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# A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial

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The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 02/10/02. The contractual start date was in July 2004. The draft report began editorial review in August 2008 and was accepted for publication in April 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

## A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial

JA Michaels,[1] WB Campbell,[2] BM King,[3] J MacIntyre,[2] SJ Palfreyman,[1*] P Shackley[1] and MD Stevenson[4]

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**Objective:** To examine the effectiveness and cost-effectiveness of antimicrobial silver-donating dressings for venous leg ulcers compared with simple non-adherent (also known as low-adherent) dressings.
**Design:** A pragmatic, prospective randomised controlled trial (RCT) and cost-effectiveness analysis of silver-donating versus low-adherent dressings in the treatment of venous leg ulcers. A non-randomised observational group was also recruited.
**Setting:** Primary and secondary care services in the north and south of England (Sheffield and Exeter).
**Participants:** Consenting patients with active ulceration of the lower leg that had been present for a period of greater than 6 weeks.
**Interventions:** Patients were randomised to receive either a silver-donating or non-silver low-adherent dressing applied beneath compression bandages or hosiery. The choice of dressing within these groups was left to clinician preference. Evaluation was by clinical assessment, supplemented by evaluation of quality of life and cost-effectiveness.
**Main outcome measures:** The primary outcome measure was complete ulcer healing at 12 weeks in the index limb. Secondary measures were costs and quality-adjusted life-years (QALYs), cost-effectiveness, time to healing, and recurrence rate at 6 months and 1 year.
**Results:** In total, 304 participants were recruited to the clinical trial: 213 to the RCT and 91 to the observational arm. Within the RCT 107 were randomised to antimicrobial dressings and 106 to the control dressings. There were no significant differences ($p > 0.05$) between the two groups for the primary outcome measure of proportion of ulcers healed at 12 weeks (59.6% for silver and 56.7% for control dressings). The overall median time to healing was also not significantly different between the two groups ($p = 0.408$). A total of 24 patients had recurrent ulcers within 1 year; the recurrence rates of 11.6% ($n = 11$) for the antimicrobial and 14.4% ($n = 13$) for the control dressings were not significant. Mean utility valuations for both the EuroQol 5 dimensions (EQ-5D) quality of life questionnaire and Short Form 6 dimensions (SF-6D) utility index showed no differences for either group at 1, 3, 6 or 12 months. Compared with the control group, the antimicrobial group had an incremental cost of £97.85 and an incremental QALY gain of 0.0002, giving an incremental cost-effectiveness ratio for the antimicrobial dressings of £489,250. Cost-effectiveness modelling of the results of the RCT showed that antimicrobial dressings were not cost-effective.
**Conclusions:** No significant differences in either primary or secondary end points were found between the use of antimicrobial silver-donating dressings and the control group of low-adherent dressings. Modelling showed that antimicrobial silver dressings were not cost-effective.
**Trial registration:** Current Controlled Trials ISRCTN72485131.

# Contents

# List of abbreviations

| | |
|---|---|
| A&E | accident and emergency |
| ABPI | ankle brachial pressure index |
| AfC | Agenda for Change |
| Ag | silver |
| AUC | area under the curve |
| BNF | *British National Formulary* |
| CEAC | cost-effectiveness acceptability curve |
| CI | confidence interval |
| CONSORT | Consolidated Standards of Reporting Trials |
| CWIS | Cardiff Wound Impact Schedule |
| DVT | deep vein thrombosis |
| EQ-5D | EuroQol 5 dimensions quality of life questionnaire |
| FLQA | Freiburger Lebessqualitas Assessment Questionnaire |
| GP | general practitioner |
| HRQoL | health-related quality of life |
| ICER | incremental cost-effectiveness ratio |
| NHP | Nottingham Health Profile |
| PCT | primary care Trust |
| QALY | quality-adjusted life-year |
| QoL | quality of life |
| RCT | randomised controlled trial |
| RR | relative risk |
| SD | standard deviation |
| SE | standard error |
| SF-36 | Short Form-36 quality of life questionnaire |
| SF-6D | Short Form 6 dimensions utility index |
| TTO | time trade-off |
| VULCAN | Venous ULcer Cost-effectiveness of ANtimicrobial dressings |
| VV | varicose veins |
| WTE | whole time equivalent |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

# Executive summary

## Background

Venous leg ulcers are a major health problem and result in considerable costs and morbidity for health services. Despite a lack of clinical evidence of cost-effectiveness, the use of dressings containing antimicrobials has become commonplace for venous leg ulcers, with a particularly rapid rise in the adoption of new silver-donating antimicrobial dressings.

## Objectives

The objective of this study was to examine the effectiveness and cost-effectiveness of antimicrobial silver-donating dressings for venous leg ulcers compared with simple non-adherent (also known as low-adherent) dressings, both used beneath compression bandaging.

The aims were to:

- Collect cost and outcome data through a randomised controlled clinical trial of silver-donating antimicrobial dressings versus non-antimicrobial low-adherent control dressings applied to venous ulcers.
- Collect data from an observational arm of the study regarding treatment, clinical outcomes and costs of the management of venous leg ulcers.
- Carry out an economic analysis alongside the clinical trial to estimate the cost-effectiveness of antimicrobial dressings for venous leg ulcers.
- Develop a cost-effectiveness model of venous ulceration and to populate this with data from the trial and published literature.
- Examine the cost-effectiveness of using antimicrobial dressings in different circumstances and with differing sets of assumptions.
- Document current routine practice regarding the use of antimicrobial agents in the treatment of venous ulcers.

## Methods

### Design

The study was a pragmatic, prospective randomised controlled trial (RCT) and cost-effectiveness analysis of antimicrobial silver-donating dressings versus low-adherent control dressings beneath compression bandaging in the treatment of venous leg ulcers.

### Setting

This was a multicentre study that recruited patients in primary and secondary care services in two areas, in the north and south of England.

### Participants

Participants were consenting patients with active venous ulceration of the lower leg that had been present for a period of greater than 6 weeks.

### Interventions

Patients were randomised to receive either silver-donating dressings or low-adherent dressings without any antimicrobial substances (control dressings), applied beneath compression bandages or hosiery. The choice of dressing within the two groups was left to clinician preference. Evaluation was by clinical assessment, supplemented by evaluation of quality of life and cost-effectiveness.

### Main outcome measures

The primary outcome measure was complete ulcer healing at 12 weeks in the index limb. Secondary measures were costs and resource use, quality-adjusted life-years (QALYs), cost-effectiveness, time to healing, and recurrence rates at 6 months and 1 year.

## Results

Recruitment was slower than anticipated due to encountering organisational, cultural and bureaucratic obstacles. In total, 304 participants were recruited to the clinical trial. A total of 213 were recruited to the RCT and 91 to the observational arm. Within the RCT, 107 were randomised to silver-donating antimicrobial dressings and 106 to the control dressings. There were no significant differences ($p > 0.05$) between the two groups for the primary outcome measure of proportion of ulcers healed at 12 weeks (59.6% for

silver and 56.7% for control dressings). The overall median time to healing was also not significantly different between the two groups ($p = 0.408$).

A total of 24 patients had recurrent ulcers within 1 year: the recurrence rates of 11.6% ($n = 11$) for the antimicrobial and 14.4% ($n = 13$) for the control dressings were not significantly different.

Mean utility valuations for both the EuroQol 5 dimensions (EQ-5D) and Short Form 6 dimensions (SF-6D) showed no statistically significant differences between the groups at 1, 3, 6 or 12 months. In comparison with the control group, the antimicrobial group had an incremental cost of £97.85 and an incremental QALY gain of 0.0002, giving an incremental cost-effectiveness ratio for the antimicrobial dressings of £489,250. Cost-effectiveness modelling of the results of the RCT showed, for the base-case model, that only included variables that were predictive of healing antimicrobial dressings were not cost-effective. Sensitivity analysis where dressing type was forced (i.e used as a predictive variable regardless of statistical significance) into the model, and a small benefit in utility that was assumed to occur at the point of healing, resulted in a small average incremental benefit for the antimicrobial dressings. However, this was not sufficient to justify the additional cost and there remained a high probability that the treatment was not cost-effective.

## Conclusions

The key finding of this study was that there was no significant difference in either primary or secondary end points between the use of antimicrobial silver dressings and the control group of low-adherent dressings. The cost analysis showed a significantly higher cost for those treated with antimicrobial dressings. Cost-effectiveness modelling showed antimicrobial dressings to be dominated by inert dressings, with there being no difference in clinical outcomes and a higher cost associated with the antimicrobial dressings.

Antimicrobial dressings have been widely adopted without positive clinical evidence and our surveys suggested that silver-donating antimicrobial dressings have become widely used. If this reflects national practice then the implication is that the National Health Service (NHS) could be spending several million pounds on dressings each year with no evidence of clinical benefit.

## Implications for health care

The results of this trial have the following implications for health care:

- The evidence suggests that there are no significant benefits in ulcer healing from using silver antimicrobial dressings beneath compression therapy.
- The use of less expensive low- or non-adherent dressings is recommended in preference to antimicrobial silver dressings.
- The results suggest that there is no indication for the regular use of antimicrobial dressings in general in promoting the healing of venous ulcers.
- The finding of very widespread use of silver-donating dressings, shown by this trial not to be cost-effective, should stimulate the NHS to encourage and facilitate recruitment of patients to large, well-designed studies of new technologies before it disseminates in an uncontrolled way.
- This trial has illustrated a number of the bureaucratic, organisational and cultural obstacles to research, which need to be addressed centrally, for improved development of cost-effective services in the long term. In particular, effective mechanisms for engaging frontline clinical staff with the NHS research agenda are urgently required.

## Recommendations for future research

The following are recommendations are made:

- The development of a disease-specific quality of life measure for venous ulcer patients that can be used in economic evaluation would be an advantage for future studies.
- The differences in healing rates between the two geographical areas of this study have implications for future research. They emphasise the need for very clear descriptions of epidemiology, treatment methods and the experience of staff engaged in compression bandaging; and they suggest an advantage to multicentre studies in different geographical areas, to produce results which can reasonably be generalised to the population as a whole.
- It is recommended that research into new treatments for leg ulcers includes mathematical modelling to establish the potential value of further clinical trials, and to assist in

appropriate trial design prior to undertaking large and expensive clinical trials.
- This study has not addressed the problems of ulcers that fail to heal after 12 weeks of compression, or the problem of patients who are unable to tolerate compression. It is uncertain whether antimicrobial dressings might have any advantages in either of those situations.
- Uncertainty also remains about the diagnosis of 'infection' in leg ulcers which might be relevant to the use of antimicrobials. These are complex areas for research, but more information would be useful to guide clinical practice.
- Further studies are needed into how clinicians make decisions regarding dressing type and, in particular, the influence of sales representatives as sources of evidence and guidance.

## Trial registration

This trial is registered as ISRCTN72485131.

# Chapter 1
# Introduction

In the last 20 years there has been a dramatic increase in the use of antimicrobial wound care products.[1] However, the evidence of any increased benefit provided by these dressings in relation to venous ulcers remains equivocal compared with that related to the effectiveness of compression. The general quality of the existing evidence has been described as poor and systematic reviews have shown no statistically significant difference between any of the dressing types in terms of the total numbers of ulcers healed.[2–4]

This study sought to address the lack of evidence by examining the cost-effectiveness of antimicrobial dressings applied beneath compression therapy in the treatment of venous leg ulcers.

## Background

### Aetiology of venous leg ulcers

Venous ulcers may result from minor trauma to the lower leg, such as a fall or bump from furniture. The initial tissue injury becomes defined as a leg ulcer when it has remained unhealed for more than 6 weeks.[5] Often there is pre-existing deterioration of the skin and subcutaneous tissues, suggestive of venous insufficiency. Demonstration of venous reflux (usually by ultrasound tests) and the exclusion of other causes confirm the diagnosis of the ulceration being venous in origin.[6]

The aetiology of venous ulcers is complex and not fully understood,[7] but is thought to be due to chronic venous hypertension resulting from venous insufficiency caused by a deficient calf-muscle pump.[8] Under normal circumstances blood returns to the heart through the contraction and relaxation of the calf and foot muscles during leg movement and exercise – the 'calf-muscle pump'. Muscular contraction increases the pressure in both the deep and superficial veins – but results in higher pressure in the deep veins because they are contained within relatively unyielding fascial compartments. When the muscles relax, retrograde flow of blood is prevented by non-return valves in the lumen of the veins. Perforating veins, which join the deep veins with the superficial veins, also contain valves which normally allow blood to flow only from superficial to deep veins.

People presenting with venous leg ulcers have venous insufficiency due to problems with the calf-muscle pump as a result of venous occlusion or incompetence of the valves in the deep, superficial or perforating veins.[9] Venous insufficiency can be classified as either primary or secondary. Primary venous insufficiency occurs when no discernible cause can be identified and can result from congenitally ineffective valves or perhaps from occupations which involve prolonged standing, which leads to a loss of elasticity in the vein walls.[10,11] Secondary venous insufficiency occurs when damage to the valves is caused by an identifiable condition such as deep vein thrombosis (DVT).[8,12]

Whatever the underlying cause, damage to the venous valves results in the blood flowing in the wrong direction (this is referred to as 'reflux' and the veins are described as 'incompetent'), pooling of blood in the veins, and exposure of the superficial veins to high pressure, i.e. superficial venous hypertension.[13] The venous hypertension results in localised oedema which traps leucocytes in the tissues: the leucocytes release oxygen-free radicals and other toxic products which produce localised tissue damage.[9] This tissue damage means that the tissues may fail to heal after even minor trauma, resulting in an ulcer.

Once a venous ulcer has occurred it often follows a cyclical pattern of healing and recurrence. Recurrence rates of between 45% and 70% at 1 year are reported.[8,14] The time taken for an ulcer to heal can be very protracted and a significant minority of patients do not achieve complete ulcer healing, or do so only after many years.[15,16]

### Epidemiology

Leg ulceration has an incidence of between 1 and 2 per 1000 in the UK population,[17] with approximately 80% being venous in origin.[7] It has been estimated that up to between 0.2% and 1% of the adult population have experienced a leg ulcer;[5,8,17] of these about 20% have an open ulcer and about 80% have a previous history of ulceration.[18] Venous ulcers are more prevalent in women and in the elderly.[19–21] These figures may well be underestimates as a result of inadequate

assessment which fails to identify venous ulcers, and also as a result of under-reporting.[22]

## Venous leg ulcers and quality of life

It is well recognised that venous leg ulcers can cause considerable morbidity and reduced quality of life (QoL).[23,24] However, the main focus of research in the area of venous ulceration has been around the effectiveness of dressings and has not tended to incorporate the impact of ulcers on QoL.[25] Studies that have examined QoL have used a number of different methodological techniques including qualitative and both generic and disease-specific QoL questionnaires. A systematic review by Herber *et al*.[26] found 24 articles that examined the impact of leg ulcers on QoL, but highlighted the problem that many of the studies did not differentiate participants by ulcer aetiology, i.e. they did not specifically examine venous ulcers.

### Qualitative studies

A key characteristic of qualitative research is to adopt the perspective of the people being studied in order to understand the impact and meanings that inform their behaviour,[27] and a number of qualitative studies have been conducted in an attempt to explore the experience of having a leg ulcer.[28–37]

A synthesis of qualitative studies[38] described leg ulceration as being a chronic, debilitating condition. The symptom that had the most impact on patients was pain, which restricts physical and social activities.[26] In addition to pain, other symptoms identified in the studies were restricted mobility,[32,33] depression[32,35,39] and an offensive smell from ulcers.[29] The impact of ulceration is magnified by the patients feeling powerless and isolated.[33,35,40] There can be a complex web of interactions between the physical, psychological and social impacts of having an ulcer.[29] One example is the impact of physical symptoms on mood, which in turn can have a social impact, which can result in any symptoms being perceived as more severe. Some of the perceived impact on QoL of having a leg ulcer has been ascribed to patients' lack of understanding about the origin and treatment of their leg ulcers.[41]

Qualitative studies have also explored the impact of venous ulceration on relationships of patients with their health-care professionals. This impact could be either negative, in terms of patients perceiving professionals as lacking empathy,[42] or positive, as a result of the psychological support provided by clinicians.[33]

### Generic quality of life measures

Generic QoL questionnaires that have been used to measure outcomes for patients with venous leg ulcers have included the EuroQol 5 dimensions (EQ-5D)[43], Short Form 36 (SF-36)[44,45] and Nottingham Health Profile (NHP).[46]

Studies that have administered these generic questionnaires to venous ulcer patients have tended to show that people with leg ulcers do differ from an age-matched normal population. Generic instruments administered to venous ulcer patients showed limited sensitivity to the healing of the ulceration. The NHP showed statistically significant ($p = 0.04$) improvements in energy and mobility,[47] but not pain related to ulcer healing. This contrasted with another study[48] that administered a number of different generic questionnaires, including the SF-36 and EQ-5D, but found only the McGill Pain Questionnaire was able to detect any changes in scores pre and post ulcer healing.

The generic measures have been developed mainly using the medical model and, with the exception of the NHP that used lay perceptions of health status, have tended to include items based on expert medical opinion or derived from existing health status measures.[49]

### Disease-specific measures

The lack of sensitivity of generic QoL measures in detecting differences due to treatments has led some researchers to evaluate disease-specific measures. These are said to be more sensitive as they highlight issues that are important to patients with a specific disease.[50,51]

Disease-specific questionnaires administered to ulcer patients have included the Cardiff Wound Impact Schedule (CWIS),[52] the Hyland ulcer-specific tool,[53] the Charing Cross Venous Leg Ulcer Questionnaire,[54] the Freiburger Lebessqualitas Assessment Questionnaire (FLQA)[55] and the Chronic Venous Insufficiency Questionnaire.[56]

The disease-specific questionnaires that have been administered to venous ulcer patients have been subject to a number of limitations. The Hyland ulcer-specific tool and CWIS were not developed

specifically for venous leg ulcers, but for all chronic wounds regardless of aetiology. Some of the tools were originally created in a foreign language and have not been validated in English.[55,56] Furthermore, the Hyland ulcer-specific tool was validated using a sample size of only 50 people.[53] Other studies did not exclude patients with ulcers of other aetiologies.[26,52] The inclusion of ulcers of mixed aetiology may confound such assessments as they vary in terms of symptoms and likely impact. For example, in terms of pain, arterial ulcers are usually more painful than venous ulcers and ulcers in diabetics are often less painful owing to associated peripheral neuropathy.

A factor that has not been examined, in either the qualitative studies or the QoL questionnaires, has been the chronic nature of leg ulcers, with cyclical healing and recurrence. When active, the ulcer is often the central issue in a patient's life, to the exclusion of everything else. A further complicating factor is separation of the impact of the ulceration from that of other co-morbidities; these patients tend to be elderly and often have arthritis and widespread atherosclerosis that impact on their QoL.

## Treatment of venous leg ulcers

The majority of leg ulcer treatment in the UK takes place in dedicated leg ulcer clinics, but it can also be given by community nurses attending patients' own homes.[57] Multilayer compression bandaging has been identified as the gold standard in the treatment of venous leg ulcers.[58,59] It has been used in one form or another for over 300 years.[21] The compression is applied in a graduated fashion with the pressure decreasing from the toe to the knee.[60] The mode of action is not clearly understood but it is postulated that the application of external pressure to the calf muscle raises the interstitial tissue pressure, decreases the superficial venous pressure and improves venous return.[58] In order to reduce the venous hypertension, sub-bandage pressures of 40 mmHg at the ankle reducing to 20 mmHg at the knee are recommended.[61] The reduction of the venous pressure and oedema allow healing of the ulcer to occur. The healing rate can vary depending on initial ulcer size and duration.[6] A mean 12-week healing rate of 70% has been reported for small ulcers in specialist leg ulcer clinics,[6] while a randomised controlled trial (RCT) that included ulcers of mixed sizes and durations reported a healing rate of 34%.[57]

There are two main methods of achieving compression on the leg – compression bandaging and graduated compression hosiery. An alternative that is occasionally used is intermittent pneumatic compression, which involves a system of inflatable boots to apply compression.

Before the application of any of type of compression patients need assessment of the arterial supply to their lower limbs including measurement of ankle brachial pressure index (ABPI), in order to exclude any arterial insufficiency.[6] This kind of arterial assessment is necessary to avoid the risk of tissue damage, including skin necrosis and even limb loss, as a result of applying compression to an ischaemic extremity.[16]

### Compression bandaging

Systematic reviews[58,59,62] have shown that compression bandages are effective in healing venous leg ulcers. Compression bandaging usually involves multiple layers of bandages, commonly based on the Charing Cross four-layer bandage system, which was developed in the late 1980s.[63] The first layer is usually a soft wool bandage which redistributes the pressure of the overlying bandage layers, cushioning bony prominences and allowing 'shaping'. The second layer is a cotton crepe bandage which provides absorbency and a smooth surface. The third layer is an elastic bandage, and is the first layer of compression; it provides around 17–20 mmHg pressure.[64] The final layer is a cohesive bandage, the second layer of compression, and provides around 23 mmHg pressure. Each of the elastic layers of bandage is applied at 50% maximum stretch and 50% overlap at each turn.[65] Laplace's law in relation to the pressure beneath compression bandages states that the external force of the bandage is dependent on the circumference of the limb to which it is applied. A bandage applied with constant tension to a limb of increasing circumference will result in a pressure gradient with the highest pressure at the ankle.[66] The application of compression bandage systems is a skilled technique: consistency in achieving the necessary sub-bandage pressures is linked to technique, training, experience and patient positioning.[61,64]

An alternative bandage regime involves the application of short-stretch bandages.[67] The mode of action of short-stretch bandages differs from that of four-layer bandage systems. There are only two layers of bandages and these are applied at full

stretch. The bandages form a tube surrounding the limb from knee to ankle and the action of the calf muscle creates pressure between the bandages and the limb.[65] The main advantages of short-stretch bandages over four-layer systems are that they can be easier to apply and patients or their carers can be taught to apply them.[68] However, a recent a recent large RCT found that four-layer systems were more cost-effective as they required fewer visits from clinicians.[18]

### Compression hosiery

Compression hosiery can take the form of either above-knee or below-knee stockings. The graduated compression applied is categorised into three 'classes', with Class 1 providing the lowest level of compression and Class 3 the highest level of compression.[10,60] Compression hosiery is most often worn once healing of ulceration has occurred in order to reduce the risk of recurrence, but new hosiery systems are becoming available for the treatment of active ulceration.[6] Patients often complain that the compression hosiery is uncomfortable and difficult to apply, with the result that problems of compliance are not uncommon.[69,70]

### Intermittent pneumatic compression

This involves the application of a boot-like system to the lower leg. Compressed air is used to inflate and deflate air bladders incorporated into a boot, which applies pressure in a wave from the ankle to the knee.[71] The patient has to wear the intermittent compression boot for approximately 4 hours a day, and either compression bandages or compression hosiery are required between the treatment episodes. The evidence for the effectiveness of pneumatic compression remains equivocal.[72]

### Dressings

Dressings are usually placed over the ulcer prior to the application of compression bandages or hosiery, with the intention of preventing the bandages from sticking to the ulcer and of promoting healing.[65] Dressings aim to promote healing by: removing excess exudate from the wound surface; providing a moist, sterile micro-environment; reducing ulcer pain; providing a barrier to micro-organisms; and providing thermal insulation.[73]

There are a large number of dressings available, ranging from simple woven gauze to products made from complex polymers. The classification of dressings is complicated by manufacturers who are increasingly marketing new dressings based on different materials with different properties, characteristics and claims about what they can do.[74] The *British National Formulary* (BNF)[75] classifies dressings on the basis of the material from which they are made, adherence and permeability. The main groups included in the BNF are alginate, hydrocolloid, low-adherent (also known as non-adherent) and vapour-permeable dressings. Newly marketed antimicrobial dressings that contain silver or honey are based on the existing dressing types and the BNF therefore classifies them based on the material to which the antimicrobial agent is bonded.

Manufacturers regularly market 'new and improved' dressings in order to access the 'explosive growth in the wound care market' which is projected to reach US$11.8 billion by 2009.[76] However, the evidence of any increased benefit provided by these dressings is limited (in contrast to the evidence for compression) and they can contribute significantly to the cost of treating a venous leg ulcer. A recently published systematic review and meta-analysis[2] found that the general quality of the existing evidence was poor, and that there appeared to be no statistically significant difference between any of the dressing types in terms of the total number of ulcers healed. The lack of evidence of effectiveness has also been highlighted for the antimicrobial dressings that have been marketed more recently.[4]

## The wound infection continuum

Chronic wounds are almost always contaminated with micro-organisms and in small numbers they do not necessarily delay healing.[77,78] Where infection occurs it is most commonly caused by bacteria. Other organisms such as fungi and protozoa (such as *Leishmania*) are rare causes, while viruses do not generally cause skin infections. The bacteria that infect leg ulcers are often commensals and their impact can be variable, depending on the numbers and type of bacteria present. The criteria used to describe bacterial loading have been loosely defined by the European Wound Management Association[79] as follows:

- *Contamination* is the presence of bacteria with no multiplication.
- *Colonisation* describes multiplication of bacteria with no host response.

