<td>83</td>
<td>187</td>
<td>90</td>
<td>91</td>
<td>181</td>
</tr>
<tr>
<td>Drug</td>
<td>$0.93</td>
<td>$3.58</td>
<td>$2.11</td>
<td>$1.03</td>
<td>$4.91</td>
<td>$2.98</td>
</tr>
<tr>
<td>District Nursing</td>
<td>$581.15</td>
<td>$124.79</td>
<td>$862.39</td>
<td>$513.19</td>
<td>$1072.88</td>
<td>$794.58</td>
</tr>
<tr>
<td>Nursing</td>
<td>$224.78</td>
<td>$517.68</td>
<td>$354.78</td>
<td>$212.44</td>
<td>$434.38</td>
<td>$324.02</td>
</tr>
<tr>
<td>Dressings</td>
<td>$92.16</td>
<td>$216.19</td>
<td>$147.21</td>
<td>$36.39</td>
<td>$148.28</td>
<td>$94.28</td>
</tr>
<tr>
<td>Bandages</td>
<td>$259.39</td>
<td>$460.70</td>
<td>$348.74</td>
<td>$258.28</td>
<td>$471.37</td>
<td>$365.41</td>
</tr>
<tr>
<td>Swab</td>
<td>$4.81</td>
<td>$20.23</td>
<td>$11.66</td>
<td>$2.78</td>
<td>$18.85</td>
<td>$10.86</td>
</tr>
<tr>
<td>Outpatient Consult*</td>
<td>$2.47</td>
<td>$7.46</td>
<td>$4.68</td>
<td>$2.36</td>
<td>$5.83</td>
<td>$4.10</td>
</tr>
<tr>
<td>Community Care **</td>
<td>$4.08</td>
<td>$14.55</td>
<td>$8.72</td>
<td>$2.38</td>
<td>$16.45</td>
<td>$9.45</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total average cost</td>
<td>$558.62</td>
<td>$1240.38</td>
<td>$877.90</td>
<td>$518.96</td>
<td>$1100.06</td>
<td>$811.12</td>
</tr>
</tbody>
</table>

* Visits to any outpatient hospital clinic  
** Visits to community-based health worker e.g. general practitioner, practice nurse, etc
5.4.7 Ulcer recurrence

Three hundred and sixty participants (98%) were contacted by telephone six months after randomisation. There was no significant difference in recurrence rates between the honey-treated and the usual care groups. Twenty participants (11%) in the honey-treated group and ten participants (6%) in the usual care group reported a new ulcer on the reference leg had occurred after the reference ulcer had healed and was present at six months after randomisation (absolute increase 5.0%, 95%CI -0.4 to 11.0%, p=0.1).
CHAPTER 6

Discussion of the HALT trial findings

6.1 Introduction

In this chapter the key findings from the HALT trial are summarised and the strengths and limitations of the trial are evaluated to assess whether the findings reflect a true estimate of the effect of honey. The results of the trial are then compared to those of previous studies, with discussion of possible reasons for the HALT trial results. Finally the clinical implications of the study are examined and recommendations for future research are made.

6.2 Summary of key findings

Findings from the HALT trial indicate that using honey-impregnated dressings in addition to compression did not significantly increase the proportion of participants with healed ulcers at 12 weeks, in comparison to usual care. Furthermore, using honey-impregnated dressings did not significantly reduce ulcer area, the incidence of infection, nor improve time to healing in comparison to usual care. Neither did the use of honey have any significant effect on ulcer recurrence. Honey-impregnated dressings did significantly increase the reports of pain, although the pain appears to have been tolerated by most. Finally, honey-impregnated dressings probably had little impact on health-related quality of life and were a more expensive treatment option than using the range of wound dressings normally available to district nurses.

6.3 Study strengths

6.3.1 Internal validity (lack of systematic error)

Internal validity is influenced by the level of systematic error or bias in RCTs. The central role of trials is to compare two or more groups that are sufficiently alike so
that only the difference in treatment explains between-group differences in outcomes.\textsuperscript{441} If the result can be explained by other reasons, then the findings may be biased. Bias is introduced by flaws in study design that cause a systematic difference in the groups being compared. One of the strengths of the HALT trial was the management of bias.

6.3.1.1 Selection bias

The purpose of randomisation is to create groups that are similar to two random samples from the same population.\textsuperscript{457} If properly randomised, both groups will be balanced for known and unknown factors that may otherwise affect the outcome. Trials that do not employ randomisation or those that do not prevent manipulation of the allocation sequence are subject to selection bias. Selection bias occurs when the outcome is affected by the way in which different participants are assigned to groups in a trial.\textsuperscript{458} Such trials can deliver a flawed, but precise estimate of effect because of selection bias.\textsuperscript{459} The most effective means of preventing selection bias is to protect the allocation sequence up to the point of randomisation. Randomisation schedules in trials with inadequate allocation concealment can be subverted,\textsuperscript{460} and such trials have been shown to overestimate treatment effects by 37-41\%.\textsuperscript{305, 395} Effective allocation concealment requires that [1] the person who generates the allocation sequence is not the person who determines participant eligibility and [2] the process of allocation involves people not otherwise associated with the trial.\textsuperscript{461} When these criteria are met, trial participants truly have an equal chance of being randomised to one group or the other.

In the HALT trial, allocation was concealed to the point of randomisation. The Research Nurses were required to contact a commercial telephone answering service. The telephone operator checked that the participant was eligible, collected information necessary for stratification, and then randomised the participant using a web-based interface connected to the CTRU's secure computer servers. Randomisation could not proceed unless the potential participant had been previously registered and all the inclusion criteria were met. It was not possible for the telephone operator to reveal the allocation of the participant in advance of randomisation or to reveal more than one allocation at a time. The participants' baseline characteristics reflect the effectiveness of the allocation concealment. If allocation concealment had been breached in some way, large differences would likely have been revealed in the baseline demography. However, the groups were
quite similar and this similarity supports the low likelihood of selection bias having an influence on the trial results.

6.3.1.2 Confounding

Although confounding is typically a systematic error in other epidemiological study designs, in RCTs it is a random error that arises from an imbalance of a confounding factor or factors between treatment groups. A confounding factor is a known or unknown variable that can predict or cause the outcome of interest and is associated with the treatment allocation. For instance, compression bandaging is known to affect healing rates in venous leg ulcers and could be a confounder if it was associated with allocation to one of the treatment groups. In the HALT trial, both groups received compression as a background therapy, and there was a balance in compression bandaging at baseline.

Where randomisation in RCTs is adequately concealed, any imbalance that occurs is a consequence of random allocation. As a random error, the likelihood of confounding is minimised by sample size. The law of large numbers will ensure groups with similar distributions of demographic characteristics, if sufficient numbers are recruited and randomised. In this way the impact of unknown extraneous variables is cancelled out. Randomisation, however, will not deliver groups that are perfectly alike. Small differences are likely and assessment of differences between the groups for baseline imbalance should focus on the impact of substantial differences in variables that are prognostic. Assessment of whether the differences are statistically significant is uninformative as randomisation ensures the distribution of the variables is due to chance.

In the HALT trial, there were minor differences between the groups for factors such as age, ethnicity (Maori), relevant medical history (deep vein thrombosis, lower limb surgery, any leg fracture), and aspirin use. The 1.4 year age difference and ethnicity are unlikely to be prognostic, and the sum of all lower limb trauma was very similar in both groups (52.9% versus 53.6%). The lower rate of aspirin use in the honey-treated participants could favour the usual care group, but it has not been clearly established whether aspirin increases ulcer healing rates. Of greater concern, perhaps, was the difference between groups for mean ulcer area and mean ulcer duration, which favoured respectively the usual care group and the honey-treated group. Both factors are known to be prognostic. However, the strong correlation between these prognostic factors and the Margolis index meant that the imbalance was controlled for by adjusting for the Margolis index.
Manipulation of the data post hoc can also introduce confounding in an RCT. For instance, an "as treated" or "treatment received" analysis explores the effect of the intervention on the outcome, by reassigning participants to groups on the basis of whether they received the intervention or control treatment. Such an analysis fails to preserve the randomised allocation sequence and any observed effect could be explained by factors other than the intervention. In the HALT trial we did not conduct any "as treated" analyses, although we did conduct a "per protocol" analysis excluding participants lost to follow up or non-compliant with allocated treatment. This analysis was intended to provide guidance to patients who might ask what sort of effect might be found if one was fully compliant with treatment. ITT analyses have been criticised as being too cautious and providing inadequate information with which to inform a patient about anticipated effects if they are fully compliant. By averaging the effect across both compliant and non-compliant participants, the effect of a policy of implementation is being tested, but using the averaged effect to inform patients about the anticipated effect may under-inform the patient who intends to be fully compliant. Creating under-expectation is not as misleading as creating over-expectation and excluding participants can introduce bias. Therefore the "per protocol" analysis should be interpreted very cautiously. It is for this reason that the primary outcome was analysed using ITT and informs the main conclusions of the HALT trial.

6.3.1.3 Attrition bias

Attrition bias can arise when there are differential rates of loss in each group in an RCT. However, attrition bias is not eliminated if there are similar rates of loss in both groups, as it cannot be assumed that loss is unrelated to the treatment. Attrition bias is minimised by ensuring that there is complete follow up and by conducting ITT analyses. ITT analyses preserve randomisation and are less likely to be biased than other types of analyses, even though the method may dilute the results and deliver a conservative estimate of treatment effect. In taking the cautious approach, ITT analyses minimise the likelihood of type I error (rejecting the null hypothesis when it should be accepted). Definitions of ITT analysis vary, with debate over whether any exclusions are appropriate. In the HALT trial, ITT analysis was taken as inclusion of all participants randomised, irrespective of treatment received, adherence, withdrawal from treatment, or loss to follow up. There were no exclusions in the primary analysis. Attrition bias did not affect the results in the HALT trial because ITT analysis was used and follow up was almost complete. Although the six participants lost to follow up were in the usual care group, they
were included in the primary analysis as treatment failures. In addition, this result was robust to sensitivity analysis, where the last value for healing state for each lost participant was carried forward to the endpoint.

6.3.1.4 Recall bias

Recall bias is systematic error due to between-group differences in the recall of information or events, and the potential for such a bias is particularly pertinent for self-reported event data. Some aspects of resource utilisation that contributed to the cost-effectiveness analyses in the HALT trial were reliant on recall. For instance, participants were asked to report whether they had visited any other health worker for leg ulcer treatment or had received antibiotics for their leg ulcer during each district nursing visit. Participants were also asked to report whether they had been admitted to hospital for treatment of their leg ulcer during the treatment period. However, there is no reason to suspect that recall bias played any role in the cost analyses. The average per participant cost of antibiotics, community care and outpatient visits was similar in both the honey-treated and the usual care groups, suggesting no systematic difference. The hospital utilisation rate was different, but probably reflected the duration of hospital stay (a total of ten days in the honey-treated group versus 40 days in the usual care group), rather than the number of participants reporting hospitalisation (three participants in the honey-treated group and six participants in the usual care group). The length of hospital stay was not self-reported data, but was recorded from the participants’ discharge summary obtained by the Research Nurse.

6.3.2 External validity

A further strength of the HALT trial is the external validity, or generalisability of the study. The generalisability of the HALT trial is grounded in its pragmatic design, the heterogeneity of the study population, and the use of an active comparison, rather than a placebo.

There are two broad types of RCTs. Trials are designed either to maximise the possibility that a treatment effect will be observed (explanatory trials) or to assist clinical decision makers (pragmatic trials). Pragmatic trials aim to measure the benefits a treatment produces under naturalistic conditions, and thus are considered to be more generalisable to patients to whom the treatment might normally be offered. This aim requires that pragmatic trials reflect the heterogeneity of patients
that would normally be encountered in clinical practice and make comparisons between clinically relevant interventions.\textsuperscript{458 473 474}

The HALT trial had broad inclusion criteria, with only those unable to consent, unable to initially tolerate compression, or who had been diagnosed with diabetes, rheumatoid arthritis or peripheral arterial disease being excluded. There was no reason that honey could not be used on the latter group of patients, but it was necessary to exclude these patients as more comprehensive vascular investigations at a hospital clinic would have been necessary to establish them as candidates for the trial. This resource utilisation was not budgeted for or available across all the study centres. Being set in the community, where most leg ulcer care takes place,\textsuperscript{108} a minimum of entry criteria increased the likelihood that the HALT trial participants were similar to those that would normally be encountered in district nursing practice. Using a community-based diagnosis of venous ulceration by district nurses provided an additional enhancement as community practice is often grounded in empirical rather than definitive diagnosis. Basing the entry criteria on presenting signs and symptoms replicated normal practice and increased the diversity of the participants, overcoming the common difficulty of applying the results of trials with tightly controlled entry criteria to the heterogeneity of clinical practice.\textsuperscript{473}

Trials that make comparisons between competing clinical strategies "have the ability to alter clinical decisions profoundly" because they are grounded in the alternatives patients and health workers normally confront.\textsuperscript{473} Head-to-head comparisons of new treatments to standard or usual care overcome the difficulties associated with generalising comparisons with placebo or no treatment. In comparing honey dressings with usual care, the HALT trial could be said to be comparing the policy of initiating treatment with a honey dressing compared to using any other dressing from the range normally available to district nurses (see Table 12, p73). Thus the usual care comparison should be regarded as a complex intervention rather than a simple one.\textsuperscript{475} There was no attempt to standardise what dressings could be used for two reasons. First, whilst it would technically have been possible to use calcium alginate dressings as a comparator to truly isolate the effect of honey, this comparison would have oriented the trial more towards an explanatory design. Furthermore, calcium alginate dressings are highly absorbent and can adhere to wound surfaces as venous ulcers re-epithelialise and lose less moisture. Removing an adherent dressing can cause tissue trauma and the type of dressing used is routinely changed to prevent this event as the ulcers begin to heal and lose less moisture (pers. comm., Anita Latta, Susan McAuley). Thus it was not feasible to use
a single type of comparison dressing. Second, standardising the dressing regimen would have required the agreement of the participating centres. While such agreement may have been possible, without physically restricting the dressings available for use in the usual care group, it was unlikely that the agreement of all the individual district nurses could be obtained due to the large numbers of nurses involved. Perhaps more importantly a systematic review of dressings for wound care found little evidence to support the assertion that modern dressings are superior to traditional dressings (e.g. tulle-gauze), or that one modern dressing is superior to others for treating venous leg ulcers.476 These findings have been confirmed by a second recent review.477 Thus there seemed no justifiable rationale to restrict the dressings used in the usual care group.

Pragmatic trials are trials where context and treatment policy are intertwined.478 The naturalistic setting of the HALT trial and the use of usual care as a comparator mean that the results from this trial should have clinical applicability to the context in which most venous ulcer care takes place. Indeed it could be argued that the results of this trial are likely to be applicable no matter what the setting. Additionally, generalisability may be rather less of an issue than it is usually made out to be.479 It has been argued that health workers do not so much generalise research findings to their patients as particularise them, and the critical question in applying research findings is to decide whether a patient is so different from participants included in a study that the results cannot be applied to the individual.464480 Thus the findings of the HALT trial should be as applicable to patients with venous leg ulcers in other settings and contexts as to settings similar to that of the HALT trial.

6.4 Study limitations

The HALT trial was subject to three potential limitations: lower than anticipated recruitment, duration of follow up and unblinded outcome assessment.

6.4.1 Low recruitment rate

Although the third largest leg ulcer trial, after the ESCHAR and VenUS I trials,153201 the HALT trial did not reach its recruitment target of 400 participants. Recruitment rates were closely monitored during the HALT trial, and while two centres recruited at the anticipated weekly rate, two of the study centres (Auckland and the Waikato centres) did not. The Auckland centre recruited about half its target, whilst the Waikato centre recruited about 80% of its target. The reason for the lower recruitment rates in these two centres is not known. Despite extending the
recruitment period from 52 weeks to 64 weeks, only 92% of the target recruitment was achieved. Continuing recruitment after 64 weeks was not possible due to the need to return the Research Nurses to their normal positions. The target of 400 participants did incorporate a 5% allowance for loss to follow up, but even if the target had been achieved with no loss to follow up, the sample size would still have been inadequate to observe a 6% absolute difference in healing rates.

6.4.2 Duration of follow up
The outcome "proportion healed" at any specific time point may not deliver to patients the type of information that they want to know. Nelson, et al. argued that patients do not want to know what the chances of the ulcer healing by 12 weeks are, but rather want to know about prognosis over longer timeframes. The same authors also suggest that selection of specific time points may deliver a misleading result as the selection is an arbitrary decision in that it does not capture the total survival experience of the groups, unlike a time-to-event analysis. At issue in the HALT trial is whether it was likely that a small non-significant effect at 12 weeks would have become a larger significant effect beyond 12 weeks. Such an effect occurred in the VenUS I trial where two different compression bandages were compared over one year's follow up. There was no significant difference between the groups when the outcome was "proportion healed ulcers at 12 weeks", but there was a significant difference when the outcome was "proportion healed at 24 weeks". In the HALT trial, the 12-week outcome was selected for three reasons. First, the 12 week healing rates were known for one of the New Zealand leg ulcer services, which provided the control event rate for the sample size calculation. Second, although there are no guidelines for outcome selection in wound care trials, many other trials of treatments for venous leg ulcers have used 12 week healing rates as the primary endpoint. Third, the resource implications of longer term follow up may have precluded the HALT trial from being funded. Although, the Kaplan-Meier plot seems to indicate convergence of the groups in the HALT trial at 12 weeks, a survival analysis cannot estimate treatment effects beyond the period of follow-up.

6.4.3 Blinding
Information bias, also called ascertainment bias and detection bias, is a flaw in measurement that results in a different quality of information between the groups being compared, or inaccuracy in estimation of effects if the bias is non-differential. Trial participants have expectations of novel treatments, and expectation can influence research findings, especially where elements of subjectivity are involved in
the outcome assessment. The simplest means to prevent information bias is to ensure that parties involved in a trial are blind to treatment allocation. Trials described as "double blind" yield smaller treatment effects than trials not described as such. Unfortunately, there has been no assessment of the effect of the extent of blinding (i.e. single versus double blinding) on treatment estimates.

It is not possible to blind participants and clinicians to treatment allocation in many wound care trials, as the interventions are obvious to participants, treatment providers and investigators. For instance, participants and treatment providers cannot be blinded in a trial comparing short stretch single layer compression bandage with a four-layer elastic bandage, although blinding the outcome assessor in such trials is possible. In the HALT trial, blinding the outcome assessor was not feasible, as the assessor could determine from staining around the ulcer, and possibly from odour, whether or not honey had been used. However, blinded verification of healing state was possible. In the HALT trial, the primary outcome involved a clinical judgment as to whether the ulcer was healed or remained open. Therefore the ulcers (or ulcer site) were photographed by the Research Nurse at the 12 week assessment. The photographs were also reviewed for blinded verification of healing status by a gerontologist (Dr Yogini Ratnasabapathy) not involved with the trial. There was substantial agreement between the Research Nurse and the blinded reviewer, similar to the kappa (0.68) found in a study of agreement between dermatologists assessing healing in photographs of venous ulcers. The absence of perfect agreement indicates an element of subjectivity was involved in the assessment of healing state. To what extent this reflects information bias on the part of the Research Nurse as opposed to difficulty in assessing healing state from a photograph cannot be determined. For instance, the photograph below (Figure 15) was assessed by the blinded reviewer as being not healed, whereas the Research Nurse.

Figure 15: Example of ulcer photograph assessed as not healed by blinded reviewer but reported as healed by the Research Nurse.
Nurse reported it as healed. Difficulty in accurately assessing photographic records of healing may lead to more false negatives than false positives. Margolis, et al. (1996) found a lower level of sensitivity (84%) than specificity (92%) in their study on agreement, suggesting that where misclassification occurs the error is more likely to lead to a healed wound being categorised as an unhealed (false negative) than an unhealed wound being categorised as healed (false positive).  

6.5 Consistency with previous research

Interest in the potential efficacy of honey in wound care has intensified in the last 10 years. The number of citations on this topic listed in MEDLINE increased from eight for the period 1980-1989 to 66 for the period 1995-2004. A similar pattern is observed for both EMBASE and CINAHL, with citations for the same periods increasing from six to 48 and from zero to 47 respectively. However, these reports were mainly single case reports or case series, and while useful for hypothesis generation, caution should be exercised considering applying such reports to clinical practice, given the lack of any sort of contemporaneous control. The systematic review in Chapter 3 found that there were no previous trials of honey in venous leg ulcers. The 18 studies included in the review were mostly positive findings in contrast to the results from the HALT trial. It is therefore important to consider how the HALT trial differed from the relevant studies in the review and how the HALT trial findings compare to findings from other relevant research.

6.5.1 Clinical outcomes

6.5.1.1 Ulcer healing

Only two other trials have considered the impact of honey on leg ulcer healing, and neither trial was comparable to the HALT trial. One trial recruited participants with burns or with leg ulcers of any aetiology, and compared a honey dressing to treatment with silver sulfadiazine, a topical antibiotic. Topical antibiotics are not advocated for treating leg ulcers in New Zealand. No other information about ulcer treatment was presented. The study did not analyse the data from burn and ulcer participants separately, therefore precluding any comparison with the findings from HALT trial. The second trial was a three arm trial that compared honey to a topical phenytoin paste, or a mixed paste of honey and phenytoin. Again, this regimen is not a treatment routinely used in New Zealand. Additionally, assignment of participants was non-random (allocation by alternate days). The trial did measure change in ulcer area, but like the HALT trial, the mean reduction in ulcer size was
not significant, although the endpoint in this trial was assessed at four weeks. However, the study specifically excluded participants with venous ulcers.

There is one other trial (n=120) of honey in venous leg ulcers currently in progress, but results are not expected until mid-2007.486 Like the HALT trial, the honey product being used is ApiNate and follow up is for 12 weeks. The primary outcome in this trial is debridement at four weeks, while ulcer healing at 12 weeks is a secondary outcome. It is unclear whether treatment with honey in this trial continues for the entire period of follow up. Combination of this trial with the HALT trial in a meta-analysis may be possible if the trials are sufficiently alike in design, as the trialist has indicated early support for the possibility (pers. comm., Georgina Gethin). Such a meta-analysis would deliver more precise information on the effect of manuka honey dressings in venous ulcer healing.

It is inappropriate to compare the findings of the HALT trial to trials of honey for treating acute wounds, such as burns. Acute and chronic wounds are very different wound environments.304 364 487 488 Acute wounds are the result of an exogenous insult and would normally follow a timely and orderly path towards repair, marked by progress through inflammatory, proliferative and remodelling phases.364 489 Chronic wounds are usually symptomatic of underlying pathology. This pathology can be either endogenous (e.g. venous insufficiency) or exogenous (e.g. infection), although the chronic wound may be initiated by a minor trauma, such as a scratch. Chronic wounds also follow a disordered path that may last years, if healing takes place at all.364 Prolonged inflammation is thought to be the major driver of chronicity, mediated by the cytokines tissue necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).487 One hundred-fold increases in TNF-α and IL-1β have been observed between the wound fluids of surgically created and chronic wounds,487 and significantly elevated levels of these proinflammatory cytokines have been reported in non-healing venous ulcers compared to healing venous ulcers.490 491 These cytokines also upregulate matrix metalloproteinase expression causing an imbalance between the proteinases normally responsible for tissue degradation during reparative phases and their inhibitors (e.g tissue inhibitors of metalloproteinases).487 Metalloproteinase activity has been found to be elevated 30-fold in chronic wounds when compared to acute wounds and is elevated in venous ulcers.492-494 Jelly bush honey, manuka honey and New Zealand pasture honey have all been found to increase TNF-α and IL-1β expression in cell lines,265 although expression of TNF-α may be dependent on the concentration of
honey. It is therefore possible that this feature of manuka honey could delay healing in venous ulceration.

6.5.1.2 Incidence of infection

Of the two other honey trials that have enrolled participants with leg ulcers, one trial did not report on the incidence of infection. The other trial did not separate leg ulcers from burns in the analysis, but reported on control of infection, although this term was not operationally defined. Unlike the HALT trial, this study found honey controlled infection rates with 8% of cases in the honey treated group having "persistent infection" after seven days treatment compared with 76% in the group treated with SSD dressings (p<0.05). However, infection in this study appears to have been associated with the presence of any bacterial species on a wound swab and bacterial presence may simply represent colonisation of the wound rather than infection.

The overall incidence of infection in the HALT trial was higher than expected at 19.5%. The point prevalence of infection in venous ulceration has been estimated to be 3%, but this estimate was obtained from a cross-sectional study of leg ulcer prevalence. Actual rates of infection over time can be inferred from trials that have reported reasons for withdrawal from treatment. In a systematic review of trials of dressings for venous leg ulcers, eight of the 27 trials reported infection as amongst the reasons for withdrawal. The rates ranged from 3% to 13%, but it is likely that these are underestimates of the actual rates of infection in the trials, unless the protocols dictated withdrawal when infection was observed. One recent trial (VenUS I) comparing short stretch compression bandaging to four layer compression bandaging reported an infection rate of 20%. The rate of infection was comparable to that of the HALT trial, as was the operational definition of infection diagnosis, reflecting current district nursing practice in the United Kingdom and New Zealand. More recently, the biopsy-confirmed infection rate in 614 patients with venous leg ulcers being screened for participation in a multicentre clinical trial in the United States of America was reported as 19.9%. Therefore, the incidence of infection in the HALT trial is very similar to that observed in other venous ulcer trials.

6.5.1.3 Health-related quality of life

No other trial of honey in the treatment of any wound has considered the impact of treatment on HRQoL. Other trials of treatments for venous leg ulceration have assessed impacts on HRQoL using SF-36, EQ5D and CVUQ, but there
would be little benefit in making comparison with the findings of these studies as they assessed the impact of treatments other than honey. However, one aspect of these studies worthy of comparison with the HALT trial is the different response rates. The response rates are pertinent, as it has been suggested by other researchers that the SF-36 is too burdensome an instrument for significant proportions of older adults, and that SF-12 offers a more concise and simpler tool. The 98% response rate in the HALT trial compared very favourably with the response rate of 86% obtained in the one other trial that used SF-36 as part of a battery of four HRQoL questionnaires in participants with venous ulcers and reported response rates. The higher response rates in the HALT trial may reflect differences in the method of obtaining the information as data collection was face-to-face in the HALT trial, whereas in Morrell, et al., data collection was via postal return. Postal surveys are known to have relatively low response rates. The response rates in the HALT trial also compare favourably with the one trial that has used SF-12 in participants with venous ulcers, where the response rates were 77% at three months. Again the differences in response rates between the HALT trial and the VenUS I trial may reflect the use of postal return.