- *Infection* is said to be present when there is invasion of healthy tissues with a host response.

Another descriptor of the continuum of wound infection is often referred to as *critical colonisation* or *subclinical infection*.[80] A state of bacterial colonisation is said to exist which verges on infection. This state has been used to justify the application of antimicrobial dressings in order to reduce the bacterial count and so to aid healing.[81,82] However, the significance of the quantity and type of bacteria in a chronic wound is still the subject of much debate, and there is also confusion about and a lack of understanding of the effect bacteria have on wounds of different aetiologies.[83]

A possible factor in the persistence of bacteria in leg ulcers is the formation of biofilms. These have been recognised as a problem in the food industry for many years, but have recently been identified as relevant to infection in humans.[79] They are composed of a complex community of micro-organisms (several different bacterial species) that attach to a surface and are encased in a sticky extracellular polymer membrane which gives protection against many antimicrobial agents (including antibiotics). They have only recently been described in connection with wounds, but are of concern as the bacteria within them can be difficult to eradicate, and therefore a persistent source of infection.[84]

Diagnosis of wound infection is not an exact science and recognition of clinical infection may be difficult. It can often be challenging to ascertain from a wound swab whether or not a wound is infected.[85,86] This can be especially difficult with leg ulcers as large numbers of different bacteria are often present – some of which are pathogens and others commensals.[87] Bacteriological investigations are helpful only insofar as they identify which organisms are present, and their sensitivities to particular antibiotics. However, the culture may not identify all the bacteria potentially causing a problem.[88] Health-care professionals need to be able to recognise clinical indicators of infection and the significance (or lack of significance) of the presence of bacteria.[89]

## Clinical indicators of wound infection in the chronic wound

The classic signs commonly used by health-care professionals to diagnose infection – pain, heat, redness and swelling, with the associated purulent discharge[90] – can be difficult to apply to venous leg ulcers.[91,92] Leg ulcer-specific criteria that may indicate infection include:

- Delayed healing. This may be the only sign of an infection. If there are no signs of healing within a 4-week period increased bacterial burden or infection should be considered.[93]
- Unexpected pain and tenderness.[94]
- Abnormal odour. This can be a sign of the presence of Gram-negative bacilli, *Pseudomonas* species or anaerobic bacteria.[91]
- 'Pocketing'. This describes the appearance of small deep lesions at the base of the wound caused by a lack of granulation tissue.[94]
- Discolouration. Granulation tissue which appears 'unusually' dark red in colour may indicate an angiogenic response to pathogens, while black discolouration may be caused by anaerobic bacteria.[92]
- Friable granulation tissue (granulation tissue that bleeds easily).[93]
- Devitalised tissue. Loose yellow debris and areas of necrosis at the base of a previously healing wound may represent localised infection.[95]

These features may be present in varying combinations and degrees. This can lead to real difficulty in assessing whether a wound is 'infected' and in need of specific antimicrobial treatment. The lack of a clear definition of infection, and lack of clarity about the significance of bacteria found on microscopy and culture, underpin the uncertainties and use of topical antimicrobials in the treatment of leg ulcers.

## Antimicrobials and chronic wounds

Antimicrobials are agents that either kill or inhibit the growth and division of micro-organisms.[79] They include antiseptics, disinfectants and antibiotics.

Historically, the main method of attempting to reduce or eliminate bacteria from a wound was by routine cleansing using an antiseptic.[83] Antiseptics are substances that inhibit the growth and development of micro-organisms and may be bacteriostatic (stop the bacteria multiplying) or bactericidal (kill the bacterial cell). Antiseptics that have been used in wounds include sodium hypochlorite, hydrogen peroxide, chlorhexidine, iodine compounds and silver nitrate solutions.[96] The use of such agents has declined owing to studies that have shown that these solutions

did little to rid wounds of harmful bacteria.[96–98] Chlorhexidine and iodine used within a wound are rapidly inactivated in the presence of the wound fluid.[99,100]

In recent years there have been concerns regarding the development of bacterial resistance and so the routine use of topical and systemic antibiotics in the treatment of leg ulcers has been discouraged.[101,102] One possible consequence of this has been the increasing use of dressings that are described as antimicrobial. Another is the recognition that such dressings can disrupt bacterial biofilms found on the surface of chronic wounds.[103]

## Antimicrobial wound dressings

In the last 20 years there has been a significant increase in antimicrobial wound care products which release low concentrations of substances that inhibit bacterial growth.[1] These can be divided into two groups – passive dressings that act on the bacteria as they pass into the dressings, and active dressings that release antimicrobial substances into the wound.[104] The dressings contain antimicrobial substances such as iodine, honey or silver. There are at least 40 of these types of dressings listed in the latest *Wound Care Handbook*[105] and the numbers are increasing.

Iodine was reportedly first used on wounds as an aqueous potassium solution in 1839 by Davies,[106] but was found to cause pain, irritation and skin discolouration. The development of povidone iodine and cadexomer iodine in 1949 led to fewer problems owing to these preparations releasing low concentrations of iodine.[84] However, there are limits to how long they can be used because of the uptake of iodine by the thyroid gland.[75]

### *Honey*

Honey has a long history of use in wound care dating back to the ancient Egyptians.[107] More recently, a type of honey called Manuka honey, derived from the tea tree, has been incorporated into wound dressings.[108] The Honey as Adjuvant Leg Ulcer Therapy (HALT) trial,[109] published in 2008, was an RCT that compared these types of dressings versus 'usual care' for venous ulcers. The trial concluded that honey-impregnated dressings did not significantly improve ulcer healing rates at 12 weeks.

### *Silver*

The antimicrobial properties of silver have been recognised for centuries in wound care, particularly for burns.[110] The earliest publication in which silver was recommended for treating wounds, including leg ulcers, was a textbook published in 1617 by General Surgeon John Woodall, who used a solution of one part silver with three parts nitric acid.[111] The introduction of antibiotics during the 1940s led to a decline in the use of silver.[110] However, in the 1960 and 1970s concerns regarding resistant bacteria, due to the widespread use of antibiotics, led to a renewed interest in the antimicrobial properties of silver.

Most of the evidence on the antibacterial effects of silver are from in vitro studies on experimental wounds.[4] The antimicrobial properties of silver are thought to be based on its property of forming ionic silver salts ($Ag^+$) in the presence of concentrated acids.[112] The mechanism by which silver affects bacteria is thought to be based on the presence of negatively-charged structures on the cell membrane that attract the positively-charged silver ions. This allows silver to attach to the surface of the micro-organisms and enter the cell.[4] The silver ions then block key metabolic pathways such as the respiratory system, and prevent cell division.[87]

The range of products containing silver covers the whole spectrum of dressing types, including hydrocolloids, film membranes, foams, alginates and tulles. There are differing claims regarding the effectiveness of these products based upon their mode of action, the ability of the dressings to release silver into the wound and the precise type of silver they contain.[1]

#### The differing properties of silver dressings

The silver dressings available vary in the type of silver preparation they contain, the amount of silver, their ability to release silver and the way in which silver is released. The dressings may contain compounds of silver nitrate, silver ion release preparations or silver-based crystalline nanoparticles; some products also include sulphadiazine (a member of the sulphonamide antibiotic group).[95,110] The silver dressings also differ in that some release silver into the wound, while others have silver bound into the dressing fabric and the antimicrobial activity is within the structure of the dressing.[4]

Differences in the methodology of the published studies make interpretation of the results difficult.[87] In addition, there have been no high quality RCTs that have compared silver wound care products in

terms of their action and mode of delivery.[113] The evidence for using silver dressings in relation to venous leg ulcers has also been described as being generally lacking.[4]

### *The choice of antimicrobial dressings for the VULCAN study*

When the trial was originally planned in 2002 it was envisaged that the likely dressings to be examined would be iodine based (See Appendix 7 for the original trial protocol). However, by the time the VULCAN study was initiated there was a trend for the increasing use of silver-containing dressings in preference to those containing iodine. This trend was confirmed in a national survey of health-care professionals caring for venous ulcers,[114] which is detailed in Chapter 2. The survey showed that, although honey and iodine preparations were in use, silver dressing were reported as being the first and second choice of dressing for venous leg ulcers by the majority of those who responded. Silver dressings have been heavily marketed by the manufacturers and there has been an increase of over 200% in the use of dressings containing silver since 1996.[4]

Based on the findings of the survey and on the fact that there was already an RCT in progress evaluating honey-impregnated dressings for venous ulcers,[109] it was decided to focus the VULCAN study on silver-donating dressings and to exclude dressings containing iodine or honey. In choosing the dressings for inclusion in the study, there was considerable discussion about both the type of dressings and how far to limit the choice (the option of a single type of silver dressing was considered). In the end the pragmatic and permissive approach was taken, as recruitment to the study would depend on the cooperation of community nurses. They are accustomed to making their own choices of dressings for each patient, guided by the local practice guidelines and their personal experience and preferences.[115] It was feared that they might not recruit patients if there were too many restrictions on their choice of dressings and the protocol did not allow them some flexibility.

Silver dressings were included in the trial if they were reported by the pharmaceutical company to actively release silver ions to the wound bed and if they could be used under compression bandages for up to 7 days. An allowance was also made in the trial protocol that any other products that fulfilled these criteria could be included if they became available during the recruitment period of the trial.

There were six active silver-releasing dressings on the UK Drug Tariff at the time the study was being set up:

- Acticoat™ (Smith & Nephew Healthcare, Hull) and Acticoat 7™ (Smith & Nephew Healthcare, Hull) are dressings that comprise two absorbent rayon and polyester layers laminated between layers of nanocrystalline silver.
- Acticoat Absorbent™ (Smith & Nephew Healthcare, Hull) is an alginate dressing incorporating nanocrystalline silver.
- Urgotul SSD™ (Urgo, Parema Medical, Loughborough) is a hydrocolloid-based dressing impregnated with a silver salt.
- Aquacel Ag™ (ConvaTec, Ickenham) is a fibrous dressing impregnated with 1.2% silver.
- Contreet Foam™ (Coloplast, Peterborough) is a polyurethane foam dressing with a permeable film backing impregnated with silver.

## Cost-effectiveness of treatments for venous ulceration

There is a lack of rigorous studies examining the economics of treatments for venous leg ulcers. The existing economic costings have been described as unsophisticated, consisting of merely summing the monetary cost of the dressings.[2] With respect to cost-effectiveness, there has been very little work in the area of leg ulcer treatment. A non-systematic review of the literature revealed just two applications of cost-effectiveness in this area. One study[109] investigated the potential impact of honey-impregnated dressings, while the other study[116] examined silver-releasing dressings.

The first of these studies[109] compared the costs and outcomes of treating venous leg ulcers using dressings impregnated with Manuka honey versus usual care. Their randomised trial of 386 participants showed no difference between the groups in terms of healing rates. The honey treatment was more costly and associated with more adverse events.

The second study[116] examined the relative cost-effectiveness of four antimicrobial dressings for leg ulcers using a Markov model validated by 'a group of wound care specialists', based on wound healing at 4 weeks. These dressings were: Contreet Foam; Aquacel Ag; Actisorb Silver; and Iodoflex. Cost-effectiveness was assessed using a short-term 4-week model and a longer-term Markov model.

Contreet Foam was found to be the most cost-effective treatment, with a cost per percentage reduction in wound area of £9.50 compared with between £16.50 and £17.50 for the other treatment options. The Markov analysis of complete healing supported these results. The authors suggested that using Contreet Foam instead of the other dressings could save the UK National Health Service (NHS) between £2.2 million and £4.4 million per year.

The cost-effectiveness of antimicrobial dressings in the treatment of venous leg ulcers is clearly an under-researched area, so the cost-effectiveness analysis undertaken in this study provides a timely contribution to a limited evidence base. The estimation of incremental cost per quality-adjusted life-years (QALYs) gained represents a significant improvement on existing work.

## Conclusion

Delayed healing and difficulties in both recognising and determining the clinical significance of infection are major problems in the management of venous leg ulcers. Following clinical assessment, decisions need to be made about what kind of dressing to use. Antimicrobial dressings containing iodine, honey and silver have been promoted for treatment for venous ulcers. Iodine-based dressings have declined in use because of concerns about the possible toxic effects on the body from use of iodine and the limited timescale for which they can be in contact with the wound. Honey dressings have been evaluated in a large RCT, the HALT trial,[109] which showed no significant advantage over 'usual care'.

The range of antimicrobial dressings which contain silver has increased in the last 5 years,[112] and they have become the most commonly used type of dressing among nurses caring for leg ulcers in the UK.[114] Dressing manufacturers are continuing to produce new silver products or silver versions of existing dressings as a way to 'meet demand'. The increasing use of these dressings has cost implications for the health service as they are significantly more expensive than non-silver dressings. Sophisticated marketing of silver products makes the decision for nurses regarding which dressing to use difficult and sometimes confusing.

Evidence on the use of antimicrobial dressings for venous leg ulcers is currently limited and equivocal.[4,113] In 2006, Palfreyman *et al*.[117] published a Cochrane review that assessed the evidence on dressings (of all kinds) for venous leg ulcers, looking at 44 studies which showed no significant difference in terms of healing between any of the dressing types. This absence of data complicates the selection of an appropriate product. Anecdotal evidence and increasing concerns regarding infection have led to a 'just in case' approach, whereby nurses often choose a silver dressing in case infection is playing a part and in the hope of enhancing healing, but without any good evidence base. Antimicrobial use needs to be selective, appropriate and proportionate,[110] based on clinical need and not used as a matter of rote or routine.[118]

There is currently no good evidence on the cost-effectiveness of using of antimicrobial dressings for venous leg ulcers and specifically with respect to silver dressings. The VULCAN trial sought to address this by evaluating the cost-effectiveness of silver-donating dressings compared with low-adherent dressings for venous leg ulcers.

# Chapter 2

# Surveys of venous ulcer services and antimicrobial dressings

## Introduction

In order to set the planned study in context and to inform its design, two surveys were undertaken:

- an informal survey of nurses attending a national vascular meeting, about the dressings they used (survey 1)
- a comprehensive survey of all areas of the UK about the existence and nature of dedicated services for venous ulcers, including their use of antimicrobial dressings (survey 2).

A further survey was undertaken during the trial to provide further information about the knowledge base and rationale for the use of antimicrobial dressings (survey 3).

## Survey 1: informal survey of nurses attending a national vascular meeting

An informal, opportunistic survey was conducted in order to gather data on the range of antimicrobial dressings in use, to inform subsequent surveys and to guide the choice of antimicrobial dressing for the trial. This was carried out by one of the authors (WBC) in November 2003 at a meeting of the Society of Vascular Nurses. Nurses were approached opportunistically between sessions of the meeting – individually or in groups. They were asked two questions related to the types and frequency of antimicrobial dressings used for venous leg ulcers in their local setting. Thirty-eight nurses (who worked in a total of 40 hospital or community Trusts) were questioned and all responded.

*Question 1. How often were antimicrobial dressings used in their hospitals or community Trusts in the treatment of venous ulcers?*

The responses are shown in *Table 1* (percentages were based on the 38 nurses questioned as the denominator).

***TABLE 1*** *Estimated frequency of use of antimicrobial dressings among 38 nurses*

| Response | *n* (%) |
|---|---|
| Always | 0 |
| Frequently | 7 (18) |
| About half the ulcers treated | 9 (24) |
| Rarely | 18 (47) |
| Never | 4 (11) |
| Total | 38 |

*Question 2. Which dressings or antimicrobial agents were used in their hospital or community Trusts in the treatment of venous ulcers?* (If more than one, they were asked to rank, but few described the use of more than one type.)

The responses are shown in *Table 2*.

***TABLE 2*** *Dressings specified by 38 nurses as being used in the 40 Trusts in which they worked*

| Dressing | *n* (%) |
|---|---|
| Flamazine™ (Smith & Nephew, Hull) | 12 (17) |
| Actisorb Silver 200™ (Johnson & Johnson, Ascot) | 11 (16) |
| Aquacel Ag™ (ConvaTec Ltd, Ickenham) | 9 (13) |
| Acticoat™ (Smith & Nephew) | 7 (10) |
| Inadine™ (Johnson & Johnson) | 6 (9) |
| Iodosorb™ (Smith & Nephew) | 4 (6) |
| Iodoflex™ (Smith & Nephew) | 4 (6) |
| Metrotop™ (Mölnlycke Health Care Ltd, Dunstable) | 4 (6) |
| Metronidazole (generic drug) | 4 (6) |
| Bactroban™ (GlaxoSmithKline, Uxbridge) | 4 (6) |
| Fucidin™ (Leo Pharma, Princes Risborough) | 2 (3) |
| Fucibet™ (Leo Pharma) | 2 (3) |
| Total number of nurses/Trusts using specified dressings | 69 |

Percentages add to up to greater than 100 owing to rounding up of values.

# Survey 2: comprehensive survey of venous ulcer services throughout the UK

## Introduction

The aims of this survey were to obtain information about the existence and organisation of venous ulcer services in each locality throughout the UK, and specifically to document details about the use and types of topical antimicrobials.

## Methods

The survey[114] was conducted between September and December 2004. A list was compiled of acute hospital Trusts throughout the UK (a total of 181). A letter was sent to a vascular surgeon (from the membership list of the Vascular Society of Great Britain and Ireland) in each Trust, explaining the intention of the planned survey (see Appendix 4).

A questionnaire (see Appendix 4) was sent to the individual identified as supervising the dedicated leg ulcer service in each hospital (or group of hospitals with a shared service) based on the responses received.

## Results

Responses were received from 177 of the 181 localities (98%). These are described in three sections: Organisation and management of the venous ulcer services; Use of different antimicrobial dressings; and Training for nurses.

### *Organisation and management of services*

Fifteen localities (8%) had no dedicated venous ulcer service, but some kind of service was said to exist in the remainder (a total of 162). Completed questionnaires were received about 111 (63%) of these services, but questionnaires were not returned from 50 (28%). Sixteen (9%) of the returned questionnaires were not completed. *Table 3* shows where the venous ulcer services were based.

The organisations managing these services were acute care (hospital) Trusts in 56 (54%) localities, primary care Trusts (PCTs) in 29 (28%) and both of these in 19 (18%). The individuals in overall charge of the services were vascular surgeons ($n = 49$), dermatologists ($n = 12$), both vascular surgeons and dermatologists ($n = 4$), nurses ($n = 31$) and others ($n = 4$).

New referrals per week were reported as 1–50 (median 5) and annual attendances as 10–4600 (median 270) based on audit (33%) or estimates (67%). Forty-five (42%) services had databases. Written guidelines existed for 76% of services. These were significantly more common in services supervised by nurses (90%) than in services supervised by doctors (64%) ($p < 0.02$). Eighty-five per cent had been developed locally – 51% based on existing national guidelines, most commonly those of the Royal College of Nursing[6] ($n = 34$) or Scottish Intercollegiate Guidelines Network[119] ($n = 19$).

### *Use of different antimicrobial dressings*

With regard to the use of specific types of antimicrobial dressings used, the first 59 responses were analysed in detail in January 2004 as part of the iterative process of selecting dressings for use in the randomised trial. Respondents had been asked to specify the antimicrobial dressings used in their area only if they had a dedicated venous ulcer service ($n = 44$). Some who said that they had not got a dedicated service nevertheless specified dressings, and these responses were included in the analysis. The general types of dressings used (i.e. iodine based, silver based, etc.) are shown in *Table 4* (see question 12, Appendix 4). *Table 4* shows the percentages for which each type of agent was listed as first choice, and the percentages for which each was listed as first, second or third choice.

This initial analysis was considered to support the decision to choose silver-based dressings in the randomised trial. A further analysis was therefore done, when all the responses had been received, of the specific types of silver-based dressings in use. Silver-based dressings were described as first or

**TABLE 3** *Location of venous ulcer clinics*

| Where clinics were based | *n* (%) |
|---|---|
| Acute hospital only | 58 (52) |
| Acute hospital and general practice surgery | 10 (9) |
| General practice surgery only | 7 (6) |
| Acute hospital and community hospital | 5 (5) |
| Community hospital only | 2 (2) |
| Community hospital and general practice surgery | 3 (2) |
| All the above | 7 (6) |
| Acute hospital and other community setting | 4 (4) |
| Other | 15 (14) |
| Total | 111 |

second choice in 54% of the questionnaires. The specific types of dressing are shown in *Table 5*.

#### *Training for nurses*

Training in arterial Doppler pressure measurements and in compression bandaging was done 'in house' in 52% and 54% respectively, on courses in 22% and 18% respectively, or both in 26%.

## Survey 3: the use of silver and other antimicrobial dressing products

### Introduction

During the course of the VULCAN trial, variations were noticed in the choices of antimicrobial dressings. Informal discussions with clinicians caring for venous leg ulcer patients highlighted that some uncertainty existed regarding the indications for antimicrobial dressings and the differing properties of the various types of dressings available.

### Methods

The survey was conducted in the two main centres participating in the VULCAN trial. The questionnaires were distributed in Sheffield between July and August 2007, and in Exeter between February and April 2008. The identification of nurses caring for leg ulcer patients in Sheffield was facilitated through the clinical effectiveness team of Sheffield PCT who posted the questionnaires to 94 general practitioner (GP) practices, 59 community nurse bases and 61 care homes. In Exeter, the sample was drawn from four district and practice nurse bases and 25 leg ulcer clinics. The relevant governance approvals were obtained from the participating centres.

A questionnaire with a covering letter was either sent or delivered by hand to the nurse base or leg ulcer clinic and this was followed up with a reminder letter or telephone call 3 weeks later if no response had been received. The items for the questionnaire were generated using a Delphi technique by repeated consultation with senior tissue viability nurses in the survey areas. A copy of the questionnaire can be seen in Appendix 4.

The aim of the items contained in the questionnaire was to explore the decisions around the choice of antimicrobial dressings made by nurses caring for venous leg ulcer patients. The questionnaire was structured into four sections. The first collected demographic information; the second examined knowledge regarding antimicrobial dressings; the third asked about sources of information and education regarding antimicrobial dressings; and the final section asked about the clinical indications for antimicrobial dressings.

The data were analysed using SPSS™ (version 15). Simple descriptive statistics were used to report item response. In assessing the differences between the centres the Mann–Whitney test for non-parametric data was used.

### Results

#### *Demographic details and response rate*

A total of 398 questionnaires were sent out and 102 responses obtained giving a response rate of 26%. The response rates varied between the two centres, but were comparable at 25% (53/214) and 27% (49/184) in Sheffield and Exeter respectively. A total of 53 (52%) of the returned questionnaires were from Sheffield and 49 (48%) from Exeter. *Table 6* shows the demographic details of the respondents.

***TABLE 4*** *Types of dressings described in the first 59 questionnaires returned*

| Type of antimicrobial agent | First choice (%) | First + second + third choice (%) |
|---|---|---|
| Iodine based | 20 | 40 |
| Silver based | 19 | 46 |
| Flamazine | 12 | 44 |
| Antibiotic based | 9 | 43 |
| Potassium permanganate | 2 | 5 |
| Other | 0 | 7 |

***TABLE 5*** *Types of silver-based dressings reported as being in use in the questionnaire responses*

| Type of topical silver agent | *n* (%) |
|---|---|
| Aquacel Ag | 31 (27) |
| Actisorb silver (200) | 21 (18) |
| Acticoat | 19 (17) |
| Acticoat 7 | 11 (10) |
| Contreet Foam | 9 (8) |
| Urgotul SSD | 4 (4) |
| Avance™ (Mölnlycke Health Care Ltd, Dunstable) | 2 (2) |
| Any silver dressing | 17 (15) |
| Total | 114 |

Percentages add to up to greater than 100 due to rounding up of values.

The majority ($n = 33$; 52%) of responders were on Agenda for Change (AfC) band 5. This was most notable in Exeter, although in Sheffield 38% ($n = 18$) did not identify their AfC band compared with only 10% in Exeter. There were significant ($p < 0.05$) differences between the two centres in terms of where respondents worked. In Sheffield 59% ($n = 29$) classed themselves as practice nurses compared with only 14% ($n = 5$) in Exeter, while in Exeter the majority of responders were community nurses (67%; $n = 24$) compared with 14% ($n = 7$) in Sheffield. Twelve described themselves as 'Other'.

A total of 82 out of 87 (94.3%) respondents stated that they used silver antimicrobial dressings on a regular basis – the remaining five did not give a response. The silver dressings most often used were Acticoat (52%; $n = 53$), Urgotul SSD (83.3%; $n = 85$), Aquacel Ag (77.5%; $n = 79$) and Actisorb (79.4%; $n = 81$). The most popular silver-containing dressings were the Acticoat range (18/102; 28.4%) and Urgotul SSD (17.6%; 18/102). The least popular was Contreet Foam (6.8%; 7/102). The non-silver antimicrobial dressing most commonly used was Inadine (21.3%; 16/75).

When asked about the frequency of antimicrobial dressings used per month, the lowest category options, '0–3' and '4–6' patients per month, accounted for 92% of responses – with the majority of responses (69%) in the 0–3 per month category.

***TABLE 6*** *Demographic details of the sample*

| | | All | | Sheffield | | Exeter | |
|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % |
| Area | Sheffield | 53 | 52.0 | | | | |
| | Exeter | 49 | 48.0 | | | | |
| | Total | 102 | 100.0 | | | | |
| Agenda for Change band | 5 | 33 | 52.4 | 8 | 42.1 | 25 | 56.8 |
| | 6 | 19 | 30.2 | 3 | 15.8 | 16 | 36.4 |
| | 7 | 10 | 15.8 | 7 | 36.8 | 3 | 6.8 |
| | 8a | 1 | 1.6 | 1 | 5.3 | 0 | 0.0 |
| | Total | 63 | 100.1 | 19 | 100.0 | 44 | 100.0 |
| | (Not recorded *n* = 8) | | | | | | |
| Area of practice | District nurse | 8 | 9.4 | 2 | 4.1 | 6 | 16.7 |
| | Community nurse | 31 | 36.5 | 7 | 14.3 | 24 | 66.7 |
| | Practice nurse | 34 | 40.0 | 29 | 59.2 | 5 | 13.9 |
| | Other | 12 | 14.1 | 11 | 22.4 | 1 | 2.7 |
| | Total | 85 | 100.0 | 49 | 100.0 | 36 | 100.1 |
| Length of time in current post | 0–1 years | 13 | 13.4 | 8 | 16 | 5 | 10.6 |
| | 2–5 years | 36 | 37.1 | 19 | 38 | 17 | 36.2 |
| | Over 6 years | 48 | 49.5 | 23 | 46 | 25 | 53.2 |
| | Total | 97 | 100.0 | 50 | 100.0 | 47 | 100.0 |
| Nurse prescriber | Yes | 25 | 26.3 | 15 | 30.6 | 10 | 21.7 |
| | No | 70 | 73.7 | 34 | 69.4 | 36 | 78.3 |
| | Total | 95 | 100.0 | 49 | 100.0 | 46 | 100.0 |

### *Knowledge about antimicrobial dressings*

The dressings that were identified most commonly as containing silver and having antimicrobial properties were Urgotul ($n = 85$; 83%), Actisorb ($n = 81$; 79%) and Aquacel ($n = 79$; 77.5%). Contreet Foam ($n = 40$; 39%) and Acticoat ($n = 53$; 52%) were the products that were listed less frequently. Nurses in Sheffield did not list Acticoat and Contreet as much as those in Exeter: only 26.9% ($n = 15$) in Sheffield compared with 78% ($n = 38$) in Exeter for Acticoat, and 25% ($n = 14$) compared with 54% ($n = 26$) for Contreet respectively.

In rating their own knowledge of wound care, the majority of respondents ($n = 72$; 73%) rated themselves as competent, while only 11% stated that they were expert. There were no significant differences between the two centres for this item.

### *Sources of evidence about antimicrobial dressings*

In examining the sources of evidence which informed their choices of dressings, the majority of respondents (71%) stated that they had seen or read some research evidence or information about antimicrobial dressings. However, it was not always clear whether this evidence was published research or manufacturers' information, nor was it clear what level of evidence had been accessed. Articles in journals were the type of evidence most often described (42%), followed by evidence provided by commercial companies and their sales representatives (32%): 18.5% of respondents reported that they had attended a conference where there was a presentation about silver. The majority of respondents (70%) stated that they used multiple sources of evidence. Aggregating those respondents who gave multiple responses and focusing on non-journal sources of evidence (i.e. company representatives, colleagues, etc.) showed that 61% relied on these sources in preference to journal sources of evidence.

The journals most frequently used as sources of articles were the *British Journal of Community Nursing* (37%; 13/35) and the *Nursing Times/Nursing Standard* (25.7%; 9/35).

With regard to training or teaching sessions about antimicrobial dressings, a majority (65%) stated that they had received some education on antimicrobial dressings and antiseptics. The most common sources of this education were company representatives (42%), followed by in-service training (39%) and dedicated courses (11%). The influence of company representatives in providing information and education was particularly marked in the Exeter area, where 58% reported that the representatives were the main source of research evidence and 58% had been on training/education organised by company representatives. One explanation for this could be that in Exeter the community tissue viability service runs a 'rolling' programme of teaching for community nurses, district nurses and practice nurses that includes input from company representatives.

### *Clinical indications for antimicrobial dressings*

The wounds on which most respondents (78%) considered using silver dressings were venous ulcers. Only 20% would use silver on a pressure sore. There were differences between the centres in terms of the type of wounds for which silver dressings would be used – these are shown in *Table 7*. In Exeter, the nurses were more likely to apply silver dressings to diabetic ulcers (69% compared with 40% in Sheffield) and post-operative surgical wounds (65% in Exeter compared with 21% in Sheffield).

When asked to describe the basis for clinical decisions on the use of silver antimicrobial dressings, the majority (64%) did not give a reason. Where reasons were given, the non-adherent nature of the dressing was the more frequent response than the antimicrobial properties of the dressing (24% compared with 18%).

## Discussion

From the point of view of planning the randomised trial, the primary aim of the first two surveys was to obtain information about the types of antimicrobial dressings in use in the UK, and the secondary aim was to find out about the existence and organisation of venous ulcer services. None of this information was available from any other source at the time the trial was being planned, and at the time of writing (May 2008) the postal survey remained the most comprehensive source of data about UK venous ulcer services.[114] With regard to the prospect of information for the future about numbers of patients treated and types of treatment used, the postal survey showed that less than half of the services had databases for collection of data and audit: this is disappointing.

The information gained about antimicrobial dressings was of great importance to the purpose

***TABLE 7*** *Type of wound for which silver dressings were considered suitable*

| Type of wound | Silver dressing suitable | All | | Sheffield | | Exeter | |
|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % |
| Venous ulcers | Yes | 79 | 78.2 | 35 | 67.3 | 44 | 89.8 |
| | No | 22 | 21.8 | 17 | 32.7 | 5 | 10.2 |
| Arterial ulcers | Yes | 35 | 34.7 | 11 | 21.2 | 24 | 49.0 |
| | No | 66 | 65.3 | 41 | 78.8 | 25 | 51.1 |
| Diabetic foot ulcers | Yes | 55 | 54.5 | 21 | 40.4 | 34 | 69.4 |
| | No | 46 | 45.5 | 31 | 59.6 | 15 | 30.6 |
| Post-operative surgical wounds | Yes | 43 | 42.6 | 11 | 21.2 | 32 | 65.3 |
| | No | 58 | 57.4 | 41 | 78.8 | 17 | 34.7 |
| Pressure sores | Yes | 18 | 19.8 | 18 | 34.6 | 0 | 0.0 |
| | No | 73 | 80.2 | 34 | 65.4 | 39 | 100.0 |
| | Missing | 12 | 11.7 | 0 | 0.0 | 11 | 22.0 |

and planning of the trial for two reasons. First, the rationale for this research had been an impression that antimicrobial dressings were being widely used in the treatment of venous leg ulcers (in the absence of good evidence of benefit). The first two surveys both confirmed that impression. The initial opportunistic survey suggested that they were used in over 50% of ulcers treatments, in some 42% of areas. Although their use was said to be 'rare' by 47% of the nurses questioned, they were reported as never being used by only 11%.

With regard to the specific types of antimicrobial dressings, the surveys prior to recruitment for VULCAN concurred in their finding that silver-based dressings were marginally the most commonly used. In addition, it was our impression (and nurses from around the UK had repeatedly told us) that silver-based dressings were being very actively promoted by manufacturers, and they were being used increasingly. They were claimed to represent the gold standard in modern antimicrobial dressings. Their cost was greater than other types of dressings (see Chapter 5 for a detailed breakdown of costs). For all these reasons silver-based dressings were considered to be the most appropriate type to select for the trial.

The surveys also provided interesting general information about leg ulcer services, showing that these were present in the majority of areas in the UK. The varying organisation and supervision of services almost certainly reflected local circumstances and different approaches to the difficulties of setting up dedicated services which operate across the funding boundaries of acute Trusts and PCTs. The drive by senior clinicians (primarily vascular surgeons and dermatologists) to establish leg ulcer services usually comes from within acute Trusts, but services are widely thought to be best delivered in the community, close to patients' homes – not least because many patients are elderly and immobile.

The role of nurses in the treatment of venous ulcers is fundamental. They need to be competent in assessment of the arterial circulation before the use of compression and skilled in the application of compression bandaging. The results suggested that there was sufficient 'in house' expertise to train nurses in about half of the clinics, but that a similar number attended courses to learn these skills. It is important to note that nurses were in overall charge of about one-third of venous leg ulcer clinics.

The third survey questionnaire took place at the end of the recruitment period for the trial. It was distributed at a time of particular instability and change within the community health-care setting as a result of the reorganisation of the PCTs that took place in 2006/2007. The merger of the four Sheffield PCTs certainly reflected the concerns that were expressed prior to the reorganisation that it would cause distraction, loss of focus and unhappy staff.[120] Community nurses were particularly affected as there were delays in appointing community matrons and merging of community nurse teams, and district nurses had to reapply for their current posts.[121] The poor response rate of 15% (9/59) compared with practice nurses (31%; 29/94) in Sheffield is likely to be a reflection of these difficulties.

There were differences between the two centres in terms of their knowledge of the dressings that contained silver. These mirrored differences in the types of dressings that were used in each centre for the randomised part of the VULCAN trial. During the trial, Urgotul was more widely used in Sheffield and Acticoat in Exeter.

The main sources of evidence on antimicrobial dressings were non-published figures, including information from colleagues, conferences and company representatives. Reliance on those easily accessible sources, rather than peer-reviewed research literature, has been highlighted previously.[122] The lack of high quality research evidence may be another reason that nurses seem to more readily use the more prolific and easier to access evidence available from company representatives and colleagues. A potential concern about company representatives as one of the main sources of evidence and training is that they are likely to have a vested interest in promoting a particular product or brand.[115,123]

The respondents to the survey seemed to have a lack of understanding about the clinical indications for the use of silver dressings and about the fact that these dressings are suitable for all types of wound. It was also interesting to note that the respondents cited the non-adherent nature of dressings as being of more importance than the antimicrobial properties of the dressing.

## Conclusion

The surveys showed that the most commonly used first- and second-choice antimicrobial dressings were the silver-containing dressings, and they provided details of the specific types of silver dressings in use. This information underpinned decision and selection of dressings for the randomised trial. In addition, the surveys found that dedicated leg ulcer services were operating in most areas of the UK, although their organisation and management varied. Fewer than half of the areas had databases for auditing their activity.

The final survey that was undertaken after the VULCAN trial had been in progress for 3 years found deficiencies in the knowledge about silver dressings and the indications for their use. Sources of knowledge varied: information from commercial companies and 'hearsay' from colleagues were more frequently used than studies published in journals. It may be that tissue viability services should increase their educational role, especially in the light of the emergence of new wound care products year upon year.

# Chapter 3
# Methods

## Introduction

The brief for the proposal was to assess the place of antimicrobial agents in the management of venous leg ulcers. The initial questionnaire survey and expert opinion described in Chapter 2 suggested that during the planning stages of the trial there had been a considerable shift from other types of antimicrobial dressings towards the use of silver-containing dressings. This seemed to be the result of commercial pressure relating to the launch of several new silver-containing dressings.

Since silver-donating dressings had become the most popular kind of antimicrobial dressing, the clinical trial was designed to be a randomised study comparing these with non-adherent dressings without any antimicrobial agent. Different local preferences for the various silver-donating dressings available led to an agreement that this would be a pragmatic trial in which the clinical staff treating the patient could choose their preferred silver-donating dressing from an approved list. The list was compiled by the Trial Steering Committee after seeking information on all the available dressings. The criterion for inclusion was that there was evidence of silver donation to the wound: dressings that contained silver, but did not 'donate' silver to the wound were excluded. The list was kept under review by the Steering Committee and new silver-donating dressings that were released onto the market during the trial were added to the approved list as appropriate.

## Methods of the clinical trial

### Setting

This was a multicentre trial that took place in community, primary and secondary care services in South Yorkshire and Devon. These services were based around Sheffield and Exeter respectively. The two areas had different demographic profiles and differing organisational arrangements for the management of patients with leg ulcers.

In the Sheffield area the service was based around three community leg ulcer clinics, which provided support and training for community nurses in the assessment and management of and bandaging techniques for patients with leg ulceration. Leg ulcer management was carried out in accordance with locally developed evidence-based guidelines that were revised shortly before the start of the study, as a collaborative venture between community nursing experts in leg ulceration, the vascular surgical service at the Northern General Hospital and the dermatology service at the Royal Hallamshire Hospital. All patients were assessed using a common protocol and data were entered onto an initial assessment form, before being recorded on a computer database and updated by communication with community nurses at regular intervals. The main support for leg ulcer services from secondary care was provided by nurse-led leg ulcer clinics, run in parallel with the vascular surgical clinics in the Northern General Hospital in Sheffield – a large teaching hospital vascular unit.

In Exeter there was a similar service, configured as a 'hub and spoke' arrangement with 39 clinics, managed through the central service for tissue viability at Franklyn House, Exeter. There were 2.5 whole time equivalent (WTE) nurses employed in this service who collaborated with nurses from the community to provide regular community clinics. There were reciprocal arrangements for nurses from the community to attend the clinic at Franklyn House for support and training. The service in Exeter had also developed local evidence-based guidelines and assessment protocols, and data of all newly assessed patients were entered into a computer database. Support from secondary care was provided by a dermatologist, who attended the clinic at Franklyn House. Referrals were made to other services as required; in particular, patients with ulcers were referred as necessary to the clinics of the individual vascular surgeons at the Royal Devon and Exeter Hospital, all of whom collaborated as a vascular unit in this medium-sized teaching hospital.

### Objectives

The overall objective of the clinical trial was to collect data on the effectiveness and cost-effectiveness of the use of antimicrobial silver-donating dressings for venous leg ulcers, compared with simple non-adherent dressings which had no antimicrobial agent. Detailed descriptions and

evaluation of the bacteriology of the wounds were outside the scope of the study.

## Aims

The aims were:

- to collect cost and outcome data through a randomised controlled clinical trial of silver-donating antimicrobial dressings versus non-antimicrobial low-adherent control dressings applied to venous ulcers
- to collect data from an observational arm of the study regarding treatment, clinical outcomes and costs of the management of venous leg ulcers
- to carry out an economic analysis alongside the clinical trial to estimate the cost-effectiveness of antimicrobial dressings for venous leg ulcers
- to develop a cost-effectiveness model of venous ulceration and to populate this with data from the trial and published literature
- to examine the cost-effectiveness of using antimicrobial dressings in different circumstances and differing sets of assumptions
- to document current routine practice regarding the use of antimicrobial agents in the treatment of venous ulcers.

## Participants

All patients with active ulceration of the lower leg that had been present for longer than 6 weeks were considered for inclusion in the trial. The following were specific exclusion criteria:

- refusal to give informed consent to participating in the RCT
- insulin-controlled diabetes mellitus
- pregnancy
- sensitivity or specific contraindications to the use of silver
- ABPI of less than 0.8 in the affected leg
- leg ulcers with a maximum diameter of less than 1 cm
- atypical ulcers, including those where there was suspicion of malignancy, coexisting skin conditions or vasculitis
- patients on oral or parenteral antibiotic treatment.

Patients with bilateral ulceration were eligible for inclusion in the trial. In this case the leg with the greatest total ulcer area was considered to be the index limb and randomisation was for that leg (but the allocated treatment was used for both legs). The primary and secondary end points relating to ulcer healing were recorded in relation to the index limb.

When there was more than one ulcer on the index leg the patient was randomised based upon the size of the largest ulcer, but the primary end point was healing of all ulcers on that leg.

## Research ethics approval and consent

Approval for the study was obtained from both the Sheffield and Exeter Local Research Ethics Committees. Research governance approval was obtained from the Sheffield and Exeter PCTs, Sheffield Teaching Hospitals NHS Foundation Trust and Royal Devon and Exeter NHS Foundation Trust.

After an interim review additional research ethics and research governance approval was obtained to allow recruitment to the trial to be extended to Rotherham, Doncaster and Chesterfield.

Patients were free to withdraw their consent and withdraw from the trial at any time.

In addition to those patients recruited to the RCT those patients who were not eligible or who declined consent for the RCT were invited to participate in the observational arm of the trial. In this arm of the study the same data were collected, but treatment choices were not affected by participation in the trial. The parallel collection of data from this group of patients had a number of benefits:

- It could be used to provide contrast and insight into those recruited to the RCT and increased the trial's external validity.
- The observational arm was a reflection of the wider population who may not necessarily have fulfilled the strict criteria for inclusion in an RCT. An assessment could be made as to the suitability of the intervention to the wider general population to whom the intervention may have been appropriate.
- The populations in the RCT and observational arms could be compared in order to determine any differences in demographic, healing and utility data. This could highlight any selection bias in recruitment to the RCT.

## Sample size

At the start of the study it was estimated that an RCT with 300 patients would be required (150 in

each group). This estimate was based on healing rates from a cost-effectiveness study by Morrell *et al.*[57] that had been undertaken in the Trent region, and on an assumption of a loss to follow-up or withdrawal rate of 25%. In the Trent study the 3-month leg ulcer healing rates were 34% and 24% in the intervention and control groups respectively.

Basing sample size calculations on these figures a two-group continuity-corrected chi-squared test with a 0.050 two-sided significance level had an 80% power to detect a difference between 25% and 44% healing rate at 3 months with a sample size of 97. A two-group continuity-corrected chi-squared test with a 0.050 two-sided significance level had an 80% power to detect the difference between proportions of 34% in group 1 and 54% in group 2 with a sample size in each group of 106. Allowing for 25% losses this would have required 142 patients to be recruited to each arm of the trial.

Recruitment was slower than expected and this necessitated an extension to the duration of the trial. Revised power calculations were carried out based upon the overall healing rates within the study and the lower than expected rates of loss of patients to follow-up. This interim analysis showed that follow-up to the primary end point was greater than 90% and the revised calculations indicated that 212 patients would provide sufficient power. The area of recruitment in South Yorkshire was extended to include Rotherham, Chesterfield and Doncaster, and the trial was extended until November 2007 in the expectation that this would result in the required number of patients ($n = 212$) being available for evaluation.

## Recruitment and randomisation procedure

The initial approach to the patient was by the clinician (usually a community nurse) with overall responsibility for management of their leg ulcer. If the patient expressed an interest in taking part then they were provided with information sheets about the trial and the treatments being compared. They were then allowed time to consider the information and met a member of the research team at their next visit or appointment.

If the patient agreed to participate in either the RCT or the observation arm then informed consent was obtained by a member of the research team. Trial numbers and randomisation were allocated through a telephone-based service which recorded details of the patient and which proffered a checklist of questions to confirm eligibility.

Treatment allocation for the randomised patients was carried out using a computer program to generate stratified block randomisation with variable block size. Stratification was on the basis of ulcer size (maximum ulcer diameter either smaller than or greater than 3 cm in any direction) and treatment centre (South Yorkshire or Devon). Patients who were not eligible for the randomised trial, but who had agreed to participate in the observational study were also logged through the telephone recruitment service. Each patient was allocated a unique trial number which remained with them throughout the trial.

## Blinding

The trial was an open-label study. It was not possible to blind either the patients or the nurses applying the dressings, because each type of dressing had different physical characteristics. A pragmatic approach was taken in that clinicians made decisions regarding the frequency of dressing changes and clinic visits, and the type and application of compression. One possible implication of this could be a confounding issue related to treatment, in that clinicians treated patients who had silver dressings applied differently from those with standard dressings. However, the research staff dealing with postal questionnaires, the staff measuring ulcer sizes based upon tracings, and the staff carrying out initial data entry and analysis were all blinded to the treatment allocation of the patient.

## Interventions

The management of patients' leg ulcers was according to normal practice, based on local and national guidelines, in every respect apart from the nature of the dressings used. The allocated dressing was covered by a multilayer compression bandage, applied by a nurse specifically trained in the technique. Dressings were changed and bandages reapplied on a weekly basis unless the clinical staff dealing with the patient felt that more frequent changes were necessary. Any decisions regarding the frequency of dressing changes were made by the clinician.

Multilayer compression bandaging (with the allocated dressing beneath) was continued until ulcers were healed, at which time a Class 2 below-knee graduated compression stocking was applied (or a Class 1 stocking if the patient could not tolerate Class 2). The allocated dressings were applied at each dressing change until the ulcers were fully healed or for the 12-week treatment

period of the trial. If there was still active ulceration after that period then the decision regarding continuation or change of dressing was made by the clinician caring for the patient. Use of the allocated dressing could be discontinued prior to 12 weeks if the clinician thought that there was evidence of sensitivity to the dressing or considered that there were adverse effects from the allocated dressing. In such cases the reason for changing or stopping the dressing was recorded.

For the treatment group the responsible clinician was able to choose a silver-donating dressing from the list that had been approved by the Steering Committee. During the progress of the trial new silver dressings that were released were considered by the Steering Committee and added to the list if they fulfilled the necessary criteria. The list of approved dressings is given in *Table 8*.

In the control group the 'standard dressing' was any non-antimicrobial low-adherent dressing from any manufacturer. Other types of dressings that did not contain antimicrobial agents could also be used at the discretion of the clinical staff. All types of dressings used were recorded.

Other interventions or treatments, such as debridement of the leg ulcer, could also be used by the clinicians if these were felt to be clinically appropriate. Any use of such additional treatment was recorded.

In those patients who were not eligible for randomisation, but who agreed to participate in the observational study, the decision regarding which type of dressing would be used was at the discretion of the clinician. Information was recorded about the dressing and bandaging applied. The baseline and weekly clinical assessments followed the protocol for the randomised trial.

***TABLE 8*** *Silver-donating dressings approved for inclusion in the VULCAN trial*

| Dressing | Manufacturer |
|---|---|
| Aquacel Ag | ConvaTec |
| Acticoat | Smith & Nephew |
| Acticoat 7 | Smith & Nephew |
| Acticoat Absorbent | Smith & Nephew |
| Contreet Foam | Coloplast |
| Urgotul SSD | Urgo |

## Outcomes

The primary outcome measure for the study was complete ulcer healing at 12 weeks in the index limb. Full healing was defined as complete epithelialisation of the ulcer with no scab.

Secondary outcome measures were:

- healing rates at 6 months and 1 year
- time to healing
- recurrence rates at 6 months and 1 year.
- health-related quality of life (HRQoL) questionnaires (EQ-5D and SF-36)
- pain and other symptoms
- costs and resource use
- cost-effectiveness
- time trade-off (TTO) valuations by the general public of health states related to venous ulceration.

In addition, information was collected at the time of each dressing change about clinical symptoms, ulcer size, adverse events and any changes in comorbidity.

## Assessment and follow-up

Initial assessments were carried out at or around the time of recruitment to the trial. These followed a standard assessment proforma for leg ulceration that was based upon one that had already been used for some years in Exeter (see Appendix 2). This recorded information about the ulcer, including previous treatments and symptoms; and about the patient's past medical history, general health and other risk factors and comorbidities.

Briefer proformas were completed at the time of each dressing change – usually once a week, but more frequently if more frequent dressing changes were required (see Appendix 3). On each occasion, details of the appearance and size of the ulcer were recorded, together with the types of dressings and bandages being used, and any changes in management. Tracings of each ulcer were carried out using the Visitrak™ system (Smith & Nephew Healthcare, Hull) which uses a digital system to determine the ulcer proportions. The tracings were used to determine the dimensions of the ulcer by one of the researchers, who was blinded to the treatment of the patient.

Full assessments (similar to the initial assessment) were completed at 3, 6 and 12 months. A form about costs and use of resources was completed at 3 months for all patients. In addition, further forms

about costs and use of resources were collected on a sample of patients at 3-monthly intervals up to 1 year.

### Quality of life data

Information about HRQoL was collected through the use of EQ-5D[43] and SF-36[45] questionnaires which were completed at recruitment, 3, 6 and 12 months. Single index utility values were calculated from the EuroQol using the UK tariff values.[124] The SF-36 data were used to generate the single Short Form 6 dimensions (SF-6D) index measure[125] and separate scores for each of the dimensions. Differences between the randomisation groups at follow-up with respect to EQ-5D scores, SF-6D scores and individual dimension scores of the SF-36 were investigated using multiple regression analysis of covariance. The average follow-up score of the QoL measures (the mean of the 1, 3, 6 and 12-month assessments) was estimated and included as the dependent variable in a linear regression model. Covariates in the model were the 'baseline QoL score' and the 'dressing type' (coded 0 for non-adherent and 1 for silver). The regression coefficient estimate for dressing type represents the difference in mean QoL follow-up score between the non-adherent and silver dressing groups after adjustment for baseline QoL. A similar analysis using EQ-5D data and SF-6D data was performed in order to investigate differences in QoL at follow-up between patients whose ulcer had healed at 12 weeks and those whose ulcer had not healed. In this analysis, the covariate 'healed at 12 weeks' (coded 0 for not healed and 1 for healed) was included in the regression model in place of 'dressing type'.