The utility of changes in scores on HRQoL domains has been an issue for clinical research. Although there were no statistically significant differences between group scores on either the EQ5D or the CXVUQ in the HALT trial, there was a difference between the groups for physical functioning on the SF-36 that favoured the honey-treated group. This difference remained after adjustment for baseline imbalance. One explanation for this result is the possibility that it was a chance effect given the number of domains being measured. Even if it was a real effect, its significance can be assessed by considering the impact of the single domain score on the physical component summary (PCS) score. The PCS provides an overview of the impact of leg ulceration on general physical status. PCS scores are standardised so that the mean is 50 with a standard deviation of ten. Each point away from 50 represents 1/10th of a standard deviation. The PCS scores for both treatment groups in the HALT trial were only about 1/10th of a standard deviation different and not statistically significant. These data suggest that if the between-group difference on physical functioning was real, its overall impact on general physical status was minimal.
6.5.1.4 Adverse events

In the two trials of honey in leg ulcers, there were no reports of adverse events in one trial,\(^2_{48}\) and the adverse events were not reported separately for burns and leg ulcers in the other trial.\(^3_{92}\) Hypergranulation and contractures were reported in the honey-treated group (one of each event), but in smaller numbers than in the SSD-treated group (three of each event). Local irritation and hypertrophic scarring were reported in the comparison group (one and seven respectively), but not in the honey-treated group. The small number of events and the probability that the events were more likely to be associated with the burns patients rather than the leg ulcer patients suggests the information is probably not meaningful for comparison with the HALT trial in any event.

There were no unexpected adverse events and no serious adverse events related to honey reported in the HALT trial. Pain was the only adverse effect with significantly more reports in the honey-treated group. Pain (including itching and burning sensations) has been observed in other clinical studies of honey.\(^3_{24}\) \(2_{52}\) \(3_{25}\) \(3_{87}\) Thirty-five percent of patients with venous ulcers in a 40-patient case series reported continuous or transient pain on application of the honey, which is comparable to the 25% of honey-treated participants in the HALT trial who reported pain. It does seem that pain was tolerated, as only four of the 31 participants who withdrew from honey treatment gave pain as their reason for withdrawal.

The district nurses attending participants in the HALT trial were encouraged to report any unexpected adverse event, whether they believed it was related to the treatment or not. There were more reports of adverse events in the honey-treated group than in the usual care group. This finding is to be expected, given that the HALT trial had an open label design and participants were likely to be more closely monitored for treatment problems when a new treatment is being introduced. More adverse events in the treatment arm were also reported in the VeNUS I trial, another open label leg ulcer trial where a new bandaging system was being compared to a system participating study centres were already familiar with.\(^1_{53}\) The relative risk of adverse events was similar to that of the HALT trial (1.2 compared to 1.3). Other open label leg ulcer trials have reported considerably lower numbers of adverse events than either the HALT trial or VeNUS I, but these trials appear to have focused only on reporting events related to ulceration, rather than any untoward medical events.\(^1_{54}\) \(5_{04}\) \(5_{05}\)
6.5.1.5 Cost-effectiveness

There have been no other trials of honey in leg ulcers that evaluated the costs of treatment with honey. Only one other trial of patients with shallow wounds and abrasions has considered the cost of treatment with honey compared with an alternative regimen. In this trial conducted in South Africa, the comparison treatment was a hydrogel (IntraSite) and honey was found to be a cheaper treatment (ZAR 0.5 versus ZAR 12.1). However, the only direct cost considered was the cost of products and as there is no information on the frequency of health worker visits, it cannot be assumed that the levels of inputs were similar in both groups. In addition, no confidence interval was calculated for the between-group difference in costs, and so the level of uncertainty associated with the cost analysis cannot be assessed. In the HALT trial, honey-impregnated dressings were a more costly treatment than usual care when only the dressing costs were considered and this finding remained stable across all the sensitivity analyses. The difference in the cost analyses from the two trials is likely to be attributable to the costs of the honey, which was much more expensive in the HALT trial at NZ$11.50 per 30 gm honey dressing. The cost of an equivalent weight dressing in the South African trial would have been ZAR 0.4, or less than NZ$0.1 in current terms (8 December 2006).

The cost-effectiveness of honey-impregnated dressings should not be considered to have been established by the HALT trial for two reasons, despite base case suggesting honey was a cheaper treatment when the full costs of treatment were incorporated into the analysis. First and foremost, the confidence interval in the primary analysis incorporated zero, so effectiveness has not been established. Although standard economic analyses would traditionally consider a dominant strategy to be one where the treatment is associated with point estimates of a cost decrease and a benefit increase, this approach would ignore the uncertainty around point estimates for the primary outcome and the ICER in the HALT trial. Critical appraisal guidelines for cost-effectiveness studies in clinical epidemiology require that a treatment’s effectiveness needs to be clearly established, before cost-effectiveness can be considered valid. Second, the analysis was sensitive to the exclusion of hospital costs. While hospitalisation is a component of leg ulcer care, the frequency of hospitalisation will be determined by local practice. The proportion of leg ulcer care delivered as inpatient hospital care has been reported as ranging from 1% to 13%, although the more recent of these data are only dated from the early 1990s. Hospitalisation in the HALT trial was a rare occurrence, with 2% of
the total number of participants receiving in patient treatment during the 12 week intervention. The small difference between the groups was likely to have been due to the play of chance, justifying testing the sensitivity of the economic analysis to the exclusion of these costs.

6.5.1.6 Ulcer recurrence

There have been no other trials that have assessed the impact of honey on leg ulcer recurrence. The possibility that honey might have an impact on ulcer recurrence was suggested by two animal studies that found tissue from honey-treated wounds had greater tensile strength than control wounds,\(^{288, 289}\) although another study has since found no difference in tissue strength between control and treated wounds.\(^ {290}\) The overall accuracy of the ulcer recurrence data in the HALT trial is limited by the information being self-report, as there was no objective assessment of whether the recurrent ulcer was at the site of the healed reference ulcer. Thus the data should be interpreted with considerable caution.

6.6 Implications of the HALT trial

6.6.1 Clinical implications

The findings of the HALT trial do not support the routine use of honey-impregnated dressings for treating venous leg ulcers. The clear clinical implication of the findings is that the focus of venous ulcer treatment should remain compression bandaging, not dressing selection. The findings of the HALT trial are consistent with two systematic reviews of dressings for wound care, both of which found little evidence to support the assertion that modern dressings are superior to traditional dressings (e.g. tulle-gauze), or that one modern dressing is superior to others for treating venous leg ulcers.\(^ {476, 477}\) Current clinical practice guidelines recommend simple, comfortable and cheap dressings should be used under compression,\(^ {151, 152, 485}\) and there should be no reason to reject these recommendations, unless there is clear empirical need and other treatments have failed.

The results of the HALT trial should be considered as applying to the use of all honeys in the treatment of venous ulcers until evidence suggests otherwise. The effect of different honeys on healing has not been compared in vivo in either the animal or the human model. The effect of different honeys on healing in vitro has also received relatively little attention in comparison to antibacterial activity. The activity of jelly bush honey, manuka honey and New Zealand pasture honey on cytokine expression has been compared to artificial honey.\(^ {265, 266}\) Although jelly bush
honey did produce significantly greater cytokine expression, all three honeys increased TNF-α, IL-1β and IL-6 expression in comparison to artificial honey. However, in vitro evidence is only relevant to guiding research questions in humans and should not have any bearing on current clinical practice.

The HALT trial findings should provide guidance for the purchasing policies of health providers. The absence of any clear effect strongly suggests that health providers should not purchase honey-impregnated dressings for general supply or routine use. Purchasers should resist any interpretation of the findings that suggests that the HALT trial established the equivalence of honey-impregnated dressings with usual care. Although such an interpretation may be tempting, an equivalence trial is designed specifically to test whether a treatment produces an effect that is sufficiently close to that of the active comparison as to be considered clinically equivalent. The margin of difference that is considered clinically equivalent must be specified a priori and the rationale for the margin justified. Such trials, if adequately powered, must recruit substantially more participants than trials designed to establish difference, as the bounds of the confidence interval must not cross the threshold that is stated to be clinically equivalent. The size of a trial attempting to demonstrate equivalence is dependent on the range of values assumed to be equivalent. For instance, assuming a control event rate of 50% healing at 12 weeks, an alpha of 0.05, a beta of 0.90, and a treatment effect of ±5% being clinically equivalent, the total sample size would need to be 4,204 to establish equivalence. If ±2.5% was set as the value for equivalence, the sample would need to be 16,817, whereas the sample size would need to be 1,051 if equivalence was assumed to be ±10%.

More attention needs to be given to current treatments which have proven efficacy as adjuvants to compression bandaging for treating venous ulceration. These treatments are outlined in section 2.6.2 (Pharmacological treatments for venous ulcers) and include pentoxifylline, MPFF and sulodexide. However, access to these treatments is limited in New Zealand, with the exception of pentoxifylline. Despite pentoxifylline increasing the relative risk of ulcer healing by almost 60%, it is not widely used in New Zealand. For people at risk of delayed healing (for instance, those that score one or two on the Margolis index), early intervention with pentoxifylline has been recommended, but only one participant in the HALT trial had been prescribed pentoxifylline at baseline. Fifty-four percent of participants in the HALT trial scored one or two on the Margolis index and potentially could
benefit from treatment with pentoxifylline, a medication that is subsidised by PHARMAC.

6.6.2 Research Implications

The HALT trial established that honey-impregnated dressings have little or no effect on venous ulcer healing at 12 weeks. Further study is justified to more precisely establish the possible size of a treatment effect. There is currently a 120 participant trial underway in Ireland, which has used the same dressing in participants with venous ulcers and is due to report in 2007. Combination of the two trials in a meta-analysis might be possible if the trials are sufficiently alike in design. Such a meta-analysis would be able to rule out a 15% treatment effect, assuming the same event rate as the HALT trial.

Future trials should consider longer follow up periods than 12 weeks in case there is a slowly accumulating treatment effect. Six month or one year follow up may be more appropriate following the experience of the VenUS I trial. Trials should also be adequately powered to observe a more modest effect than that anticipated in the HALT trial. The similarity of effect sizes in the ITT and per-protocol analyses, suggest that a 12-week effect of between 5% and 10% needs to be considered.

To ensure future trials can contribute to systematic reviews, triallists should make certain their reports are consistent with the requirements of the Consolidated Statement on Reporting of Trials. Trials should also consider using pragmatic rather than explanatory study designs in order to enhance the clinical applicability of the findings.

Clinical scientists should also have a role in future investigations. There is uncertainty over the role of cytokines in venous ulcer healing. There is a possibility that non-healing venous ulcers, in particular, may over-express cytokines. Honey has been shown to increase expression of the same cytokines and it is therefore possible that the use of honey-impregnated dressings in slow-to-heal or non-healing venous ulcers may further delay healing. The effect of honey on cytokine expression in slow-to-heal or non-healing venous ulcers needs to be established before further trials are conducted in this field.
CHAPTER 7

Conclusion

"Put the hydraulics right and the ulcer will take care of itself; this is the gist of the method." 144

Dickson-Wright, 1930

The main aim of this thesis was to investigate the effect of honey on wound healing by conducting [1] a systematic review of trials of honey in wound care and [2] a randomised controlled trial of honey-impregnated dressings for treatment of venous leg ulcers.

The findings from the systematic review were that:

- Publication bias is likely to be present.

- Honey may be an effective treatment for partial thickness burns in comparison to conventional dressing materials, such as paraffin gauze and polyurethane film dressings.

- Honey may delay healing in mixed partial and full thickness burns.

- Honey does not appear to benefit healing in other acute wounds, such as lacerations and abrasions.

- No recommendation could be made with respect to the treatment of chronic wounds with honey.

The findings of the HALT trial were that:
Honey-impregnated dressings did not significantly increase the proportion of patients with healed leg ulcers at 12 weeks, or have any significant positive effect on time to healing, change in ulcer area, or the incidence of infection or overall health-related quality of life.

Using honey-impregnated dressings was more expensive when community care costs were considered, but uncertainty remains about the cost-effectiveness of honey-impregnated dressings when the costs of hospitalisation are included.

Participants allocated to treatment with honey-impregnated dressings experienced more pain than control participants, but this appears to have been tolerated in most instances.

The implications of these findings are:

- At present honey cannot be recommended for clinical use in chronic wounds, such as venous leg ulcers. A reappraisal of the clinical implications of this thesis is required after the completion of a meta-analysis of the HALT trial and the Irish trial. This meta-analysis will also guide any research implications.

- A definitive trial investigating honey for treatment of burns is warranted. While the systematic review described in this thesis provided some encouraging results, there remains the possibility that such results were influenced by publication bias.
Appendix 1

Additional tables
### APPENDIX Table 1: Costs for miscellaneous resource utilisation (2005)

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<tr>
<th>Item</th>
<th>Source</th>
<th>Unit cost (NZ$)</th>
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<td>Subsidy for general practitioner consultation</td>
<td>Ministry of Health</td>
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APPENDIX Table 2: Retail unit cost (2005) of dressings used in different study centres to treat participants' leg ulcers.
### APPENDIX Table 2 (continued): Retail unit cost (2005) of dressings used in different study centres to treat participants’ leg ulcers

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</tr>
<tr>
<td>Varolast</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>Smith &amp; Nephew</td>
<td>12.00</td>
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<tr>
<td>Viscopaste</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>Smith &amp; Nephew</td>
<td>15.78</td>
<td></td>
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<tr>
<td>Zip zoc</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>Smith &amp; Nephew</td>
<td>15.21</td>
<td></td>
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</tr>
</tbody>
</table>
# APPENDIX Table 4: Unit cost (2005) of antibiotics used to treat participants’ infected leg ulcers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Dose (grams)</th>
<th>Price, NZ$ (subsidy)</th>
<th>Full subsidy</th>
<th>Unit price (NZ$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin</td>
<td>Apo-Amoxicin</td>
<td>500</td>
<td>17.33</td>
<td>Yes</td>
<td>0.0347</td>
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<tr>
<td>Amoxycillin + potassium clavulanate</td>
<td>Augmentolin</td>
<td>20</td>
<td>6.40</td>
<td>Yes</td>
<td>0.3200</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Ranbaxy-cefaror</td>
<td>100</td>
<td>28.90</td>
<td>Yes</td>
<td>0.2890</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Keflex</td>
<td>20</td>
<td>6.00</td>
<td>Yes</td>
<td>0.3000</td>
</tr>
<tr>
<td>Phenoxy-methylpenicillin</td>
<td>Celecss VK</td>
<td>50</td>
<td>8.15</td>
<td>Yes</td>
<td>0.1630</td>
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<tr>
<td>Ciprofloxxin</td>
<td>Cipflox</td>
<td>28</td>
<td>8.31</td>
<td>Yes</td>
<td>0.2968</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Dalacin C</td>
<td>16</td>
<td>11.39</td>
<td>Yes</td>
<td>0.7119</td>
</tr>
<tr>
<td>Clotrimazole 1% cream (tube)</td>
<td>Clomazole</td>
<td>15</td>
<td>1.83 (0.55)</td>
<td>No</td>
<td>0.5500</td>
</tr>
<tr>
<td>Co-trimoxazole + sulphamethoxazole</td>
<td>Trisul</td>
<td>500</td>
<td>17.00</td>
<td>Yes</td>
<td>0.0340</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>Diclocil</td>
<td>24</td>
<td>8.65 (3.83)</td>
<td>No</td>
<td>0.1596</td>
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<tr>
<td>Doxycycline</td>
<td>Doxine</td>
<td>250</td>
<td>10.10</td>
<td>Yes</td>
<td>0.0324</td>
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<tr>
<td>Erythromycin</td>
<td>ERA</td>
<td>100</td>
<td>44.58 (29.90)</td>
<td>No</td>
<td>0.2990</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>Staphlex</td>
<td>500</td>
<td>68.50</td>
<td>Yes</td>
<td>0.1370</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Trichozole</td>
<td>100</td>
<td>17.50</td>
<td>Yes</td>
<td>0.1750</td>
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<tr>
<td>Roxithromycin</td>
<td>Romicin</td>
<td>50</td>
<td>29.90</td>
<td>Yes</td>
<td>0.5980</td>
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<tr>
<td>Trimefoprim</td>
<td>TMP</td>
<td>50</td>
<td>7.90</td>
<td>Yes</td>
<td>0.1580</td>
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</tbody>
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**APPENDIX Table 5: Costs per hour (2005) for health professionals consulted by participants**

<table>
<thead>
<tr>
<th>Practitioner</th>
<th>Salary (NZ$)</th>
<th>Source</th>
<th>Cost/hour (NZ$)</th>
<th>Direct:indirect care ratio</th>
<th>Duration of contact (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>District Nurse</td>
<td>53,851</td>
<td>NZNO MECA 2004-2006, Registered Nurse, Step 5</td>
<td>25.89</td>
<td>1:1.21</td>
<td>-</td>
</tr>
<tr>
<td>Nurse Specialist</td>
<td>53,851</td>
<td>NZNO MECA 2004-2006, Registered Nurse, Step 5</td>
<td>25.89</td>
<td>1:0.55*</td>
<td>30</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>93,000</td>
<td>NZNO MECA 2004-2006, Senior Nurse, Step 8</td>
<td>44.58</td>
<td>1:0.55</td>
<td>30</td>
</tr>
<tr>
<td>Practice Nurse</td>
<td>43,680</td>
<td>NZNO 2004-2005 Practice Nurse MECA Practice Nurse 5th year</td>
<td>21.00</td>
<td>1:0.18</td>
<td>13</td>
</tr>
<tr>
<td>Laboratory Nurse</td>
<td>43,680</td>
<td>NZNO 2004-2005 Practice Nurse MECA Practice Nurse 5th year</td>
<td>21.00</td>
<td>1:0.18*</td>
<td>13</td>
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<tr>
<td>Orthotist</td>
<td>56,638</td>
<td>Allied Health MECA 2006</td>
<td></td>
<td>0.73*</td>
<td>29</td>
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<tr>
<td>Medical Officer (Registrar)</td>
<td>114,540</td>
<td>DHB Resident Doctors MECA 2005-2006 Year 5, Category A</td>
<td>45.89</td>
<td>1:0.55*</td>
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<tr>
<td>Medical Officer Specialist Scale (Medical)</td>
<td>137,105</td>
<td>DHB Medical Specialists MECA 2006</td>
<td>54.93</td>
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<td>Medical Officer Specialist Scale (Surgical)</td>
<td>137,500</td>
<td>DHB Medical Specialists MECA 2006</td>
<td>54.93</td>
<td>1:0.35</td>
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* Assumed same ratio as for nurse practitioners
* Assumed same ratio as for practice nurses
* Assumed same ratio as for community physiotherapists
### APPENDIX Table 6 Resources consumed by treatment group

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<thead>
<tr>
<th>Resource</th>
<th>Honey</th>
<th>Usual care</th>
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<tr>
<td>Drugs (total number of tablets)</td>
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<td></td>
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<tr>
<td>Penicillins</td>
<td>910</td>
<td>1,375</td>
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<tr>
<td>Cephalosporins</td>
<td>69</td>
<td>55</td>
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<tr>
<td>Sulfonamides</td>
<td>310</td>
<td>372</td>
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<tr>
<td>Macrolides</td>
<td>128</td>
<td>319</td>
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<tr>
<td>Lincosamides</td>
<td>0</td>
<td>36</td>
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<tr>
<td>Fluoroquinolones</td>
<td>124</td>
<td>142</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>14</td>
<td>45</td>
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<tr>
<td>Antifungals</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td><strong>District nursing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing visits</td>
<td>2,316</td>
<td>2,196</td>
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<tr>
<td>Wound swabs</td>
<td>61</td>
<td>55</td>
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<tr>
<td><strong>Dressings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional</td>
<td>173</td>
<td>449</td>
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<tr>
<td>Modern</td>
<td>181</td>
<td>657</td>
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<tr>
<td>Medicated</td>
<td>604</td>
<td>1,378</td>
</tr>
<tr>
<td>Honey</td>
<td>1,957</td>
<td>2</td>
</tr>
<tr>
<td>Dressing packs</td>
<td>2,316</td>
<td>2,196</td>
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<tr>
<td><strong>Compression systems</strong></td>
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<td></td>
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<tr>
<td>Compression stockings</td>
<td>2</td>
<td>8</td>
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<tr>
<td>Proprietary multi-layer</td>
<td></td>
<td></td>
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<tr>
<td>Profore</td>
<td>525</td>
<td>587</td>
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<tr>
<td>Proguide</td>
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<td>39</td>
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<tr>
<td>Prolite</td>
<td>106</td>
<td>53</td>
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<tr>
<td>Non-proprietary multi-layer</td>
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<tr>
<td>Orthopaedic wool</td>
<td>1,086</td>
<td>1,154</td>
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<tr>
<td>Crepe bandage</td>
<td>1,089</td>
<td>1,198</td>
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<tr>
<td>Elastic bandage</td>
<td>587</td>
<td>639</td>
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<tr>
<td>Cohesive</td>
<td>1,015</td>
<td>1,047</td>
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<tr>
<td>Proprietary single layer</td>
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<tr>
<td>Short stretch</td>
<td>146</td>
<td>69</td>
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<td>Long stretch</td>
<td>228</td>
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<td><strong>Outpatient consults</strong></td>
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<td>Consultant</td>
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<td>Nurse practitioner</td>
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<td>Registrar</td>
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<td>Other</td>
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<td>8</td>
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<td><strong>Community care</strong></td>
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<td>General practitioner consult</td>
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<td>63</td>
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<td>Nurse specialist consult</td>
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<td>1</td>
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<td>0</td>
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<tr>
<td>Laboratory nurse consult</td>
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<td>1</td>
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<td><strong>Hospitalisation</strong></td>
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<tr>
<td>Total days</td>
<td>10</td>
<td>40</td>
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</tbody>
</table>

Traditional dressings included absorbent gauze dressings and non-adherent dressings. Modern dressings included hydrogels, hydrocolloids, hydrofibres, calcium alginites and polyurethane foams. Medicated dressings included iodophor dressings, silver-impregnated dressings and zinc paste bandages.
Appendix 2

Systematic review data extraction form
### Study Details

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<th>Column</th>
<th>Value</th>
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### Notes

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Cochrane Systematic Review

Data extraction form

Honey as a topical treatment for wounds

Reviewer initials: [ ]

Date of data extraction: [ ] [ ] [20]
### Quality assessment

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<tr>
<td></td>
<td></td>
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<td>Randomisation</td>
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**If No, method of allocation**

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<thead>
<tr>
<th>14. Allocation concealment</th>
<th>Adequate</th>
<th>Uncertain</th>
<th>Inadequate</th>
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</table>

| 15. Participants blinded    |          |           |            |
| 16. Investigators blinded   |          |           |            |
| 17. Outcome assessor blinded|          |           |            |
| 18. Complete follow-up      |          |           |            |
| 19. Intention to treat analysis |      |           |            |
| 20. Balanced baseline characteristics of participants | | | |

### Participants

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
<th>Total</th>
<th>Tick if unknown</th>
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<tbody>
<tr>
<td>21. Male</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>22. Mean age</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>23. Median age or SD</td>
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<td></td>
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<td>24. Age range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. Other</td>
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<td></td>
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<td></td>
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</tbody>
</table>

27. Characteristics of patient population (inclusion criteria):

28. Characteristics of patient population (exclusion criteria):
Trial Design

29. Type of RCT (tick ONE only)
   - ○ Parallel
   - ○ Cross over

30. Duration of treatment: ____________________________

31. Duration of follow-up (post treatment to study end): ____________________________

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<tr>
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<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td>32.</td>
<td>Compliance measured</td>
<td>Treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If Yes, give % compliant

Intervention

33. Treatment:

   Product composition: ____________________________

   Dose: ____________________________

   Other: ____________________________

   Brand: ____________________________

   Frequency: ____________________________

34. Comparison:

   Product composition: ____________________________

   Dose: ____________________________

   Other: ____________________________

   Brand: ____________________________

   Frequency: ____________________________

35. Co-intervention
   - ○ Yes
   - ○ No

   If Yes, describe
   ____________________________________________
   ____________________________________________
   ____________________________________________
   ____________________________________________
### Outcome measures

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<tr>
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<th>No</th>
<th>Comments (eg. method of measurement)</th>
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<td>36.</td>
<td>O</td>
<td>O</td>
<td>Complete healing</td>
</tr>
<tr>
<td>37.</td>
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<td>O</td>
<td>Time to healing</td>
</tr>
<tr>
<td>38.</td>
<td>O</td>
<td>O</td>
<td>Infection</td>
</tr>
<tr>
<td>39.</td>
<td>O</td>
<td>O</td>
<td>% change in wound size</td>
</tr>
<tr>
<td>40.</td>
<td>O</td>
<td>O</td>
<td>% graft take</td>
</tr>
<tr>
<td>41.</td>
<td>O</td>
<td>O</td>
<td>Pain</td>
</tr>
<tr>
<td>42.</td>
<td>O</td>
<td>O</td>
<td>Quality of life</td>
</tr>
<tr>
<td>43.</td>
<td>O</td>
<td>O</td>
<td>Adverse events (please list)</td>
</tr>
</tbody>
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### Flow diagram

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<tr>
<th>No.</th>
<th>Treatment</th>
<th>Control</th>
<th>All</th>
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<tr>
<td>44.</td>
<td>Number eligible</td>
<td></td>
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<tr>
<td>45.</td>
<td>Excluded or withdrew pre-randomisation</td>
<td></td>
<td></td>
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<tr>
<td>46.</td>
<td>Number randomised</td>
<td></td>
<td></td>
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<tr>
<td>47.</td>
<td>Lost to follow-up or excluded post-randomisation</td>
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<tr>
<td>48.</td>
<td>Withdrawn</td>
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<td></td>
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<tr>
<td>49.</td>
<td>Number analysed at treatment end</td>
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<td></td>
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<tr>
<td>50.</td>
<td>Number analysed at end follow-up</td>
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</table>
### Dichotomous results at end of treatment

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td># assessed</td>
<td># with outcome</td>
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<tr>
<td>51. Primary outcome</td>
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<td>52. Secondary outcomes</td>
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<td>Control</td>
<td>Treatment</td>
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<tr>
<td>Mean</td>
<td>SD/SE</td>
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<td>N</td>
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</table>

<table>
<thead>
<tr>
<th>Continuous results (baseline)</th>
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</thead>
<tbody>
<tr>
<td>53. Primary outcome</td>
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<tr>
<td>54. Secondary outcomes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous results (end treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55. Primary outcome</td>
</tr>
<tr>
<td>56. Secondary outcomes</td>
</tr>
</tbody>
</table>
### Time to event results

57. Event:

<table>
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<tr>
<th>Time</th>
<th>Treatment</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
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<td>N = [ ]</td>
<td>N = [ ]</td>
</tr>
<tr>
<td></td>
<td>N with event</td>
<td>N w/out event</td>
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58. Adverse Events and Side Effects Collected

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61. Flow Diagram/Other Notes

62. Data extraction checked

Initials:  
Date: day  month  year
Appendix 3

Ethical approval for HALT trial
Please include the reference no. and study title in all correspondence/telephone calls.