## Methods of economic analysis

The economic analysis was in two parts. The first was a relatively straightforward analysis of cost-effectiveness using trial data, while the second used cost-effectiveness modelling to extrapolate beyond the trial. In addition to extending beyond the trial time horizon, the modelling complements the trial evaluation by facilitating an analysis of alternative scenarios and subgroups and the rigorous investigation of uncertainty surrounding parameter estimates. The modelling results are arguably more generalisable than those of the trial evaluation and consequently the two may differ.

In view of the primary outcome of the trial being the numbers of patients healed at 12 weeks, this analysis was carried out using data from the first 3 months of the trial. Data beyond this point were used in the cost-effectiveness modelling, which adopts a lifetime perspective.

### Assessment of costs

The perspective adopted was that of the UK NHS and Social Services, with all costs reported in 2007 prices. Data were collected in the clinical forms on patients' use of the following resources: frequency of attendance at ulcer clinics; frequency of nurse home visits; number and type of dressings applied; and number and type of bandages applied. In addition, a patient resource use questionnaire (see Appendix 6) was administered at 3 months, which asked patients to indicate their use of resources in relation to their leg ulcer during the first 3 months of the trial. Questions were asked on the following: use of hospital outpatient services [accident and emergency (A&E) admissions and hospital admissions]; GP contacts; chiropody contacts; prescribed compression hosiery; prescribed antibiotics; and any other prescribed medicines.

### Resource use and costs

A breakdown of the individual items of resource use and the corresponding unit cost applied to each item is given in *Table 9*. The table does not include A&E attendances or hospital admissions as there were none of these among the trial patients. In addition, the table does not list the unit cost data for each specific dressing, bandage, hosiery, antibiotic and other medicine as it is not practical to attempt to summarise these data due to the large variation in type, size and dosage. All unit costs for these were taken from the *BNF*.[75]

The unit costs for ulcer clinic visits were obtained by observing a sample of clinics in Exeter and Sheffield and recording the clinic duration, patient throughput and type and grade of staff in attendance. In Exeter a convenience sample of five separate clinics (which had contributed the most patients out of the total of 39 clinics) were observed over 30 weeks. In Sheffield all three clinics were observed over 10 weeks. This allowed the estimation of average patient cost per clinic visit at each location. Unit costs for staff in attendance at the clinics were obtained from Curtis.[126] Costs related to home visits by community nurses were also obtained form Curtis.[126]

In estimating the costs of compression hosiery, antibiotics and other medicines a number of assumptions were made. With respect to dressings

***TABLE 9*** *Breakdown of sources for resource use and corresponding unit cost data*

| Resource | Unit cost (2007 prices) | Source |
|---|---|---|
| Ulcer clinic visit | £30.72 per patient (Exeter)<br>£39.78 per patient (Sheffield) | Observation of clinics and Curtis[126] |
| Nurse home visit | £24.00 per visit | Curtis[126] |
| Dressings | Dressing-specific costs | BNF[75] |
| Bandages | Bandage-specific costs | BNF[75] |
| GP contacts | £35.87 per consultation | BNF[75] |
| Chiropody contacts | £9.00 per consultation | Curtis[126] |
| Compression hosiery | Hosiery-specific costs | BNF[75] |
| Antibiotics | Antibiotic-specific costs | BNF[75] |
| Other medicines | Medicine-specific costs | BNF[75] |

and bandages, it was assumed that these were changed at every ulcer clinic visit and/or nurse home visit. With respect to hosiery, unless otherwise stated, it was assumed that class II hosiery was prescribed. It was also assumed that hosiery was prescribed in pairs irrespective of whether ulceration was unilateral or bilateral. With respect to antibiotics and other medicines, when the specific drug was not recorded and when alternative drugs existed, the cost of the cheapest drug was used. When dosage was not specified, a standard leg ulcer prescription was assumed, using a standard prescription from the BNF or guided by expert opinion. It was also assumed that patients were taking the drugs/creams up to the time when their ulcer healed and that each prescription was for a period of 1 month. This means that if an ulcer healed after, say, 1 month and 1 day, 2 months' prescriptions were costed.

Patient HRQoL was assessed using the EQ-5D[43] and the SF-6D,[125] the latter being derived from the administration of the SF-36.[45] Both the EQ-5D and the SF-6D allowed the estimation of QALYs. The EQ-5D responses were converted to health-state utility values using the UK tariff values,[124] while the SF-6D utilities were derived using the algorithm developed by Brazier and Roberts.[125]

QALYs were estimated using an area under the curve (AUC) approach.[127] The estimation of QALYs at 3 months was done in two ways. With the first approach, patient responses at baseline and 3 months were used to map out the AUC, whereas with the second approach the baseline, 1-month and 3-month points were used. While the latter approach provides a more precise estimate of QALYs, the inclusion of the 1-month values increases missing values and consequently decreases the number of patients on which the estimation is based. Therefore, the first approach was used in the initial analysis, while the second approach was used to investigate whether the use of more precise estimates of QALYs changed the results. Separate analyses were performed for the EQ-5D and SF-6D derived QALY estimates. In addition, the impact on the results of imputing missing EQ-5D and SF-6D data was also investigated. The imputation method adopted was as follows. Where possible, baseline and/or 1-month values were carried forward to substitute for any missing values. Where carrying forward was not possible, i.e. when baseline or baseline plus 1-month values were missing, the 1-month or 3-month values were carried backwards. For individuals with no responses at baseline, 1 and 3 months, the mean baseline value for their randomisation group was assigned as their baseline value and carried forward.

## Assessment of cost-effectiveness

In order to assess the relative cost-effectiveness of the alternative types of dressing at 3 months, data on cost and outcome were brought together to estimate incremental cost-effectiveness ratios (ICERs), specifically the incremental cost per QALY gained of silver-donating antimicrobial dressings relative to the control non-adherent dressings.

The ICER for silver dressings can be located on the cost-effectiveness plane (*Figure 1*), which is a two-dimensional space in which the origin represents the comparator intervention – in this case the non-adherent dressings. The *x*-axis represents the average difference in effectiveness per patient between the antimicrobial dressings and the control dressings, while the *y*-axis represents the

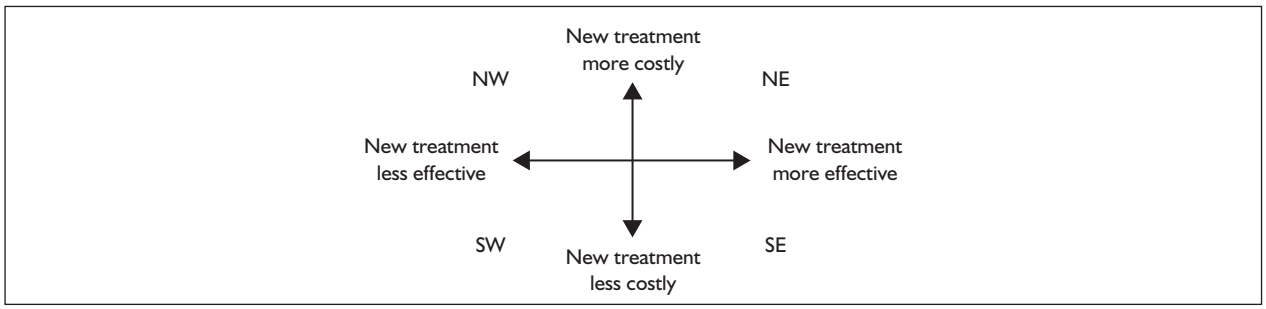


***FIGURE 1*** *The cost-effectiveness plane.*

average difference in cost per patient between the dressings. The four quadrants are conventionally referred to as points on the compass, namely north-west (NW), north-east (NE), south-west (SW) and south-east (SE). The ICERs can be plotted as points on this plane, with the slope of the line from the origin to the ICER representing the value of the ICER. Treatments with ICERs located in the NW quadrant (more costly, less effective) are said to be dominated by the comparator treatment, while treatments with ICERs located in the SE quadrant (less costly, more effective) are said to dominate the comparator treatment. In practice most new treatments are located in the NE quadrant where increased effectiveness is achieved at increased cost. In this instance the decision to adopt the new treatment will depend upon whether the ICER lies below the acceptable ceiling ratio of the decision maker. If the decision maker's willingness to pay for a unit of effectiveness ($\lambda$) is greater than the ICER, then on efficiency grounds the treatment should be recommended for adoption.

The point estimates of the ICERs are subject to uncertainty and it is therefore important that this uncertainty is taken into account. Because of the problems associated with estimating confidence intervals (CIs) for ratio statistics, the approach of non-parametric bootstrapping is adopted to represent the uncertainty surrounding the ICER estimates.[128] Cost-effectiveness acceptability curves (CEACs), which summarise the evidence in support of the silver dressings being cost-effective for a range of values of $\lambda$, are also presented.[129] A full probabilistic sensitivity analysis was undertaken as part of the modelling.[130]

The probabilistic interpretation of the CEAC was from a Bayesian perspective. In effect the CEAC provides information to decision makers on the level of uncertainty associated with a potential decision to recommend the use of a new or additional intervention. For example, a 0.82 probability of an intervention being cost-effective at a ceiling ratio of £30,000 per QALY, say, implies an error probability (i.e. the probability of making a wrong decision) of 0.18 (1–0.82). In making a decision regarding the potential recommendation of a new intervention, the decision maker must weigh up these probabilities against one another. Alternatively, instead of deciding whether or not to recommend the new intervention on the basis of the currently available evidence, the decision maker may demand an expected value of perfect information analysis to compare the expected cost of the uncertainty with the value of conducting further research to reduce the uncertainty.

## Analysis of data

Details of the economic analysis and cost-effectiveness modelling are given in Chapter 6.

Analysis of all outcomes was on an intention to treat basis. Data from the assessments and questionnaires were coded and analysed using SPSS and EXCEL. Differences in means and continuous variables were estimated using Student's *t*-tests and analysis of variance and differences in proportions using a chi-squared test. Categorical data were compared using Fisher's exact test, chi-squared or chi-squared test for trend as appropriate.

Survival analysis was carried out using Kaplan–Meier techniques. Exploratory analysis of factors influencing healing rates used regression techniques based upon a Cox proportional hazards model. The utility values estimated from the QoL data were analysed using linear regression analysis of covariance with mean follow-up utility score as the dependent variable, with the covariates of baseline utility score and dressing type/healed at 12 weeks.

# Chapter 4

# Results – clinical trials

## Recruitment

Between March 2005 and November 2007 a total of 304 patients were recruited to the clinical trial. A total of 213 were recruited to the RCT [107 randomised to receive silver dressings and 106 non-adherent dressings – see the Consolidated Standards of Reporting Trials (CONSORT) diagram, *Figure 2*] and 91 were recruited to the observational study. An additional six patients were initially recruited to the observational arm of the study but were subsequently randomised when they became eligible for the RCT; their outcomes were analysed within the RCT and are not included in the results for the observational arm of the study.

The original protocol estimated a sample size of 150 patients in each group but over the first year of the trial it became evident that recruitment was falling below the expected number. A particular reason for this was the change in structure of the PCTs and reconfiguration of community services, which coincided with the trial. The disruption and uncertainty generated by the merger of the PCTs was widely recognised.[120,121] Recruitment depended upon patients being identified by nurses in the community: they reported that the disruption caused by the reorganisation had a considerable impact on their inclination and ability to recruit. In the Sheffield area there was a complete reorganisation and restructuring with a large number of voluntary redundancies among nurses, district nurse bases being merged and staff having to reapply for their current posts. These changes had a profound effect on morale in the community nursing services and made it difficult to persuade district nurses to take on the additional work required to identify and recruit patients.

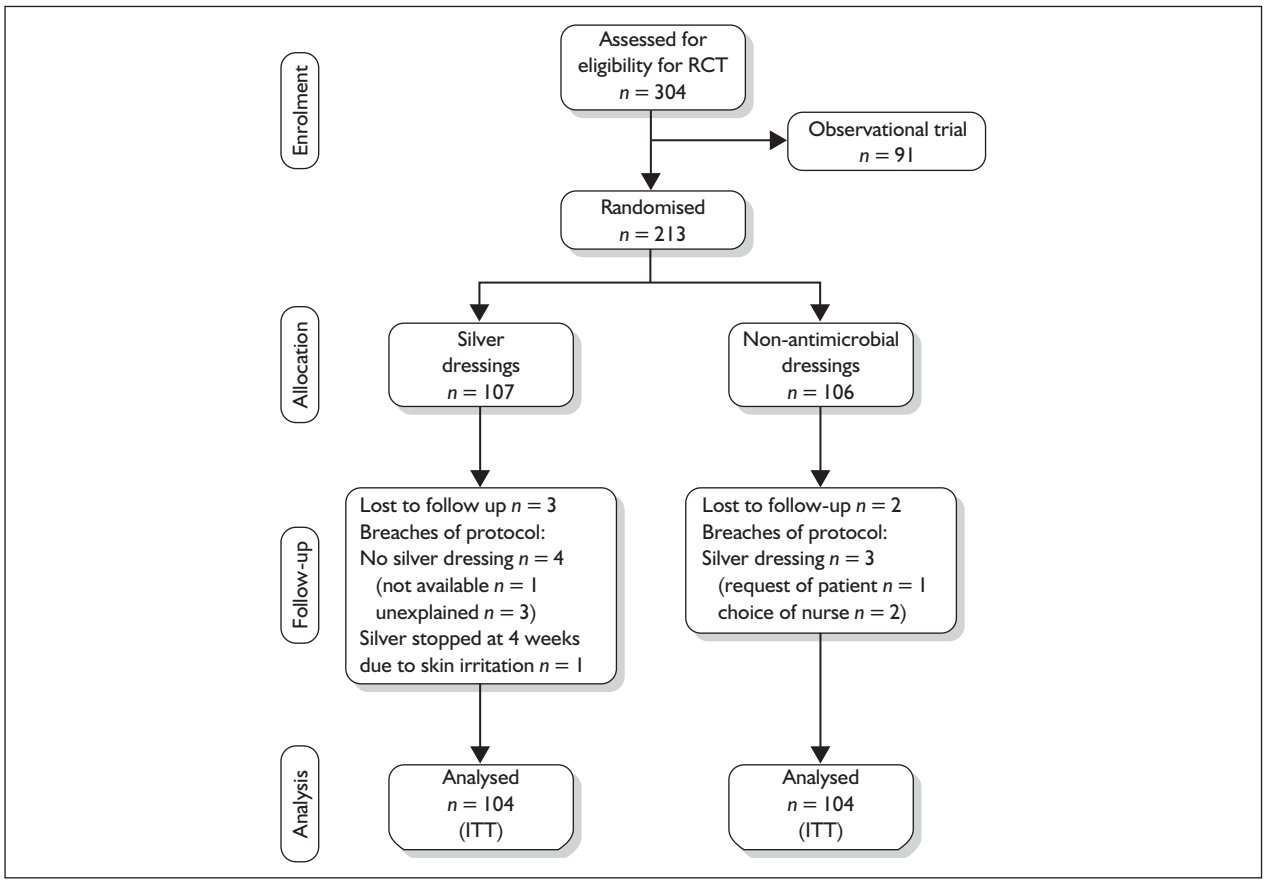


***FIGURE 2*** *CONSORT diagram showing recruitment to RCT. ITT, intention to treat.*

As a result of the restructuring it became more difficult to gain access to the nurses dealing with venous leg ulcers. There was increasing management of leg ulcer patients by practice nurses within general practices, who often had a very small caseload of patients with ulcers. Financial restraints also meant that it was difficult for community nursing staff to attend educational meetings, which would have provided more opportunities to publicise the trial and encourage recruitment.

An interim review of recruitment in mid-2006 showed that although total recruitment levels were lower than expected the follow-up to the primary end point was more complete than had been predicted when the sample size estimations were carried out. As a result of this, the overall recruitment target was reduced and the recruitment period was extended to the end of November 2007.

## Demographics

Among the 304 patients recruited (213 into the RCT and 91 into the observation study), 172 (57%) were female and the average age was 69.3 years. One hundred and forty-five (48%) were recruited in Sheffield and 159 (52%) in Exeter. The patients recruited in Sheffield had a slightly lower average age and a higher proportion of males compared with Exeter. More details are given in *Table 10*.

In the RCT 107 patients were allocated to the antimicrobial silver dressing arm and 106 to the control arm. These patients were evenly matched for demographic features (*Table 11*). The patients in the RCT were stratified by ulcer size and recruitment centre. At initial recruitment, 30 patients in each group (28%) had been stratified in the larger size category having a maximum ulcer diameter of 3 cm or more.

All analysis of the RCT is carried out on an intention to treat basis.

## Follow-up

Data were available on complete ulcer healing at the primary end point of 12 weeks on all but five of the 213 patients in the RCT, giving a total follow-up to the primary end point of 97.7%. One patient was lost after moving away from the area, one underwent surgical treatment for varicose veins and withdrew from the trial, and three other patients withdrew from the trial (no further information available).

A summary of the allocation and follow-up of patients is given in the CONSORT diagram in *Figure 2* and a CONSORT statement[131] (see Appendix 1).

There were no deaths within the first 12 weeks following recruitment. A total of 11 patients died during the first year following recruitment, four in each arm of the RCT and three in the observational study. None of these deaths was directly related to leg problems (ischaemic heart disease = 4, cancer = 4, chest infection = 2, cerebrovascular disease = 1).

## Dressings and breaches of protocol

Of the 213 randomised patients, seven (3.3%) did not receive their allocated treatment. Three patients who had been allocated to the control group were treated with silver dressings, one at the request of the patient and two through choice of the nursing staff carrying out the dressings. Four patients allocated to antimicrobial dressings were not treated with silver dressings. In one case lack of availability of the silver dressing was given as the reason and the ulcer healed before the dressing was available, while in the other three the breach of protocol was unexplained.

One patient was started on a silver-donating dressing which was subsequently changed after 4 weeks when it was noted that there was a reaction to the dressing. This was not reported to the research team by the community nurse until after the weekly assessments had been submitted, by which time the reaction had settled and the ulcer had healed. Two patients were started on Silvercel dressings (Johnson & Johnson Wound Management, Ascot). Silvercel had been considered by the Trial Steering Committee for addition to the list of approved dressings, but was never formally added because responses to some questions from the Steering Committee were not received from the manufacturer.

A list of the dressings approved for the trial is given in *Table 8*. The most common antimicrobial dressing used was Urgotul Ag (39.6%) followed by Acticoat 7 (27.5%) and Aquacel Ag (16.1%). Most patients (96%) remained on the same dressing throughout the 12-week treatment period or until

***TABLE 10*** *Demographics of patients recruited to RCT and observational study*

| | Exeter | | Sheffield | | Total | |
|---|---|---|---|---|---|---|
| | **RCT** | **Obs** | **RCT** | **Obs** | **RCT** | **Obs** |
| Number of patients | 99 | 60 | 114 | 31 | 213 | 91 |
| Age (SD) | 74.3 (12.8) | 70.7 (17.7) | 67.3 (16.7) | 67.7 (14.6) | 70.5 (15.4) | 69.7 (16.7) |
| Female:male | 62:37 | 39:21 | 53:61 | 18:13 | 115:98 | 57:34 |

Obs, observational study.

***TABLE 11*** *Features of patients allocated to arms of RCT (no significant differences)*

| | Antimicrobial | Control | Total |
|---|---|---|---|
| Number of patients | 107 | 106 | 213 |
| Age (SD) | 68.8 (16.7) | 72.4 (13.7) | 70.6 (15.3) |
| Female:male | 53:54 | 62:44 | 115:98 |
| Left:right | 56:51 | 60:46 | 116:97 |
| Sheffield:Exeter | 56:51 | 58:48 | 114:99 |
| Size > 3 cm:< 3 cm | 30:77 | 30:76 | 60:153 |

the ulcer had healed. The type of silver-donating dressing was changed in three patients during the period of the trial owing to the unavailability of a particular dressing or nurse preference. Most patients in the control group (87/106; 82%) were treated with low adherence knitted viscose non-adherent dressings throughout the initial 12-week treatment period. The other non-antimicrobial dressings used for some or all of the treatment period in the other cases were Urgotul (non-silver-containing version), Biatain™ (Coloplast), Atrauman™ (Paul Hartmann Ltd, Heywood) and Allevyn™ (Smith & Nephew).

There were geographical differences in preferences for particular types of silver dressings: Urgotul was more commonly used in Sheffield, and Acticoat 7 or Aquacel Ag were more commonly used in Exeter (*Table 12*).

## Patient characteristics

There was a high incidence of pre-existing disease and comorbidity in this group of patients (*Table 13*). The proportions of participants with a number of specific comorbidities were different between the treatment arms. For example, 45.8% of participants had a previous history of hypertension in the silver-donating antimicrobial group compared with 34% in the control group. However, there were no statistically significant differences between the arms of the randomised trial with respect to these factors.

Overall, 56.3% of patients reported previous episodes of leg ulceration (49.7% in the index limb). A history of venous problems in the legs was common, with 21.1% of patients having had deep vein thrombosis (16.0% in the index limb). A total

***TABLE 12*** *Dressings used in antimicrobial arm of RCT*

| Dressing | Exeter | Sheffield | Total |
|---|---|---|---|
| Urgotul SSD | 6 | 53 | 59 |
| Acticoat 7 | 41 | 0 | 41 |
| Aquacel Ag | 19 | 5 | 24 |
| Contreet Foam | 6 | 5 | 11 |
| Other/unspecified | 10 | 4 | 14 |

***TABLE 13*** *Incidence of comorbidities, smoking history and selected drug history in RCT arms and observational trial*

| | Antimicrobial, *n* (%) | Control, *n* (%) | Total, *n* (%) |
|---|---|---|---|
| Number of patients | 107 | 106 | 213 |
| ***Comorbidity*** | | | |
| Hypertension | 49 (45.8) | 36 (34.0) | 85 (39.9) |
| Osteoarthritis | 35 (32.7) | 29 (27.4) | 64 (30.0) |
| History of myocardial infarction or cardiac failure | 16 (15.0) | 14 (13.2) | 30 (14.1) |
| Anaemia | 12 (11.2) | 6 (5.7) | 18 (8.5) |
| Rheumatoid arthritis | 14 (13.1) | 20 (18.9) | 34 (16.0) |
| History of stroke or transient cerebral ischaemia | 10 (9.3) | 7 (6.6) | 17 (8.0) |
| ***Smoking history*** | | | |
| Smoker | 18 (16.8) | 21 (19.8) | 39 (18.3) |
| Ex-smoker | 31 (29.0) | 24 (22.6) | 55 (25.8) |
| ***Current drugs*** | | | |
| Aspirin | 13 (12.1) | 10 (9.4) | 23 (10.8) |
| Diuretics | 15 (14.0) | 10 (9.4) | 25 (11.7) |
| Warfarin | 3 (2.8) | 10 (9.4) | 13 (6.1) |
| Atenolol | 10 (9.3) | 10 (9.4) | 20 (9.4) |

of 54.5% reported a history of having varicose veins and 22.5% had previously undergone treatment for varicose veins; 21.1% had suffered previous episodes of phlebitis; and 18.3% of patients reported a family history of leg ulceration. More details of these figures are given in *Table 14*.

At the time of recruitment the ulcer had been present for more than 12 weeks in 39.1% of patients.

Examination of the ulcer showed the presence of slough in 62.9% and necrosis in 6.1% of all the ulcers in the trial. Granulation tissue was observed in 62% and epithelialisation in 29.6% of ulcers. Exudation of fluid from the ulcer was troublesome for 74.6% patients and 13.1% reported that odour was a problem. A detailed breakdown of the findings on examination is given in *Table 15*.

The distribution of ulcer sizes, measured at the time of recruitment both as the maximum diameter and as the area measured using the Visitrak, are shown in *Figure 3*. There was no significant difference in ulcer size distribution between the two arms of the trial.

## Ulcer healing

*Table 16* shows the proportion of ulcers healed in the two arms of the RCT at the primary end point of 12 weeks and the secondary end points of 6 months and 1 year.

The overall proportions healed were 59.6% versus 57.3% for the antimicrobial dressing group versus the control group at 12 weeks, 85.3% versus 78% at 6 months and 96.0% versus 95.7% at 12 months. The relative risk (RR) of healing for the silver dressings versus the control dressings was 1.06 (95% CI 0.80 to 1.40) at 12 weeks. The RRs of healing at 6 months and 1 year were 1.34 (95% CI 0.88 to 2.03) and 1.03 (95% CI 0.51 to 2.08) respectively. None of the differences was statistically significant.

Overall median time to healing was not significantly different between the two groups ($p = 0.408$ Cox proportional hazard) at 67 days (95% CI 54 to 80) for antimicrobial dressings and 58 days (95% CI 43 to 73) for the control group. The hazard ratio for silver versus control dressings was 1.13 (95% CI 0.85 to 1.51). Large ulcers healed significantly more slowly than small ulcers ($p = 0.05$ Cox proportional hazard), with a median of 101 days (95% CI 43 to 73) versus 52 days (95% CI 46 to 57) respectively for those above and below 3 cm in initial diameter. The hazard ratio for large versus small ulcers was 1.55 (95% CI 1.15 to 2.10).

In order to investigate predictors of healing at 12 weeks, a binary logistic regression was performed with 'healed at 12 weeks' as the dependent variable,

***TABLE 14*** *Ulcer history and aetiological factors for patients in RCT*

| | **Antimicrobial, *n* (%)** | **Control, *n* (%)** | **Total, *n* (%)** |
|---|---|---|---|
| Number of patients | 107 | 106 | 213 |
| ***History of venous problems*** | | | |
| Ulcer in index leg | 56 (52.3) | 44 (41.5) | 100 (46.9) |
| Ulcer (either leg) | 61 (57.0) | 52 (49.1) | 113 (53.1) |
| VV (index leg) | 51 (47.7) | 54 (50.9) | 105 (49.3) |
| VV (either leg) | 58 (54.2) | 58 (54.7) | 116 (54.5) |
| Previous DVT (index leg) | 15 (14.0) | 19 (17.9) | 34 (16.0) |
| Previous DVT (either leg) | 21 (19.6) | 24 (22.6) | 45 (21.1) |
| VV surgery (index leg) | 20 (18.7) | 18 (17.0) | 38 (17.8) |
| VV surgery (either leg) | 23 (21.5) | 25 (23.6) | 48 (22.5) |
| Previous phlebitis (index leg) | 20 (18.7) | 17 (16.0) | 37 (17.4) |
| Previous phlebitis (either leg) | 25 (23.4) | 20 (18.9) | 45 (21.1) |
| ***Risk factors*** | | | |
| Fixed ankle (index leg) | 15 (14.0) | 18 (17.0) | 33 (15.5) |
| Fixed ankle (either leg) | 17 (15.9) | 18 (17.0) | 35 (16.4) |
| Fixed hip (index leg) | 15 (14.0) | 11 (10.4) | 26 (12.2) |
| Fixed hip (either leg) | 15 (14.0) | 11 (10.4) | 26 (12.2) |
| Ulcer present over 12 weeks | 39 (36.4) | 43 (40.6) | 82 (38.5) |
| Family history of ulcer | 21 (19.6) | 18 (17.0) | 39 (18.3) |
| ***Leg symptoms*** | | | |
| Swelling (index leg) | 45 (42.1) | 53 (50.0) | 98 (46.0) |
| Swelling (either leg) | 50 (46.7) | 57 (53.8) | 107 (50.2) |
| Claudication (index leg) | 5 (4.7) | 6 (5.7) | 11 (5.2) |
| Claudication (either leg) | 5 (4.7) | 7 (6.6) | 12 (5.6) |
| Aching (index leg) | 29 (27.1) | 35 (33.0) | 64 (30.0) |
| Aching (either leg) | 29 (27.1) | 35 (33.0) | 64 (30.0) |
| Pain (index leg) | 21 (19.6) | 24 (22.6) | 45 (21.1) |
| Pain (either leg) | 20 (18.7) | 23 (21.7) | 43 (20.2) |

DVT, deep vein thrombosis; VV, varicose veins.

with the selection of covariates being based on clinical judgement. *Table 17* shows the variables that were included in the regression and their definitions, while *Table 18* shows the results.

The non-significant chi-squared statistic in the Hosmer–Lemeshow goodness of fit test indicate that the data fit the regression model well. Significant predictors of healing at 12 weeks were location, gender and ulcer size. The odds ratios for these variables indicated that: the odds of the ulcer healing within 12 weeks were decreased by 0.509 in Sheffield compared with Exeter; they were increased by a factor of 2.156 for females compared with males; and decreased by a factor of 0.425 for large compared with small initial ulcer size (greater or less than 3 cm initial diameter). Further development of modelling relating to the factors affecting healing is presented in Chapter 7. The proportion of ulcers healing over time is shown by allocated treatment, size of ulcer and gender in *Figure 4*.

## Modelling of time to ulcer healing

The analysis was undertaken by pooling all data points from patients consenting to randomisation in order to provide maximal data. The location of

***TABLE 15*** *Ulcer characteristics for patients in RCT*

| | **Antimicrobial, *n* (%)** | **Control, *n* (%)** | **Total, *n* (%)** |
|---|---|---|---|
| Number of patients | 107 | 106 | 213 |
| ***On examination*** | | | |
| Slough | 70 (65.4) | 64 (60.4) | 134 (62.9) |
| Necrosis | 6 (5.6) | 7 (6.6) | 13 (6.1) |
| Granulation | 68 (63.6) | 64 (60.4) | 132 (62.0) |
| Epithelialisation | 26 (24.3) | 37 (34.9) | 63 (29.6) |
| ***Problems reported by patients*** | | | |
| Exudate | 79 (73.8) | 80 (75.5) | 159 (74.6) |
| Odour | 16 (15.0) | 12 (11.3) | 28 (13.1) |
| ***Leg signs*** | | | |
| Visible VV (index leg) | 73 (68.2) | 78 (73.6) | 151 (70.9) |
| Visible VV (either leg) | 79 (73.8) | 81 (76.4) | 160 (75.1) |
| Oedema (index leg) | 62 (57.9) | 67 (63.2) | 129 (60.6) |
| Oedema (either leg) | 66 (61.7) | 73 (68.9) | 139 (65.3) |
| Eczema (index leg) | 37 (34.6) | 20 (18.9) | 57 (26.8) |
| Eczema (either leg) | 38 (35.5) | 23 (21.7) | 61 (28.6) |
| Staining (index leg) | 71 (66.4) | 66 (62.3) | 137 (64.3) |
| Staining (either leg) | 74 (69.2) | 75 (70.8) | 149 (70.0) |
| Induration (index leg) | 25 (23.4) | 18 (17.0) | 43 (20.2) |
| Induration (either leg) | 29 (27.1) | 18 (17.0) | 47 (22.1) |
| Atrophy/blanching (index leg) | 29 (27.1) | 29 (27.4) | 58 (27.2) |
| Atrophy/blanching (either leg) | 31 (29.0) | 31 (29.2) | 62 (29.1) |
| Ankle flares (index leg) | 71 (66.4) | 69 (65.1) | 140 (65.7) |
| Ankle flares (either leg) | 76 (71.0) | 72 (67.9) | 148 (69.5) |

VV, varicose veins.

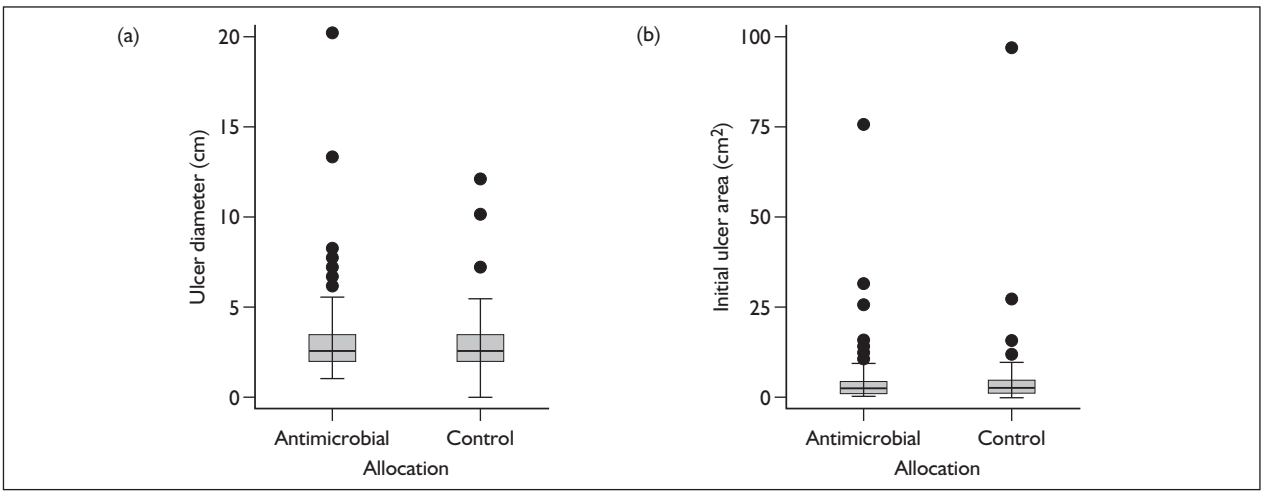


***FIGURE 3*** *Initial ulcer size for patients in RCT arms. Box and whisker plots showing median (central line), 25th and 75th centiles (box), 10th and 90th centiles (whiskers) and outliers. (a) Maximum measured diameter at recruitment (cm). (b) Measured area based upon first Visitrak tracing.*

***TABLE 16*** *Ulcer healing at primary end point of 12 weeks and secondary end points of 6 months and 1 year for patients in RCT*

| | | 12 weeks | | 6 months | | 1 year | |
|---|---|---|---|---|---|---|---|
| | ***n*** | **No. healed** | **% (95% CI)** | **No. healed** | **% (95% CI)** | **No. healed** | **% (95% CI)** |
| Silver | 107 | 62/104 | 59.6 (50.2 to 69.1) | 87/102 | 85.3 (78.4 to 92.2) | 95/99 | 96.0 (92.1 to 99.8) |
| Control | 106 | 59/104 | 56.7 (47.2 to 66.3) | 78/101 | 77.2 69.1 to 85.4) | 90/94 | 95.7 (91.7 to 99.8) |
| Total | 213 | 121/208 | 58.2 (51.5 to 64.9) | 165/203 | 81.3 (75.9 to 86.7) | 185/193 | 95.9 (93.0 to 98.7) |
| *p*-value ($\chi^2$ test) | | 0.32 | | 0.48 | | 0.63 | |

***TABLE 17*** *Variables in binary logistic regression*

| Variable | Definition |
|---|---|
| Healed | Ulcer healed at 12 weeks: 1 = yes; 0 = no |
| Dressing | Type of dressing: 1 = silver; 0 = non-adherent |
| Comorbity | Whether the patient had comorbid conditions:[a] 1 = yes; 0 = no |
| Location | Treatment centre location: 1 = Sheffield; 0 = Exeter |
| Age | Age of patient (continuous variable) |
| Gender | Gender of patient: 1 = female; 0 = male |
| Ulcer size | Size of ulcer: 1 = large; 0 = small |

a Comorbidity was defined as having at least one of osteoarthritis, rheumatoid arthritis, myocardial infarction, cardiac failure, stroke or transient ischaemic attack.

***TABLE 18*** *Results of binary logistic regression (n = 212)*

| Variable | Coefficient | Standard error | Odds ratio |
|---|---|---|---|
| Dressing | 0.074 | 0.296 | 1.077 |
| Comorbidity | 0.222 | 0.362 | 1.248 |
| Location | –0.675[a] | 0.307 | 0.509 |
| Age | –0.018 | 0.012 | 0.982 |
| Gender | 0.768[a] | 0.309 | 2.156 |
| Ulcer size | –0.855[b] | 0.322 | 0.425 |
| Constant | 1.579 | 0.836 | 4.852 |

a $p \leq 0.05$.
b $p \leq 0.01$.
Hosmer–Lemeshow test: $\chi^2 = 7.279$; $p = 0.507$.

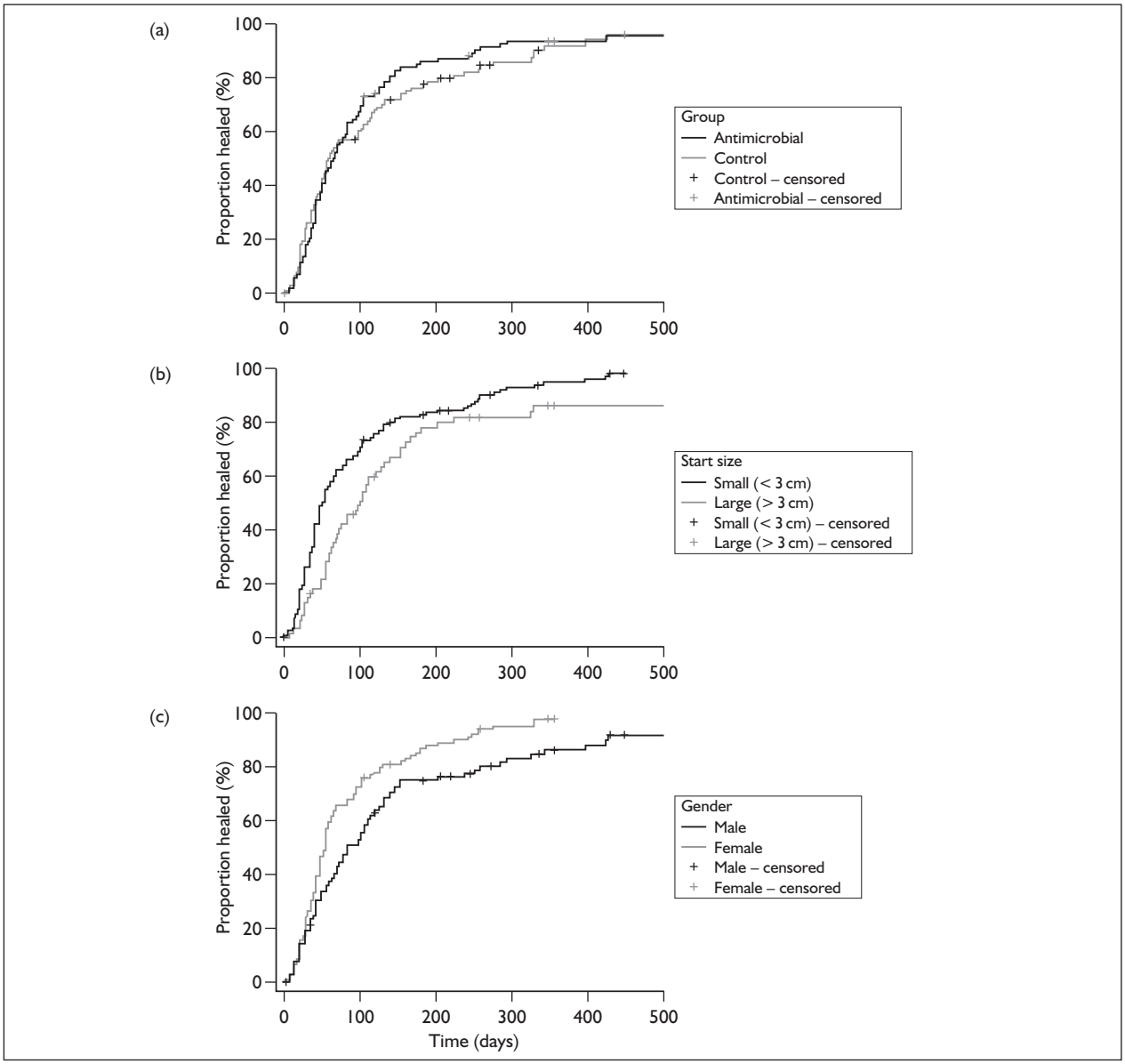


***FIGURE 4*** *Kaplan–Meier survival plots showing proportion of ulcers healed over time.(a) Antimicrobial dressings versus control dressings. (b) Large versus small ulcers. (c) Male versus female participants in the RCT.*

the centre (either Sheffield or Exeter) was included within the survival model in order to capture any population demographics that were not explicitly contained within the questionnaire. All data analyses were conducted in STATA version 10 (© STATACorp LP, College Station, Texas, USA).

A preliminary analysis investigated the change in hazard rate across time to determine the most appropriate survival model. The change in hazard can be seen in *Figure 5*.

There were few patients (1.4% of the total) where the follow-up time was greater than 500 days and thus data after this period should be treated with caution. Excluding these data, there was a clear trend for a decreasing hazard, i.e. as the time with an ulcer increased, the probability of healing in the next time unit decreased.

On this evidence an exponential model, where the hazard remains constant across time, was rejected. A Weibull model (which incorporates a parameter to increase or decrease the failure rate in relation with time) was therefore selected as the most appropriate mode as this distribution was also assumed to be clinically plausible. The Weibull model produced a good fit ($p < 0.000$) and had additional advantages (compared with a flexible baseline hazard) of being less influenced by small

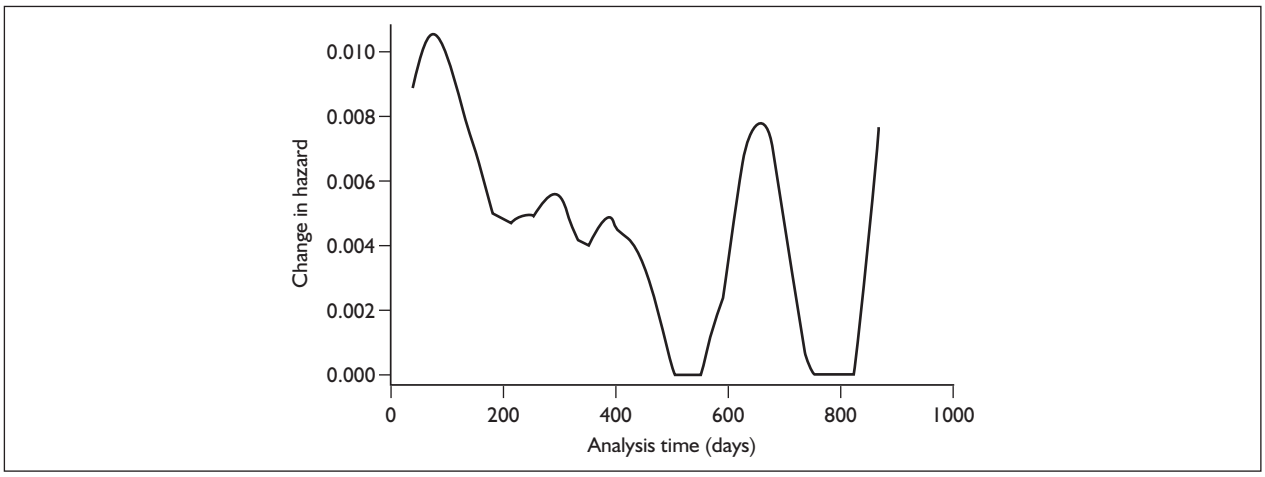


***FIGURE 5*** *Change in hazard (i.e. rate of healing) in relationship to analysis time (smoothed hazard estimate).*

patient numbers in later time periods and of being already included within modelling packages.

Two survival analysis scenarios were formally evaluated and these are detailed below.

## Survival analysis 1

This used only those parameters that were shown to be significant predictors of time to healing.

Stepwise analyses (both forward and backward) were conducted using a significance cut-off level of 10%. Both analyses selected the same combination of parameters as significant predictors of time to healing. These variables are shown in *Table 19*.

The predictive variables were assumed to affect the scale parameter of the underlying Weibull distribution. In all cases the shape parameter was assumed constant. In all instances a hazard ratio below 1 indicates that the greater the value for the parameter, the longer the predicted time to healing. Conversely, where the hazard ratio is greater than 1, the greater the value for the parameter, the shorter the predicted time to healing. Ulcer size was a continuous variable; all other variables are binary, with 1 meaning the presence of the condition. For categorical variables such as gender, a footnote is provided in the table.

The primary characteristic of interest, the dressing type applied, was not statistically significant. If it were assumed that the predicted healing times were equal regardless of dressing type then the cost-effectiveness analysis would be reduced to that of cost minimisation.

## Survival analysis 2

This used only those parameters that were shown to be significant predictors of time to healing plus the forced inclusion of dressing type.

In this model dressing type was forced into the model; this meant that it was included and used as a predictive variable regardless of statistical significance. The results for this scenario are shown in *Table 20*. The hazard ratio for dressing type was 1.190. The predicted healing time was therefore lower when the dressing type was 1 (i.e. antimicrobial dressings). There were wide CIs around the hazard ratio. The probability that the hazard ratio was greater than 1 was 86.6% with a corresponding probability of the hazard being below 1 of 13.4% – which equates to the respective probabilities that the antimicrobial or control dressings were clinically more efficacious.

The shape parameter for the Weibull distribution was 1.350 (95% C.I. 1.211 to 1.505). The scale of the Weibull distribution was dependent on the characteristics of individual patients. It should be noted that as this interval does not include unity this means that statistically the exponential distribution, which is a Weibull distribution with a shape of 1, was not appropriate.

In order to ensure that no correlations between the variables were influencing the results, analyses were undertaken to examine the correlations between those variables included within the model. These are shown in *Table 21*. Only two correlations were greater than 0.2 – the relationship between gender and osteoarthritis and that between centre and fixed ankle – and both of these are below 0.3. No

***TABLE 19*** *Significant predictors of time to healing*

| Predictor | Hazard ratio | *p*-value | 95% CI for hazard ratio |
|---|---|---|---|
| Ulcer size (cm) | 0.728 | 0.000 | 0.654 to 0.811 |
| Leg affected[a] | 0.542 | 0.000 | 0.402 to 0.732 |
| Ankle flare | 1.972 | 0.000 | 1.423 to 2.734 |
| Gender[b] | 1.715 | 0.001 | 1.234 to 2.384 |
| Stroke or TIA | 1.972 | 0.001 | 1.475 to 4.367 |
| Osteoarthritis | 0.609 | 0.003 | 0.437 to 0.849 |
| Centre[c] | 0.642 | 0.006 | 0.469 to 0.878 |
| VV surgery | 0.591 | 0.008 | 0.399 to 0.874 |
| Fixed ankle | 0.588 | 0.016 | 0.381 to 0.906 |
| Eczema | 0.664 | 0.021 | 0.469 to 0.939 |
| DVT | 0.697 | 0.073 | 0.470 to 1.034 |
| Ache | 1.331 | 0.092 | 0.954 to 1.857 |

DVT, deep vein thrombosis; TIA, transient ischaemic attack; VV, varicose veins.
a 0 = right; 1 = left.
b 0 = male; 1 = female.
c 0 = Exeter; 1 = Sheffield.

***TABLE 20*** *Significant predictors of time to healing plus forced inclusion of dressing type*

| Predictor | Hazard ratio | *p*-value | 95% CI for hazard ratio |
|---|---|---|---|
| Ulcer size (cm) | 0.726 | 0.000 | 0.652 to 0.809 |
| Leg affected[a] | 0.555 | 0.000 | 0.412 to 0.749 |
| Ankle flare | 1.925 | 0.000 | 1.386 to 2.673 |
| Gender[b] | 1.753 | 0.001 | 1.258 to 2.443 |
| Stroke or TIA | 2.425 | 0.001 | 1.407 to 4.180 |
| Osteoarthritis | 0.619 | 0.005 | 0.444 to 0.862 |
| Centre[c] | 0.635 | 0.005 | 0.464 to 0.869 |
| VV surgery | 0.608 | 0.012 | 0.412 to 0.895 |
| Fixed ankle | 0.582 | 0.014 | 0.377 to 0.898 |
| Eczema | 0.644 | 0.014 | 0.453 to 0.914 |
| DVT | 0.723 | 0.113 | 0.484 to 1.080 |
| Ache | 1.334 | 0.080 | 0.965 to 1.873 |
| Dressing type[d] | 1.190 | 0.266 | 0.876 to 1.616 |

DVT, deep vein thrombosis; TIA, transient ischaemic attack; VV, varicose veins.
a 0 = right; 1 = left.
b 0 = male; 1 = female.
c 0 = Exeter; 1 = Sheffield.
d 0 = non-adherent, 1 = silver.

correlations were more negative than –0.2. Little correlation was found between the parameters and so none was likely to affect the selection of parameter values when populating the model.

In addition to the two scenarios reported, analyses were also undertaken to examine the effect of including all non-statistically significant parameters in the model rather than just dressing type. This allowed the examination of whether other factors were influencing time to healing. In these additional analyses the $p$-value for dressing became less significant ($p = 0.470$ compared with the previous value of 0.266). This indicated that

***TABLE 21*** *Correlation between parameters in survival model*

| | Parameter | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** |
| 1. Ulcer size | 1.000 | | | | | | | | | | | | |
| 2. Dressing type | –0.033 | 1.000 | | | | | | | | | | | |
| 3. Centre | 0.063 | –0.024 | 1.000 | | | | | | | | | | |
| 4. Leg affected | –0.021 | –0.043 | –0.058 | 1.000 | | | | | | | | | |
| 5. Gender | –0.067 | –0.090 | –0.162 | 0.102 | 1.000 | | | | | | | | |
| 6. Osteoarthritis | –0.035 | 0.058 | –0.026 | –0.038 | 0.256 | 1.000 | | | | | | | |
| 7. Stroke or TIA | –0.024 | 0.051 | –0.038 | –0.009 | 0.063 | 0.147 | 1.000 | | | | | | |
| 8. DVT | 0.082 | –0.037 | 0.183 | –0.012 | –0.076 | –0.013 | –0.025 | 1.000 | | | | | |
| 9. VV surgery | –0.048 | 0.022 | –0.131 | 0.057 | 0.037 | 0.016 | –0.092 | 0.029 | 1.000 | | | | |
| 10. Ache | 0.075 | –0.065 | 0.139 | 0.106 | 0.071 | 0.040 | –0.004 | 0.137 | –0.038 | 1.000 | | | |
| 11. Eczema | 0.034 | 0.177 | –0.138 | –0.022 | –0.187 | 0.136 | 0.018 | –0.053 | –0.032 | –0.072 | 1.000 | | |
| 12. Ankle flare | –0.106 | 0.013 | –0.078 | 0.015 | 0.068 | –0.045 | –0.079 | 0.083 | 0.052 | 0.063 | 0.034 | 1.000 | |
| 13. Fixed ankle | 0.004 | –0.041 | 0.243 | –0.025 | 0.031 | 0.059 | –0.030 | 0.001 | –0.132 | 0.059 | –0.054 | 0.009 | 1.000 |

DVT, deep vein thrombosis; TIA, transient ischaemic attack; VV, varicose veins.

the results of dressing type influence on healing rate observed in the data, or results more extreme, would occur by chance in almost one out of two RCTs conducted with identical patient numbers, were the null hypothesis that dressing type had no effect on healing correct.