9 December 2003.

Mr Andrew Jull
Clinical Trials Research Unit
University of Auckland
PB 92 019
Auckland

Please include the reference no. and study title in all correspondence/telephone calls.

Dear Andrew,

Honey as adjuvant therapy for leg ulcers (HALT): a randomised controlled trial: Protocol V#1, 20/08/03: PIS/Cons V#2, 1/12/03
Multicentre:
Auckland Lead: Waikato WAI/03/09/062: CTR/03/09/145

Information Brochure/Consent Form V#2, 1/12/03 covering:
Andrew Jull
Anita Latta
Susan McAuley
Julie Betts
Catherine Hammond

University of Auckland
Auckland District Health Board
Home Healthcare Papakura
Community Services, Health Waikato
Nurse Maude Assn, Christchurch

Thank you for your amendments, received 4 December 2003.

The above multicentre study (lead Auckland) has been given ethical approval by Auckland Ethics Committee X on behalf of the Waikato and Canterbury Ethics Committees.

Certification
It is certified as not being conducted principally for the benefit of the manufacturer and may be considered for coverage under ACC.

Accreditation
This Committee is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, March 2002.

Approved Documents:
- Protocol V#1, 20/08/03
- Information brochure V#2, 1/12/03

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider, within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Progress Reports
The study is approved until 1 April 2006. The Committee will review the approved application annually. A progress report is required for this study on 9 December 2004. A form should come off our database requesting this information prior to the review date. Please note that failure to complete and return this form may result in the withdrawal of ethical approval.

A final report is also required at the conclusion of the study.
Requirements for SAE Reporting
Please advise the Committee as soon as possible of the following, if applicable:

- withdrawal from the market for any reason
- all serious adverse events which result in the investigator or sponsor breaking the blinding code at the time of the SAE or which result in hospitalisation or death.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Yours sincerely,

[Signature]

Pat Chainey
Administrator, Committee X

Cc: Auckland DHB Research Office
Appendix 4

HALT trial protocol
A randomised controlled trial of a honey-impregnated dressing for venous leg ulcers

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**Wound Mapping Grids provided by:**
USL Medical Ltd, PO Box 15-645, New Lynn, Auckland. Ph: (09) 827 3149

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**Comvita New Zealand Ltd**

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Overview

Title of Study: Honey as adjuvant therapy for leg ulcers (HALT): a randomized controlled trial

Investigators and Study Centres: This a collaborative study designed and coordinated jointly by independent investigators at the Clinical Trials Research Unit (University of Auckland), the Honey Research Unit (University of Waikato), the Dept of General Practice and Primary Care (University of Auckland), the Leg Ulcer Team, Auckland District Health Board, South Auckland Health, Health Waikato, and the Nurse Maude Association, Christchurch. The overall design and conduct of this investigator-initiated study will be the responsibility of the Steering Committee.

Study Period: November 2003 – Feb 2006

Clinical Phase: Phase III

Objectives: The primary aim of the study is to evaluate whether a honey dressing as an adjuvant to compression therapy is more effective at healing venous and mixed venous/arterial leg ulcers compared to usual therapy (compression plus usual dressing regimens) at 12 weeks. Secondary outcomes include time to healing, percentage change in ulcer size, ulcer recurrence within six months, cost per healed leg ulcer, adverse events, incidence of infection, and health-related quality of life.

Duration of Treatment: The maximum duration of treatment is 12 weeks (12 weeks treatment or less if the ulcer heals within 12 weeks).

Study Design and Methodology: An open label randomized controlled trial of a honey dressing will be performed. Participants will be randomized to a honey dressing (alginate gel dressing impregnated with manuka honey) or to usual care (with compression bandaging as standard therapy in both arms). The reference ulcer will be photographed at baseline and 12 weeks, and wound tracings made. Assessment of health-related quality of life will also be carried out at baseline and at the end of the study treatment period. The patient will continue to receive district nursing care as per normal protocol. During each district nursing visit data will be collected on products used for the ulcer treatment, concomitant treatments, adverse events, antibiotic use, GP visits, and signs of infection. If the ulcer healed within the 12-week treatment period, participants will be followed up by telephone at 6 months to determine if the ulcer recurred.

Number of Subjects: Recruitment and randomization of 400 participants is planned.

Diagnosis and Main Criteria for Inclusion: Patients are eligible for inclusion if they have:

- A venous leg ulcer, or a mixed venous/arterial leg ulcer of primarily venous origin
- Are receiving or able to receive compression bandaging from the district nursing service
- Are able to give informed consent.

Test Product:
- Manuka honey dressing + compression bandaging
Reference Therapy:
- Usual care (any dressing type) + compression bandaging

Criteria for Evaluation:

Primary Outcome:
- Proportion of participants with healed venous leg ulcer at 12 weeks. Complete healing is defined as full epithelialisation of the ulcer. The reference ulcer will be the largest ulcer at baseline, where the participant has multiple ulcers. In such a case all the participant's ulcers will be treated with the allocated treatment.

Secondary outcomes
- Time to healing
- Percentage change in ulcer size
- 6-month recurrence
- Incidence of wound infection
- Use of rescue antibiotics
- Costs per healed ulcer
- Health-related quality of life

Statistical Methods:
Sample size: The sample size of 400 people (200 in each group) will provide 90% power (with \( p = 0.05 \)) to detect a 30% relative increase (RR 1.30) in the proportion of participants with completely healed leg ulcers in the intervention group at 12 weeks.

Statistical analysis: Simple incidence rates, relative risks and 95% CIs will be obtained for all binary variables with multiple logistic regression analysis conducted if important confounding is shown to exist. Continuous data (such as time to healing) will be analysed using Cox regression modelling. Prior to undertaking any Cox regression modelling, the effectiveness of the interventions on time to healing will be analysed using Kaplan-Meiers curves to compare the differences between the two groups. Cox proportional hazards regression analysis will be used to assess time-to-event data. Sensitivity analysis will also be carried out to determine the effect of missing data from patients that are lost to follow-up or death. A health service perspective will be employed in analyzing costs per healed ulcer at 12 weeks.

Funding:
This study is being funded by a Health Research Council of New Zealand project grant, with product from Comvita New Zealand Ltd (ApiNate dressings), and USL Medical Ltd (800 wound mapping grids supplied free-of-charge). In addition, Comvita provided an unconditional $50,000 cash grant to assist with the operational costs of the trial.
Background

Prevalence of Leg Ulceration

Leg ulceration is a chronic, relapsing, and remitting condition. Leg ulcers are defined as any break in the skin below the knee of six or more weeks duration. Overall, the point prevalence for leg ulceration of any kind in New Zealand is quite low at 39 per 100,000 population, but this increases steeply with age (see Table 1).\(^1\) With the population aged over 65 projected to increase from 12% to 20% over the next 25 years,\(^2\) the number of people with new leg ulcers can be expected to double. The commonest type of leg ulcer is venous ulceration, representing between 50 and 80% of all leg ulcers.\(^3-10\)

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Economic Implications of Leg Ulceration

Leg ulcers represent a significant cost to community services as they are slow to heal and the majority of patients require nursing care at least once per week plus general practitioner consultations.\(^11\) It has been estimated that district nurses in Auckland spend approximately 25% of their time on venous ulcer management.\(^12\) An audit of a New Zealand district nursing service in 1999 found the average cost of treatment with compression was $906 for a first time ulcer and $1205 for a recurrent ulcer (pers. comm. Richard Milne). The actual cost ranged from $156 to $5626 depending on time to healing. A Dunedin-based study of five general practices found that care of patients aged over 40 with a venous leg ulcer cost twice that of the average patient. This study suggested that over $50 million is spent annually on venous leg ulcer care in New Zealand.\(^11\)

Effects of Leg Ulceration on Health

Leg ulcers are reported as having an impact on virtually every aspect of daily life. Pain is common, sleep is often impaired, mobility and work capacity tend to be restricted, personal finances are often adversely affected,\(^13\) and social activities are restricted due to fear of injury and poor body image.\(^14\) In New Zealand leg ulceration has been shown to have a significant adverse impact on health-related quality of life as measured by the SF-36.\(^15\) The differences between people with leg ulcers, population controls and the New Zealand population norms are most pronounced with respect to the cases’ ability to perform the physical aspects of their social roles. However, leg ulceration appears to adversely affect health-related quality of life on all the domains measured by SF-36, and the impact is comparable with that of other common conditions such as diabetes and arthritis.
Treatments for Venous Ulceration

The therapeutic mainstay in the management of venous ulceration is graduated compression bandaging. Healing rates in venous ulcers are significantly improved by the application of compression therapy, but generally only 55% of patients will be healed by 12 weeks. Compression bandages can be categorized as low compression (achieving approximately 14mmHg pressure at the ankle) or high compression (achieving 23mmHg pressure at the ankle). High compression bandaging is more effective at healing venous ulcers than low compression bandaging. High compression can be achieved using a variety of multilayer bandaging systems, with no one system being more effective than another. Compression bandaging should only be applied in the absence of significant arterial disease. The threshold normally employed for the use of compression is an ankle brachial pressure (ABI) index of 0.8. An ABI is the ratio of the systolic blood pressure at the arm over the systolic blood pressure at the ankle. A normal adult value for the ABI is between 0.9 and 1.2. Levels lower than 0.8 are thought to indicate the presence of moderate arterial disease. Selected patients with an ABI of between 0.6-0.8 can safely receive reduced levels of compression bandaging with appropriate monitoring.

Few adjuvants to compression bandaging are known to be effective. However, two drugs may be useful adjuvants to compression in selected patients. Pentoxifylline, a rheological agent, has a moderate effect on healing when used in addition to compression, but is only registered for use where other treatments have failed. Another drug treatment likely to be beneficial is Daflon, a semi-synthetic flavanoid consisting of 90% diosmin and 10% hesperidin. However, Daflon is not available in New Zealand. Simple treatments that can be used in conjunction with compression and which accelerate healing could reduce the cost of leg ulcer treatment. One such treatment that has recently received considerable media attention in New Zealand is manuka honey.

3.5 Honey as a Potential Treatment

Honey is an ancient treatment for wounds, with records of it being employed by early Egyptians, Assyrians, Chinese, Greeks and Romans, as well as being recommended as a salve by early physicians, such as Hippocrates. Honey is plant nectar and saccharine modified by the honeybee Apis mellifera. Honey contains approximately 35% glucose, 40% fructose, 5% sucrose, and 20% water, as well as many other substances, such as amino acids, vitamins, minerals and enzymes. In addition, manuka honey (derived from the NZ tree Leptospermum scoparium) also has a unique constituent that enhances its bacteriocidal action (Unique Manuka Factor – UMF). The microscopic actions of honey may be multiple. Honey appears to draw fluid from the underlying circulation, providing both a moist environment and topical nutrition that may enhance tissue growth. Moist wound beds have been demonstrated to heal faster than dessicated wounds, and topical application of nutrients may increase the deposition of granulation tissue. Histologically, honey appears to stimulate tissue growth in animal and human controlled trials, with early reparative changes noted, fewer inflammatory changes, and improved epithelialisation. Clinically, reports have also noted the debriding action of honey, making surgical debridement unnecessary. Although there is an almost complete lack of research to show that debridement enhances ulcer healing, it is accepted clinical opinion that debridement of devitalised tissue promotes ulcer healing.

Animal Studies

Animal studies have found that the topical application of honey on standardized wounds increases epithelialisation and the depth of granulation tissue, and decreases the area of the wounds in comparison to control treatments.
treated lesions have less necrosis and inflammatory markers, and have been found to be less fragile than untreated lesions.  

**Human Studies**

A series of human studies suggest topical honey may accelerate wound healing. In a trial of 40 people with small, uninfected pressure ulcers, patients received either honey or normal saline dressings. The mean number of days to healing in this trial significantly favoured the honey-treated group (8.20 versus 9.93 days, _p<0.001_). In a trial involving burn patients, 92 people were treated with either honey or a polyurethane dressing (OpSite). The mean time to healing in this study also significantly favoured the honey-treated group (10.8 versus 15.3 days, _p<0.001_). In another trial, 50 patients with moderate burns (10 to 40% of body area) were treated with either honey or a commonly employed topical antibiotic (silver sulfadiazine - SSD). The mean age, burn surface area and mechanism of injury were similar in all patients involved. All honey-treated patients were healed by day 21 compared to 84% of the SSD-treated group (absolute risk difference 16%, 95% CI -0.42-34.65%). The trend to accelerated healing was significant when 100 patients with moderate burns (10 to 40% of body area) were treated with either honey or boiled potato peel. All honey-treated patients in this study were healed by day 21 compared to 80% in the potato skin treated group (risk difference 20%, 95% CI 8.9-31.1%). In a larger trial, 450 participants with moderate partial thickness burns were treated with topical honey or one of four comparisons (Soframycin, Vaseline-impregnated gauze, OpSite, or an open wound). Mean time to healing favoured the honey-treated group (8.8 versus 13.5 days, _p<0.001_).  

There have been no controlled trials of honey as a treatment for leg ulceration. However, in a pilot study of 10 patients with 11 slow-to-heal leg ulcers (seven venous, one arterial, two neuropathic and one traumatic) treated with a daily application of honey for eight weeks, one ulcer increased in size, six did not change and four reduced in size by more than 25%.  

**Clinical Safety Summary**

As of June 2003, 1204 participants in nine controlled trials have been exposed to multifloral honey as a topical treatment. Honey appears to be generally well tolerated in clinical trials, with no adverse effects reported in four studies. In a double-blind trial, 78 atopic patients with pollen sensitivity were challenged with either 30 gram of honey (n=46), or 30 gram comparison cane sugar syrup (n=32), both taken orally. Minor symptoms (eg headache, itching, gastrointestinal complaints) were reported in both groups, with fewer reports in the honey group (26%) than in the comparison group (41%). In a New Zealand case series of leg ulcers treated with manuka honey, three out of 10 patients treated reported stinging for up to 15 minutes following the application of honey, and one participant withdrew from the study as a consequence.  

**Rationale for Clinical Trial Involving Manuka Honey**

Despite limited studies of its efficacy to date, manuka honey is promoted as a healing aid and is currently available as an over-the-counter remedy in New Zealand and other countries. However, the clinical effectiveness of both honey and manuka honey continues to be disputed, and there have been no randomized controlled trials on the effect of honey on leg ulcers. In view of the lack of definitive evidence, an independently led trial of manuka honey as an adjuvant to compression bandaging is required to assess its effectiveness as a treatment for venous leg ulcers.
Objectives
The primary aim of the trial is to determine whether a manuka honey dressing (plus compression) is more effective at healing venous/mixed leg ulcers compared to usual care (plus compression) at 12 weeks. Secondary objectives include measurement of time to healing, percentage change in ulcer size, ulcer recurrence within six months, costs per healed ulcer, adverse events, the incidence of infection, and health-related quality of life.

Study Design
The study is an open label randomised controlled trial. The district nurse will identify potential participants, obtain consent from them to be contacted by the research nurse if the patient is interested in the trial and notify the research nurse. The research nurse will see those who consent to participate in the study at two scheduled visits, and may contact them once by phone. The visits occur at baseline (Visit 1) and at 12 weeks after the randomised treatment commences (Visit 2). The participant will be telephoned at six months after randomisation to collect information on ulcer recurrence. At Visit 1, after consent has been obtained, a clinical history will be obtained, details of lifestyle and current ulcer and concurrent treatments will be recorded, the ulcer measured (by tracing and digital photography) and three health-related quality of life questionnaires (SF36, Charing Cross Ulcer Questionnaire and EuroQoL) completed. At Visit 2, the reference ulcer will be measured and photographed and the 3 health-related quality of life questionnaires completed. If the ulcer has healed, the leg that had the reference ulcer will be photographed. The district nurse will continue to visit (at approximately weekly intervals) throughout the study period and manage the participant as per their normal protocols. Following each visit by the district nurse to the participant, the district nurse will record bandaging materials used, the presence of clinical signs of infection, antibiotics used, adverse events, and general practitioner visits.
Study Plan Schematic

District nurse screens for potential participants, obtains consent to contact, leaves brochure and notifies research nurse

Telephone contact by research nurse

Visit 1
Research nurse visits participant and consents participant
Reasons for non-participation recorded

Research nurse registers and randomises participant

Research nurse conducts baseline assessments and leaves study treatment (if randomised honey)

Baseline assessments
- Demographic questionnaire
- Clinical history and ulcer measurement and photography
- Concurrent treatment
- SF36 Questionnaire
- EuroQoL Questionnaire
- Charing Cross Ulcer Questionnaire

Following each visit the district nurse records details on study Case Record Form (CRF)

District nurse assessments
- Details of products used (secondary dressings and compression type)
- Presence of clinical signs of infection
- Use of antibiotics/GP visits
- Adverse events

Visit 2
At 12 weeks, the research nurse completes outcome assessment

Outcome assessments
- Ulcer measurement and photography
- SF36 Questionnaire
- EuroQoL Questionnaire
- Charing Cross Ulcer Questionnaire

Phone call
At 6 months, the research nurse will contact the participant

Outcome assessments
- 6 month recurrence (self-reported)
- Compression stocking use
Ethical Approval and Informed Consent

Ethics Committee
Ethical approval of the study protocol and protocol-related documents will be sought from the Auckland Ethics Committee, the Waikato Ethics Committee and the Canterbury Ethics Committee, with the Auckland Ethics Committee being the lead ethics committee.

SCOTT Committee
MedSafe has considered whether an application to SCOTT for exemption under S30 of the Medicines Act 1981 is necessary. After consultation with counterparts in the Australian Therapeutic Goods Agency, MedSafe has decided an application to SCOTT is unnecessary as the manuka honey dressing is not considered to be a medicine, but rather a medical device.

Informed Consent
District nurses will screen patients for potential participants. If a patient meets the inclusion criteria, and expresses interest in participating in the trial, the district nurse will obtain written consent to forward the patient's name and telephone number to the research nurse (refer Appendix 2). The district nurse will leave a participant information brochure (refer Appendix 3) with the patient. After contact by the research nurse, if the patient wishes to participate in the study, Visit 1 will be arranged and informed consent will be obtained during that visit if the patient wishes to participate in the trial (refer Appendix 4).

Recruitment
Patients with venous or mixed leg ulcers will be recruited from the Central Auckland, South Auckland, Waikato and Christchurch district nursing regions. The district nurses involved in leg ulcer care will identify people potentially meeting the inclusion criteria, obtain consent to pass on people's details, and having done so notify a research nurse. The research nurse will then contact the potential participants, verify that they meet the inclusion criteria, and arrange to interview them at a time and place convenient to the potential participant. At this meeting the research nurse will explain the trial and obtain informed consent if the patient wishes to participate, and collect baseline data required to register and randomise the participant [see section 10.1 for more details].

Baseline Inclusion/Exclusion Criteria

Inclusion Criteria
Participants over the age of 18 years are potentially eligible for inclusion if they satisfy the following criteria:

- They have a leg ulcer of venous origin, or primarily venous origin (as determined by clinical history and examination, and an ABPI of > 0.7 within last three months)
- They are being treated with or able to be treated with compression bandaging at one of the study centres.
- They are able to give informed consent.
Exclusion Criteria

- Leg ulcer of aetiology other than venous.
- Unable to tolerate compression bandaging.
- History of diabetes, rheumatoid arthritis or significant peripheral vascular disease
- Doppler determined ABPI < 0.7
- Allergy to either honey or calcium alginate.

Randomisation Assignment

Consented participants will be randomly assigned a unique randomisation number by a central telephone randomisation service upon registration. The central telephone service will be provided by First Contact via an 0800 number. The allocation sequence will be stratified by study centre and prognostic index (based on size and duration of ulcer)\(^4\), using a range of block sizes generated by the study statistician.

Blinding

Blinding of the participants, district nurses and research nurses will not be possible as all will be aware of the assigned treatment. However, the observer responsible for measurement of the ulcer size will be blinded to treatment allocation. Digital photographs of the ulcer will be forwarded to the Clinical Trials Research Unit. An analyst blind to treatment allocation will measure the ulcer area and the average of the two measures will be taken as the measured ulcer area. Where the ulcer has healed at endpoint, an analyst independent of the study will verify whether healing has occurred.

Post-randomisation

Definitions

"Study treatment" is defined as the manuka honey dressing. "Control treatment" is that treatment employed by the district nurse, and might consist of one of several alternatives normally used in leg ulcer care eg. a calcium alginate or a silicone-impregnated vicose dressing.

Instructions

Following randomisation, the research nurses will leave a labeled pack with the patient. The pack will contain case report forms (Form C), adverse events case report forms (Form X), and 20 samples of the study treatment if the patient has been allocated to manuka honey dressing. The district nurse will either (i) apply the manuka honey dressing if the participant is allocated to the study treatment, or (ii) use a dressing of their choice if the participant is allocated to control treatment.

Where the participant is randomised to the study treatment, the district nurse will cover the leg ulcer with the manuka honey dressing and then apply a compression bandaging system. The choice of compression system will be at the clinician’s discretion, but must not be compression stockings. The manuka honey dressing can be applied directly to the ulcer surface, smooth side down. There is no need to trim the dressing.
Where the participant is randomised to the control treatment, the district nurse will cover the leg ulcer with a dressing of their choice and then apply a compression bandaging system. The choice of compression system will be at the clinician's discretion, but must not be compression stockings.

**Concomitant Therapy**
Throughout the study, participants' GPs and doctors are free to provide whatever ancillary treatments are required for the appropriate medical management of study subjects. If a concurrent medication or therapy is administered, the generic name of the medication or supplement and the date(s) and frequency of administration will be recorded on "Concomitant Medication" Case Report Form (CRF) M.

**Study Visits**

**Summary of Study Visits and Procedures Completed at Each Visit**

<table>
<thead>
<tr>
<th>Visit Description</th>
<th>Visit 1 (Research nurse)</th>
<th>District Nurse Visits</th>
<th>Visit 2 (Research nurse)</th>
<th>Telephone follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 1-12</td>
<td>Week 12</td>
<td>6 month Phone call</td>
</tr>
<tr>
<td></td>
<td>Randomisation A, B</td>
<td>DN visits C+</td>
<td>Endpoint D</td>
<td>E</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent obtained</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Demographic data</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Max ulcer width/length</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Brief clinical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Record ABI</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ulcer measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer tracing</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Digital photography</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Other data collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Quality of life measures</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Report ulcer healing</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Concomitant medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Dressing count</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Type of compression</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Additional dressings</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- GP visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Signs of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ulcer recurrence</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Study treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Manuka honey dressing</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

+ Form C is a multi-use form and one form will be completed during each district nurse visit

**Visit 1: Registration & Randomisation**
The following procedures will be performed:

1. Assess participant for eligibility.
2. Obtain informed consent.
3. Trace reference ulcer and measure maximum width and length (refer Appendix 5).
4. Register and randomize participant as soon as ulcer tracing is completed.
5. Complete brief clinical history and record ABI.
6. Review concomitant medication.
7. Carry out assessments of health-related quality of life (refer Appendix 6).
8. Photograph leg ulcer (refer Appendix 5).
9. Provide study treatment if allocated to manuka honey dressing.
10. Leave case report forms (CRFs) and labels.

Visit 2: Following Treatment of 12 Weeks Duration:
The following procedures will be performed 12 weeks after randomisation:
1. If allocated to study treatment count remaining dressings.
2. If ulcer unhealed [a] trace ulcer and [b] photograph leg ulcer.
3. If ulcer healed photograph leg where ulcer was present.
4. Carry out assessments of health-related quality of life (Appendix 6).

6-month Follow-up Phone Call:
The following procedure will be performed 6-months after randomisation.
1. Carry out assessment of 6-month self-reported leg ulcer recurrence
2. Carry out assessment of self-reported compression hosiery use

Adverse Event Reporting

Adverse Events
All adverse events (AEs) will be recorded on the Adverse Event Form (X).
Timely and complete reporting of all AEs is necessary to identify events that are treatment related or potentially treatment related, thereby allowing: (1) a greater understanding of the overall safety profile of the treatment; (2) appropriate modification of study protocols; and (3) adherence to regulatory requirements.

Reporting Safety Information
An AE is any untoward clinical occurrence in a participant and does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the product. In this study, this includes any illness, sign, symptom, or clinically significant abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the treatment(s) under study. Following the questioning and examination of the participant, all AEs must be recorded and described on the appropriate Adverse Event Form. If known, the name of the underlying illness or disorder (ie. the diagnosis) should be recorded, rather than its individual symptoms. Participants experiencing AEs that cause interruption or discontinuation of study treatment, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate.
Non-serious Adverse Events
An AE that is not designated as serious, as defined in section 16.4 below, will be recorded at each visit in the appropriate section of Form X.

Serious Adverse Events
An event that is serious may require expeditious handling to comply with regulatory requirements.
A serious adverse event or reaction is any untoward medical occurrence that:
- Results in death;
- Is life-threatening
  (Defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.);
- Requires inpatient hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a cancer;
- Is an important medical event
  (Defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject/subject or may require intervention (eg. medical, surgical) to prevent one of the other serious outcomes listed in the definition above.)

Contact for Notification of Serious Adverse Events:
Serious adverse events will be reported to the Study Coordinator within three days of detection. Should a district nurse become aware of a serious adverse event that occurs within 30 days after stopping the study treatment, the serious adverse event should be reported in accordance with the procedures specified in the protocol.
All adverse events that are serious and definitely, probably or possibly related to the study treatment will be reported to the Ethics Committee responsible for the study. This notification will be in the form of a Safety Update (ie a 15-day letter) issued by the Study Coordinator. Otherwise aggregate safety data will be reported to the Ethics Committee at six-monthly intervals.