The CI around the coefficient in the Weibull model for dressing type was 0.813 to 1.567. Although not statistically significant, the estimated probability of antimicrobial dressings having a predicted healing time that was shorter than that for non-adhesive dressings was 76.5%. This compares with an 86.6% probability of a beneficial effect when the only non-significant variable allowed was dressing type. Any analyses undertaken that included all non-significant variables within the model would produce more unfavourable results to antimicrobial dressings than allowing the sole inclusion of dressing type.

## Recurrence

Among those patients whose ulcers had healed within the first year of the randomised trial ($n = 185$ patients) a total of 24 had recurrent ulceration, with no significant difference in rates between the antimicrobial dressing and control groups (*Table 22*).

In an exploratory analysis there were no factors relating to history, comorbidities, symptoms, ulcer features or treatment that significantly predicted the risk of recurrence.

## Quality of life and utility valuation

A TTO valuation of health states related to venous ulceration was undertaken by a sample of a 160 members of the general population. However, when analysing the results the study did not integrate with the other data collected during the study and added little additional information. The data were not thought to be suitable for inclusion in the modelling. A decision was therefore made not to include the results from the TTO study in the final report.

*Table 23* shows the mean EQ-5D health-state values and the difference between the means at baseline, 1, 3, 6 and 12 months for patients in the non-adherent and antimicrobial groups. Regression analysis of covariance indicated that there was no significant difference between the groups with respect to mean follow-up EQ-5D values after adjusting for baseline values.

*Table 24* shows the mean SF-6D health-state values and the difference between the means at baseline, 1, 3, 6 and 12 months for patients in the non-adherent and antimicrobial groups. As with the EQ-5D data, regression analysis of covariance indicated that there was no significant difference between the groups with respect to mean follow-up SF-6D values after adjusting for baseline values.

*Table 25* shows the mean EQ-5D health-state values at baseline, 1, 3, 6 and 12 months for patients who had healed at 12 weeks and those who had not healed. Regression analysis of covariance indicated that there was no significant difference between the groups with respect to mean follow-up EQ-5D values after adjusting for baseline values.

The mean difference between the EQ-5D values at baseline and 3 months was 0.0436 for those who had healed ($n = 93$) and 0.0311 for those who had not healed ($n = 52$), giving a mean difference of 0.00251.

*Table 26* shows the mean SF-6D health-state values at baseline, 1, 3, 6 and 12 months for patients who had healed at 12 weeks and those who had not healed. Regression analysis of covariance indicated that the coefficient on the covariate 'healed at 12 weeks' was positive and significant (coefficient = 0.041; $p = 0.002$). This means that patients whose ulcer had healed at 12 weeks had a significantly better mean SF-6D score at follow-up after adjusting for baseline values.

*Table 27* shows the mean scores for the eight dimensions of the SF-36 at baseline, 1, 3, 6 and 12 months for the control and antimicrobial dressing groups. Regression analysis of covariance indicated that there was no significant difference between the groups with respect to any of the dimensions' mean follow-up scores after adjusting for baseline values.

## Observational study

Ninety-one patients were recruited to the observational study. Compared with patients in the RCT there were no significant differences in age or gender; but patients were more likely to be from Exeter, a lower proportion of ulcers were on the left side, and there was a greater proportion of large ulcers (*Table 28*).

***TABLE 22*** *Recurrence rates within the first year following randomisation*

| | Antimicrobial | Control | Total |
|---|---|---|---|
| Number of patients | 107 | 106 | 213 |
| Data available | 99 | 94 | 193 |
| Primary healing | 95 | 90 | 185 |
| Recurrence | 11 (11.6%) | 13 (14.4%) | 24 (13.0%) |

***TABLE 23*** *Mean EQ-5D health-state values for control and antimicrobial dressings*

| | Control | Antimicrobial | Difference in means |
|---|---|---|---|
| Baseline | 0.6536 ($n=94$) | 0.6446 ($n=98$) | 0.0090 |
| 1 month | 0.6973 ($n=72$) | 0.6963 ($n=82$) | 0.0010 |
| 3 months | 0.7004 ($n=76$) | 0.7255 ($n=81$) | –0.0246 |
| 6 months | 0.6808 ($n=64$) | 0.7214 ($n=70$) | –0.0406 |
| 12 months | 0.6752 ($n=58$) | 0.7526 ($n=61$) | –0.0774 |

***TABLE 24*** *Mean SF-6D health-state values for non-adherent and antimicrobial dressings*

| | Control | Antimicrobial | Difference in means |
|---|---|---|---|
| Baseline | 0.6792 ($n=83$) | 0.6544 ($n=89$) | 0.0248 |
| 1 month | 0.7016 ($n=67$) | 0.6829 ($n=74$) | 0.0187 |
| 3 months | 0.7029 ($n=68$) | 0.6864 ($n=73$) | 0.0165 |
| 6 months | 0.6764 ($n=49$) | 0.6890 ($n=67$) | –0.0126 |
| 12 months | 0.6662 ($n=53$) | 0.7092 ($n=55$) | –0.0430 |

***TABLE 25*** *Mean EQ-5D values at baseline, 1, 3, 6 and 12 months for patients who had healed and not healed at 12 weeks*

| | Not healed at 12 weeks | Healed at 12 weeks | Difference in means |
|---|---|---|---|
| Baseline | 0.5792 ($n=79$) | 0.6978 ($n=113$) | –0.1186 |
| 1 month | 0.6588 ($n=67$) | 0.7262 ($n=87$) | –0.0677 |
| 3 months | 0.6474 ($n=59$) | 0.7531 ($n=98$) | –0.1057 |
| 6 months | 0.6974 ($n=53$) | 0.7050 ($n=81$) | –0.0076 |
| 12 months | 0.6495 ($n=51$) | 0.7639 ($n=68$) | –0.1144 |

***TABLE 26*** *Mean SF-6D values at baseline, 1, 3, 6 and 12 months for patients who had healed and not healed at 12 weeks*

| | Not healed at 12 weeks | Healed at 12 weeks | Difference in means |
|---|---|---|---|
| Baseline | 0.6426 ($n=70$) | 0.6826 ($n=102$) | –0.0400 |
| 1 month | 0.6743 ($n=61$) | 0.7051 ($n=80$) | –0.0308 |
| 3 months | 0.6622 ($n=55$) | 0.7149 ($n=86$) | –0.0527 |
| 6 months | 0.6586 ($n=48$) | 0.7014 ($n=68$) | –0.0428 |
| 12 months | 0.6606 ($n=45$) | 0.7078 ($n=63$) | –0.0472 |

***TABLE 27*** *SF-36 dimension scores (0–100)[a] at baseline, 1, 3, 6 and 12 months for the non-adherent and silver dressing groups*

| SF-36 dimension | Randomised group | Score at baseline (SE) (*n*) | Score at 1 month (SE) (*n*) | Score at 3 months (SE) (*n*) | Score at 6 months (SE) (*n*) | Score at 12 months (SE) (*n*) |
|---|---|---|---|---|---|---|
| Physical functioning | NA | 47.02 (3.17) (*n* = 94) | 52.93 (3.47) (*n* = 75) | 54.61 (3.47) (*n* = 81) | 48.25 (4.11) (*n* = 62) | 46.34 (4.30) (*n* = 59) |
| | Ag | 48.76 (2.77) (*n* = 99) | 46.74 (3.15) (*n* = 87) | 50.77 (3.40) (*n* = 84) | 47.35 (3.49) (*n* = 75) | 55.12 (3.94) (*n* = 63) |
| Social functioning | NA | 62.46 (2.67) (*n* = 95) | 64.94 (3.09) (*n* = 77) | 68.04 (2.85) (*n* = 81) | 66.84 (3.34) (*n* = 66) | 62.71 (3.53) (*n* = 59) |
| | Ag | 59.60 (2.56) (*n* = 99) | 63.18 (2.75) (*n* = 86) | 68.43 (2.58) (*n* = 82) | 63.11 (2.75) (*n* = 75) | 64.37 (3.21) (*n* = 63) |
| Role – physical | NA | 33.98 (4.37) (*n* = 90) | 43.49 (5.16) (*n* = 73) | 51.92 (5.10) (*n* = 78) | 51.64 (5.78) (*n* = 61) | 43.06 (5.93) (*n* = 54) |
| | Ag | 35.31 (4.03) (*n* = 97) | 41.88 (4.53) (*n* = 80) | 41.14 (4.70) (*n* = 79) | 41.44 (4.93) (*n* = 73) | 43.55 (5.60) (*n* = 62) |
| Role – emotional | NA | 66.67 (4.42) (*n* = 91) | 72.69 (4.77) (*n* = 72) | 73.25 (4.50) (*n* = 76) | 81.36 (4.65) (*n* = 59) | 64.85 (6.32) (*n* = 55) |
| | Ag | 66.84 (4.36) (*n* = 94) | 67.49 (4.61) (*n* = 81) | 70.09 (4.62) (*n* = 78) | 67.37 (5.05) (*n* = 71) | 72.22 (5.32) (*n* = 60) |

| SF-36 dimension | Randomised group | Score at baseline (SE) (*n*) | Score at 1 month (SE) (*n*) | Score at 3 months (SE) (*n*) | Score at 6 months (SE) (*n*) | Score at 12 months (SE) (*n*) |
|---|---|---|---|---|---|---|
| Mental health index | NA | 73.75 (1.91) (*n* = 94) | 77.32 (2.07) (*n* = 76) | 80.21 (1.80) (*n* = 78) | 74.91 (2.25) (*n* = 63) | 74.39 (2.43) (*n* = 57) |
| | Ag | 73.96 (1.82) (*n* = 99) | 74.65 (1.99) (*n* = 85) | 75.10 (1.92) (*n* = 82) | 74.34 (1.92) (*n* = 74) | 77.41 (2.12) (*n* = 63) |
| Energy/vitality | NA | 54.31 (2.00) (*n* = 94) | 54.44 (2.59) (*n* = 75) | 56.39 (2.54) (*n* = 77) | 56.98 (2.77) (*n* = 63) | 50.09 (3.34) (*n* = 57) |
| | Ag | 50.26 (2.08) (*n* = 98) | 51.73 (2.13) (*n* = 84) | 54.03 (2.25) (*n* = 81) | 51.42 (2.48) (*n* = 74) | 52.62 (2.95) (*n* = 63) |
| Pain index | NA | 58.91 (2.74) (*n* = 96) | 64.50 (3.06) (*n* = 77) | 67.49 (3.07) (*n* = 81) | 65.80 (3.57) (*n* = 64) | 63.55 (4.21) (*n* = 57) |
| | Ag | 52.19 (2.65) (*n* = 99) | 61.89 (2.85) (*n* = 86) | 63.28 (2.83) (*n* = 82) | 60.59 (3.01) (*n* = 75) | 61.91 (3.43) (*n* = 63) |
| General health perceptions | NA | 59.80 (2.49) (*n* = 91) | 61.43 (2.66) (*n* = 73) | 62.95 (2.63) (*n* = 74) | 61.46 (3.15) (*n* = 63) | 57.49 (3.36) (*n* = 53) |
| | Ag | 59.36 (2.23) (*n* = 95) | 58.89 (2.14) (*n* = 83) | 58.03 (2.44) (*n* = 81) | 56.70 (2.25) (*n* = 73) | 58.10 (2.66) (*n* = 61) |

Ag, silver; NA, non-adherent.
a Higher scores indicate better health.

***TABLE 28*** *Demographic features of patients in RCT and observational study*

| | Observation | RCT | Total |
|---|---|---|---|
| Number of patients | 91 | 213 | 304 |
| Age (SD) | 69.7 (16.7) | 70.6 (15.3) | 70.3 (15.8) |
| Female:male | 57:34 | 115:98 | 172:132 |
| Left:right | 46:45 | 116:97 | 162:142 |
| Sheffield:Exeter | 31:60 | 114:99 | 145:159 |
| Size > 3 cm:< 3 cm | 41:50 | 60:153 | 101:203 |

***TABLE 29*** *Incidence of comorbidities, smoking history and selected drug history in RCT and observational trial*

| | Observation, *n* (%) | RCT, *n* (%) | Total, *n* (%) |
|---|---|---|---|
| Number of patients | 91 | 213 | 304 |
| ***Comorbidity*** | | | |
| Hypertension | 43 (47.3) | 85 (39.9) | 128 (42.1) |
| Osteoarthritis | 32 (35.2) | 64 (30.0) | 96 (31.6) |
| History of myocardial infarction or cardiac failure | 13 (14.3) | 30 (14.1) | 43 (14.1) |
| Anaemia | 7 (7.7) | 18 (8.5) | 25 (8.2) |
| Rheumatoid arthritis | 7 (7.7) | 34 (16.0) | 41 (13.5) |
| History of stroke or transient cerebral ischaemia | 4 (4.4) | 17 (8.0) | 21 (6.9) |
| ***Smoking history*** | | | |
| Smoker | 17 (18.7) | 39 (18.3) | 56 (18.4) |
| Ex-smoker | 28 (30.8) | 55 (25.8) | 83 (27.3) |
| ***Current drugs*** | | | |
| Aspirin | 10 (11.0) | 23 (10.8) | 33 (10.9) |
| Diuretics | 10 (11.0) | 25 (11.7) | 35 (11.5) |
| Warfarin | 8 (8.8) | 13 (6.1) | 21 (6.9) |
| Atenolol | 5 (5.5) | 20 (9.4) | 25 (8.2) |

Information was available about the types of dressings used on 82 patients: 43 with antimicrobial silver-donating dressings, 37 with control dressings and two with iodine dressings.

The incidence of comorbidities, smoking history and medication was similar to that in the RCT (*Table 29*) with the exception of diabetes, which was present in 11/91 (12%) of observational patients, this being an exclusion criterion for randomisation.

Other risk factors and ulcer history were similar to those in the RCT (*Table 30*), as were clinical features (*Table 31*).

Healing was slower in the observational group than in the RCT – 87% compared with 95.9% respectively being healed by 1 year, although the difference did not reach statistical significance (*Table 32*).

***TABLE 30*** *Ulcer history and aetiological factors for patients in RCT and observational trial*

| | **Observation, *n* (%)** | **RCT, *n* (%)** | **Total, *n* (%)** |
|---|---|---|---|
| Number of patients | 91 | 213 | 304 |
| ***History of venous problems*** | | | |
| Ulcer (index leg) | 51 (56.0) | 100 (46.9) | 151 (70.9) |
| Ulcer (either leg) | 58 (63.7) | 113 (53.1) | 171 (80.3) |
| VV (index leg) | 50 (54.9) | 105 (49.3) | 155 (72.8) |
| VV (either leg) | 59 (64.8) | 116 (54.5) | 175 (82.2) |
| Previous DVT (index leg) | 14 (15.4) | 34 (16.0) | 48 (22.5) |
| Previous DVT (either leg) | 18 (19.8) | 45 (21.1) | 63 (29.6) |
| VV surgery (index leg) | 26 (28.6) | 38 (17.8) | 64 (30.0) |
| VV surgery (either leg) | 30 (33.0) | 48 (22.5) | 78 (36.6) |
| Previous phlebitis (index leg) | 23 (25.3) | 37 (17.4) | 60 (28.2) |
| Previous phlebitis (either leg) | 23 (25.3) | 45 (21.1) | 68 (31.9) |
| ***Risk factors*** | | | |
| Fixed ankle (index leg) | 6 (6.6) | 33 (15.5) | 39 (18.3) |
| Fixed ankle (either leg) | 6 (6.6) | 35 (16.4) | 41 (19.2) |
| Fixed hip (index leg) | 4 (4.4) | 26 (12.2) | 30 (14.1) |
| Fixed hip (either leg) | 4 (4.4) | 26 (12.2) | 30 (14.1) |
| Ulcer present over 12 weeks | 37 (40.7) | 82 (38.5) | 119 (55.9) |
| Family history of ulcer | 19 (20.9) | 39 (18.3) | 58 (27.2) |
| ***Leg symptoms*** | | | |
| Swelling (index leg) | 48 (52.7) | 98 (46.0) | 146 (68.5) |
| Swelling (either leg) | 50 (54.9) | 107 (50.2) | 157 (73.7) |
| Claudication (index leg) | 14 (15.4) | 11 (5.2) | 25 (11.7) |
| Claudication (either leg) | 14 (15.4) | 12 (5.6) | 26 (12.2) |
| Aching (index leg) | 37 (40.7) | 64 (30.0) | 101 (47.4) |
| Aching (either leg) | 37 (40.7) | 64 (30.0) | 101 (47.4) |
| Pain (index leg) | 19 (20.9) | 45 (21.1) | 64 (30.0) |
| Pain (either leg) | 19 (20.9) | 43 (20.2) | 62 (29.1) |

DVT, deep vein thrombosis; VV, varicose veins.

***TABLE 31*** *Ulcer characteristics for patients in RCT and observational study*

| | Observation, *n* (%) | RCT, *n* (%) | Total, *n* (%) |
|---|---|---|---|
| Number of patients | 91 | 213 | 304 |
| ***On examination*** | | | |
| Slough | 58 (63.7) | 134 (62.9) | 192 (90.1) |
| Necrosis | 4 (4.4) | 13 (6.1) | 17 (8.0) |
| Granulation | 55 (60.4) | 132 (62.0) | 187 (87.8) |
| Epithelialisation | 29 (31.9) | 63 (29.6) | 92 (43.2) |
| ***Problems reported by patients*** | | | |
| Exudate | 70 (76.9) | 159 (74.6) | 229 (107.5) |
| Odour | 10 (11.0) | 28 (13.1) | 38 (17.8) |
| ***Leg signs*** | | | |
| Visible VV (index leg) | 55 (60.4) | 151 (70.9) | 206 (96.7) |
| Visible VV (either leg) | 62 (68.1) | 160 (75.1) | 222 (104.2) |
| Oedema (index leg) | 41 (45.1) | 129 (60.6) | 170 (79.8) |
| Oedema (either leg) | 48 (52.7) | 139 (65.3) | 187 (87.8) |
| Eczema (index leg) | 25 (27.5) | 57 (26.8) | 82 (38.5) |
| Eczema (either leg) | 28 (30.8) | 61 (28.6) | 89 (41.8) |
| Staining (index leg) | 62 (68.1) | 137 (64.3) | 199 (93.4) |
| Staining (either leg) | 65 (71.4) | 149 (70.0) | 214 (100.5) |
| Induration (index leg) | 24 (26.4) | 43 (20.2) | 67 (31.5) |
| Induration (either leg) | 25 (27.5) | 47 (22.1) | 72 (33.8) |
| Atrophy/blanching (index leg) | 38 (41.8) | 58 (27.2) | 96 (45.1) |
| Atrophy/blanching (either leg) | 42 (46.2) | 62 (29.1) | 104 (48.8) |
| Ankle flare (index leg) | 57 (62.6) | 140 (65.7) | 197 (92.5) |
| Ankle flare (either leg) | 62 (68.1) | 148 (69.5) | 210 (98.6) |

VV, varicose veins.

***TABLE 32*** *Ulcer healing at primary end point of 12 weeks and secondary end points of 6 months and 1 year comparing RCT and observational study*

| | RCT, *n* (%) | Observation, *n* (%) | Total, *n* (%) | *p*-value ($\chi^2$ test) |
|---|---|---|---|---|
| Number of patients | 213 | 91 | 304 | |
| 12 weeks | 121/208 (58.2) | 42/86 (48.8) | 163/294 (55.4) | 0.54 |
| 6 months | 165/203 (81.3) | 58/80 (72.5) | 223/283 (78.8) | 0.45 |
| 1 year | 185/193 (95.9) | 67/77 (87.0) | 252/270 (93.3) | 0.07 |

# Chapter 5
# Results – cost-effectiveness

## EQ-5D data

This analysis is based on 141 patients in the RCT arm of the trial who provided EQ-5D responses at baseline and 3 months, of whom 74 were in the antimicrobial dressing group and 67 were in the control dressing group. These 141 patients comprise a self-selected group on the basis that they completed and returned their questionnaires. Tests of differences between these patients and those who did not return their questionnaires revealed that the self-selected group had a higher proportion of patients whose ulcer had healed at 12 weeks ($\chi^2 = 6.14$; $p = 0.013$) and a higher proportion of patients from Exeter ($\chi^2 = 12.30$; $p < 0.001$).

*Table 33* shows the average number of ulcer clinic visits, community nurse home visits, GP contacts and chiropody contacts per patient for the control and antimicrobial dressing groups. The numbers of clinic/home visits was used as a surrogate for the numbers of dressings and bandages used, as these were both changed at each visit.

The only statistically significant difference was in relation to mean number of ulcer clinic visits per patient, with antimicrobial patients having more visits than control patients (8.00 versus 5.61 respectively).

With respect to numbers of prescriptions for hosiery, antibiotics and other medicines, 41 control patients were prescribed hosiery compared with 42 antimicrobial patients, 12 control patients were prescribed antibiotics compared with 21 antimicrobial patients, and seven control patients were prescribed other drugs compared with five antimicrobial patients. Chi-squared tests revealed that none of these differences was significant.

*Table 34* shows the average cost per patient of each item of resource use and the average total cost per patient for the control and antimicrobial dressing groups.

The biggest contributor to total costs for both groups was the cost of attending the ulcer clinics, accounting for between 61% and 66% of total costs. Ulcer clinic costs were significantly higher in the antimicrobial dressings group, as were dressing costs. The mean total cost per patient is also significantly higher for the antimicrobial group.

*Table 35* shows the point estimate of the ICER for antimicrobial dressings relative to control dressings.

Antimicrobial silver dressings were associated with an incremental cost of £97.85 and an incremental QALY gain of 0.0002 compared with control dressings. When combined, these data gave an

***TABLE 33*** *Average number of visits/contacts per patient (EQ-5D data)*

| | Average number of visits/contacts per patient (95% CI) | |
|---|---|---|
| **Resource** | **Control** | **Antimicrobial** |
| Ulcer clinic visits[a] | 5.61 (4.55 to 6.67) ($n = 67$) | 8.00 (6.92 to 9.08) ($n = 74$) |
| Community nurse home visits | 9.58 (5.45 to 12.71) ($n = 12$) | 10.57 (7.42 to 13.72) ($n = 7$) |
| GP contacts | 2.00 (1.06 to 2.94) ($n = 9$) | 2.09 (1.53 to 2.65) ($n = 11$) |
| Chiropody contacts | 1.82 (1.39 to 2.24) ($n = 22$) | 1.60 (1.25 to 1.95) ($n = 20$) |

a Statistically significant difference.

***TABLE 34*** *Average cost per patient by item of resource (EQ-5D data)*

| | Average cost per patient (£) (95% CI) | |
|---|---|---|
| **Resource** | **Control** | **Antimicrobial** |
| Ulcer clinic visit[a] | 196.06 (156.95 to 235.18) | 275.39 (236.83 to 313.95) |
| Nurse home visit | 41.19 (16.53 to 65.86) | 24.00 (5.85 to 42.15) |
| Dressings[a] | 5.73 (2.96 to 8.49) | 30.62 (25.47 to 35.78) |
| Bandages | 55.22 (46.41 to 64.02) | 66.49 (58.62 to 74.37) |
| GP contacts | 9.64 (2.56 to 16.71) | 10.18 (3.65 to 16.71) |
| Chiropody contacts | 5.37 (3.14 to 7.60) | 3.89 (2.20 to 5.59) |
| Compression hosiery | 6.17 (4.61 to 7.73) | 5.02 (3.62 to 6.41) |
| Antibiotics | 0.23 (–0.03 to 0.49) | 1.11 (0.16 to 2.06) |
| Other medicines | 0.51 (–0.01 to 1.02) | 1.27 (–0.19 to 2.72) |
| Total cost[a] | 320.12 (277.42 to 362.82) | 417.97 (375.01 to 460.93) |

a Statistically significant difference.

***TABLE 35*** *Point estimate of ICER for antimicrobial relative to control dressings*

| Dressing | Cost (£) (95% CI) | QALYs (95% CI) | Incremental cost (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| Control | 320.12 (277.42 to 362.82) | 0.1702 (0.1549 to 0.1856) | – | – | – |
| Antimicrobial silver donating | 417.97 (375.01 to 460.93) | 0.1704 (0.1571 to 0.1837) | 97.85 | 0.0002 | 489,250 |

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

ICER for antimicrobial dressings of £489,250 per QALY gained.

Bootstrapping the point estimate of the ICER for antimicrobial dressings resulted in 30% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), 11% being located in the SE quadrant (less costly, more effective), and 13% being located in the SW quadrant (less costly, less effective). The largest proportion of the replications (46%) is located in the NW quadrant, where antimicrobial dressings are more costly and less effective and therefore dominated by control dressings.