Participant Withdrawal
If, at any time after randomisation, significant intolerance to the study treatment is suspected, the treatment (or control) can be withdrawn. Should participants require discontinuation of study treatment for any reason (see below), or if they elect to cease taking treatment, follow-up visits and data collection should continue as scheduled as if they were continuing with the randomized treatment.
Participants may have the study treatment withdrawn if one or more of the following occurs:

1. The participant makes a voluntary decision to withdraw from follow-up, or from the treatment.
2. The participant has any clinical adverse event, intercurrent illness, or other medical condition that indicates to the investigator that continued treatment with the study treatment is not in the best interest of the participant (see Section 14.1.2). The study treatment must be withdrawn if the participant is admitted to hospital.
3. The study is terminated. If the participant discontinues treatment due to an adverse event, the participant should be followed until the event resolves or there is a return to clinically acceptable medical status. Participant deaths or serious adverse events (see Section 14.2), which occur within 30 days of discontinuation should be reported to the Study Coordinator.

Clinical Supplies

**Study Treatment Identification**
Comvita New Zealand Ltd will supply the following study treatment(s):

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>INGREDIENTS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuka honey dressing</td>
<td>Manuka honey UMF 12+ Calcium alginate</td>
<td>10cmx10cm Dressing</td>
</tr>
</tbody>
</table>

**Handling and Dispensing of Study Treatment**
Comvita New Zealand Ltd will be responsible for assuring that the quality of the study treatment is adequate for the duration of the trial. Comvita have an accredited "medical honey supplier" programme to ensure the quality of honey that is delivered to them. The manuka honey dressings are also produced to ISO EN 46000 standards by a British facility that produces medical devices to the European CE Mark standard. These standards are independently verified. The honey dressings will have been sterilized during manufacturing. The packaging of dressings will meet the requirements of the Medicines Regulations 1984, and those of MedSafe.

All treatment supplies that will be used in the study must be maintained under the direct responsibility of the manufacturer or investigator. The dressings can be stored at ambient room temperature. The bulk of the study treatments will be stored by Comvita and monthly supplies will be dispatched to the study centres. It is the investigator's responsibility to ensure that an accurate record of treatments issued and returned is maintained.

**Following randomisation** each participant will receive one of the following treatments:

**Group 1: Usual care**

<table>
<thead>
<tr>
<th>WEEK</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>Usual care</td>
</tr>
</tbody>
</table>

**Group 2: Manuka honey dressing**

<table>
<thead>
<tr>
<th>WEEK</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>20 individually packaged sterile dressings</td>
</tr>
</tbody>
</table>

**Packaging and Labelling**
Each participant will be given a Participant Kit containing:

- The study treatment where the participant is allocated to the manuka honey dressing.
Directions for using the manuka honey dressing if the participant has been allocated to treatment

Contact details for the study

District Nursing Case Record Forms (Form C)

Adverse Event Forms (Form X)

Labels

Treatment Supply Records at Study Site

It is the responsibility of the Study Coordinator to ensure that an inventory of study treatment disposition is maintained. Records or logs will include:

- Amount received from manufacturer and placed in inventory at CTRU
- Amount transferred to the research nurses for storage
- Label ID numbers or batch number.
- Dates of treatment inventory movement.
- Unique participant identifier (when allocated).
- Amount dispensed to each participant.
- Initials of person responsible for each treatment inventory entry.

The study treatment will only be dispensed by the research nurse.

Study Treatment on Completion of Study

Upon completion or termination of the 12-week study period, unused study treatments can continue to be used by the patient until the supply is finished. The manuka honey dressing is not commercially available, but other honey dressings are. These could be purchased by the patient for their continued use if they desire.

Statistical Considerations

Sample Size

A sample size of 400 people (200 in each group) will provide 90% power at \( p = 0.05 \) to detect a 30% relative increase (RR 1.30) in the proportion of participants with completely healed leg ulcers in the intervention group at 12 weeks. The relative increase equates to an increase in healed ulcers from 55% to 71% at 12 weeks, an increase that has been suggested by the burns studies. The recruitment rate for the Auckland Leg Ulcer Study was 68%. This rate is exceptional, showing that people with leg ulcers tend to be very motivated to participate in studies. However, a lower recruitment rate of 45% has been assumed for HALT. Based on these figures it is estimated that it will take up to 15 months to recruit 100 people from each of the four centers.

A 10% dropout rate has been allowed for in this trial. This is congruent with the CTRU’s previous experience in a trial involving older people. The dropout rate for the Frailty Intervention Trial in Elderly Subjects (FITNESS) was 9%. HALT has been powered at 90% and the dropout rate would have to exceed 30% before power is reduced below 80%.
Statistical Analysis

Baseline Characteristics
Data on demographic characteristics (sex, age, ethnicity), smoking status, alcohol use, history of ulceration, ulcer size, co-morbidities, and mobility will be collected. Since any differences between randomised groups at baseline could only have occurred by chance, no formal significance testing will be conducted.

Effects of Treatment
Data from the trial will be entered into an Oracle database at the Clinical Trials Research Unit, then extracted into SAS (version 8) for analysis. All data analysis will be carried out on an intention-to-treat basis. Simple incidence rates, relative risks and 95% CIs will be obtained for all binary variables in the first instance, with subsequent multiple logistic regression analysis conducted if important confounding is shown to exist. Continuous data (such as time to healing) will be analysed using Cox regression modelling. However, prior to undertaking any Cox regression modelling, the effectiveness of the interventions on time to healing will be analysed using Kaplan-Meiers curves to compare the differences between the two groups using the log rank test. Cox proportional hazards regression analysis will be used to assess time-to-event data, thereby taking into account known covariates and the varying times since randomisation. The proportionality assumption will be checked using standard graphical techniques. Sensitivity analysis will also be carried out to determine the effect of missing data from patients that are lost to follow-up or death. A health service perspective will be used in analyzing the cost data.

Tolerability of Manuka Honey Dressing
All randomised participants will be included in this analysis. Comparison of the frequency of treatment withdrawal because of suspected intolerance between the manuka honey group and the placebo group will be tested using the methods of Mantel and Haenszel. The number of participants discontinuing treatment prematurely for any reason will be summarized by treatment group and by reasons for discontinuation. The incidence of all suspected adverse treatment reactions and ulcer infections will be summarized by treatment group.

Data Safety and Monitoring Committee (DSMC)
This is a study of a treatment already in clinical use. The treatment is low-risk on a relatively minor condition and no interim analyses are planned. A DSMC has been established, consisting of two CTRU staff (Mr Stephen Vander Hoorn [Chair], Dr Carlene Lawes) and one member external to CTRU (Associate Professor Ngaire Kerse). Members have no conflicts on interest and are not involved with the HALT trial. The DSMC will draw up their own terms of reference and will be free to review any information or study process in addition to the reviews of safety data. The study statistician will provide the DSMC with reports on safety data.

In addition, an external monitor will monitor the study conduct. The monitor will audit each centre to ensure that the study protocol is being adhered to. At least ten complete participant records at each study centre (10% of the anticipated participant recruitment) will be reviewed over two visits. The first audit will take place after five patients have been recruited by the study center. The second audit will take place approximately six months later, after 50 participants have been recruited (further visits may be scheduled at the discretion of the monitor following discussion with the study coordinator). The monitor will also audit all records to ensure the existence of all randomised participants, that the participants meet the inclusion criteria and have
provided informed consent, and that the study treatment is appropriately stored. The monitor will also visit each centre at study close-out.

**Administrative Section**

**Study Management**

The Auckland Leg Ulcer Team, Home Health Services South Auckland, Community Services Health Waikato, and the Nurse Maude Association, Christchurch will be responsible for identifying potential participants, and some data collection. The Clinical Trials Research Unit will perform participant registration, central coordination, randomisation, some data collection, data management and data analysis. The Steering Committee will oversee the overall design and management of the study. The Study Management Committee will be responsible for the operational conduct of the study (refer Appendix 1). All study funds will be managed by Auckland UniServices Ltd., the research contract management arm of the University of Auckland.

**Adherence to the Protocol**

Except for changes to eliminate an immediate hazard to participants, the approved protocol will be followed as specified. Any significant protocol deviation will be documented in the CRF file.

**Protocol Revisions**

All revisions will be discussed with, and approved by, the Steering Committee. If the revision is an Administrative Letter, the Study Coordinator will submit it to the Ethics Committee(s) for their information. If the revision is an Amendment, the Study Coordinator will sign it and submit the Amendment to the Ethics Committee(s) for review and approval or favorable opinion prior to implementation. Documentation of approval, signed by the chairperson or designee of the Ethics Committee(s), must be sent to the Study Coordinator.

If an Amendment substantially alters the study design or increases the potential risk to the subject:

1. the consent form will be revised and submitted to the Ethics Committee(s) for review and approval or favorable opinion;
2. the revised form will be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and
3. the new form will be used to obtain consent from new subjects prior to enrolment.

**Case Report Form Procedures**

The Case Report Form (CRF) will be completed legibly in ink at the time of the participant visit. Participants are to be identified by initials, birth date, and registration number. All requested information will be entered on the CRF in the spaces provided. An item will be documented with an asterisk (*) if unavailable or a dash (\-) if not applicable; no blank spaces will be left. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction will be initialed and dated by the person making the correction.
The completed CRF will be processed electronically via the Internet. The research nurse will enter the data from the paper CRFs. All computerized forms will be electronically signed by the authorized study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date. Validation ranges will be set up to ensure notification of any numeric values outside of set ranges. At least 10% of the records will be double-keyed by CTRU data management.

**Periodic Reports to Ethics**
The Study Coordinator will provide annual reports of the progress, or completion, termination or discontinuation of the study to the Ethics Committee.

**Records Retention**
The Study Coordinator shall retain study treatment disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by the Privacy Legislation and the Health (Retention of Health Information) Regulations 1996 (16 years from date of termination of study).
If any Investigator withdraws from the study (eg. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg. another Investigator). Notice of such transfer will be given in writing to the Clinical Trials Research Unit.

**Ownership of Data and Publication**
The Clinical Trials Research Unit will retain ownership of study data and reserve the right to publish the results upon completion of the trial. All investigators will be acknowledged in the final report, and in publications resulting from the study.
Study Acknowledgement

STUDY ACKNOWLEDGMENT

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will undertake to complete the study within the time designated.

I will provide copies of the protocol and access to all information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the treatment and the study.

I understand that the study may be terminated or enrollment suspended at any time if it becomes necessary to protect the best interests of the study participants.

Printed name and signature

Date

Study Coordinator

Date

References

55. Latham N. A clinical trial of resistance training and vitamin D to improve physical health in frail older adults [PhD]. University of Auckland, 2002.
Appendix 1 – Terms of Reference

The HALT steering committee will consist of the investigators who are responsible for developing and maintaining the study design, statistical analysis, presentation and publication of results. The committee will meet at least once every six months to review problems and issues raised by the Study Management Committee. Members who live outside of Auckland may attend the meetings, or participate via conference call.

The HALT Study Management Committee is responsible for the daily operation of the study. Meetings will be held weekly while the study is in development, then as required when the study is underway. The Study Management Committee will deal with study problems, recruitment, and logistical issues.

Appendix 2 – Consent to contact letter

Appendix 3 – Informed Consent Procedures and Form

Informed Consent

Written consent MUST be obtained from all participants. The signed consent will be filed in the participant’s study file. For written consent to be valid the participant must be suitably informed of the study so that they can make an independent choice about whether to participate. The participant should receive a copy of the consent form at the study visit. Issues to be covered in the information sheet should be reviewed carefully with each participant. Do not assume that every person has read the information sheet or that they can read. The consent form should be signed and dated by the participant. The potential participant should have details (refer information sheet) regarding:

- The purpose of the study.
- An explanation of who the researchers are.
- An explanation of why the participant qualifies for the study.
- The type of participants studied and the number likely to be involved.
- The length of the study.
- The length of time and the procedure of the assessment, interventions, including any special tests.
- The potential risks/benefits to the person.

The potential participant should be informed (See information sheet) that:

- The supply of information by the participant is entirely voluntary.
- The participant may refuse to answer any of the questions or refuse any of the clinical examination. They do not have to give a reason for doing so.
- All participants have the right to access their data and/or to remove it from the study.
- All participants have the right to have questions answered.
- A person outside of the study is available to be contacted should they have any concerns i.e. a health advocate.
The participant should be aware (See information sheet) that:

- Personal information will be collected about them but that this information will be kept strictly confidential.
- That the information will be kept in a locked cabinet at the study site and/or in a locked room at the Clinical Trials Research Unit, School of Medicine, University of Auckland.
- All computerised information will be password protected on a computer.
- No one, other than the study investigators, will have access to this data.
- All information will be published or presented in a way that no individual can be identified.
- Unless otherwise requested, the participant’s GP will be informed that they have entered the study and of the study results when complete.

Appendix 4 – Patient Information Brochure

Appendix 5 – Ulcer measurements

Ulcer measurements will be made on visits 1 and 2. Measurements will be made using digital photography and wound tracing.


  An acetate ring of appropriate diameter (4, 6 or 8cm) will be laid over the leg, around the ulcer. The ring will be of sufficient diameter to [1] surround the ulcer while [2] ensuring that the vertical axis of the ring is visible on the leg. This allows for correction for convexity of the leg and more accurate determination of the area of the ulcer. The center of the ring is cut out to ensure no contact with the ulcer, and the acetate is single use only.

- **Wound tracing:** A 10 x 10cm single use acetate, supplied by USL Ltd, will be used to trace the outline of the leg ulcer. The acetate will be laid over the leg ulcer and an indelible spirit pen will be used to trace the outline. The backing of the acetate will be removed and the tracing attached to the CRF. The backing will be disposed of in the rubbish. If the ulcer is larger than 10 x 10cm, two A4 acetate sheets will be employed in the same manner as the 10 x 10cm acetate, one A4 sheet being used as a backing and disposed off after the tracing. A measure of maximum length and width will be taken from the acetate to calculate ulcer area for the purposes of stratification prior to randomization.

Appendix 6 – Health-related Quality of Life Questionnaires

**SF-36:**
Charing Cross:

EuroQol:
Appendix 5

Statistical analysis plan for the HALT trial
Statistical Analysis Plan

A randomised controlled trial of a honey-impregnated dressing for venous leg ulcers

Clinical Trials Research Unit
Clinical Trials Research Unit

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Study: Honey as adjuvant leg ulcer therapy trial (HALT)

Title: A randomised controlled trial of a honey-impregnated dressing for venous leg ulcers

Author of analysis plan: Varsha Parag

Version: Final

Version date: 31 January 2006

Who else was involved in the discussion of the analysis:

Stephen Vander Hoorn, Andrew Jull, Laura Wilkinson-Meyers, Natalie Walker, Anthony Rodgers, Peter Molan

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas. The CTRU author/reviewer also finds this plan to be in compliance with ICH-E9 as well as CTRU SOP BS-0004.

Varsha Parag
Study Statistician

Date

Stephen Vander Hoorn
Biostatistics Manager

Date

Andrew Jull
Investigator

Date

Anthony Rodgers
Investigator

Date
1. Introduction

The purpose of the Statistical Analysis Plan (SAP) is to provide detailed statistical analysis methods that will be performed in the HALT study. This document is intended to be separate from the protocol and provides additional details about the analysis methodologies. The scope of this SAP is intended to cover ONLY those main analyses described in the protocol. For additional research questions outside the scope of the main protocol analyses, please refer to separate SAPs.

This SAP is intended to comply with CTRU's internal procedure for generation of analysis plans (BS-0004), the general principles outlined in the FDA's Guidance for Industry ICH E9 (Statistical Principles for Clinical Trials www.fda.gov/cder/guidance/ICH_E9-fnl.pdf) and the Consort Statement.

It is assumed that the study documentation provided by data management follows standard operating procedures. In particular, data management study documentation (DM-1002), design and development of case report forms (DM-1006), validation of study forms (DM-1007) and study log (DM-1003). These procedures describe the process for setting up and maintaining study documentation, recording decisions affecting data handling, as well as methods of data capture and the algorithms to ensure accurate data are collected and maintained. It is assumed that the SAP will use data from a locked database that has been verified against the clinical record and is a true record of the data collected from the participant. Any data that are missing will be flagged and assumed to be undiscoverable.

The analysis plan will also outline the proposed layout of tables/figures that will be presented.

2. Study objectives

The primary aim of the trial is to determine whether a manuka honey dressing (plus compression) is more effective at healing venous/mixed leg ulcers compared to usual care (plus compression) at 12 weeks. Secondary objectives include measurement of time to healing, change in ulcer size, ulcer recurrence within six months, costs per healed ulcer, adverse events, the incidence of infection and health-related quality of life.

3. Study design

An open label randomized controlled trial of a honey dressing will be performed on venous leg ulcers. Participants will be randomized to a honey dressing (alginate fibre dressing impregnated with manuka honey) or to usual care, with compression bandaging as standard therapy in both arms. The reference ulcer will be photographed at baseline and 12 weeks, and wound tracings made. The participant will continue to receive district nursing care as per normal protocol. During each district nursing visit data will be collected on products used for the ulcer treatment, concomitant treatments, adverse events, antibiotic use, GP visits, and signs of infection (form C). If the ulcer heals within the 12-week treatment period, participants will be followed up by telephone at 6 months to determine if the ulcer recurred.
3.1. Study centers
Participants will be recruited through district nursing teams involved in leg ulcer management in Central Auckland, South Auckland, the Waikato region and Christchurch.

3.2. Randomisation
Consented participants will be randomly assigned a unique randomisation number by a central telephone randomisation service upon registration. The allocation sequence will be stratified by study center and prognostic index (based on size and duration of ulcer), using a range of block sizes generated by the study statistician.

3.3. Sample size
The sample size of 400 people (200 in each group) will provide 90% power (with p = 0.05) to detect a 30% relative increase (RR 1.30) in the proportion of participants with completely healed leg ulcers in the intervention group at 12 weeks. The relative increase equates to an increase in healed ulcers from 55% to 71% at 12 weeks.

3.4. Inclusion/exclusion criteria
Participants are eligible for inclusion if they:
- are over the age of 18 years
- have a leg ulcer of venous origin, or primarily venous origin (as determined by clinical history and examination, and an ABI of > 0.7 within last three months)
- are receiving or able to receive compression bandaging from the district nursing service
- are able to give informed consent

Exclusion criteria:
- leg ulcer of aetiology other than venous
- unable to tolerate compression bandaging
- history of diabetes, rheumatoid arthritis or significant peripheral vascular disease
- Doppler determined ABI < 0.7
- allergy to either honey or calcium alginate

4. Study outcomes

4.1. Primary outcome
The primary outcome is the proportion of participants with healed venous leg ulcer at 12 weeks. Complete healing is defined as full epithelialisation of the ulcer. The reference ulcer will be the largest ulcer at baseline, where the participant has multiple ulcers. In such a case all the participant's ulcers will be treated with the allocated treatment.

4.2. Secondary outcomes
Secondary outcomes include:
- time to healing
- change in ulcer size from baseline to 12 weeks
- incidence of infection during 12 week study period
• adverse events during 12 week study period
• health-related quality of life at 12 weeks
• costs per healed ulcer during 12 week study period
• ulcer recurrence within six months

5. Variable definitions

• Leg ulcer: A leg ulcer is defined as an area of broken skin on the lower leg that has remained unhealed for six weeks or more, or an area of broken skin on the lower leg of a person that has a previous history of leg ulcers.

• Venous ulcer: A venous ulcer is a leg ulcer that has been caused by chronic venous insufficiency. Venous ulceration is diagnosis by the presence of clinical signs of chronic venous insufficiency (e.g. haemosideran pigmentation, varicose veins, and induration of the leg), shallow, irregularly shaped ulcer that is moist, and an absence of other causes of ulceration eg arterial disease.

• Ankle Brachial Index (ABI): The ABI is an index of arterial insufficiency in the lower leg. It is obtained by taking resting blood pressures using the arm and the ankle. The ratio of the ankle pressure to arm pressure when the participant is horizontal should be 1.0. Ratios lower than 1.0 indicate a degree of arterial insufficiency. Ratios lower than 0.8 indicate moderate arterial insufficiency.

• Healing: the primary outcome is determined from the ulcer status at the 12-week assessment (form D, Q2.01). Where a 12-week assessment is not available, the ulcer status will be set to a failure (not healed). Sensitivity analysis will be conducted where the missing ulcer status at 12 weeks will instead be set to the last ulcer status value on form C (Q2.01).

• Infection: Where the ulcer was assessed as being infected and the participant was treated by antibiotics for ulcer infection.

• Ulcer size: The size of the reference ulcer at baseline and 12 weeks was measured using the method proposed by Solomon et al.² Measurement of a two-dimensional plane such as a photograph of an ulcer will underestimate the 3-dimensional surface area of the ulcer because of the curvature of the leg. An acetate circle was placed over the ulcer to allow the estimation of a correction factor for the curvature of the leg. Digital photographs of the reference ulcer were measured twice and the average of the two measures was taken. If both digital photographs were unable to be used then the wound tracing was measured twice and the average of these two measures was used as the ulcer area instead. Note at 12 weeks, ulcers that had healed were not measured, so these ulcer sizes will be set to zero.

• Adverse events: Any non-serious adverse event (eg stinging, itching and allergies) experienced by the participant was recorded during the 12 week study period. Serious adverse events eg death, life-threatening event, or hospitalisation for medical condition were also recorded. All adverse events were described as being related, possibly related, unlikely to be related or unrelated to the treatment by the district nurse or site investigator.

• Time to healing: The date the ulcer healed will be taken as the last date on the district nurse form (form C) when the ulcer was indicated to be healed (Q2.01).

• Short-Form 36 (SF36) questionnaire: The SF36³ is a 36-item self-administered instrument to measure generic health-related quality of life. Participants perceived health is measured across 8 domains (physical...
functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health). Additionally, two summary component scores (physical and mental) will be obtained.

- Charing Cross Venous Ulcer Questionnaire (CCVUQ): The CCVUQ is a 21-item self-administered disease-specific instrument to measure health-related quality of life across four domains (social function, domestic activities, cosmesis and emotional status).
- EuroQol 5D (EQ5D): The EQ5D is a 6-item self-administered generic instrument to measure health-related quality of life across 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The instrument can also generate a utility associated with a health state.

5.1. New variables to create

- Total Venous Clinical Severity Score (VCSS): sum 10 individual items to get total score (Form B, Q: 6.10-6.16, 6.18-6.20)
- Ulcer area: calculated using measured circle and ulcer area from the digital photographs, and formula from Solomon et al.²
  - measured circle area: \( mc = \frac{(b626\text{circle}_\text{area}_\text{a}+b627\text{circle}_\text{area}_\text{b})}{2} \)
  - measured ulcer area: \( mu = \frac{(b628\text{ulcer}_\text{area}_\text{a}+b629\text{ulcer}_\text{area}_\text{b})}{2} \)
  - ulcer area = \( mu + ((1-(\text{mc}/b625\text{circle}_\text{diam}))*\text{mu/mc})*\text{mu} \)
  Note if the digital photographs were unable to be used then the average of the measured ulcer areas from the wound tracings was used instead. Also at 12 weeks, the ulcer area for healed ulcers was set to zero.
- Infection: Form C, any of Q5.02 to Q5.06=Yes and Q6.01=Yes
- Date ulcer healed (time to healing): last date on the form C when the ulcer was indicated to be healed (Q2.01)
- SF36 domains and summary scores
- CCVUQ domains
- EQ5D domains

6. Statistical analysis

All statistical analyses will be preformed using SAS version 9.1 (SAS Institute Inc. Cary NC) and SPPLUS. All statistical tests will be two-tailed and a 5% significance level maintained throughout the analyses. All treatment evaluations will be performed on the principle of 'intention to treat' unless otherwise specified. No adjustments for multiplicity are planned for the secondary endpoints, adverse events or other endpoints.

Summaries of continuous variables which are normally distributed will be presented as means and standard deviations or medians and inter-quartiles for skewed data, while categorical variables will be presented as frequencies and percentages. Continuous variables will be compared with t-tests or Mann-Whitney tests and categorical data with Chi-squared tests as appropriate.

The study statistician and an investigator (Andrew Jull) named on this SAP will conduct all the analyses. The investigator will be blinded to the treatment allocation (all results will be presented as treatment A and B). The results will be unblinded once the final statistical report has been completed.
6.1. Blind review

A pre-analysis review will be conducted before the primary analyses, where both the study statistician and the investigator will be blinded to treatment allocation. The purpose of this review is to establish rules for a per protocol analysis and to reconsider the analysis plan (e.g., adjustment for potential confounders) in light of recent research. Any amendments (and the rationale) must be justified and documented in the SAP.

A per protocol analysis involves looking at the major protocol violations such as cross-over treatments, withdrawals and lost to follow-up or deaths (where the ulcer will be assumed not to have healed). The potential confounders for adjustment to be looked at will include stratification factors (study center and prognostic index), age, sex, ethnicity, measured ulcer size and venous clinical severity score. It should be emphasized that any alterations to the SAP from that originally proposed could seriously undermine the credibility of the trial so need to be discussed with the study management committee.

6.2. CONSORT statement

All participants who were invited to participate in this trial should be accounted for and a CONSORT statement prepared. The reasons for non-participation will be discussed in relation to the external validity of the trial and the pattern of protocol violations considered as potential sources of bias. Reasons for early withdrawal will be listed for all participants that prematurely discontinued treatment or the study. The age and sex of participants that were registered but not randomised will be compared to the participants that were randomised.

6.3. Randomisation and baseline information

The number of participants who were registered, fulfilled eligibility criterion, together with reasons for exclusion, and number randomised by study center will be summarised in table 1. Baseline demographic variables (age, sex, ethnicity), smoking status, alcohol use, history of ulceration, ulcer size, mobility, quality of life and relevant clinical variables will be summarised for each treatment group and for the difference between the treatment groups in table 2. Baseline medical history and medications will be summarised for each treatment group and for the difference between the treatment groups in table 3.

6.4. Primary outcome analyses

6.4.1. Unadjusted and adjusted analyses

The absolute risk difference in the proportion of participants with healed venous leg ulcer at 12 weeks between the treatment groups will be calculated. In addition, the number needed to treat (NNT) with the intervention to achieve an improvement in healed venous leg ulcers over a 12 week period compared to the control will be calculated.

The adjusted analyses will be conducted using logistic regression containing the stratification factors (study center and prognostic index) and any confounders shown to exist in 6.1. The odds ratio obtained from the logistic regression will be converted to an absolute risk difference and NNT.

The likelihood ratio test between the unadjusted and adjusted logistic regression models will be used to assess whether the covariates in the adjusted model significantly improves the goodness of fit of the model. If the goodness of fit for the adjusted analyses is significantly better than the unadjusted analyses then the adjusted analyses will also be reported. If there is no significant difference between
the unadjusted and adjusted analyses, then relative risk for the unadjusted analysis will be reported. Odd ratios for the adjusted analysis will only be reported if the difference between adjusted and unadjusted analysis is significant.

6.4.2. Sensitivity analyses
Sensitivity analyses will be conducted on the primary outcome where participants with a missing 12-week assessment will have their ulcer status set to the last ulcer status on form C.

Sensitivity analyses will also be conducted on the primary outcome where a per protocol analysis will be done excluding participants that have major protocol violations (see 6.1).

6.4.3. Subgroup analyses
If the treatment effect for the primary outcome is significant (i.e. p<0.05), then subgroup analyses will be reported. It is planned that the following subgroup analyses be carried on the primary outcome: by study center, prognostic index, sex, age, ethnicity, ulcer size and duration, and compression system. The model will include the subgroup variable along with it’s interaction with treatment. A test of whether the treatment effect differs across the levels of the subgroup will be constructed by assessing the significance of the interaction term. The results of the subgroup analyses will be treated with caution as this study was not powered for these analyses. Figure 1 will contain a forest plot of the subgroup results for the primary outcome.

6.5. Secondary outcome analyses
The distribution of all continuous endpoints will be assessed for normality and skewed data will be subjected to an appropriate transformation before analysis.

6.5.1. Time to healing
Time to healing will be analysed using Cox regression modelling. However, prior to undertaking any Cox regression modelling, the effectiveness of the treatments on time to healing will be analysed using Kaplan-Meiers curves (figure 2) to compare the differences between the two groups using the log rank test. Cox proportional hazards regression analysis will be used to assess time-to-event data, thereby taking into account known covariates from 6.4 and the varying times since randomisation. The proportionality assumption will be checked using standard graphical techniques.

If the treatment effect for this outcome is significant (i.e. p<0.05), then subgroup analyses will be reported. It is planned that the following subgroup analyses be carried out: by study center, prognostic index, sex, age, ethnicity, ulcer size and duration, and compression system. The model will include the subgroup variable along with it’s interaction with treatment. A test of whether the treatment effect differs across the levels of the subgroup will be constructed by assessing the significance of the interaction term.

6.5.2. Change in ulcer area
The percentage and absolute change in ulcer area from baseline to 12 weeks will be assessed using ANCOVA (analysis of covariance). This analysis will include adjustment for known covariates from 6.4; the adjusted analysis will only be reported if there is significant difference between the unadjusted and adjusted analyses. Figure 3 will contain a frequency plot of the change in the ulcer area from baseline to 12 weeks by treatment.
If the treatment effect for this outcome is significant (i.e. \( p<0.05 \)), then subgroup analyses will be reported. It is planned that the following subgroup analyses be carried out: by study center, prognostic index, sex, age, ethnicity, ulcer size and duration, and compression system. The model will include the subgroup variable along with its interaction with treatment. A test of whether the treatment effect differs across the levels of the subgroup will be constructed by assessing the significance of the interaction term\(^{11}\).

6.5.3. Incidence of infection
The incidence of leg ulcer infection during the 12 week study period will be compared between the treatment groups using the chi-squared test.

6.5.4. Adverse events
The safety data collected during the study will provide comparisons of the intervention with usual care. All safety data will be summarized in the form of frequency distributions, descriptive statistics and tabulations. Incidence of all adverse events will be summarized according to the templates for line listings and tables as shown in tables 5 and 6. Separate tables for specific types of adverse events may be created, for example ulcer pain as in table 7. Line listings will be produced in order to examine the serious and/or treatment related adverse events and multiple adverse events of the same type for the same participant, see tables 8 to 10. The incidence rate ratios comparing the two treatment arms will be calculated and presented as in table 11.

6.5.5. Quality of life
The 12 week SF-36 domains and summary scores, CCVUQ domains and the EQ5D domains will be summarised for each treatment group and for the difference between the treatment groups in table 4. Note if the quality of life data is found to be non-normal both medians and means will be reported.

6.5.6. Costs
The objective of the economic analysis is to assess the costs and consequences of using manuka honey dressing as an adjuvant to compression therapy in community-based participants with venous or mixed venous/arterial leg ulcers. The evaluation will aim to (a) identify (b) model, (c) measure and (d) value the immediate and long term costs and consequences of using the manuka honey dressing, and compare the resulting costs and consequences to the outcomes that would be expected with usual care. Information on district nursing time per visit, frequency of visits, dressing materials used at each visit, compression bandages used at each visit, number of general practitioner visits for leg ulcer care, number of other health professional visits for leg ulcer care, and prescribing for ulcer care e.g. antibiotic use has been collected to facilitate this analysis. Travelling time will not be incorporated due to the variation between rural/urban mix of the study centers. Dressings and bandages will be costed at their New Zealand retail price in the first instance, with the study center costs employed in a sensitivity analysis. The final results will report on both the cost effectiveness (cost per healed ulcer at 12 weeks) and the cost utility (cost per QALY) using the EQ-5D. The analysis will use a health services perspective.

6.5.7. Ulcer recurrence within 6 months
The self-reported recurrence rate of the ulcer at 6 months will be compared between the treatment groups using the chi-squared test.

6.6. Verifying ulcer healing
The primary analysis is being conducted on whether the ulcer has healed at 12 weeks as determined by the study research nurse. A blinded verification of ulcer
healing status is being conducted by a blinded reviewer independent of the study. A sensitivity analysis of comparing the impact of verification (verified healed or not healed) on the primary outcome will be performed. The level of agreement between ulcer healing reported by the research nurse and the reviewer will be calculated using a weighted Kappa statistic.

7. Prioritisation of analyses

<table>
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<tr>
<th>Output</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Data cleaning</td>
<td>January 2006</td>
</tr>
<tr>
<td>Data lock of baseline and 12 week forms</td>
<td>1 February 2006</td>
</tr>
<tr>
<td>Analysis of primary endpoint</td>
<td>February 2006</td>
</tr>
<tr>
<td>Analysis of secondary endpoints</td>
<td>February-April 2006</td>
</tr>
<tr>
<td>Preparation of statistical report</td>
<td>March-April 2006</td>
</tr>
<tr>
<td>Data lock of 6 month form</td>
<td>31 March 2006</td>
</tr>
<tr>
<td>Completed review, discussion and any revisions to statistical report</td>
<td>April 2006</td>
</tr>
</tbody>
</table>

Note the ordering of tasks above implies the ordering of analysis

8. List of tables and figures

Table 1. Eligibility criteria
Table 2. Baseline information
Table 3. Baseline medical information
Table 4. Health-related quality of life
Table 5. Adverse event counts
Table 6. Adverse events: Number observed by relation to treatment and severity
Table 7. Adverse events: Number observed by relation to treatment and severity, for ulcer pain only
Table 8. List of adverse events that were related to treatment and serious
Table 9. List of adverse events that were related to treatment and non-serious
Table 10. Line listing of multiple adverse events of the same type for the same participant
Table 11. Adverse events analysis

Figure 1. Primary outcome: subgroup results
Figure 2. Kaplan-Meiers curve of time to healing by treatment
Figure 3. Change in ulcer area from baseline to 12 weeks by treatment

9. References


Manual of Procedures
1.1.1 Overview of participant flow

1. DN visits - leaves PIS and sends you C2C letter
   - Register participant - Form A (telephone)
     - Use next reg_num in sequence from Reg_num master list. Start participant progress chart
     - Does not meet any exclusion criteria
       - NO
       - YES
         - Visit 1: Randomisation & baseline assessment
           - YES
             - File in excluded participants folder. DO NOT Collect any further data
             - Meets all inclusion criteria
               - YES
                 - Randomise and complete data collection
                 - Complete Forms B, Q and Z, (and M if necessary). Leave participant kit. Obtain photocopy copy of front sheet from DN clinical record and verify ABI
                 - 12 weeks data collect by DNs - Form C
                   - Visit 2: 12 week follow-up
                     - Complete Forms D, (M and X if necessary). Update Form Z.
                   - 6-month follow-up by telephone
                     - Complete Forms D, (M and X if necessary). Update Form Z.
1.1.2 Registering a patient as a potential participant

Receive consent to contact letter

Assign next registration number in sequence from master list, and complete Form A: Registration

Telephone new contact using preferred time if possible

If participant does not have a phone, complete Form A at first visit

Does the contact meet 1 or more of the exclusion criteria

NO

YES

Arrange convenient time for a baseline visit

Sign off Form A and enter details on website

Log details on Participant Progress Chart & update Recruitment Progress Chart

Sign off Form A & enter details on website

File in Form A Folder

Explain that the contact does not meet the criteria for the trial

File Form A in Excluded Participants folder
1.1.3 Randomisation and baseline assessment: Visit 1

Discuss participation in the trial, answer any questions, and consent the patient if they agree to participate.

Answer Q2.01 to 2.06

Does the patient meet all the inclusion criteria?

YES

Complete questions up to Q3.05

Phone First Contact
0800 800 710 & tell the operator you "have a patient to be randomised into the honey trial"

Record treatment allocation and complete Forms B, Q, M (if necessary) & Z

Complete participant kit - label forms C & X, leave instructions for honey dressing if appropriate

Complete letter informing GP their patient is a participant in the HALT trial

NO

Does the participant object to their GP being informed of their participation in HALT?

YES

Obtain copy of front sheet from district nurse record. Enter data from Forms B, Q and M on website. File all forms (including Z) in the participant's CRF Folder, Secure Folder in locked drawer, Update the Recruitment Progress Chart, Participant Progress Chart and put HALT participation sheet in patient's Clinical Record.

NO

Do NOT randomise.

On return to office, throw away unused registration labels & update participant progress chart

File Form patient's Form A and B in Excluded Patients Folder, Secure Folder in Locked drawer
1.1.4 12-week follow-up: Visit 2

Visit participant 12 weeks after randomisation (Visit 1)

Is the reference ulcer healed?

YES

Photograph the reference ulcer

Photograph the leg at the site of the reference ulcer

Complete Form D & administer Form Q

Has the participant started on any new medications since Visit 1?

YES

Update Form M (or start new Form M if one not completed previously)

NO

Has the participant had any adverse events since the last district nurse visit?

YES

Complete Form X

NO

Has the participant’s contact details changed since Visit 1?

NO

Complete new Form Z with new details only

YES

Enter data from Forms D, Q M & X on website. File all forms (including Z) in the participant’s CRF Folder. Secure Folder in locked drawer. Update the participant progress chart.
1.1.5 Adverse event management

Receive Form X from district nurse

Adverse event detected during Visit 2

Complete Form X

Is the Adverse Event a Serious Adverse Event?

NO

YES

Notify Study Manager by phone as soon as possible after receiving Form X

Complete Serious Adverse Event Notification and file in the Trial Master File

Enter form via web and file in participant's CRF folder
1.1.6 Obtaining more honey dressings

Estimate during the first week of the month the number of new recruits anticipated in coming month

Review amount of product still at hand

Are more honey dressings required?

YES

Email required amount to the study manager by the first Wednesday of the month

Update Inventory log in Trial Master File

When product received, check batch number matches sample label in Trial Master File. Notify Study Manager if any problems

Update Inventory log in Trial Master File

NO

Email Study Manager by first Wednesday of the month that no product is required
1.1.7 Troubleshooting

Is it a local problem eg. cannot start computer or computer will not print?

YES
Contact your DHB helpdesk

NO

Can you access the Internet?

YES
Telephone First Contact 0800 800-710, give them the study name and tell them you have a connection problem

NO

Are you having problems with the website?

YES
1. Take a screen shot;
2. Note the time of the event;
3. Note what you did immediately before the error
PHONE the Study Manager

NO

Any other problems contact the Study Manager

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2 Guidelines for Completing Forms

This section includes information to assist with the completion of the forms on paper and on the website. General points relevant to all the forms are given first, followed by specific points relevant to individual forms.

In addition to these form guidelines, carefully read the instructions on the front of all forms. If your question is not answered, please contact Andrew Jull, Study Manager at (09) 373-7599 extn. 84744, 021 108-8923, or by emailing halt@ctru.auckland.ac.nz. The study manager will refer problems to whomever necessary.

2.1.1 Paper forms

The HALT research nurse will complete the Forms A, B, D, E, L, M (if necessary), and Z. The research nurse will also complete a Form X after Visit 2 if necessary.

Use a black ballpoint pen to complete forms. Fill in the participant identifiers on every form. Wherever possible use a registration label to indicate the registration number. The research nurse must [1] fill in the participant identifiers and [2] attach registration labels to every page of all Forms C and Forms X left with the participant for completion by the attending district nurse.

Participant initials are to be recorded using the first name and the first three letters of the last name.

- If the participant is known by a name other than their legal first name eg. William Richard (known as Rick) Johns, use their legal first name (ie WJOH).
- If the last name consist of three letters or less eg. Eddie Kaa, use the initial of the first name and the initial of the last name (ie. EK).
- If the last name starts with Mc or Mac eg. McDuggan or MacDougal, use Mc followed by the next capitalised initial (ie. McD for MacDougal).
- If the last name is hyphenated eg. John Smith-Jones, use the initial of the first name and the first three letters of the last name that appears before the hyphen (ie. JSMI).

When completing CRFs:

- Tick circles.
- Write numbers in boxes.
- Print all text in CAPITAL LETTERS
- Complete every section and answer every question on every form unless specifically instructed otherwise.
- Sign off the form as completed

2.1.2 Correcting errors on paper forms

If you make an error when completing a paper form for the first time, strike out the error with a single line (so that the corrected data is still legible) and print the correction clearly alongside. Write your initials and the date next to the correction. Do not use correction fluid.

2.1.3 Entering data from paper form onto the website

See the HALT Website Users' Guide

Data from all forms will be entered onto the HALT website by the research nurse within 24 hours of data collection, or receipt of the form. Follow instructions provided on website. Complete every section and answer every question on every form unless specifically instructed otherwise. Sign off the form as completed, by submitting the final section and re-entering your password.
2.1.4 Overdue Form C

A report will be generated if a Form C has not been loaded within the previous 10 days and the participant's ulcer has not been reported as having healed. The HALT Research Nurse will need to follow up with the district nursing service and identify if a Form C has not been completed or the district nurse visit has not been able to complete a visit.

2.1.5 Data query reports

A data query is automatically generated by our databases to check for possible errors. A data query is raised when the information entered falls outside specified values eg. if the ulcer width is greater than 50cm. If the value is correct, you can confirm it. However, if the value is incorrect, you can correct it.

See the HALT Website Users' Guide on how to resolve data queries.

2.1.6 Protocol violations

If you have any situations that occur where it is not possible to follow the guidelines in this manual or the HALT study protocol record the violation on the protocol violation notification in the Trial Master File. Fax the notification form to the Study Manager - (09) 373-1710, and retain the original in the Trial Master File.

Examples of protocol violation include:

- Any situation where the questionnaires could not be completed
- External factors that have influenced a planned follow-up visit
- The participant is not receiving the treatment to which he/she was randomised.

2.1.7 Patients off study treatment

All follow-up and all forms are required for patients regardless of whether they are using the study treatments to which they were randomised or whether they are still receiving district nursing care. Complete all sections of all forms as usual.
3 Guidelines for completing specific forms

3.1.1 Form A – Registration

Form A is to be completed for every potential participant notified to the HALT Research Nurse by consent to contact letter. This form provides information on the numbers of patients screened for participation.

- Registration number – participant registrations are to be consecutive. Use the registration number next in sequence from any previously assigned number on the Master Reg_Num List in the Trial Master File.
- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual

Q3.01 Ask the participant if their doctor has told them they have diabetes. If answer “yes”, exclude.

Q3.02 Ask the participant if their doctor has told them they have rheumatoid arthritis. If the answer is “yes” exclude. NB. This only applies to participants with rheumatoid arthritis; participants with osteoarthritis are not to be excluded.

Q3.03 Ask the participant if they are allergic to calcium alginate dressings. If the participant does not understand, explain calcium alginate dressings are the seaweed dressings. Only exclude participants who are certain they have an allergy.

Q3.04 Ask the participant if they are allergic to honey. If the participant does not understand, ask if they cannot eat honey. Only exclude participants who are certain they have an allergy.

- If the participant answers “yes” to any exclusion criteria, they are NOT eligible for the HALT trial. Please thank the participant for their interest, and explain

  that there are certain criteria to be in the honey trial and your current circumstances do not meet those criteria. However, if there are any changes in your circumstances or if you have any questions about the trial, please feel free to contact me again. My number is ...
3.1.2 Form B – Randomisation and baseline assessment

Complete Form B at Visit 1. Form B must not be completed until informed consent has been obtained. This form will provide information on participant characteristics, disease severity, lifestyle factors, and baseline ulcer size.

- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual

Section 2: Inclusion criteria
Q2.01 - Please verify from the participant's clinical record.
2.06

- If the answer is "no" to any inclusion criteria, the participant is NOT eligible for the HALT trial. Please thank the participant for their interest, and explain that there are certain criteria to be in the honey trial and your current circumstances do not meet those criteria. However, if there are any changes in your circumstances or if you have any questions about the trial, please feel free to contact me again. My number is ...

Section 3: Ulcer assessment
Chose the largest ulcer as the reference ulcer if the participant has more than one ulcer. Obtain a tracing of the reference ulcer (see page 31 for details on how to obtain wound tracing).

Q3.01 To answer yes to this question the reference ulcer must have been present for more than 6 months to the best of the participant’s memory
Q3.02 Measure across the tracing of the reference ulcer at its maximum width. Record the measure to the nearest millimetre.
Q3.03 At 90 degrees to the maximum width, measure the maximum length of the ulcer. Record the measure to the nearest millimetre.
Q3.04 Record the measure as estimated if a wound tracing could not be obtained from the participant. Record the measure as actual if the measure was obtained from a wound tracing.
Q3.05 Record the site of all leg ulcers and identify the reference ulcer.

Section 4: Treatment allocation
For further information on randomising participants, review page 30.

Q4.01 Record the allocated treatment (the operator will ask you to repeat the treatment allocation back to him/her).

Section 5: Demographics
Q5.01 - Use the flipchart and ask the participant to identify their ethnicity.
Q5.09 Record all ethnic groups the participant indicates they belong to.

Q5.10 Record any other ethnicity the participant indicates. Record text in CAPITAL LETTERS.

Q5.11 To record "yes" the participant must be the sole human occupant of the dwelling.

Q5.12 A private house, unit or apartment is defined as a dwelling the participant rents, owns or otherwise occupies, and is not in a retirement village.

Q5.13 Record text in CAPITAL LETTERS.

Section 6: Ulcer history

Q6.01 Obtain the participant's ABI from their district nursing record.

Q6.10 Occasional pain = occasional pain that does not restrict activity or require analgesia

- Daily pain that requires occasional use of pain relief = daily pain with moderate activity limitation, with occasional use of analgesia (no pattern discernible)
- Daily pain that requires regular use of pain relief = daily pain that severely limits activity or requires regular use of analgesia

Q6.11 Varicose veins must be greater than 4mm in diameter to qualify as varicosities.

Q6.12 Presume venous oedema if there is a significant effect of standing vs limb elevation and other evidence of venous disease (eg varicose veins). Pitting or spongy oedema does not qualify. Onset of venous oedema must be daily – record timing of first onset during the day eg. daily in the afternoon if oedema first appears in after 1200pm.

Q6.13 Focal pigmentation over varicose veins should be recorded as no pigmentation. Focal means confined to a small, related area.

Q6.14 Cellulitis refers to area of inflammation or erythema, not infection. Significant venous eczema means eczema that is inflamed.

Q6.15 An ulcer means a skin break with dermal involvement.

Q6.17 Record total number of ulcers. If ulcers present on both legs, record total number of ulcers on both legs.

Q6.20 Record frequency that participant has worn compression in last week.

- Wears bandages most of the time = 5-6 days
- Wears bandages all the time = 7 days (it is acceptable for the participant to have removed them that morning prior to your visit)

Q6.21.1 N.B. This question determines whether the ulcer at this visit will be part of the HALT sub-study. It is only on the paper CRF for South Auckland centre, but will appear on the website for all centres. Research nurses in Auckland, Waikato and Christchurch centres should always enter 'No' for this question on the website as they are not

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involved in the sub-study. Research nurse at South Auckland centre must enter 'Yes' or 'No' on both the paper CRF and website as follows: Enter ‘Yes’ if:
   - At least one successful photo was obtained using the pxt camera phone for the reference ulcer.
Otherwise, enter ‘No’.

Section 7: Dressing and compression system
Record the dressing and compression system used when you have rebandaged the participant’s leg.

Q7.01 – Only answer these questions if the participant has been allocated to Q7.15 “Usual Care”.

Q7.14 Record text in CAPITAL LETTERS.

Q7.16 – All these questions for all participants
Q7.23

Q7.23 Record text in CAPITAL LETTERS.

Section 8: Health

Q8.01 To record “yes” the participant must have had investigative imaging and been told by a doctor that they have had a DVT.

Q8.09 Record text in CAPITAL LETTERS.

Q8.14 To record “yes” to Q8.14, the participant must be taking medication prescribed by a doctor or nurse practitioner. Dietary supplements, vitamins and complementary medications DO NOT qualify, even if prescribed.

Section 9: Lifestyle

Q9.09 To record “yes” the participant must have had a drink once per week for 1 in every two weeks during the past year.

Q9.10 If the participant answers yes to Q9.09, ask how many glasses, bottles or casks of wine they have had on an average week – use the flipchart to calculate the number of standard drinks of wine per week.

If the participant drinks sherry or port, include these in the calculation of standard drinks of wine per week.

Q9.11 If the participants answers yes to Q9.09, ask how many nips or bottles of spirits they have had on an average week – If bottles, you will need to identify what size can or bottle they are referring to. Use the flipchart to calculate the number of standard drinks of spirits per week.

Q9.12 If the participants answers yes to Q9.09, ask how many cans or bottles of beer they have had on an average week – you will need to identify what size can or bottle they are referring to. Use the flipchart to calculate the number of standard drinks of beer per week.

Q9.13 You may choose to use the flipchart to assist the participant with selecting a mobility option.
Section 10: Questionnaires
Give the participant the questionnaire booklet to complete. Follow script for Form Q. If the participant has visual problems, please read the questions and possible responses aloud for them. DO NOT interpret the questions.

Q10.01 To record “yes” the participant must have completed all the questions to the SF-36 on pages 2, 3 and 4 in Participant Questionnaire. See 1 and 2 below if the participant refuses to do the questionnaire or does not complete all the questions to the SF-36.

Q10.02 If the participant does not answer some questions or complete all the SF-36 questionnaire, record their reason[s] in CAPITAL LETTERS.

Q10.03 To record “yes” the participant must have completed all the questions to the Charing Cross Ulcer Questionnaire on pages 5 and 6 in Participant Questionnaire. See 1 and 2 below if the participant refuses to do the questionnaire or does not complete all the questions to the Charing Cross Ulcer Questionnaire.

Q10.04 If the participant does not answer some questions or complete all the Charing Cross Ulcer Questionnaire, record their reason[s] in CAPITAL LETTERS.

Q10.05 To record “yes” the participant must have completed all the questions to the EQ-5D Questionnaire on pages 7 and 8 in Participant Questionnaire. See 1 and 2 below if the participant refuses to do the questionnaire or does not complete all the questions to the EQ-5D Questionnaire.

Q10.06 If the participant does not answer some questions or complete all the EQ-5D Questionnaire, record their reason[s] in CAPITAL LETTERS.

1. If the participant refuses to fill out the questionnaires, they are not required to do so. However, gently emphasize that:
   - This information is as important as the other data
   - That it will provide helpful health-related information
   - That it is simple to fill out

2. If the participant does not complete the questionnaire, ask the participant if they had trouble understanding any of the questions and why. Reread the question[s] to them verbatim – DO NOT rephrase the question. If the question[s] is still unanswered, accept the incomplete questionnaire and record their reason[s] in Q10.02, Q10.04 and Q10.06 in CAPITAL LETTERS.

3. If the participant requests clarification, DO NOT explain what the question means. Simply reread it verbatim and suggest the participant use his/her own interpretation of the question.

4. If the participant is having trouble with the response choices, or want to answer something different than what is on the form, guide them to respond with one of the pre-set categories by saying

   *I know it may be hard to think this, but which of these answers most closely says what you are thinking or feeling.*

Before you leave
- Enter the participant’s initials and date of birth and attach a registration label on every page of each form C in the participant kit.
- Enter your fax number on page 1 of each Form C.
- Attach the allocated treatment label to page 1 (SECTION 3) of every form C in the participant kit.
- Enter the participant’s initials and date of birth and attach a registration label on every page of each form X in the participant kit.
- Enter your fax number on page 1 of each Form X.

After completing the baseline visit you will need to obtain a photocopy of the front sheet from the participant's district nursing records. This information must include the participant’s name, date of birth and NHI number. Retain this in the participant’s CRF folder – the independent Study Monitor will use this information during the monitoring visit.
3.1.3 Form C – District Nurse form

Form C is to be completed by the district nurses after each visit to the participant. This form will provide information on change in the participant’s ulcer status and data for cost analysis.

The HALT Research Nurse is to ensure that:
- Fifteen (15) copies of this form are to be left in the participant kit
- A registration label is attached to each page on each form
- Participant identifiers are filled out on each page on each form
  - Date of birth – use dd/mm/yyyy format eg. 01/12/1937
  - Participant initials – follow guidelines on page 9 of this manual
- The fax number for the HALT Research Nurse is recorded on page 1 of each form
- The treatment allocation is recorded on page 1, Section 3 of each form.

Section 1: Assessment date
Q1.01 Use dd/mm/yyyy format eg. 01/12/2005
Q1.02 District nurse to record time they arrived in the car at the participant’s address.

Section 2: Ulcer healing
Q2.01 To record “yes” to this question, the ulcer must be completely resurfaced with epithelium (epithelialisation). The presence of a scab does not necessarily preclude healing; gently remove the scab to determine whether there is complete epithelialisation underneath.