*Figure 6* shows the CEAC for antimicrobial dressings relative to control dressings. The probabilities that antimicrobial dressings are cost-effective at ceiling ratios of £10,000, £30,000 and £50,000 per QALY are 0.37, 0.40 and 0.40 respectively.

Repeating the above analysis using the more precise estimates of the QALYs enjoyed by patients up to 3 months has little impact on the results. Consequently, this analysis is not reported.

The imputation of missing EQ-5D values had little impact on the results, with the probability that antimicrobial dressings are cost-effective at a ceiling ratio of £30,000 per QALY being the same as that in the initial analysis, i.e. 0.40.

## SF-6D data

This analysis was based on 118 patients who provided SF-6D responses at baseline and 3 months, of whom 63 were in the antimicrobial dressing group and 55 were in the control dressing group. As with the EQ-5D data, these 118 patients comprise a self-selected group. Tests of differences between the selected and non-selected patients revealed that the patients in the self-selected group had a higher mean age (72.7 years versus 67.7 years; $p = 0.023$) and that the self-selected group had a higher proportion of patients from Exeter ($\chi^2 = 7.01$; $p = 0.008$).

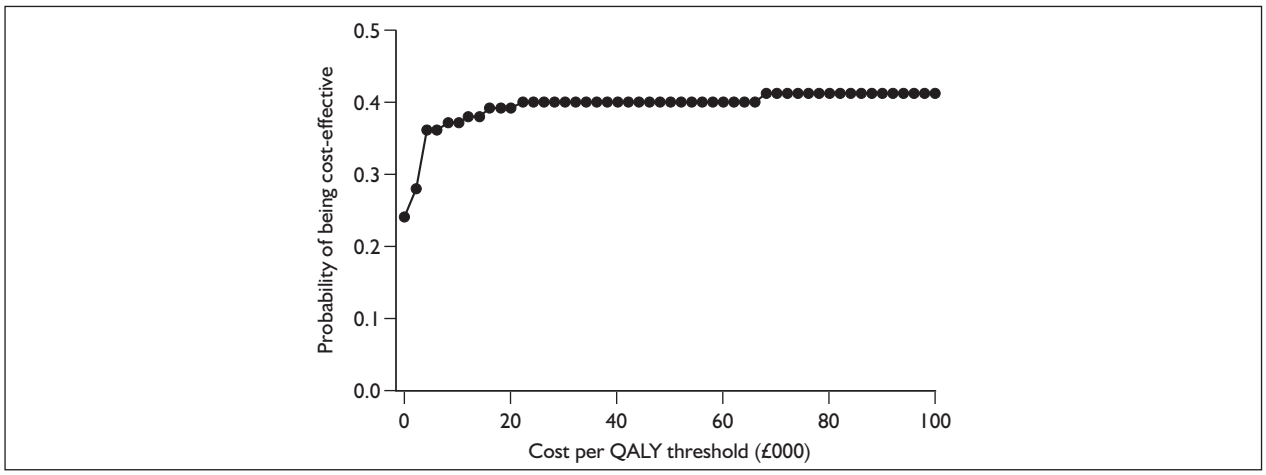


***FIGURE 6*** *Cost-effectiveness acceptability curve for antimicrobial dressings relative to control dressings (EQ-5D data). QALY, quality-adjusted life-year.*

*Table 36* shows the average number of ulcer clinic visits, nurse home visits, GP contacts and chiropody contacts per patient for the control and antimicrobial dressing groups. For the same reasons as outlined above regarding the EQ-5D data, use of bandages and dressings is not reported separately.

As with the EQ-5D data, the only statistically significant difference was in relation to mean number of ulcer clinic visits per patient, with antimicrobial dressing patients having more visits than control patients (8.68 versus 5.60 respectively).

With respect to numbers of prescriptions for hosiery, antibiotics and other medicines, 33 control patients were prescribed hosiery compared with 35 antimicrobial patients, seven control patients were prescribed antibiotics compared with 15 antimicrobial patients, and four control patients were prescribed other drugs compared with two antimicrobial patients. Chi-squared tests revealed that none of these differences was significant. *Table 37* shows the average cost per patient of each item of resource use and the average total cost per patient for the control and antimicrobial dressing groups.

As with the EQ-5D data, the biggest contributor to total costs for both groups was the cost of attending the ulcer clinics, accounting for between 61% and 70% of total costs. As before, ulcer clinic costs were significantly higher in the antimicrobial dressing group, as were dressing costs. Once again, the mean total cost per patient was also significantly higher for the antimicrobial group. *Table 38* shows the point estimate of the ICER for antimicrobial dressings relative to control dressings.

Compared with control dressings, antimicrobial dressings were associated with an incremental

***TABLE 36*** *Average number of visits/contacts per patient (SF-6D data)*

| | Average number of visits/contacts per patient (95% CI) | |
|---|---|---|
| **Resource** | **Control dressing** | **Antimicrobial dressing** |
| Ulcer clinic visits[a] | 5.60 (4.38 to 6.82) (*n* = 55) | 8.68 (7.51 to 9.85) (*n* = 63) |
| Nurse home visits | 9.40 (5.61 to 13.19) (*n* = 10) | 9.25 (2.84 to 15.66) (*n* = 4) |
| GP contacts | 2.13 (1.08 to 3.17) (*n* = 8) | 2.33 (1.48 to 3.19) (*n* = 6) |
| Chiropody contacts | 1.70 (1.27 to 2.13) (*n* = 20) | 1.60 (1.14 to 2.06) (*n* = 15) |

a Statistically significant difference.

***TABLE 37*** *Mean cost per patient by item of resource (SF-6D data)*

| | Average cost per patient (£) (95% CI) | |
|---|---|---|
| **Resource** | **Control** | **Antimicrobial** |
| Ulcer clinic visit[a] | 196.08 (150.88 to 241.291) | 300.95 (259.03 to 342.88) |
| Nurse home visit | 41.02 (13.44 to 68.59) | 14.10 (–0.66 to 28.85) |
| Dressings[a] | 6.08 (2.87 to 9.29) | 31.78 (25.83 to 37.72) |
| Bandages | 53.83 (44.51 to 63.14) | 66.77 (58.89 to 74.65) |
| GP contacts | 11.09 (2.56 to 19.61) | 6.83 (0.58 to 13.09) |
| Chiropody contacts | 5.56 (3.15 to 7.97) | 3.43 (1.63 to 5.22) |
| Compression hosiery | 6.21 (4.38 to 8.04) | 4.71 (3.26 to 6.16) |
| Antibiotics | 0.28 (–0.03 to 0.59) | 1.22 (0.11 to 2.32) |
| Other medicines | 0.28 (–0.05 to 0.61) | 0.34 (–0.19 to 0.88) |
| Total cost[a] | 320.43 (271.14 to 369.72) | 430.13 (381.80 to 478.46) |

a Statistically significant difference.

***TABLE 38*** *Point estimate of ICER for antimicrobial dressings relative to control dressings*

| Dressing | Cost (£) (95% CI) | QALYs (95% CI) | Incremental cost (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| Control | 320.43 (271.14 to 369.72) | 0.1736 (0.1656 to 0.1816) | – | – | – |
| Antimicrobial | 430.13 (381.80 to 478.46) | 0.1667 (0.1603 to 0.1732) | 109.70 | –0.0069 | Dominated |

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

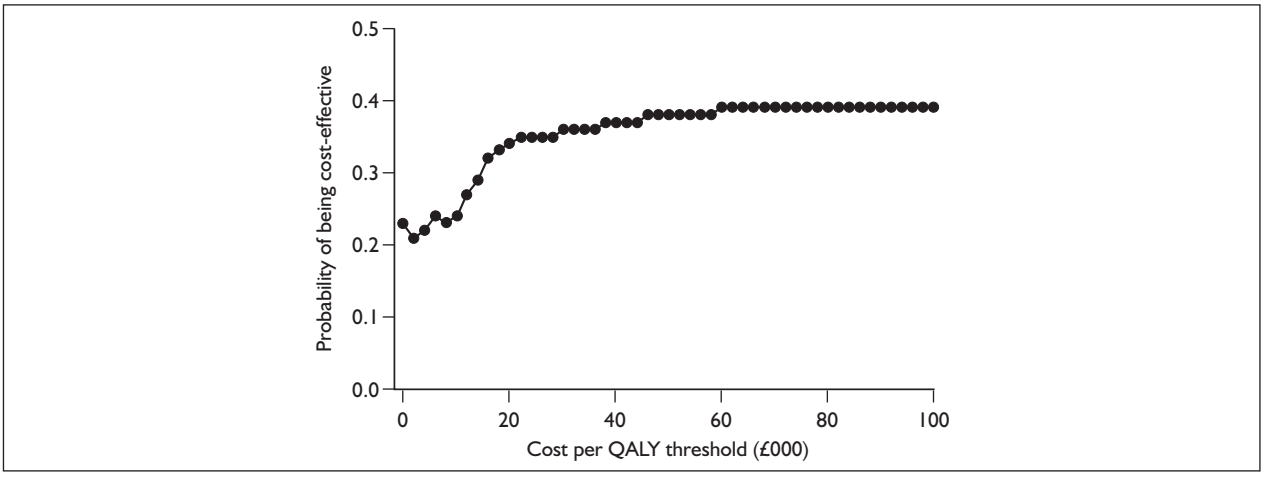


***FIGURE 7*** *Cost-effectiveness acceptability curve for antimicrobial dressings relative to control dressings (SF-6D data). QALY, quality-adjusted life-year.*

cost of £109.70 and an incremental QALY loss of –0.0069. Thus, antimicrobial dressings were dominated by control dressings.

Bootstrapping the point estimate of the ICER for antimicrobial dressings resulted in 28% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), 12% being located in the SE quadrant (less costly, more effective), and 11% being located in the SW quadrant (less costly, less effective). As was the case with the EQ-5D data, the largest

proportion of the replications (49%) is located in the NW quadrant, where antimicrobial dressings are more costly and less effective and therefore dominated by control dressings.

*Figure 7* shows the CEAC for antimicrobial dressings relative to control dressings. The probabilities that antimicrobial dressings are cost-effective at ceiling ratios of £10,000, £30,000 and £50,000 per QALY are 0.24, 0.36 and 0.38 respectively.

As was the case with the EQ-5D analysis, repeating the above analysis using the more precise estimates of the QALYs enjoyed by patients up to 3 months has little impact on the results. Consequently, this analysis is not reported.

The imputation of missing SF-6D values also had little impact on the results, with the probability that antimicrobial dressings are cost-effective at a ceiling ratio of £30,000 per QALY being 0.34, which is slightly lower than the 0.36 in the initial analysis.

# Chapter 6
# Modelling

Modelling was undertaken in order to allow the results from the clinical trial to be applied beyond the study population and in order to assess the uncertainty associated with a finite trial population. It also allows the consideration of alternative scenarios, which can identify those parameters which have most influence on the cost-effectiveness results. Probabilistic sensitivity analyses can also allow the uncertainty in the decision, associated with the uncertain values of model inputs, to be quantified and to provide information on the likelihood of an intervention being cost-effective at different cost per QALY thresholds. Inevitably, the construction of the model will introduce some simplifications compared with the decisions required within the 'real world'; however, we have attempted to keep any potential biases to a minimum.

## The structure of the model

### Model assumptions

A cohort of hypothetical patients were simulated, as later described, and duplicated, with one assumed to receive antimicrobial silver dressings and one assumed to receive a control dressing. For each patient, in each cohort, the time to ulcer healing was predicted using the distributions estimated from the trials, which were detailed in Chapter 4. For simplicity, the time to healing has been rounded to the nearest week (with a minimum of 1 week). For computational efficiency, a discrete simulation methodology was employed.

During the healing process it has been assumed that both costs and utility losses are incurred because of the ulcer – both costs and benefits were discounted at 1.035 per annum,[132] which equates to a discount rate of 1.00066 per week. Total costs and QALYs were calculated for the hypothetical cohort who received antimicrobial dressings and those who received the control dressings. The incremental costs and QALYs of silver dressings compared with the control dressings were used to calculate the cost–utility. A schematic of the model is depicted in *Figure 8*.

The model assumed that patients will not die without the ulcer healing – on the basis that this was unlikely to affect the results, as only a small percentage of ulcers remain unhealed at 5 years. From UK life tables,[133] it can be seen that only patients aged 86 and older have an expected survival duration of less than 5 years. Applied to the study cohort this represents a minority of patients (24% in Exeter and 9% in Sheffield). This again suggests that the assumption that people do not die with an unhealed ulcer is unlikely to affect these results.

The assumption of ulcer healing based on the average values for each of the patient characteristics resulted in a predicted 99.8% of

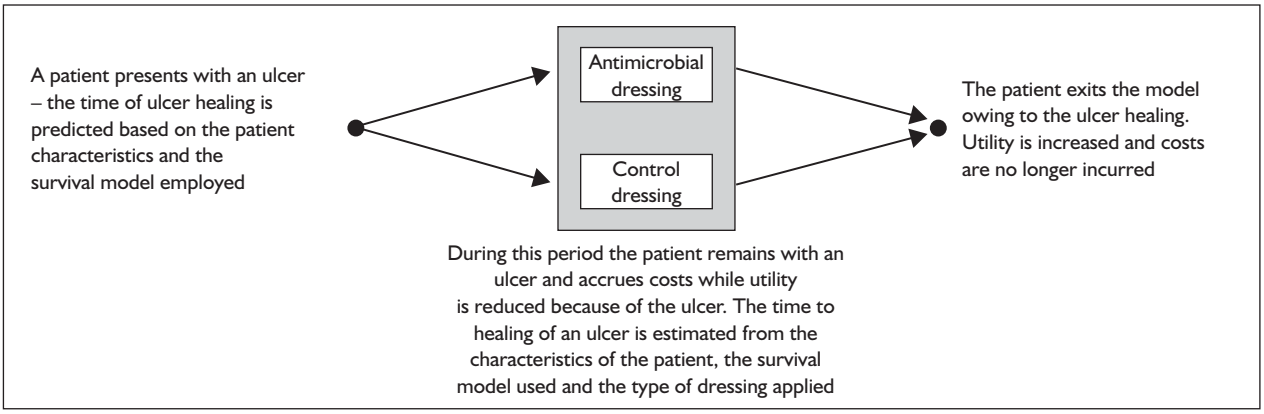


***FIGURE 8*** *A schematic of the model.*

ulcers healing in patients presenting in Sheffield and virtually all of those presenting in Exeter. Note that these values cannot be directly compared with those observed in the trials, as these patients did not all have average values for each variable considered.

We have further assumed that ulcers do not recur within the model. This assumption was based on a small number of patients having a recurrent ulcer within the RCT which would result in large uncertainty in constructing distributions to predict the time of recurrence. In the real world, where patients do recur it is recommended that they be assumed to be a new presentation and be treated in accordance with the strategy deemed to be cost-effective.

Finally, the utilities used to populate the model were those derived from the analysis of the responses to the EQ-5D, using the UK tariffs.[124] The decision to exclude the utilities derived from the SF-6D was made on the basis that EQ-5D tariffs are preferred by the National Institute for Clinical Excellence (NICE).[134]

### Modelling package used

This model could be constructed in many platforms. We used SIMUL8 (© Simul8 Corporation, Boston, USA) as it was a program that did not require significant computational times, that could automatically sample from a Weibull distribution, could handle cohorts containing a large number of individual patients and could be easily automated to run probabilistic sensitivity analyses.

## Population of the model

### Simulating the characteristics of patients presenting with a leg ulcer

The results of the RCT showed that centre, either Exeter or Sheffield, was a significant predictor of time to healing as a consequence of the different demographic characteristics of the sample. In order to allow for this, the model was run separately for both the Exeter and Sheffield centres. The patients presenting to each centre were simulated from the individual centre data, with a statistical distribution assumed to approximate the size of ulcer.

For patients presenting in Exeter the distribution of ulcer size was approximated by 1 plus a lognormal distribution with a normal distribution of the logarithm having a mean of 0.325 and a standard deviation of 0.757. The goodness of the fit is shown in *Figure 9*.

The same methodology was applied for patients presenting in Sheffield. The distribution of ulcer size was approximated by 1 plus a lognormal distribution. The distribution of the logarithm was normal with a mean of 0.500 and a standard deviation of 0.767. The fit is shown in *Figure 10*.

Excluding ulcer size, all the remaining variables were binary in distribution, as the values took either 1 or zero. Data were taken from each centre and fitted to a beta distribution where alpha represents the number of successes (defined as a 1) and beta the number of failures defined as a zero. The beta distributions fitted to each predictive variable are shown in *Table 39*. These were used in the probabilistic sensitivity analyses. These variables were not strongly correlated, as shown in *Table 21*, and therefore could be sampled independently for each patient.

### Estimating the costs of ulcer treatment per week

The costs per week of the antimicrobial and control dressings were calculated as £32.15 [standard error (SE) £1.66] and £24.62 (SE £1.65) respectively. These costs were sampled in the probabilistic sensitivity analyses.

### Estimating the disutility of an ulcer

From a naive analysis comparing the utility score for patients with an ulcer with those patients without an ulcer, the utility decrement for having an ulcer was found to be 0.10576 (SE 0.04509). However, an alternative approach was also modelled which subtracted the gain in utility from baseline to 12 weeks for patients who did not heal from the gain in utility for those who did heal. One advantage of doing this was that an allowance was made for potential comorbidities present in the leg ulcer population. Using this method, the decrement of having an ulcer was estimated to be 0.00251 (SE 0.04556) based on the mean difference in EQ-5D values between healed and unhealed ulcers (see Chapter 4 for a detailed breakdown of utility estimation).

One limitation of the resulting distributions is that they allow the possibility of a patient's utility to decrease when the ulcer heals, which is clinically implausible. To remove this possibility, statistical distributions were fitted to the normal

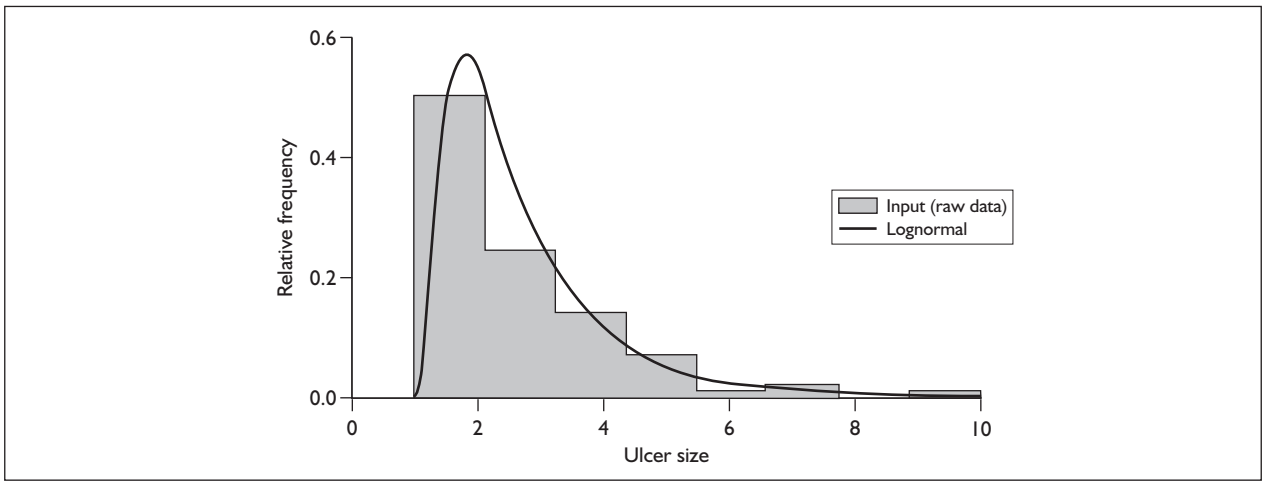


***FIGURE 9*** *Statistical distribution fitted to ulcer size for patients presenting in Exeter.*

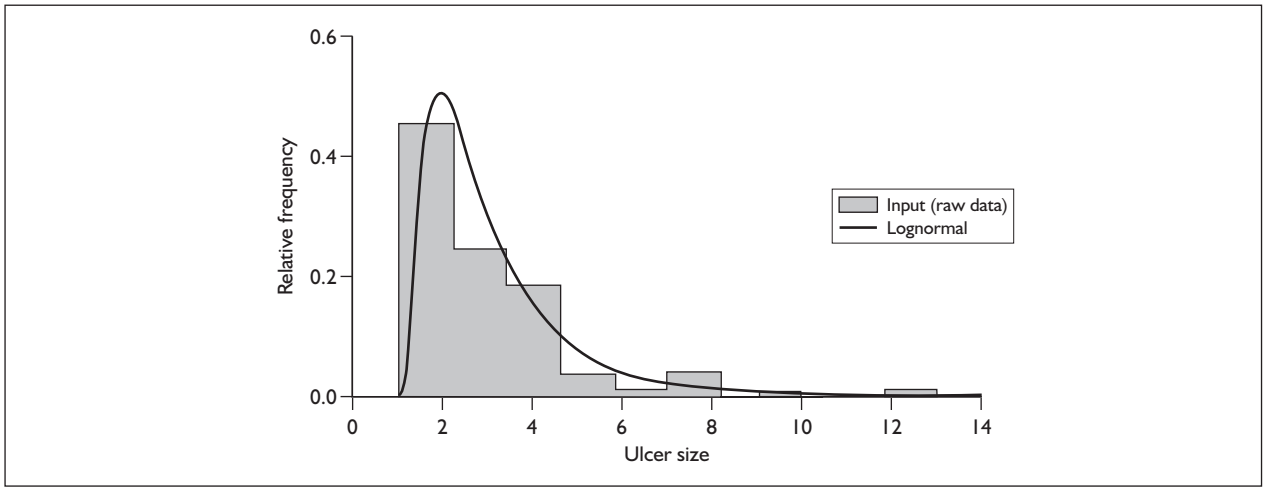


***FIGURE 10*** *Statistical distribution fitted to ulcer size for patients presenting in Sheffield.*

distributions. These were calibrated to maintain the mean value and with a similar median value, but the lower bound was zero so that the healing of an ulcer could not be associated with a decrease in utility. The best fitting distribution was chosen to replace the normal distribution.

This resulted in a Weibull distribution with a shape of 5 and a scale of 0.115 for the naive analysis, and a shape of 1.2 and a scale of 0.00267 for the alternative approach. One limitation is that the upper 95% CIs of the normal distribution were lower for the Weibull distributions than for the normal distributions. However, this was deemed preferable to having a model that was potentially clinically implausible where there was a potential for a decrease in utility on healing of the ulcer. The Weibull distribution is not bounded at 1, which could theoretically produce implausible values. To check that this was not the case, 10,000 samples from the Weibull distribution fitted for the naive analyses were drawn, with the maximum value being 0.183.

## Estimating the number of individual patients that needed to be simulated in order to provide robust answers

The analyses combined the individual time to healing from a cohort of individual patients. In the model a balance needed to be struck between too few patients and too many patients. If there were insufficient patients in the model this could result in the outcome measures being dependent on the random numbers selected and so be potentially inaccurate. Alternatively, too many patients would mean additional computational time that would provide no discernible benefit.

To investigate the likely number of patients required, an exploratory analysis examined the

***TABLE 39*** *Distributions of patient characteristics that were predictive of time to healing.*

| | Exeter | | Sheffield | |
|---|---|---|---|---|
| | **Mean** | **Alpha, beta** | **Mean** | **Alpha, beta** |
| Leg affected[a] | 0.576 | 57, 42 | 0.518 | 59, 55 |
| Gender[b,c] | 0.626 | 62, 37 | 0.465 | 53, 61 |
| Osteoarthritis | 0.313 | 31, 68 | 0.289 | 33, 81 |
| Stroke or TIA | 0.091 | 9, 90 | 0.070 | 8, 106 |
| DVT[d] | 0.131 | 13, 86 | 0.281 | 32, 82 |
| VV surgery | 0.232 | 23, 76 | 0.132 | 15, 99 |
| Ache[d] | 0.232 | 23, 76 | 0.360 | 41, 73 |
| Eczema[c] | 0.333 | 33, 66 | 0.211 | 24, 90 |
| Ankle flare | 0.697 | 69, 30 | 0.623 | 71, 43 |
| Fixed ankle[d] | 0.061 | 6, 93 | 0.237 | 27, 87 |

DVT, deep vein thrombosis; TIA, transient ischaemic attack; VV, varicose veins.
a 0 = right; 1 = left.
b 0 = male; 1 = female.
c Significantly higher rate in Exeter ($p < 0.05$).
d Significantly higher rate in Sheffield ($p < 0.05$).
The mean is defined as alpha/(alpha + beta).

relationship between the modelled average time to healing for patients presenting in Exeter and the number of patients simulated. Midpoint values were used for the model where dressing type was forced into the model as a predictive variable. The results are shown in *Figure 11*.

It can be seen that the results begin to stabilise when 60,000 patients are simulated. To ensure that we were confident sufficient patients were generated we opted to simulate 100,000 patients per simulation run.