Section 3: Allocated treatment and dressing
Answer Q3.01-3.02 only if the participant was allocated to HONEY.
Q3.01 To record “yes” to Q3.01 the participant must have been allocated to honey and still receiving the honey dressing.
Q3.02 Record text in CAPITAL LETTERS.

Answer Q3.03-3.17 only if the participant was allocated to USUAL CARE, or allocated to honey but now using another dressing.
Q3.17 Record text in CAPITAL LETTERS.

Section 4: Bandaging
Q4.03 Record text in CAPITAL LETTERS.
Q4.10 Record text in CAPITAL LETTERS.

Section 5: Infection
Q5.01 To record “yes” to Q5.01 clinical signs of infection must be present.
Q5.06 To record “yes” to Q5.06, a wound swab can have been sent anytime since the last district nurse visit, including the current visit. Answer “yes” if a pus aspirate or tissue biopsy was sent instead of a wound swab.
Q5.07 Use dd/mm/yyyy format eg. 01/12/2005
Section 6: Antibiotics

Q6.01 To record "yes" to Q6.01, the antibiotic must have been prescribed for treatment of the leg ulcer.

Q6.02 Record generic name in CAPITAL LETTERS.

Q6.03 Record the prescribed duration of the course of antibiotics.

Q6.04 Record generic name in CAPITAL LETTERS.

Q6.05 Record the prescribed duration of the course of antibiotics.

Section 7: Health professional

Q7.01 To record "yes" to Q7.01, the visit to or by another health professional must have been for treatment associated with the leg ulcer.

Q7.02 Record type of health professional in CAPITAL LETTERS eg. OCCUPATIONAL THERAPIST or NATUROPATH.

Q7.03 Record the number of visits since the last district nurse visit

Q7.04 Record type of health professional in CAPITAL LETTERS eg. OCCUPATIONAL THERAPIST or NATUROPATH.

Q7.05 Record the number of visits since the last district nurse visit

Section 8: Adverse events

Q8.01 An Adverse Event includes any illness, sign, symptom, or clinically significant abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the treatment(s) under study. It also includes Serious Adverse Events.

Section 9: Completion of visit

Q9.01 District nurse to record the time that they departed from the participant's address in the care after completing all tasks associated with the visit.

Section 10: Signature

Q10.01 District nurse to print name in CAPITAL LETTERS, sign and date Form C.
3.1.4 Form D – 12-week follow-up

Complete Form D at Visit 2, 12 weeks after randomisation. This form will provide information on change in the participant's ulcer.

- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual

Section 2: Ulcer assessment

Q2.01 To record "yes" to this question, the ulcer must be completely resurfaced with epithelium (epithelialisation). The presence of a scab does not necessarily preclude healing; gently remove the scab to determine whether there is complete epithelialisation underneath. Check Q3.05 on Form B to identify site of reference ulcer.

Q2.02
- Occasional pain = occasional pain that does not restrict activity or require analgesia
- Daily pain that requires occasional use of pain relief = daily pain with moderate activity limitation, with occasional use of analgesia (no pattern discernible)
- Daily pain that requires regular use of pain relief = daily pain that severely limits activity or requires regular use of analgesia

Q2.03 Varicose veins must be greater than 4mm in diameter to qualify as varicosities.

Q2.04 Presume venous oedema if there is a significant effect of standing Vs limb elevation and other evidence of venous disease (eg varicose veins). Pitting or spongy oedema does not qualify. Onset of venous oedema must be daily – record timing of first onset during the day eg. daily in the afternoon if oedema first appears in after 1200pm. Occasional oedema does not qualify.

Q2.05 Focal pigmentation over varicose veins should be recorded as no pigmentation. Focal means confined to a small, related area.

Q2.06 Cellulitis refers to area of inflammation or erythema, not infection. Significant venous eczema means eczema that is inflamed.

Q2.08 An ulcer means a skin break with dermal involvement.

Q2.09 Record total number of ulcers. If ulcers present on both legs, record total number of ulcers on both legs.

Q2.12 Record frequency that participant has worn compression in last week.
- Wears bandages most of the time = 5-6 days
- Wears bandages all the time = 7 days (it is acceptable for the participant to have removed them that morning prior to your visit)
Section 3: Questionnaires
Give the participant the questionnaire booklet to complete. Follow script for Form Q. If the participant has visual problems, please read the questions and possible responses aloud for them. DO NOT interpret the questions.

Q3.01 To record “yes” the participant must have completed all the questions to the SF-36 on pages 2, 3 and 4 in Participant Questionnaire. See 1 and 2 below if the participant refuses to do the questionnaire or does not complete all the questions to the SF-36.

Q3.02 If the participant does not answer some questions or complete all the SF-36 questionnaire, record their reason[s] in CAPITAL LETTERS.

Q3.03 To record “yes” the participant must have completed all the questions to the Charing Cross Ulcer Questionnaire on pages 5 and 6 in Participant Questionnaire. See 1 and 2 below if the participant refuses to do the questionnaire or does not complete all the questions to the Charing Cross Ulcer Questionnaire.

Q3.04 If the participant does not answer some questions or complete all the Charing Cross Ulcer Questionnaire, record their reason[s] in CAPITAL LETTERS.

Q3.05 To record “yes” the participant must have completed all the questions to the EQ-5D Questionnaire on pages 7 and 8 in Participant Questionnaire. See 1 and 2 below if the participant refuses to do the questionnaire or does not complete all the questions to the EQ-5D Questionnaire.

Q3.06 If the participant does not answer some questions or complete all the EQ-5D Questionnaire, record their reason[s] in CAPITAL LETTERS.

1. If the participant refuses to fill out the questionnaires, they are not required to do so. However, gently emphasize that:
   - This information is as important as the other data
   - That it will provide helpful health-related information
   - That it is simple to fill out

2. If the participant does not complete the questionnaire, ask the participant if they had trouble understanding any of the questions and why. Reread the question[s] to them verbatim – DO NOT rephrase the question. If the question[s] is still unanswered, accept the incomplete questionnaire and record their reason[s] in Q3.02, Q3.4 and Q3.06 in CAPITAL LETTERS.

3. If the participant requests clarification, DO NOT explain what the question means. Simply reread it verbatim and suggest the participant use his/her own interpretation of the question.

4. If the participant is having trouble with the response choices, or want to answer something different than what is on the form, guide them to respond with one of the pre-set categories by saying

   I know it may be hard to think this, but which of these answers most closely says what you are thinking or feeling.
Q3.07 To record "yes" to Q3.07, the participant must be taking medication prescribed by a doctor or nurse practitioner. Dietary supplements, vitamins and complementary medications DO NOT qualify, even if prescribed.

Q3.08 An Adverse Event includes any illness, sign, symptom, or clinically significant abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the treatment(s) under study. It also includes Serious Adverse Events.

Section 4: Additional information
Q4.02 Record text in CAPITAL LETTERS.
Q4.04 Record text in CAPITAL LETTERS.
Q4.05 Record text in CAPITAL LETTERS.

Section 5: Ulcer photography
Q5.01 Take two photographs of the reference ulcer. If the reference ulcer has healed, take two photographs of the site of the healed leg ulcer. This information is necessary to verify healing has occurred.

Q5.01.1 N.B. This question determines whether the ulcer at this visit will be part of the HALT sub-study. It is only on the paper CRF for South Auckland centre, but will appear on the website for all centres. Research nurses in Auckland, Waikato and Christchurch centres should always enter 'No' for this question on the website as they are not involved in the sub-study. Research nurse at South Auckland centre must enter 'Yes' or 'No' on both the paper CRF and website depending on the following criteria. Enter 'Yes' if:
- The ulcer is NOT healed AND...
- At least one successful photo was obtained using the pxt camera phone.
Otherwise, enter 'No'
3.1.5 Form E – 6-month follow-up
Complete Form E at 6 months after randomisation. This form will provide information on ulcer status after the trial treatment has completed.

- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual

Section 1: Assessment date
Q1.01 Record date of telephone contact.

Section 2: Ulcer recurrence
Q2.01 Record “yes” to Q2.01 if the participant reports a new leg ulcer has occurred on the same leg as the original reference ulcer (check Q3.05 in Form B). NB the participant does not need to have an active ulcer currently, as the ulcer may have healed again.

Q2.02 Record “yes” to Q2.02 if they currently have an ulcer on the same leg as the reference ulcer (check Q3.05 in Form B).
3.1.6 Form L – Laboratory results

Complete a Form L each time a participant is reported as having had a wound swab taken. This form will provide information for the cost analyses and microbiology.

- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual

Q1.02 Record date of laboratory report

Q1.03 To record "yes" to Q1.03 the report must identify the species of bacteria or report mixed species present. If only skin flora is reported, record "no".

Q1.09 Record text in CAPITAL LETTERS.

Q1.11 Record text in CAPITAL LETTERS.

Q1.12 Please record who the report was sent to (this will facilitate the monitoring of source information if necessary). Tick "GP" if the report was sent to the participant’s GP, "District nurse" if the report was sent to the district nursing service, "laboratory database" if the information was obtained directly from a laboratory database or web page.
3.1.7 Form M – Concomitant medications

Complete Form M if the participant is taking any medication prescribed by a doctor or nurse practitioner. Dietary supplements, vitamins and complementary medications DO NOT qualify, even if prescribed. This form will provide information for the cost analysis.

- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual
- Record the GENERIC name of the drug
- Record the total daily dose ie if prescribed 400mg three times per day, record the dose at 1200mg
- Record the units used. The following abbreviations are acceptable

<table>
<thead>
<tr>
<th>Drop</th>
<th>Drops (gutt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IU</td>
<td>International unit</td>
</tr>
<tr>
<td>g</td>
<td>Grams</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>mcg</td>
<td>Micrograms</td>
</tr>
<tr>
<td>ml</td>
<td>Millilitres</td>
</tr>
<tr>
<td>tab</td>
<td>Tablets</td>
</tr>
<tr>
<td>Puff</td>
<td>Puffs</td>
</tr>
<tr>
<td>Unit</td>
<td>Units</td>
</tr>
</tbody>
</table>

- Record date of first prescribed dose if known.
- Record date of treatment stopped.
3.1.8 Form Q – Participant questionnaire

Ensure Form Q is completed by the participant at Visit 1 and Visit 2.

- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual

Form Q utilises the following self-reported health-related quality of life (HRQoL) questionnaires:

- **Short Form 36 (SF-36):** This is a generic measure commonly employed in clinical trials. It consists of 36 questions that measure HRQoL generally across eight domains – physical functioning, role limitations due to physical functioning, bodily pain, vitality, general health, social functioning, role limitations due to emotional function, and mental health.

- **Charing Cross Venous Ulcer Questionnaire (CCVUQ):** This a HRQoL measure designed specifically for people with venous leg ulcers. It consists of 21 questions that measure how HRQoL is affected by the participant's leg ulcer.

- **EuroQol (EQ-5D):** This a short HRQoL measure that can be useful in when assessing cost-effectiveness. It consists of general questions.

The questionnaires are to be completed by the participant wherever possible. They usually take about 10-15 minutes to complete.

The following is a suggested script to use when giving the questionnaire booklet to the participants.

We would like to better understand how you and other persons in this study feel, how well you are able to do your usual activities and how you rate you own health. To help us better understand these things about you and other people, please complete this questionnaire about your health.

*The questionnaire is simple to fill out. Be sure to read the instructions on the top of the second page (point them out). Remember, this is not a test and there are no right or wrong answers. Choose the response that best represents the way you feel. I will quickly review the questionnaire when you are done to make sure all the items have been completed.*

*You should answer these questions yourself. Spouses and other family members or visitors should not help you.*

After the administration of the questionnaire, check that all questions are completed correctly. Make that the details at the front of the form (date, visit number, name of administrator) are complete. If there is any missing information, contact the participant and try and obtain the required information from them. Any logic / data queries will be referred back to study nurses, i.e. missing information.

If the participant is unable to complete the survey, accept the survey as incomplete, and record the reason for any missing data on the Form B (Q10.01-10.06) for visit 1 or Form D for Visit 2 (Q3.01-3.06).
If the participant has **VISUAL** problems, the research nurse may read the questionnaire out aloud for the participant. No-one, other than the participant should provide answers or input to the questions. If a participant has difficulty answering a question, reread it to them verbatim, but do **NOT** rephrase the question.

Table 1. DOs and DON'Ts of questionnaire administration

<table>
<thead>
<tr>
<th>DOs</th>
<th>DON'Ts</th>
</tr>
</thead>
<tbody>
<tr>
<td>DO have participants fill out the questionnaire or answer the questions by themselves</td>
<td>DON'T allow spouses or family members to help the participant to respond to questionnaire</td>
</tr>
<tr>
<td>DO request and encourage participants to fill out the questionnaire</td>
<td>DON'T force or command participants to fill out the questionnaire</td>
</tr>
<tr>
<td>DO tell participants to answer a question based on what they think the question means</td>
<td>DON'T force or command participants to fill out a particular question</td>
</tr>
<tr>
<td>DO read or repeat a question verbatim</td>
<td>DON'T interpret or explain a question</td>
</tr>
<tr>
<td>DO encourage participants to fill out all questions</td>
<td>DON'T accept an incomplete questionnaire without first encouraging the participant to fill out unanswered questions</td>
</tr>
<tr>
<td>DO thank participants for filling out the questionnaire</td>
<td>DON'T minimise the importance of the questionnaire</td>
</tr>
</tbody>
</table>

Complete the box on front page. Tick "baseline" if the questionnaire was administered during Visit 1 or 12-week assessment if the questionnaire was administered during Visit 2.
3.1.9 Form X – Adverse events

A Form X is to be completed whenever an Adverse Event is detected. An Adverse Event includes any illness, sign, symptom, or clinically significant abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the treatment(s) under study. The district nurses must be instructed to complete a Form X whenever an untoward clinical occurrence occurs.

- Date of birth – use dd/mm/yyyy format eg. 01/12/1937
- Participant initials – follow guidelines on page 9 of this manual

The HALT Research Nurse must fill in their fax number so the district nurse can forward a completed Form X. If the district nurse faxes the form, the original is to be retained in the patient’s clinical record.

Section 1

- An Adverse Event is any untoward clinical occurrence in a participant. An Adverse Event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the product. It also includes serious adverse events.
- The underlying illness or disorder (ie. the diagnosis) should be recorded if known, otherwise presenting symptoms should be recorded.
- The district nurse must indicate the severity of the AE according to the codeframe in the Form X instructions and whether the district nurse believes the AE was caused by the dressing being used on the ulcer (irrespective of dressing type).

Section 2

A Serious Adverse Event (SAEs) is any untoward medical occurrence that:

- Results in death
- Is life-threatening (an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a cancer;
- Is an important medical event (a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject/subject or may require intervention eg. medical, surgical to prevent one of the other serious outcomes listed in the definition above)

Section 4

Upon receipt of the Form X the Halt Research Nurse must:

1. Document the date of receipt Q4.01
2. Check Q2.01 to determine whether it is a serious adverse event (SAE).

If the Form X reports a SAE:

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1. Contact the study manager by phone as soon as possible after receiving the Form X. Phone: (09) 373-7599 extn 84744 or 021 108-8923
2. Document the date the study manager has been informed (Q4.02) and complete a Serious Adverse Event Notification in the Trial Master File
3. Fax the Form X to (09) 373-1710.
3.1.10 Form Z – Contact details

This information is crucial for retaining contact with the participant and to provide information to the participant's general practitioner. The Form Z should be updated with each new contact:

- Record the participant's full name and address, including home/mobile telephone number(s) and email address. If the participant lives in two places over course of the year, record the main place of residence.

- Ask the participant to identify a close family member or friend, who may be able to provide the participant's contact details if our records at follow-up are no longer accurate. Complete the contact details for this person.

- Complete name and contact details of the current GP. If the subject has no usual GP, supplementary questions “who was the last GP you saw?” or “who would you go to if you became ill?” may be used. A GP name and practice address is usually adequate to identify the GP; the extra contact details should be obtained by contacting the GP surgery directly; explain that the GP's patient is participating in the HALT Trial and the details are necessary in the unlikely event we need to contact the GP.

Contact details of the participant, alternate contact and their general practitioner must be updated at every assessment.

If the contact details of the participant or their general practitioner change, then fill in a new Form Z.

The information contained on this forms is confidential. File completed Forms Z in the participant's CRF Folder and store in a locked filing cabinet.
4 Recruitment process

4.1.1 Material required for Visit 1 (randomisation and baseline assessment)

- Research Nurse ID
- Copy of Participant Information Sheet
- Consent forms
- Copy of letter giving ethical approval to study
- Copy of study protocol & manual of operations
- Registration labels
- Treatment allocation labels
- Copy of study protocol & manual of operations
- Registration labels
- Treatment allocation labels
- Copy of Quality of Life questionnaire (Form Q)
- Participant kit box including:
  - 15 copies of Form C (District nursing)
  - 5 copies of Form X (Adverse Events)
  - Box of 20 honey dressings (if allocated to honey)
  - Honey dressing instructions (if allocated to honey)
- Black ballpoint pen
- Indelible fine tip marker pen
- Ruler
- USL wound mapping grid
- Digital camera
- Cell phone (pocket phone - South Auckland centre only)
- Back-up alkaline batteries for camera
- Flipchart
- Manual of procedures

4.1.2 Recruiting people who do not speak English

English does not need to be the participant's first language. If the participant requires a translator, arrange a translator through your normal service, notify the Study Manager (halt@ctru.auckland.ac.nz) and arrange for Auckland Uniservices Ltd to invoice.

4.1.3 Obtaining consent

Written consent MUST be obtained from all participants. The signed consent will be filed in the participant's study file. For written consent to be valid the participant must be suitably informed of the study so that they can make an independent choice about whether to participate. The participant should receive a copy of the consent form at the study visit. Issues to be covered in the information sheet should be reviewed carefully with each participant. Do not assume that every person has read the information sheet or that they can read. The consent form should be signed and dated by the participant. The potential participant should have details (refer information sheet) regarding:

The study description, including
- A statement of the purpose of the study
- An explanation of who the researchers are.
- An explanation of why the participant qualifies for the study.
- An explanation that this is a randomised study, therefore they might not receive the honey dressing.
- The type of participants studied and the number likely to be involved.
Tell the operator if the participant meets the inclusion criteria. Participation:

- That the supply of information by the participant is entirely voluntary.
- That the participant may refuse to answer any of the questions or refuse any of the clinical examination. They do not have to give a reason for doing so.
- That the participant’s health care will not be affected in any way should they choose to withdraw from the study.
- All participants have the right to access their data and/or to remove it from the study.
- All participants have the right to have questions answered.
- A person outside of the study is available to be contacted should they have any concerns i.e. a health advocate.

Data Collection:

- Personal information will be collected about them but that this information will be kept strictly confidential.
- That the information will be kept in a locked cabinet at the study site and/or in a locked room at the Clinical Trials Research Unit, School of Population Health, University of Auckland.
- All computerised information will be password protected on a computer.
- No one, other than the study investigators, will have access to this data.
- All information will be published or presented in a way that no individual can be identified.
- Unless otherwise requested, the participant’s GP will be informed that they have entered the study and of the study results when complete.

4.1.4 Randomising the participant

Complete questions 2.01-2.06 on Form B. All questions must be answered "yes" for the participant to meet the HALT Trial inclusion criteria. If the participant does not meet the inclusion criteria, please thank the participant and explain:

that there are certain criteria to be in the honey trial and your current circumstances do not meet those criteria. However, if there are any changes in your circumstances or if you have any questions about the trial, please feel free to contact me again. My number is ...

If the participant meets the inclusion criteria, proceed to obtaining answers to questions 3.01 - 3.03, and documenting the site of the reference ulcer (Q3.04). When you have obtained this information, telephone First Contact on 0800 800 710. Use your cell phone for this purpose. If you cannot obtain a cell phone signal, request to use the participant’s telephone and explain the call will be made to a free call 0800 number.

Tell the operator at First Contact you "have patient to be randomised into the honey trial". The operator will ask you:

- To verify that the inclusion criteria are all answered "YES".
- Has the ulcer been present for more than 6 months?
- The maximum width of the reference ulcer – please give your response in millimetres.
- The maximum length of the reference ulcer – please give your response in millimetres.
The operator will proceed to randomise the participant. The participant will be allocated to either honey or usual care. The operator will read out the allocated treatment and ask you to repeat the treatment allocation back to him/her.

Record the allocated treatment on Form B, Q4.01. Randomisation is now complete. Proceed to record the participant responses to the remainder of Form B.

4.1.5 Participant kit
Leave a kit with the participant. Tape a HALT participant kit front sheet to the box, and put an address label on the front sheet so the participant and the district nurses know how to get in touch with you. Leave the following in the kit:
- 15 copies of Form C (District nursing)
- 5 copies of Form X (Adverse Events)
- Box of 20 honey dressings (if allocated to honey)
- Honey dressing instructions (if allocated to honey)
- Instructions for filling out the Form C (download from Study Documents on the HALT website)

4.1.6 Informing the participant’s GP
Unless the participant indicates otherwise on the consent form, notify the participant’s current GP (as identified on Form Z) of their involvement in the HALT Trial. Use the form letter provided. More copies of the form letter can be obtained from the HALT Website (see the Study Documents menu).

5 Obtaining a wound tracing
A 10 x 10cm single use acetate, supplied by USL Ltd, will be used to trace the outline of the leg ulcer.

1. Lay over the acetate over the reference ulcer
2. Trace an outline of the reference ulcer with a indelible spirit pen. The outer edge of the tracing line should equal the border between the reference ulcer and intact skin. NB. If you are having trouble distinguishing between soggy skin and ulcers, try cooling the acetate in the fridge for a few minutes. When place the acetate on the skin – ulcerated areas should steam up, whereas intact skin does not.
3. Remove the backing of the acetate and dispose in the rubbish.
4. For the baseline measure prior to randomisation, lay the acetate on a hard flat surface. Measure the maximum width of the reference ulcer to the nearest millimetre. Measure the maximum length of the reference ulcer to nearest millimetre. NB. The measurement of maximum length must be at 90° to the measure of maximum width.

If the ulcer is larger than 10 x 10cm, use two A4 acetate sheets in the same manner as the 10 x 10cm acetate, one A4 sheet being used as a backing and disposed off after the tracing.

6 Obtaining a photograph using the digital camera
Chose a mylar ring that encloses the leg ulcer and is completely visible when the leg is viewed side-on. Position cross-lines on mylar ring so that they are in line with the vertical axis of the leg. Select auto on the program wheel and turn the camera on. Ensure:
1. The auto flash is on (Flash icon should be visible on the LCD screen)

2. The macro option is on (flower icon should be visible on the LCD screen)

3. If the LCD screen does not start when the camera is turned on, press the display button.

Position the camera directly over the ulcer, about 20 cm above the ulcer. Gently press down on the shutter button to auto-focus on the ulcer. ZOOM in to ensure all the following are visible in the LCD viewfinder:

1. The complete circle of the mylar ring
2. The registration label, and
3. The ring size number.

Once satisfied with the image of the LCD, press the shutter button firmly down and hold still as the screen blacks out. A photo has been taken.

Review the image – choose the arrow on this switch

Ensure the image is in focus and the following are visible:

1. The complete circle of the mylar ring
2. The registration label
3. The ring size number

Repeat the process for a second image.

6.1.1 Troubleshooting photos:

- If photo overexposed (eg. photo very pale or image lost in white light), you may be positioning the camera to close to the leg when using the flash (and getting reflected light on the lens). Position the camera further away from the leg and zoom in to get a closer picture).

- If the leg ulcer is larger than the largest mylar ring, lay gladwrap over the ulcer, ensuring it is smooth on the ulcer surface and lay on largest mylar ring that will be completely visible when the leg is viewed side-on. You will probably need to turn off the flash as this will cause reflections to show up in the photo. Therefore the photo needs to be taken with as much natural light as possible ie. Sit the participant right by an unshaded window or (on a porch if possible).

- If mylar ring that encloses the ulcer without touching is not completely visible in the digital photo, lay gladwrap over the ulcer, ensuring it is smooth on the ulcer surface and lay on largest mylar ring that will be completely visible when the leg is viewed side-on. You will probably need to turn off the flash as this will cause reflections to show up in the photo. Therefore the photo needs to be taken with as much natural light as possible ie. Sit the participant right by an unshaded window or (on a porch if possible).
7 Obtaining a photograph using the pxt camera phone (South Auckland centre only)

Use the same basic principles listed above to take the photos with the pxt camera phone (also see section below: General Information – How to use the I-mate JAM pxt camera phone for details on phone usage).

Wherever possible, ensure there is good light before taking the photo as the pxt phone does not have an in-built flash.

8 Material required for Visit 2 (12-week follow-up)
- Research Nurse ID
- The participant's CRF Folder
- Copy of Forms D, M, X and Z
- Registration labels
- Copy of Quality of Life questionnaire (Form Q)
- Black ballpoint pen
- Indelible fine tip marker pen
- USL wound mapping grid
- Digital camera.
- Pxt phone – South Auckland centre only
- Manual of procedures
- Back up alkaline batteries for camera

9 Monitoring visits
An auditor will visit each site after 5 participants have been randomised and again after 50 participants have been randomised. Review the Monitoring SOP in the LCC Trial Master File for more specific information.

The site visit will include:
- Viewing all study materials to make sure they are the latest version
- Examining completed study records and discussing any problems with data recording
- Feedback from the data management team about any specific data entry problems occurring at the site
- Viewing storage of completed records
- Discussion of any general issues or problems that are being encountered at the site.
10 General information

10.1.1 How to remove camera batteries

1. Place camera upside down on table. Pull button towards your right.

2. Battery hatch will spring out slightly and open

10.1.2 How to charge the camera batteries

1. Select NiMH (Nickel metal) on switch before putting batteries into charger.

2. Place NiMH batteries into charger. Positive pole of battery must be pointing towards the top of the charger.

3. Connect AC Adaptor to top of battery pack and plug into power source.

4. Red LED lights will come on, indicating charging is in progress. The lights will go out when the battery is fully charged. Charging should take about 3 hours.

5. Unplug battery charger when not in use.

Note
- It is normal for the batteries to become hot during charging.
- New batteries may need to charged and discharged several times before their optimum charge life is achieved.
- Do NOT try to recharge alkaline batteries. Only use NiMH batteries.
- If the NiMH batteries lose their charge while the camera is in use, use the alkaline replacement batteries until the NiMH batteries have been recharged.
- If you require new NiMH batteries, Please contact Andrew Jull, Study Manager, 09 373-7599 extn 84744; email halt@ctru.auckland.ac.nz; mobile 021 108-8923.
10.1.3 How to remove the flash card from the camera and put in card reader

1. Insert your thumbnails into joint and push away from you.

2. Open card hatch and press down on black card release button.

3. Pull card out gently.

4. Put the card into card reader. Note: the card will only go in one way.

5. Press card down firmly. You will now be able to upload photos.

6. Connect the card reader to the computer. Look for a USB connection either on the side of the keyboard, or at the back of the computer.
10.1.4 How to remove the compact flash card from the card reader

Complete steps 1 – 3, and remove the card once the computer confirms it is safe to remove the device.

10.1.5 How to use the i-mate JAM pxt phone (South Auckland centre only)

For detailed information please refer to the User Guide supplied with the i-Mate. The following can be used as a quick-reference guide, or contains items that were configured specifically for CTRU usage of the device.

11 Common Terms:

- **Start menu**: This menu is accessible from the top-left corner of the screen. It is represented by the standard windows icon (4-colored flag symbol), with the word ‘start’ written next to it.
12 Sending messages (User Guide Chapter 8):
- To launch the message program tap Start -> messaging
- Messaging presents 2 pieces of information in the top toolbar. On the right is the 'sort by' item, and on the left is the folder name. By tapping on the folder name, you can check that you are using the correct messaging account called 'halt1'
- Another way to check this is to select Accounts -> halt1 from the menu at the bottom of the screen
- By selecting halt1 as the messaging account you can send e-mails and attachments to CTRU staff
- Other accounts (e.g. text messaging) are accessible in the same way, however only the halt1 account allows e-mail to be sent
- If sending images via e-mail, please send to the following address: haltphone@ctru.auckland.ac.nz

13 Using the camera (User Guide Chapter 10):
- The camera can be activated pressing the camera button on the left hand side of the device, or by tapping Start -> camera
- To take a picture, press the camera button again, or press the middle button in the centre of the navigation pad

14 Tips for using the camera:
- Press the shutter down slowly, and continue to hold it down when taking a picture. This is a work-around for the lag it takes to capture the image.
- A focal distance of about 40 cm appears to render better images
- Try to prevent high contrast areas on the image e.g. highly lit areas vs. dark areas.
- Adjusting contrast etc (as outlined on page 162 of the manual) can render better images in some circumstances

15 Connecting the device to your PC:
- Use the supplied USB cable to connect the device to the PC
- Make sure that the supplied synchronisation software is installed. The software can be found on the CD-ROM that comes with the device
- Once the software is installed, and the device is connected, the device can be browsed using Windows Explorer.
- The images on the device can be copied to the PC, and uploaded as per standard image upload procedure.
Appendix 7

Apinate user guidelines for the HALT trial
Guidelines for the use of ApiNate dressings

ApiNate is the brand name of a dressing, which is a combination of an alginate dressing impregnated with UMF honey.

Wound Cleansing: Wounds dressed by honey are cleaned the same as wounds when using other dressings. With ulcers that are granulating it is unnecessary to clean the wound bed itself when using Apinate, as the high osmolarity of honey results in continual washing of the wound bed with exudate. However it is important to clean the surrounding skin and leg of the patient in order to maintain skin hygiene. This is normally achieved satisfactorily with the use of soap and water.

Applying ApiNate to wounds: It is necessary when to make sure the dressing is in direct contact with the wound bed. In the case of ulcers that have a crater or cavity you need to cut the Apinate to size, to fit the base of the wound. Continue to fill the cavity with layers of Apinate until the dressing has filled the cavity to the level of the surrounding skin. Apply a final piece of Apinate that covers the entire dressing and overlaps the surrounding skin by approx 0.5 cm. It is not necessary when applying compression bandaging to cover the Apinate with any other type of dry dressing prior to applying bandaging.

ApiNate dressings can sometimes be quite stiff when unpackaged. This can make it difficult to place them on a wound in such a way that they conform to the wound bed. The stiffness of the dressings is due to the process of pressing the honey into the alginate dressing. A tip to resolve this problem is to hold one edge of the dressing in each hand and alternately move your hands back and forwards. This “loosens” the dressing and makes it more malleable when applying to the wound.

Wound maceration: Honey itself does not macerate skin. Its high osmolarity means it is more likely to keep skin dry by drawing intercellular fluid away from the skin into the dressing. For these reasons it is safe to overlap ApiNate onto the skin surrounding the wound. Wound maceration, when using ApiNate indicates either not enough ApiNate is in contact with the wound or the dressing is not being changed frequently enough to manage the level of exudate.

Inflammation of surrounding skin: Honey has anti-inflammatory properties, again mostly due to its osmolarity. In the case of wounds that have a margin of surrounding inflammation it is recommended to cover this area with ApiNate as the honey will decrease the inflammation.

Pain: Honey is known to cause pain or a stinging sensation for some patients. This is due to the acidity of honey and is usually isolated to the 10-30 minutes after honey is applied to a wound. Any pain greater than this indicates a possible reaction to the honey, or the wound bed is inflamed to the point that honey is not tolerated. This would suggest an inflammatory process is underway, such as infection or other inflammatory disorder.

Pain is not experienced by all patients and varies greatly from patient to patient. It is also influenced by the format of the honey, with the application of liquid honey (as almost a bolus dose) inducing the most pain. ApiNate with its slow release of honey into the wound (as the wound ooze and is drawn up into the dressing releasing the
honey) should not cause more than a slight stinging sensation, for a short period of time, for some patients. If the patient is experiencing stinging that is causing pain for more than 30 minutes, and at a level that they can’t comfortably ignore, or is uncontrolled by regular pain relief, the treatment should be discontinued and reasons for the pain identified.

Large wounds: As the largest size ApiNate dressing available is a 10x10 size, wounds larger than this will be difficult to dress. In this situation it will be necessary to use more that one ApiNate dressing to cover the wound. You can butt the dressings up against one another or overlap them slightly.

Staining: Honey can leave a brown stain on skin surrounding the margin of an ulcer. It is normally associated with a build up of honey on the skin, particularly epithelial tissue that becomes scab or callus like in appearance, which often surrounds ulcers when healing. It is not permanent and will disappear as the ulcer epithelializes and the skin returns to its pre-ulcer state.

Storage of dressings: The properties of honey are destroyed when honey is exposed to excessive heat or light. Do not store the dressings in a situation where they will be exposed to direct sunlight for any length of time or stored anywhere where temperatures will exceed 25 degrees Celsius. It is not necessary to refrigerate the dressings. Storage at room temperature out of direct sunlight is fine.

Julie Betts
NP™ Wound Care
Health Waikato
Appendix 8

Participant information sheet & consent forms for the HALT trial
You are invited to take part in...

Honey as Adjuvant Leg Ulcer Therapy Trial

A study of manuka honey for leg ulcer treatment

- Main investigators: -

Andrew Jull, Dr Natalie Walker, & Dr Anthony Rodgers • Clinical Trials Research Unit
Faculty of Medical & Health Sciences • University of Auckland • Private Bag 92019 • Auckland

Professor Peter Molan • Honey Research Unit • University of Waikato • Private Bag 3105 • Hamilton

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
**Introduction:** You are invited to take part in a study of manuka honey for leg ulcer treatment. Your participation in this study is entirely voluntary (your choice). Please read this brochure carefully and think about whether you would like to take part in the study. Whether you take part or not is entirely your own decision. If you do agree to take part in this study you are free to withdraw from the study at any time, without having to give a reason, and this will in no way affect your continuing health care.

**Why do a clinical trial?**
There has been a lot of public interest in the effects of manuka honey on ulcer healing. Some studies on burns suggest honey might help healing, but there is almost no scientific evidence on manuka honey in leg ulcers. A clinical trial would provide an answer about whether manuka honey has an effect on healing in leg ulcers. In this clinical trial, half of the participants will receive a manuka honey dressing and the other half will receive usual care. Comparing ulcer healing in the two groups will show whether there is any difference in ulcer healing.

**What are the aims of this study?**
The main aim is to find out whether using honey in addition to compression bandaging has any effect on venous leg ulcer healing. The study also aims to find out about time to healing, infection, 6-month recurrence, quality of life, and the costs of treatment.

**What is a manuka honey dressing?**
The manuka honey dressing is made of a standard dressing material (calcium alginate) containing manuka honey. Normal honey becomes more liquid (‘runny’) when it is heated, even gently. The manuka honey dressing ensures the honey does not run, but stays in contact with your leg ulcer.

**What types of people can be in the study?**
To take part in this study you must:
- Have a venous leg ulcer, or a leg ulcer that is mostly caused by venous disease
- Be aged eighteen years or older
- Be able to wear compression bandages
- Be able to give informed consent yourself.

If you fit any of the following criteria, you will not be able to participate in this study:
- If you have an allergy to honey or to alginate wound dressings
- If you are currently using honey on your leg ulcer
- If your leg ulcer is due to another condition, such as rheumatoid arthritis, diabetes, malignancy or peripheral vascular disease.

**How many people will be in the study?**
In total 400 people with leg ulcers from throughout New Zealand will be involved in this study. These people will be recruited from district nursing services that treat people with venous leg ulcers.

**What happens if I decide to take part?**
If you decide to take part in the study, a research nurse will visit you in your home twice. During the first visit the research nurse will check that you meet all the entry criteria for the trial. If you meet the entry criteria the research nurse will ask you some more questions, measure your ulcer and ask you to complete three questionnaires about your health. You do not have to answer all the questions, and you may stop the interview at any time. The research nurse will also photograph your leg ulcer.

A district nurse will continue to look after your leg ulcer. Each time the district nurse returns to treat your leg ulcer, he or she will examine your leg ulcer and ask you questions about your leg ulcer.
After 12-weeks treatment, the research nurse will return, measure and photograph your leg ulcer (if it is still present) and ask you to complete three questionnaires about your health.

When the 12-weeks of study treatment are finished, you will return to your normal treatment plan (if your ulcer is still present). We will also contact you by phone six months later to find out if the ulcer is still present, or if you have a new ulcer.

**Will I be having the manuka honey or usual care?**

Whether you have the honey dressing or usual dressings will be decided at random (ie. as if by a flip of a coin) by a computer. Half the participants will be treated with the manuka honey dressing and half will be treated with usual dressings. The district nurse who normally treats your leg ulcer will apply the dressing to be used on your leg ulcer.

**Will it cost me anything to be in this study?**

No, there will be no cost to you to be involved in this trial. The honey dressing being tested will be supplied to you free of charge.

**What are the risks and benefits of the study?**

Taking part in this study will take some of your time (about 1 1/2 hours per visit by the research nurse) and require you to undergo several measurements (eg. ulcer tracings) and to answer some questionnaires. None of the measurements are dangerous.

The study treatments are well tolerated but the honey dressing may cause stinging for some people. Usually the stinging stops after a few minutes, but even if it continues, the stinging does not affect healing. If the stinging continues, taking panadol can help. If this does not help, you can remove the dressing and contact the district nurses for a new type of dressing.

Any time an ulcer is uncovered eg. for ulcer measurement, the chance of infection is increased. However, our research nurses will be registered nurses, trained in ulcer management, and sterile equipment will be used to reduce the risk of wound infection.

You may also have a friend, family or whanau support to help you understand the risks and/or benefits of this study and any other explanation you may require.

Participating in the study will contribute to important information for leg ulcer care. Companies that manufacture honey may benefit commercially from this information. Your participation in the study will be stopped should any harmful effects appear or if the investigator feels that it is not in your best interest to continue.

**What is the time span of the study?**

Although the study treatment only runs for 12 weeks, people will be recruited into the study over a 12-month period. Consequently the study is expected to finish in February 2006.

**Will I get a copy of the results?**

Once the study is finished, you will be sent a summary of the main findings. The full scientific report will be published some months later in a medical journal.

**If I need an interpreter, can one be provided?**

Yes. If you wish the visit to be conducted in your own language, an interpreter can be provided. Also, an interpreter can be provided to help you better understand this information brochure if you need one.
How confidential will the information you collect from me be?

All information collected from you will be treated as STRICTLY CONFIDENTIAL. The information you provide the researchers will be stored in a secure place by the Clinical Trials Research Unit for 10 years. All computerised information will be password protected. The information will only be available to a small team of researchers. No material that could personally identify you will be used in any reports on this study. Your GP will be informed of your participation in this study, unless you prefer otherwise.

Your rights:

You do not have to take part in this study. If you chose not to take part, any care or treatment you are currently receiving will not be affected. If you have any queries or concerns about your rights as a participant in this study, you may wish to contact a Health & Disability Advocate at the Health Advocates Trust:

- Auckland – phone 0800 555 050
- Waikato – phone 0800 423 638
- Christchurch – phone 0800 377 766

For Maori health support, contact:

**Auckland**: Mata Forbes, RGON, Co-ordinator/Advisor, Maori Health Services, Auckland District Health Board, phone 307 4949 ext. 23939 or 021 348 432.

**South Auckland**: Brian Emory, Group Manager, Maori Health, Counties Manukau District Health Board, phone 276 0000.

**Waikato**: Rose Smith, Member, Kaumatua Kaunihera; Iwi affiliations Raukawa, Waikato, Maniapoto, phone 027 294 8553; email smithro@waikatodhb.govt.nz.

**Christchurch**: Annette Finlay, Te Kai Hapai Tikanga Maori, Te Komiti Whakarite, phone (03) 364 0640, ext. 88797; email annettef@cdhb.govt.nz.

Compensation:

In the unlikely event that your participation in the study caused you a physical injury you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum payable. There is no compensation for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your rights to sue the investigators. **Should you have any questions about ACC, contact your nearest ACC office (freephone 0800 735 566), the ACC website www.acc.co.nz/claimscare/making-a-claim/medical misadventure/index.html, or the investigator.**

Finally:

This study has received approval from the Auckland Ethics Committee on 1 December 2003 on behalf of the Waikato and Canterbury Ethics Committees. You may also wish to discuss the study with your General Practitioner.

If you would like some more information about the study please feel free to contact the HALT study manager, Andrew Jull, at the Clinical Trials Research Unit.

Freephone: 0800 783-764 • Ph: (09) 373 7599 ext. 84744 • Email: halt@ctru.auckland.ac.nz

Please keep this brochure for your information
Thank you for reading about this study
Honey for leg ulcers (HALT) trial: To participate the patient must meet all of the following criteria (district nurse please tick)

- Be 18 years or older
- Have a venous leg ulcer
- Have an ABI measured within the last three months
- Have an ABI > 0.7
- Be able to tolerate compression bandaging

Patient consent to be contacted

I, ____________________________ (please print name in full), agree to be contacted by the research nurse for the HALT trial, a study investigating the effect of manuka honey dressings on venous leg ulcer healing. I understand that this initial interest in the study does not mean that I have to participate in the HALT Trial.

Contact Details:

Address: __________________________________________

________________________________________________

Telephone: Home: (___) ____________ Mobile: ________________

Email: ______________________________________________

The best day and time to contact me is:

Mon/ Tue/ Wed/ Thur/ Fri, at __________ or AM / PM

(please circle the most convenient day and time)

Signature: ____________________________________ Date ____________
Consent Form

Honey as adjuvant therapy for leg ulcers (HALT)

Please circle as appropriate:

<table>
<thead>
<tr>
<th>English</th>
<th>Maori</th>
<th>English</th>
<th>Samoan</th>
<th>Tongan</th>
<th>Cook Island</th>
<th>Niuean</th>
</tr>
</thead>
<tbody>
<tr>
<td>I wish to have an interpreter.</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.</td>
<td>Yes</td>
<td>Oo te mana’o ia i ai se fa’amatala upu.</td>
<td>Oku ou fiema’u ha fakatonulea.</td>
<td>Ka inangaro au i tetai tangata uri reo.</td>
<td>Fia manako au ke fakaanga e taha tagata fakahokohoko kupu.</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>Ae</td>
<td>Ioe</td>
<td>Io</td>
<td>Ae</td>
<td>E</td>
</tr>
</tbody>
</table>

I have read and I understand the information sheet dated ____________ for volunteers taking part in the study designed to investigate the effects of dressings containing manuka honey on the healing of venous leg ulcers.

1. I have had the opportunity to discuss this study with the investigator. I am satisfied with the answers I have been given.
2. I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.
3. I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future or my continuing health care.
4. I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
5. I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.
6. I understand the compensation provisions for this study.
7. I have had time to consider whether to take part.
8. I know whom to contact if I have any side effects to the study.
9. I know whom to contact if I have any questions about the medication or the study.
10. I agree to an approved auditor appointed by the ethics committee or regulatory authority or their approved representative and approved by the Auckland ethics committee reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

Yes/No I consent to the researchers having access to my district nursing records and laboratory reports of ulcer swabs taken during my participation in the HALT trial. I understand that any information obtained will be dealt with in confidence.
Yes/No I wish to receive a copy of the results. I understand that there may be a delay between data collection and the publication of the study results.

Yes/No I agree to my GP or other current healthcare provider being informed of my participation in this study and being provided with a copy of my results of all investigations conducted during the study.

<table>
<thead>
<tr>
<th>Participant to complete:</th>
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</thead>
<tbody>
<tr>
<td>I ______________________</td>
</tr>
<tr>
<td>of ______________________</td>
</tr>
<tr>
<td>_________________________</td>
</tr>
</tbody>
</table>

hereby consent to take part in this study about the effect of manuka honey on leg ulcers

<table>
<thead>
<tr>
<th></th>
<th>Signature of participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>_________________________</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Date</td>
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</table>

<table>
<thead>
<tr>
<th>Researcher to complete:</th>
</tr>
</thead>
<tbody>
<tr>
<td>________________________</td>
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<td></td>
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<tr>
<td>________________________</td>
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<tr>
<td>________________________</td>
</tr>
</tbody>
</table>

A copy of this consent form to be retained by the participant and a copy to be placed in the district nursing files.
Appendix 9

Case record forms for the HALT trial
Complete Form A to register person as potential participant.

Attach the registration number next in sequence to that assigned to the immediately previous participant.

If the patient does not have any exclusion criteria, inform the patient you will visit the patient the day of the next district nurse visit.

When completing the Case Record form:
- Write participant initials on every page – use initial of first name and first three letters of last name. If last name consists of three or less letters eg. Kaa, use initial of first name and initial of last name. If the last name is hyphenated, eg. John Smith-Jones, use the initial of the first name and the first three letters of the last name that appears before the hyphen (eg. JSM).
- Answer all questions. DO NOT LEAVE BLANK SPACES.
- Tick circles, write numbers in boxes.
- If the data are unavailable put an asterisk ***.
- If the data are not applicable put a dash -. 

1. Date of assessment

1.01 Date of assessment

2. Participant details

2.01 Participant's date of birth

2.02 Participant's initials

2.03 O Male or O Female

3. Exclusion criteria

Yes No

3.01 O Diagnosed with diabetes (told by a doctor they have diabetes)

3.02 O Diagnosed with rheumatoid arthritis (told by a doctor they have rheumatoid arthritis)

3.03 O Already using honey on any leg ulcer

3.04 O Known allergy to calcium alginate dressings

3.05 O Known allergy to honey (unable to eat honey)

If the patient meets any of the exclusion criteria, they are NOT eligible to participate in the trial. Sign, and date the form, enter the data on the web form and file the paper copy in the Excluded Patients Folder. Do not complete any further forms.

4. Signature

4.01 Signature printed name
Complete Form B if participant is registered for the trial and does not meet any exclusion criteria. Use registration number previously assigned to participant on Form A.

Once the participant has met the inclusion criteria, and the details about the ulcer size have been obtained, phone 0800 800 710 to randomise the participant.

When completing the Case Record Form:
- Write participant initials and date of birth on every page – use initial of first name and first three letters of last name. If last name consists of three or less letters, eg. Kaa, use initial of first name and initial of last name. If the last name is hyphenated, eg. John Smith-Jones, use the initial of the first name and the first three letters of the last name that appears before the hyphen (eg. JSMI).
- Answer all questions. DO NOT LEAVE BLANK SPACES.
- Tick circles, write numbers in boxes.
- If the data are unavailable put an asterisk ‘*’.
- If the data are not applicable put a dash ‘-‘.

Once Form B is completed, enter data from the form via the website and file paper copy in the Excluded Participants Folder.

---

1. Assessment date

1.01 [ ] [ ] [ ] 2 0 1 Date of assessment

day month year

2. Inclusion criteria

All of the following criteria must have been met for the participant to be registered:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.01</td>
<td>O</td>
</tr>
<tr>
<td>2.02</td>
<td>O</td>
</tr>
<tr>
<td>2.03</td>
<td>O</td>
</tr>
<tr>
<td>2.04</td>
<td>O</td>
</tr>
<tr>
<td>2.05</td>
<td>O</td>
</tr>
<tr>
<td>2.06</td>
<td>O</td>
</tr>
</tbody>
</table>

If No, to any of the above, THE PARTICIPANT IS NOT ELIGIBLE IN THE TRIAL. DO NOT RANDOMISE THE PARTICIPANT. Stop here, sign and date the form. Enter data on web form and file the paper copy in the Excluded Participants Folder. Do not complete any further forms.
Form B: Randomisation and baseline assessment

3. Ulcer assessment

- If the participant has more than one leg ulcer, select the largest leg ulcer as the reference ulcer. Obtain wound tracing of the reference ulcer, and file in case record folder.

3.01  Yes  No  Has the reference ulcer been present for more than six months

- Obtain the maximum length and width from the wound tracing. If unable to obtain a wound tracing, obtain an estimated measure directly from the reference ulcer.

3.02  Maximum width of reference ulcer

3.03  Maximum length of reference ulcer (at 90 degree angle to width)

3.04  Was measure (tick ONE only)

   ○ Estimated
   ○ Actual

- Document all leg ulcers in Q3.05 and identify the reference ulcer with a capital ‘R’.

3.05  Site of reference ulcer

![Diagram of legs with views](image)
4. Treatment allocation

- Please telephone 0800 800 710 to randomise participant. Tell the operator at First Contact "I have a participant to be randomised into the honey trial". The operator will ask you for the answers to the questions 2.01 - 3.03. When the participant has been randomised, record the treatment allocation below (tick ONE only).

4.01 ○ Allocated to honey
    ○ Allocated to usual care

5. Demographics

What is the participant's ethnicity [use flipchart]

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.01</td>
<td>○</td>
</tr>
<tr>
<td>5.02</td>
<td>○</td>
</tr>
<tr>
<td>5.03</td>
<td>○</td>
</tr>
<tr>
<td>5.04</td>
<td>○</td>
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<tr>
<td>5.05</td>
<td>○</td>
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<tr>
<td>5.06</td>
<td>○</td>
</tr>
<tr>
<td>5.07</td>
<td>○</td>
</tr>
<tr>
<td>5.08</td>
<td>○</td>
</tr>
<tr>
<td>5.09</td>
<td>○</td>
</tr>
</tbody>
</table>

If other, please specify

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.10</td>
<td></td>
</tr>
</tbody>
</table>

5.11 ○  |  | Does the participant live alone |

5.12 What is the participant's usual dwelling place (tick ONE only) [use flipchart]

- Private house, unit or apartment
- House, unit or apartment in retirement village
- Room in rest home
- Other

If other, please specify

5.13 ▶ If other, please specify

HALT (Honey as Adjacent Leg Ulcer Therapy Trial) • Form B: Randomisation and baseline assessment • Version 01 • April 2004

© The concepts and information contained in this document are the property of the Clinical Trials Research Unit. Use or copying of this document in whole or part constitutes an infringement of copyright.
6. Ulcer history

6.01 [ ] Doppler determined ABI (obtained from clinical records)

6.02 [ ] How long has the participant had this ulcer

6.03 [ ] Is this the first leg ulcer the participant has ever had

6.04 [ ] How old was the participant when they first developed a leg ulcer

6.05 [ ] How many times has the participant had leg ulcers (include current episode)

Clinical signs of infection

6.06 [ ] Erythema

6.07 [ ] Pus

6.08 [ ] Increasing pain (persistently more pain than normal in the last week)

6.09 [ ] Local swelling

Venous clinical severity score

6.10 Pain – does the participant have (tick ONE only)

[ ] No pain

[ ] Occasional pain

[ ] Daily pain that requires occasional use of pain relief

[ ] Daily pain that requires regular use of pain relief

6.11 Varicose veins – does the participant have (tick ONE only)

[ ] No varicose veins

[ ] A few, scattered, branch varicose veins

[ ] Multiple varicose veins, but confined either to calf or thigh

[ ] Extensive varicose veins: thigh and calf distribution

6.12 Onset of venous oedema – does the participant have (tick ONE only)

[ ] No daily oedema

[ ] Daily in the evening only

[ ] Daily in the afternoon

[ ] Daily in the morning
### 6.13 Skin pigmentation on ulcerated leg – does the participant have (tick ONE only)

- No or focal low intensity pigmentation (tan) (focal pigmentation over varicose veins does not apply)
- Diffuse pigmentation, but limited in area and old (brown)
- Diffuse pigmentation over most of gaiter distribution (lower 1/3 of ulcerated leg) or recent pigmentation (purple)
- Wider distribution of pigmentation (above lower 1/3 of ulcerated leg) and recent pigmentation

### 6.14 Inflammation – does the participant have (tick ONE only)

- No inflammation
- Mild cellulitis, but limited to marginal area around ulcer
- Moderate cellulitis, involves most of gaiter area (lower 1/3 of ulcerated leg)
- Severe cellulitis (lower 1/3 of ulcerated leg and above) or significant venous eczema

### 6.15 Induration – does the participant have (tick ONE only)

- No induration
- Focal induration, circummalleolar (<5cm in diameter)
- Medial or lateral induration (lower 1/3 of ulcerated leg)
- Induration of the entire lower third of leg or more

### 6.16 Number of active ulcers – does the participant have (tick ONE only)

- No ulcers
- 1 ulcer
- 2 ulcers
- more than 2 ulcers

#### 6.17 If more than 2 ulcers, how many __ ulcers in total

### 6.18 Active ulceration – how long has the participant had the reference ulcer (tick ONE only)

- No ulcers
- Less than 3 months
- Between 3 months and 1 year
- More than 1 year

### 6.19 Active ulcer – what is the greatest diameter of the reference ulcer (tick ONE only)

- None
- Less than 2cm diameter
- 2 – 6 cm diameter
- More than 6 cm diameter
6.20 Compressive therapy – how frequently does the participant use compression bandages (tick ONE only)

- Not at all
- Intermittent use of bandages
- Wears bandages most of the time
- Wears bandages all the time

Ulcer photography
- Please take two photographs of the reference ulcer.

6.21 Enter date ulcer photographed

7. Dressing and compression system

IF ALLOCATED TO USUAL CARE, answer all questions in section 7. IF ALLOCATED TO HONEY, go to question 7.16.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.01</td>
<td>Alginate eg. Kaltostat</td>
<td></td>
</tr>
<tr>
<td>7.02</td>
<td>If Yes, size</td>
<td></td>
</tr>
<tr>
<td>7.03</td>
<td>Hydrofibre eg. Aquacel</td>
<td></td>
</tr>
<tr>
<td>7.04</td>
<td>If Yes, size</td>
<td></td>
</tr>
<tr>
<td>7.05</td>
<td>Foam eg. Lyofoam</td>
<td></td>
</tr>
<tr>
<td>7.06</td>
<td>If Yes, size</td>
<td></td>
</tr>
<tr>
<td>7.07</td>
<td>Hydrogel eg. Intrasite</td>
<td></td>
</tr>
<tr>
<td>7.08</td>
<td>If Yes, size</td>
<td></td>
</tr>
<tr>
<td>7.09</td>
<td>Silicon vicryl eg. Adaptic</td>
<td></td>
</tr>
<tr>
<td>7.10</td>
<td>If Yes, size</td>
<td></td>
</tr>
<tr>
<td>7.11</td>
<td>Hydrocolloid eg. Duoderm</td>
<td></td>
</tr>
<tr>
<td>7.12</td>
<td>If Yes, size</td>
<td></td>
</tr>
<tr>
<td>7.13</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>7.14</td>
<td>If Other, please specify</td>
<td></td>
</tr>
<tr>
<td>7.15</td>
<td>If Other, size</td>
<td></td>
</tr>
</tbody>
</table>
Participant initials

Participant date of birth
day month year

Registration number

Affix registration label here

Yes No

7.16  O  O  Is a paste bandage, (eg. Zipzoc) being used

7.17  Please document which compression system is currently being used on the reference ulcer (tick ONE only)

O  Short stretch bandage
O  Long stretch bandage
O  ProGuide
O  Profore Lite
O  Profore
O  Unna boot
O  District nurse’s own system

Which products were used in making up this system of compression?

Yes No

7.18  O  O  Orthopaedic wool
7.19  O  O  Crepe bandage
7.20  O  O  Cohesive bandage
7.21  O  O  High stretch elastic bandage
7.22  O  O  Other

7.23  If Other, please specify

8. Health

Has the participant ever had any of the following:

Yes No

8.01  O  O  A DVT or blood clots in the leg
8.02  O  O  A hip joint or knee joint replaced
8.03  O  O  A fractured leg
8.04  O  O  Treatment for varicose veins

If Yes, which treatments for varicose veins

Yes No

8.05  O  O  Surgery
8.06  O  O  Sclerosis (injections)
8.07  O  O  Laser
8.08  O  O  Other

8.09  If other, please specify
Form B: Randomisation and baseline assessment

Participant initials  Participant date of birth  Registration number

Affix registration label here

Is the participant currently taking any of the following medications?

Yes  No
8.10  O  O  Pentoxifylline (Trental)
8.11  O  O  Aspirin
8.12  O  O  Prednisone
8.13  O  O  Zinc
8.14  O  O  Other

If Yes, to any of 8.10-8.14, complete a Concomitant medications form (Form M)

9. Lifestyle

Smoking status  [use flipchart]

Yes  No
9.01  O  O  Ever smoked cigarettes regularly (ie. most days for at least a year)

If Yes,

Yes  No
9.02  O  O  Current cigarette smoker (ready made or roll your own)

If No,  age in years last smoked regularly

9.04  If Yes,  average number of cigarettes smoked per day

Yes  No
9.05  O  O  Ever smoked pipes or cigars regularly (ie. on most days for at least a year)

If Yes,

Yes  No
9.06  O  O  Current pipe or cigar smoker

If No,  age in years last smoked regularly

9.08  If Yes,  average number of pipes or cigars smoked per day
Alcohol intake [use flipchart]

9.09 Currently drink alcohol once per week or more (most weeks for at least the last year)

9.10 Average number of standard drinks of wine consumed per week

9.11 Average number of standard drinks of spirits consumed per week

9.12 Average number of standard drinks of beer consumed per week

Mobility [use flipchart]

9.13 How does the participant usually walk/move around (tick ONE only)

- Easily without any aids
- Slowly without any aids
- With aid of stick or a walker
- Only with the help of one other person
- Only with the help of two people
- Independently in a wheelchair
- Mainly bed bound or chair bound

10. Questionnaires

- Give participant questionnaire booklet to fill out. Check for completeness after administration.

10.01 SF-36 completed

10.02 If No, please document why

10.03 Charing Cross Ulcer questionnaire completed

10.04 If No, please document why

10.05 EQ-5D completed

10.06 If No, please document why

If Yes, to 10.01,10.03,or 10.05, please enter data from questionnaires via the website and file the paper copy in the Case Record Folder.
Before you leave:

- Enter participant's initials and date of birth and attach registration label on every page of each Form C in the participant kit.

- Attach allocated treatment label to page 1 (Section 3) of every Form C in the participant kit.

- Enter participant's initials and date of birth and attach registration label on every page on each Form X in the participant kit.

11. Signature

11.01

<table>
<thead>
<tr>
<th>Signature</th>
<th>Printed name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>
1. **Assessment date**

1.01 [ ] [ ] [2] [0] Date of assessment

1.02 [ ] [: ] Time visit started (24hr clock)

2. **Ulcer healing**

2.01 Yes No

- Yes: Has the reference ulcer healed (restoration of entirely unbroken skin after removal of all scabs)
  - If No, go to section 3
  - If Yes, go to section 6

3. **Allocated treatment and dressing**

The participant was allocated to [ ] (Research nurse to attach label here).

**IF ALLOCATED TO HONEY**

3.01 Yes No

- Yes: Is the honey dressing still being used on the patient's leg ulcer.

3.02 If No, please document why not:

- If No, go to 3.03
- If Yes, go to 4.01
IF ALLOCATED TO USUAL CARE (or allocated to honey, but now using another dressing), which dressings were used on the patient’s leg ulcer this visit.

3.03 Yes
   No
   Alginate eg. Kaltostat

3.04 If Yes, size
   cm x cm

3.05 Yes
   No
   Hydrofibre eg. Aquacel

3.06 If Yes, size
   cm x cm

3.07 Yes
   No
   Foam eg. Lyofoam

3.08 If Yes, size
   cm x cm

3.09 Yes
   No
   Hydrogel eg. Intrasite

3.10 If Yes, size
   grams

3.11 Yes
   No
   Silicon vicryl eg. Adaptic

3.12 If Yes, size
   cm x cm

3.13 Yes
   No
   Hydrocolloid eg. Duoderm

3.14 If Yes, size
   cm x cm

3.15 Yes
   No
   Other

3.16 If Other, please specify

3.17 If Other, size
   cm x cm
Form C: District Nurse form

4. Bandaging

   Yes   No

4.01   ☐   ☐ Is a paste bandage (e.g., Zipzoc) being used

4.02   ☐   ☐ Is the participant using compression on the leg ulcer

4.03   ☐   ☐ If No, please document why not

4.04   ☐   ☐ If Yes, please document which system is being used (tick one only)
   ☐ Short stretch bandage
   ☐ Long stretch bandage
   ☐ ProGuide
   ☐ Profore Lite
   ☐ Profore
   ☐ Unna boot
   ☐ District nurse’s own system:
   ▶ Which products were used in making up this system of compression

   Yes   No

4.05   ☐   ☐ Orthopaedic wool

4.06   ☐   ☐ Crepe bandage

4.07   ☐   ☐ Cohesive bandage

4.08   ☐   ☐ High stretch elastic bandage

4.09   ☐   ☐ Other

4.10   ☐   ☐ If Other, please specify

5. Infection

   Yes   No

5.01   ☐   ☐ Does the leg ulcer appear to be infected

   ☐   ☐ If Yes, which signs are present

   Yes   No

5.02   ☐   ☐ Erythema

5.03   ☐   ☐ Pus

5.04   ☐   ☐ Increasing pain (persistently more pain than normal in the last week)

5.05   ☐   ☐ Local swelling

   ☐   ☐ If Yes,

   Yes   No

5.06   ☐   ☐ Has a wound swab been taken

5.07   ☐   ☐ If Yes, specify date sent

Page 3 of 4
6. Antibiotics

   | Yes | No |
   ---|-----|----|
6.01 |     | O  | Has the participant started taking antibiotics for their leg ulcer since last district nursing visit

   > If Yes, please specify what drug(s)

   6.02 | Drug 1

   6.03 | Duration of treatment:  ___ days

   6.04 | Drug 2

   6.05 | Duration of treatment:  ___ days

7. Health professional visit

   | Yes | No |
   ---|-----|----|
7.01 |     | O  | Has the participant visited another health practitioner for their leg ulcer since last district nurse visit

   > If Yes, please specify type of practitioner

   7.02 | Practitioner 1

   7.03 | Number of visits:  ___

   7.04 | Practitioner 2

   7.05 | Number of visits:  ___

8. Adverse events

   | Yes | No |
   ---|-----|----|
8.01 |     | O  | Has the participant had any adverse events since the last district nursing visit, e.g. stinging, infection

   > If Yes, please complete Form X, and post the form X via internal mail to the HALT research nurse.

9. Completion of visit

9.01 | Time visit completed (24hr clock)

   hour:  ___  min:  ___

10. Signature

   10.01 | signature

   |    |    |
   ---|----|---|
   day:  ___  month:  ___  year:  ___
Complete Form D 12 weeks from date of randomisation.

Write participant initials and date of birth on every page – use initial of first name and first three letters of last name. If last name consists of three or less letters eg. Kaa, use initial of first name and initial of last name. If the last name is hyphenated, eg. John Smith-Jones, use the initial of the first name and the first three letters of the last name that appears before the hyphen (eg. JSJ).

When completing Case Record Form:
- Answer all questions. DO NOT LEAVE BLANK SPACES.
- Tick circles, write numbers in boxes.
- If the data are unavailable put an asterisk **.
- If the data are not applicable put a dash -.

Once Form D is completed, enter data from the form via the website and file the paper copy in the Case Record Folder.

1. Assessment date

1.01 [____] [____] [2 0] Date of assessment

2. Ulcer assessment

- Check question 3.05 Form B to identify site of reference ulcer.

Yes   No

2.01  O  O  Is the reference ulcer healed (restoration of entirely unbroken skin after removal of all scabs)

Venous clinical severity score

2.02 Pain – does the participant have (tick ONE only)

O  No pain
O  Occasional pain
O  Daily pain that requires occasional use of pain relief
O  Daily pain that requires regular use of pain relief

2.03 Varicose veins – does the participant have (tick ONE only)

O  No varicose veins
O  A few, scattered, branch varicose veins
O  Multiple varicose veins, but confined either to calf or thigh
O  Extensive varicose veins: thigh and calf distribution
2.04 Onset of venous oedema – does the participant have (tick ONE only)

- No daily oedema
- Daily in the evening only
- Daily in the afternoon
- Daily in the morning

2.05 Skin pigmentation on the ulcerated leg – does the participant have (tick ONE only)

- No or focal low intensity pigmentation (tan) (focal pigmentation over varicose veins does not apply)
- Diffuse pigmentation, but limited in area and old (brown)
- Diffuse pigmentation over most of gaiter distribution (lower 1/3 of ulcerated leg) or recent pigmentation (purple)
- Wider distribution of pigmentation (above lower 1/3 of ulcerated leg) and recent pigmentation

2.06 Inflammation – does the participant have (tick ONE only)

- No inflammation
- Mild cellulitis, but limited to marginal area around ulcer
- Moderate cellulitis, involves most of gaiter area (lower 1/3 of ulcerated leg)
- Severe cellulitis (lower 1/3 of ulcerated leg and above) or significant venous eczema

2.07 Induration – does the participant have (tick ONE only)

- No induration
- Focal induration, circummalleolar (<5cm in diameter)
- Medial or lateral induration (lower 1/3 of ulcerated leg)
- Induration of the entire lower third of leg or more

2.08 Number of active ulcers – does the participant have (tick ONE only)

- No ulcers
- 1 ulcer
- 2 ulcers
- More than 2 ulcers

2.09 If more than 2 ulcers, how many [___] ulcers in total

2.10 Active ulceration – how long has the participant had the reference ulcer (tick ONE only)

- No ulcers
- Less than 3 months
- Between 3 months and 1 year
- More than 1 year
### 2.11 Active ulcer – what is the greatest diameter of the reference ulcer *(tick ONE only)*
- None
- Less than 2cm diameter
- 2 – 6 cm diameter
- More than 6 cm diameter

### 2.12 Compressive therapy – how frequently does the participant use compression bandages *(tick ONE only)*
- Not at all
- Intermittent use of bandages
- Wears bandages most of the time
- Wears bandages all the time

### 3. Questionnaires

Give participant questionnaire booklet to fill out. Check for completeness after administration.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.01</td>
<td>SF-36 completed</td>
<td></td>
</tr>
<tr>
<td>3.02</td>
<td></td>
<td>If No, <em>please document why</em></td>
</tr>
<tr>
<td>3.03</td>
<td>Charing Cross Ulcer questionnaire completed</td>
<td></td>
</tr>
<tr>
<td>3.04</td>
<td></td>
<td>If No, <em>please document why</em></td>
</tr>
<tr>
<td>3.05</td>
<td>EQ-5D completed</td>
<td></td>
</tr>
<tr>
<td>3.06</td>
<td></td>
<td>If No, <em>please document why</em></td>
</tr>
</tbody>
</table>

- If Yes, to 3.01, 3.03, or 3.05, please enter data from questionnaires via the website and file the paper copy in the Case Record Folder.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.07</td>
<td>Have concomitant medications changed since the baseline visit?</td>
<td></td>
</tr>
<tr>
<td>3.08</td>
<td>Has the participant had any adverse events since the previous <em>district nurse</em> visit?</td>
<td></td>
</tr>
<tr>
<td>3.09</td>
<td>Has the participant’s contact details or GP changed since the start of the honey trial?</td>
<td></td>
</tr>
</tbody>
</table>

- If Yes, please update/complete Form M, enter data via website and file paper copy in Case Record Folder.
- If Yes, please complete Form X, enter data via website and file paper copy in Case Record Folder.
- If Yes, please complete a new Form Z and file in Case Record Folder.
4. Additional information

4.01 Yes No
Would the participant recommend using the allocated treatment to others?

4.02 If No, please specify why

4.03 Yes No
Did the participant experience any problems with the allocated treatment?

4.04 If Yes, please specify

4.05 How does the participant feel the allocated treatment compared to any other dressing they have used?

5. Ulcer photography

5.01 Please take two photographs of the reference ulcer.

5.01 Enter date ulcer photographed

5.02 Obtain wound tracing of the reference ulcer, remove backing and file in case record folder.

6. Signature

6.01 Signature

6.02 Printed name
• Complete Form E 9 months from date of randomisation.

• Write participant initials and date of birth on every page – use initial of first name and first three letters of last name. If last name consists of three or less letters eg. Kaa, use initial of first name and initial of last name. If the last name is hyphenated eg John Smith-Jones, use the initial of the first name and the first three letters of the last name that appears before the hyphen (eg JSMJ).

• When completing Case Record Form:
  - Answer all questions. DO NOT LEAVE BLANK SPACES.
  - Tick circles, write numbers in boxes.
  - If the data are unavailable put an asterisk ‘*’.
  - If the data are not applicable put a dash ‘-’.

• Enter data from the form via the website and file paper copy in the Case Record Folder.

<table>
<thead>
<tr>
<th>1. Assessment date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01 2012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Ulcer recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>2.01</td>
</tr>
<tr>
<td>2.02</td>
</tr>
<tr>
<td>2.03</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.01</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

HALT (Honey as Adjunct Leg Ulcer Therapy Trial) • Form E: 6 month follow-up • Version 01 • April 2004

© The concepts and information contained in this document are the property of the Clinical Trials Research Unit. Use or copying of this document in whole or part constitutes an infringement of copyright.
Complete Form L each time a wound swab has been obtained.

- Fill in participant initials and date of birth - use initial of first name and first three letters of last name. If last name consists of three or less letters, eg. Kaa, use initial of first name and initial of last name. If last name is hyphenated, eg. John Smith-Jones, use the initial of the first name and the first three letters of the last name that appears before the hyphen (eg. JSMI).

- Once Form L is completed, enter data from the form via the website and file the paper copy in the Case Record Folder.

When completing Case Record Form:
- Answer all questions. DO NOT LEAVE BLANK SPACES. Tick circles, write numbers in boxes. If the data are unavailable put an asterisk '*'. If the data are not applicable put a dash '-'.

1. Swab results

1.01 Date wound swab obtained

1.02 Date wound swab results reported by laboratory

1.03 Bacterial species identified

1.04 Mixed species

1.05 Staphylococcus

1.06 Streptococcus

1.07 Pseudomonas

1.08 Other gram negative species

1.09 If Yes, please specify

1.10 Other

1.11 If Other, please specify

1.12 Source of information (tick ONE only)

- GP report
- District Nurse report
- Laboratory Database

2. Signature

2.01 Signature

2.02 Printed name

Registration number

Affix registration label here
Form M: Concomitant Medications

Complete a Form M for each randomised participant who takes any medications during the study. Write participant's initials, date of birth and registration number on every completed page of this form, including the signature page. If the data will never be available put an asterisk '*'. If the data are not applicable put a dash '-'.

Complete this form at baseline and update at 12 week endpoint assessment.

<table>
<thead>
<tr>
<th>Generic name (please print)</th>
<th>Total daily dose</th>
<th>Units</th>
<th>Date of first dose</th>
<th>If stopped, date last dose taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. NIFEDIPINE not adalat</td>
<td>eg. 50</td>
<td>eg. mg</td>
<td>day month year</td>
<td>day month year</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
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<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
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<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
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<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
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<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
</tbody>
</table>
Form M: Concomitant Medications

<table>
<thead>
<tr>
<th>Generic name (please print)</th>
<th>Total daily dose</th>
<th>Units</th>
<th>Date of first dose</th>
<th>If stopped, date last dose taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. NIFEDIPINE not adalat</td>
<td>eg. 50</td>
<td></td>
<td>day month year</td>
<td>day month year</td>
</tr>
<tr>
<td>10.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>11.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>12.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>13.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>14.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>15.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>16.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>17.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>18.</td>
<td></td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
</tbody>
</table>

2. Signature

2.01

signature                  printed name  day month year

Enter the data via the website and file the paper record in the Case Record folder.
Form X: Adverse Events

Complete Form X whenever an adverse event is detected. Please complete all sections of this form. If the data are unavailable put an asterisk '*'. If the data are not applicable put a dash '-' . Tick circles.

Definitions of severity:
- Mild = Awareness of event but easily tolerated by participant
- Moderate = Discomfort causing some interference with usual activity
- Severe = Inability to carry out usual activity

When form completed, hand deliver or fax Form X to the HALT research nurse at _________. If faxed, retain original in patient's clinical record.

<table>
<thead>
<tr>
<th>Diagnosis/symptom</th>
<th>Onset date</th>
<th>Severity</th>
<th>Event caused by dressing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day</td>
<td>month</td>
<td>year</td>
</tr>
<tr>
<td>1.01</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.02</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.03</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.04</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.05</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.06</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.07</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.08</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
<tr>
<td>1.09</td>
<td></td>
<td></td>
<td>2 0</td>
</tr>
</tbody>
</table>
# Form X: Adverse Events

## 2. Serious Adverse Event

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

2.01  **Is a serious adverse event being reported (see categories below)**

2.02  **If Yes,** tick ONE only (the most serious)

- Death
- Life-threatening
- Hospitalisation
- Persistent or significant disability/incapacity
- Cancer
- Congenital abnormality
- Medically important event

## 3. Signature

3.01  **Signature**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
</table>

3.01  **Printed name**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>

## 4. RESEARCH NURSE USE ONLY

4.01  **Date received by research nurse**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

4.02  **Date study manager informed**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
# Form Z: Contact details

<table>
<thead>
<tr>
<th>Participant</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant initials</td>
<td>Participant date of birth</td>
<td>Registration number</td>
<td></td>
</tr>
<tr>
<td></td>
<td>day</td>
<td>month</td>
<td>year</td>
</tr>
</tbody>
</table>

Affix registration label here

**Participant**

1. **Title:** [square]  **First name(s):**  **Last name:**
2. **Address:**
3. **City:**  **Postcode:**
4. **Home phone number:** ( )  **Work phone number:** ( )
5. **Mobile phone number:**  **Email address:**

**Alternate contact** (friend or relative not living with the participant)

6. **Title:** [square]  **First name(s):**  **Last name:**
7. **Address:**
8. **City:**  **Postcode:**
9. **Home phone number:** ( )  **Work phone number:** ( )
10. **Mobile phone number:**  **Email address:**
11. **Relationship to participant:**

**General practitioner**

12. **Title:** [square]  **First name(s):**  **Last name:**
13. **Practice name:**
14. **Address:**
15. **City:**  **Postcode:**
16. **Home phone number:** ( )  **Work phone number:** ( )
17. **Mobile phone number:**  **Email address:**

**Signature of investigator**

18. [signature]  [printed name]  |  |  |

Complete this form at the initial visit and file in the participant's Case Record Folder.
Participant Questionnaire

- The questionnaires are to be completed by the participant wherever possible.
- If the participant has visual problems, the Researcher may administer the questionnaires.
- Encourage the participant to fill out all questionnaires.

Research Nurse to complete: (tick ONE only)
- Baseline
- 12 week assessment

signature  printed name  day month year

Participant initials
Participant date of birth
day month year
Registration number
Affix registration label here
- SF-36 Questionnaire -

This questionnaire asks for your views about your health, how you feel and how well you are able to do your usual activities.

Please answer every question. Some questions may look like others, but each one is different. Answer each question by ticking the circle that best represents your response.

1. In general, would you say your health is: (tick ONE circle only)

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general NOW? (tick ONE circle only)

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

3. The following questions are about activities you might do during a typical day. Does your health NOW limit you in these activities? If so, how much? (tick ONE circle only)

<table>
<thead>
<tr>
<th>ACTIVITIES</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.01 Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.02 Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.03 Lifting or carrying groceries</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.04 Climbing several flights of stairs</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.05 Climbing one flight of stairs</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.06 Bending, kneeling or stooping</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.07 Walking more than one kilometre</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.08 Walking half a kilometre</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.09 Walking 100 metres</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>3.10 Bathing or dressing yourself</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (tick ONE circle on each line)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.01</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>4.02</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>4.03</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>4.04</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.01</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>5.02</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>5.03</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks? (tick ONE circle only)

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

(tick ONE circle on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.01</td>
<td>Did you feel full of life?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.02</td>
<td>Have you been a very nervous person?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.03</td>
<td>Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.04</td>
<td>Have you felt calm and peaceful?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.05</td>
<td>Did you have a lot of energy?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.06</td>
<td>Have you felt down?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.07</td>
<td>Did you feel worn out?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.08</td>
<td>Have you been a happy person?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9.09</td>
<td>Did you feel tired?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

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

(tick ONE circle only)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

11. How TRUE or FALSE is each of the following statements for you? (tick ONE circle on each line)

<table>
<thead>
<tr>
<th></th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.01 I seem to get sick a little easier than other people</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>11.02 I am as healthy as anybody I know</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>11.03 I expect my health to get worse</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>11.04 My health is excellent</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
- Charing Cross Ulcer Questionnaire -

This questionnaire is designed to allow us to get a better understanding of how your leg ulcer affects your life. Please try and answer every question. If you are unsure about how to answer a question, please give the best answer you can.

12. I have pain from my ulcer: 

<table>
<thead>
<tr>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>A good bit of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

13. Having a leg ulcer stops me from doing the following:

<table>
<thead>
<tr>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>A good bit of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

13.01 Meeting friends and relatives

13.02 Going on holiday

13.03 Enjoying my hobbies

13.04 Driving or using public transport

14. How true or false is each of the following statements for you when considering your leg ulcer:

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

14.01 My ulcer has slowed me down in general

14.02 My ulcer has put a strain on my personal relationships

14.03 The ooze from my ulcer is a problem

14.04 I spend a lot of time thinking about my ulcer

14.05 I am worried that my ulcer will never heal

14.06 I am fed up with the amount of time it takes to treat my ulcer

Page 5
15. I am unhappy about the appearance of my legs because of the ulcer and/or dressings:
   (tick ONE circle only)

<table>
<thead>
<tr>
<th>Definitely not</th>
<th>Occasionally</th>
<th>Often</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

16. My leg ulcer prevents me from the following household duties:
   (tick ONE circle on each line)

<table>
<thead>
<tr>
<th></th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>A good bit of the time</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.01 Cooking</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>16.02 Cleaning</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>16.03 Shopping</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>16.04 Gardening</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

17. I feel depressed because of my leg ulcer:
   (tick ONE circle only)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

18. Please state how much of a problem to you the following factors are regarding the dressings for your leg:
   (tick ONE circle on each line)

<table>
<thead>
<tr>
<th></th>
<th>A huge problem</th>
<th>A big problem</th>
<th>A moderate problem</th>
<th>A little problem</th>
<th>No problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.01 The bulkiness of them</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>18.02 The appearance of them</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>18.03 They influence the clothes I wear</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

19. I have difficulty walking because of my leg ulcer:
   (tick ONE circle only)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

Page 6
- EQ-5D Health Questionnaire -
(English version for New Zealand)

By placing a tick in one box in each group below, please indicate which statements best
describe your own health state today.
(tick ONE circle only)

<table>
<thead>
<tr>
<th>Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. I have no problems in walking about</td>
</tr>
<tr>
<td>o</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. I have no problems with self-care</td>
</tr>
<tr>
<td>o</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual Activities (eg. work, study, housework, family or leisure activities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22. I have no problems with performing my usual activities</td>
</tr>
<tr>
<td>o</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain/Discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. I have no pain or discomfort</td>
</tr>
<tr>
<td>o</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiety/Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>24. I am not anxious or depressed</td>
</tr>
<tr>
<td>o</td>
</tr>
</tbody>
</table>
25. To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is **today**, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
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