## The scenarios modelled

A total of three scenarios were explicitly modelled, the base case plus two additional scenarios. These are detailed in *Table 40*.

## Methodology for calculating the results

The results of the modelling are presented in a variety of formats. Initially, the deterministic cost per QALY is presented, which was calculated using the mid-point values for each parameter. Probabilistic sensitivity analyses[130] were then conducted both to determine a more accurate estimate of the cost per QALY and to provide a quantification of the uncertainty in the model. These are shown using CEACs[129] and plot the probability that an algorithm will be the most cost-effective at each value for willingness to pay, from zero to £200,000 per QALY. One thousand configurations were used for the probabilistic sensitivity analyses which sampled values for the influence of each predictive variable on the time to healing in addition to the underlying Weibull distribution; these samples were undertaken using multivariate normal distribution techniques in order that the correlation between parameters was preserved within each configuration. Cost and disutility data were additionally sampled for each configuration. Provisional statistical analyses, using a willingness to pay of £20,000, showed that this number of configurations was adequate to ensure that the uncertainty in the mean cost per QALY value was not so large as to affect the decision on cost-effectiveness of the intervention.

## Model results

### Base-case scenario

In the base-case scenario dressing type did not affect healing time and so the utility decrement of an ulcer did not affect the results. In this scenario the time to healing was unaffected by the dressing used, i.e. there was no difference in healing rates between the dressings. Therefore the incremental weeks of healing provided by the antimicrobial silver dressing were zero. As the cost per week of treatment with the antimicrobial dressings was significantly more expensive, the antimicrobial

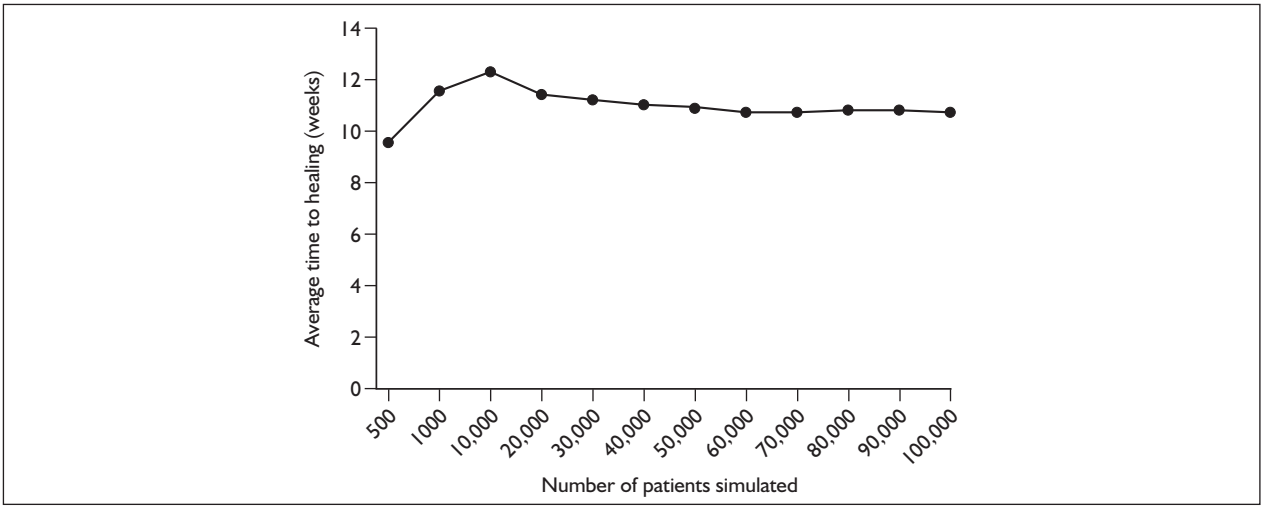


***FIGURE 11*** *The relationship between modelled average time to healing and number of patients simulated.*

***TABLE 40*** *The scenarios modelled*

| Scenario | Survival analysis | Assumed utility decrement of an ulcer |
|---|---|---|
| Base case | Only significant predictive variables were included | Not applicable as dressing type was not significant |
| 1 | Significant predictive variables were included plus dressing type even though this was not statistically significant | Mean 0.00251<br>Modelled with a Weibull with a shape of 1.2 and scale of 0.00267 |
| 2 | Significant predictive variables were included plus dressing type even though this was not statistically significant | Mean 0.10576<br>Modelled with a Weibull with a shape of 5 and scale of 0.1150 |

dressings were dominated by the control dressings. The aim of undertaking the modelling of the CEAC results allowed an assessment regarding the uncertainty surrounding the estimates.

## Scenario 1

Deterministic and stochastic results for scenario 1 are provided in *Table 41*. It can be seen that the mean cost per QALY was high at more than £600,000 per QALY for the antimicrobial dressings. Cost-effectiveness acceptability curves are provided in *Figures 12* and *13*. It can be seen that the probabilities of silver dressings having a cost per QALY below either £20,000 or £30,000 are low – 27% and 32% respectively.

## Scenario 2

Deterministic and stochastic results for scenario 2 are shown in *Table 42*. It can be seen that the cost per QALY was much reduced and was consistently below £20,000. Cost-effectiveness acceptability curves are provided in *Figures 14* and *15*. It can be seen that the probabilities of the antimicrobial silver dressings having a cost per QALY below either £20,000 or £30,000 were 53% and 62% respectively.

The results of the cost-effectiveness modelling showed that antimicrobial dressings in the baseline scenario, where only those variables that were predictive of ulcer healing were included, were not cost-effective. This was also the case in scenario 1, where the mean utility decrement of 0.00251 was used. However, scenario 2, which used the alternative method of calculating the mean utility decrement (i.e. 0.10576) and where dressing type was forced into the model, showed that antimicrobial dressings were potentially cost-effective.

## Summarising the results

These results indicate that antimicrobial dressings are highly unlikely to be cost-effective compared with control dressings. An approach of only including statistically significant predictive

***TABLE 41*** *Incremental costs and QALYs of silver dressings compared with non-adhesive dressings (per patient treated)*

| | | Incremental costs of antimicrobial dressings compared with control dressings (£) | Incremental QALYs of antimicrobial dressings compared with control dressings | Cost per QALY of antimicrobial dressings compared with control dressings (£)[a] |
|---|---|---|---|---|
| Exeter | Deterministic | 39 | $5.9 \times 10^{-5}$ | 653,000 |
| | Stochastic | 41 | $6.2 \times 10^{-5}$ | 662,000 |
| Sheffield | Deterministic | 63 | $9.7 \times 10^{-5}$ | 646,000 |
| | Stochastic | 66 | $1.0 \times 10^{-4}$ | 665,000 |

QALY, quality-adjusted life-year.
a To the nearest thousand.

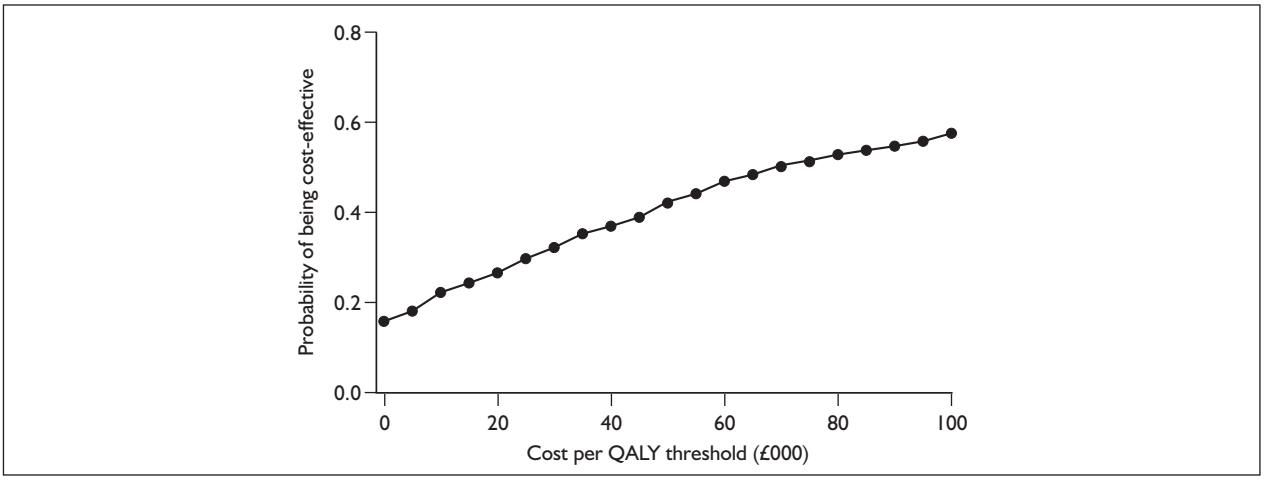


***FIGURE 12*** *Cost-effectiveness acceptability curve for Exeter demographic (scenario 1). QALY, quality-adjusted life-year.*

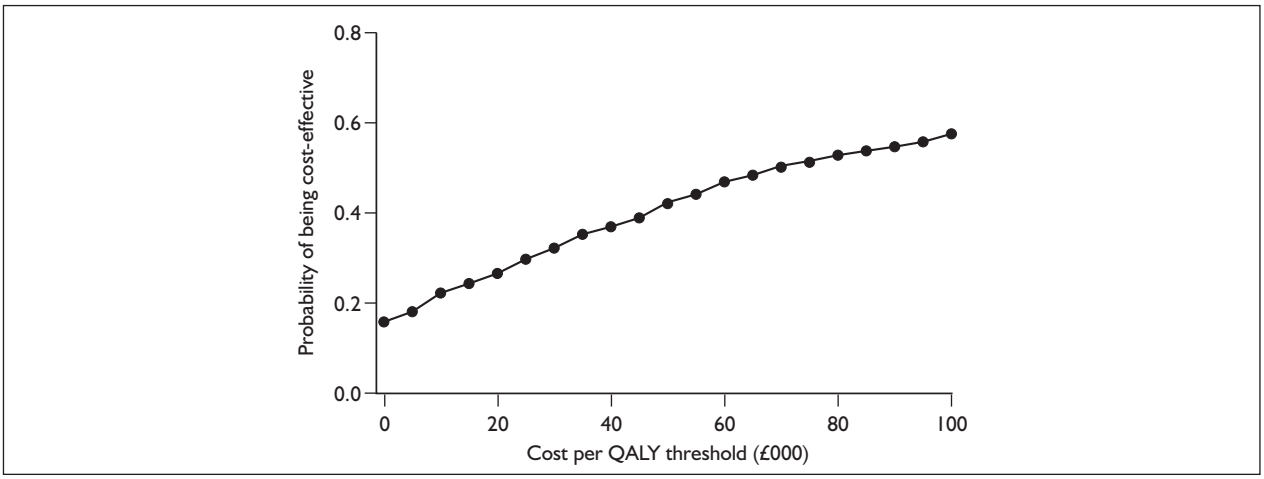


***FIGURE 13*** *Cost-effectiveness acceptability curve for Sheffield demographic (scenario 1). QALY, quality-adjusted life-year.*

variables indicates that the control dressings will always be cost-effective. When the type of dressing is used as a predictive variable the results are dependent on the utility gain associated with an ulcer healing; we believe that the gain experienced by patients who have an ulcer heal (0.00251) is most appropriate where it produces a high cost per QALY and approximately a 1 in 4 chance of being cost-effective. If the utility gain is estimated by comparing patients without an ulcer with

***TABLE 42*** *Incremental costs and QALYs of silver dressings compared with non-adhesive dressings (per patient treated)*

| | | Incremental costs of silver dressings compared with non-adhesive dressings (£) | Incremental QALYs of silver dressings compared with non-adhesive dressings | Cost per QALY of silver dressings compared with non-adhesive dressings (£)[a] |
|---|---|---|---|---|
| Exeter | Deterministic | 39 | 0.0025 | 15,500 |
| | Stochastic | 41 | 0.0025 | 16,100 |
| Sheffield | Deterministic | 63 | 0.0041 | 15,300 |
| | Stochastic | 66 | 0.0041 | 16,200 |

QALY, quality-adjusted life-year.
a To the nearest hundred.

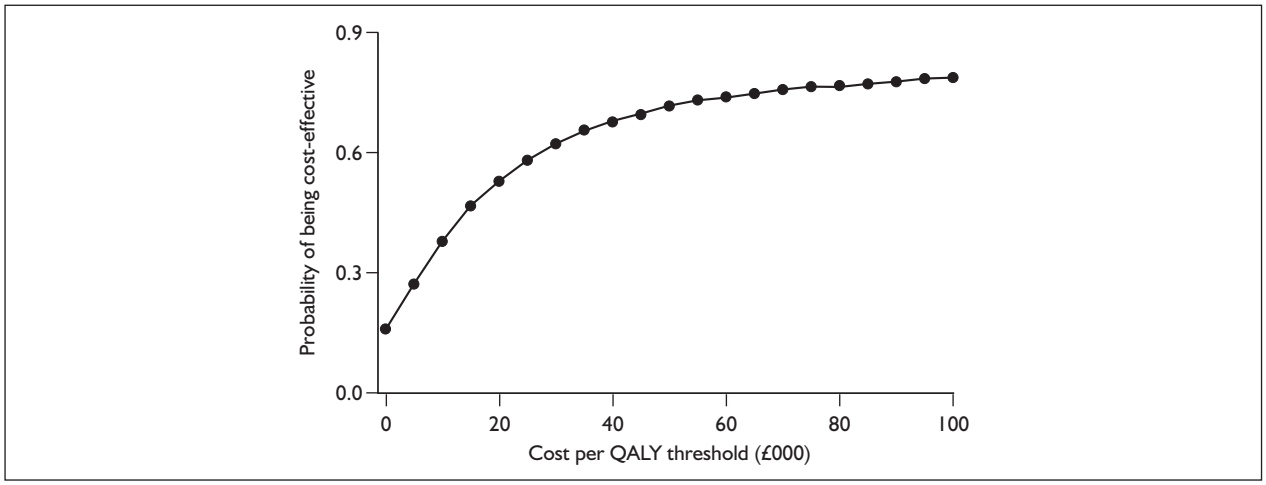


***FIGURE 14*** *Cost-effectiveness acceptability curve for Exeter demographic (scenario 2). QALY, quality-adjusted life-year.*

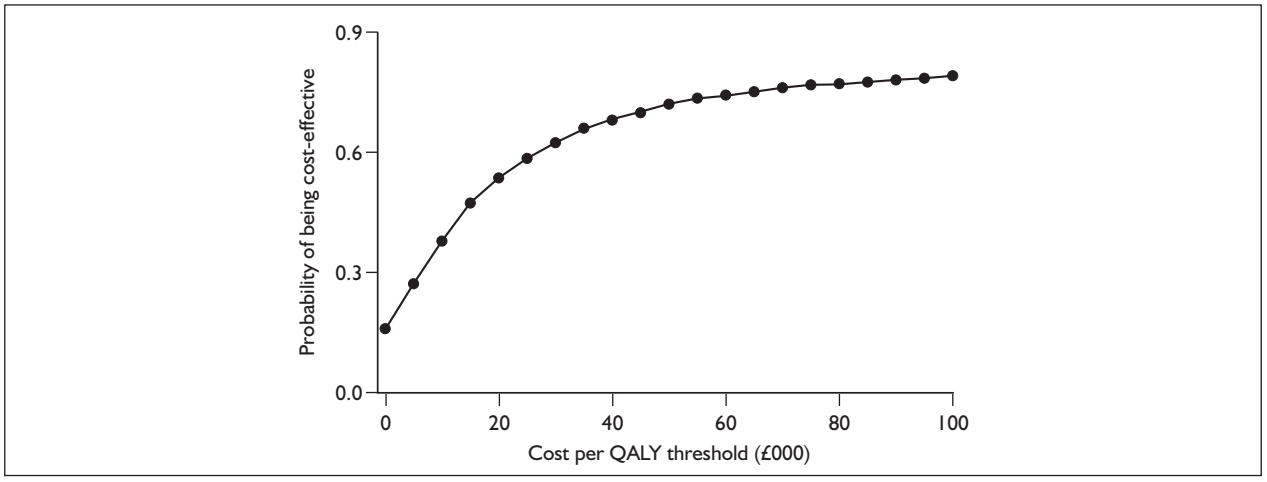


***FIGURE 15*** *Cost-effectiveness acceptability curve for Sheffield demographic (scenario 2). QALY, quality-adjusted life-year.*

those with an ulcer the gain is larger (0.10576) but potentially confounded by underlying comorbidities. It is only in this scenario that antimicrobial dressings appear to be cost-effective with a mean cost per QALY below standard thresholds used in the UK, with an estimated probability of approximately 1 in 2 of being cost-effective.

# Chapter 7
# Discussion and conclusions

This study was undertaken to inform the management of venous ulcers, which are common, distressing, and costly to the NHS.[135] Over recent years there have been significant improvements in the management of leg ulcers, in the light of research which has shown the benefits of multilayer compression bandaging.[58,59,136] There has been substantial improvement in some aspects of their treatment in recent years, based on good research evidence. In particular, there has been widespread adoption of multilayer compression bandaging with the organisation of leg ulcer services into specialist clinics and the application of bandages by nurses who have been specifically trained in their application.[58,59,136]

In contrast to the consistency of practice and good quality evidence regarding the benefits of particular bandaging methods, there is considerable variability in the use of dressings applied directly to the ulcerated area, and reviews of the evidence have shown no clear advantages for any particular dressing type.[2,113] Despite this, new and relatively expensive dressings continue to be introduced and to become widely used, with significant cost implications for health-care providers.

This trial was set up to investigate whether dressings containing antimicrobial agents have any advantages for the most clinically important end point – the healing of venous leg ulcers. The current published evidence relating to the silver dressings is related to the antibacterial effects of silver from in vitro studies on experimental wounds.[4] The mechanism of action of silver in vitro through ionic silver salts ($Ag^+$) and the attraction of the positively charged silver ions to bacterial membranes have been detailed.[4,87] What is not known is how this affects the healing of a venous ulcer on a 'real' patient. The dressings may reduce the bacterial count, but this may not have any effect on healing or the action of the silver may inhibit healing. In the end what matters to the patient is whether their ulcer heals and if adding a silver dressing will facilitate this or speed it up.

At the time of developing the protocol there was evidence of widespread adoption of silver-containing dressings that were being marketed for use in venous leg ulcers. These had been shown to exhibit antimicrobial activity,[3,95] but there was no convincing evidence that they improved healing or other clinical outcomes.[137] In addition, there was some evidence suggesting that silver dressings might induce rapid death of cells that are involved in wound healing.[138]

In view of the increased market share of silver-donating dressings and decreasing use of other antimicrobials that had previously been widely used, such as povidone iodine, the study focused on silver-donating antimicrobial dressings. The decision to include all silver-donating dressings rather than choosing a specific dressing was a pragmatic one, in that widespread promotion and adoption had resulted in different practices and preferences among district nurses responsible for managing leg ulcers. Initial discussions suggested that recruitment would be hampered if the choice of dressing was restricted to a single product.

The key finding of the study has been that there was no significant difference between the use of silver-donating antimicrobial dressings and non-adherent dressings without any antimicrobial agent, in either the primary or any of the secondary end points. Overall healing rates in the RCT were 58% at 12 weeks, 81% at 6 months and 96% at 1 year with a median time to healing of 67 days for the antimicrobial dressings and 58 days for the control group. The findings in relation to the lack of benefit from silver antimicrobial dressings were robust, with no suggestion of particular dressing types or population subgroups for whom the dressings were beneficial.

The overall rate of healing in this study compares favourably with previous studies.[2,18,136] A study by Morrell *et al.*[57] that was carried out in one of the same regions as and in a similar population to the current study showed a 12-week healing rate in the treatment group (treated in community leg ulcer clinics) of 34%. This study had been carried out over 10 years earlier, so the comparatively low healing rate compared with the current study may be explained by advances in leg ulcer management. These have included the production of national and local guidelines which recommend early intervention by compression bandaging

applied by nurses with appropriate training.[6] Such improvements have been documented following the introduction of specialist clinics elsewhere.[139] In addition, studies suggest reductions in overall prevalence of venous leg ulcers,[5,140] although this has not been a universal finding.[141]

With regard to the study population, there were some exclusions, including screening of ABPIs and exclusion of patients with comorbidities such as diabetes, which might also have resulted in the recruitment of a population with an improved chance of healing. However, other recent studies, such as a trial of honey-impregnated dressings, had similar exclusion criteria and used similar compression bandaging, with similar rates of healing to the current study.[109] Moreover, exclusion of patients with reduced ABPIs is usual in everyday practice.

Our study showed a low recurrence rate compared with some previously published reports; only 12% of those who healed had recurrence of their ulcers by the end of the first year. Once again this may be related to changes in practice – specifically the widespread use of compression hosiery after initial ulcer healing.[62,142]

The study found substantial differences between the population and the healing rates in the two participating centres. This may relate partly to demographic and social differences: the population in South Yorkshire had a higher proportion of men, lower average patient age and greater rates of comorbidities associated with poorer healing rates. There are likely to be other socioeconomic differences that were not recorded in the study as well as some differences in service provision. There is evidence elsewhere for regional differences in prevalence and healing of venous leg ulcers.[139–141]

One of the difficulties that was encountered in the trial was the recruitment of patients and this was largely related to the reconfiguration of services. South Yorkshire underwent major changes in the provision of community services with a revision of the PCT structure and a reduction in the number of district nurses during the trial. This had a significant impact on morale and recruitment to the trial. It also led to changes in the provision of ulcer services with some management being returned to the care of practice nurses, as opposed to treatment in specialist clinics. Thus a larger number of nurses, each having less experience in the condition, would have been managing leg ulcers. Although it was not possible to determine whether this may have affected healing rates within this trial, concern has been expressed that care for venous ulcer patients by practice nurses is less than optimal.[143] In addition, studies have suggested that better healing rates can be obtained by more specialised services focused on specialist community clinics.[57]

During the trial there were no adverse events that were identified as being related to the dressing. Owing to the multiple comorbidities in this population there were numerous other medical events, including ischaemic heart disease, pulmonary disease, cancer and thromboembolic disease. These events were as might be expected in this population and, other than one patient in whom a silver dressing was stopped because of redness of the wound, there was nothing to suggest any specific complications of the treatment. Sensitivity to silver products has rarely been reported,[87] and was not seen within the trial or cited as a reason for exclusion of any initial patients during the recruitment period.

The cost analysis demonstrated a significantly higher cost for the group of patients treated with silver antimicrobial dressings. Detailed analysis of the cost differences showed that this was partly due to the increased cost of the dressings themselves, but also in part due to the increase in the number of dressing changes in the antimicrobial group. This was related to an increase in the frequency of dressing changes, rather than a longer duration of dressings.

The protocol of the study called for weekly dressing changes, but it was left to the discretion of the nurse responsible for the dressings to decide if more frequent dressings were required, and it would appear to be the case that more frequent dressing changes were used in the antimicrobial group. The reasons for more frequent dressing changes in the antimicrobial dressings group were not clear: they may have been related to some concerns about the duration of activity of the antimicrobial agent, concern about the level of exudate, discomfort or other symptoms. Whatever the reasons, they were not sufficient to alter the overall outcomes.

## Quality of life

This study demonstrated some of the difficulties in measuring QoL in patients with venous leg ulceration. While it is clear that patients put considerable value on obtaining healing of their ulcers, the conventional generic QoL measures

appear to be quite insensitive to the effects of ulcer healing.[48,144] This may reflect the fact that in this elderly group with significant comorbidities the disutility largely depends upon the underlying condition rather than the presence of ulceration. The development of a disease-specific measure for QoL, particularly for patients with leg ulcers, might provide greater sensitivity to assess significant differences in outcome in this group of patients.

The study demonstrated a difference in utility, as measured by the EuroQol tariff, between the healed and unhealed patients at the end of 3 months of approximately 0.1. This is in keeping with values that have been found in previous studies using generic scales[144] and similar values have been used in previous cost-effectiveness studies.[145] However, the comparisons of utility between healed and unhealed patients within such studies may reflect confounding due to the poorer healing among those with multiple comorbidities, rather than real differences due to the healing of the ulcer.

One way to try to eliminate this effect is to restrict analysis to paired data considering differences in the change in utility between those who do or do not heal. This results in a much smaller utility difference that does not reach statistical significance. It is likely that these calculations are an oversimplification because changes in QoL related to leg ulcer healing are not a sudden stepwise change at the point of healing, but are likely to be related to the ulcer symptoms and may improve gradually during the healing process.

The evidence from the generic HRQoL scores, particularly the SF-36, is inconclusive in that there was no strong evidence for particular dimensions that are affected by leg ulceration, that distinguished between those treated with antimicrobial or inert dressings or that correlated with the healing of leg ulcers. Previous evidence of QoL estimates in patients with leg ulceration has been of poor quality[26] and the previous use of generic questionnaires suggests that they are not sensitive to the healing of leg ulcers.[48] One explanation may be because the utility associated with leg ulceration is relatively small compared with the other comorbidities that are experienced by this group of patients. However, it may also be that the questionnaires are insensitive to factors that determine QoL in patients with leg ulcers. Such factors may not be included in the items addressed by these health status measures, which have been developed largely on the basis of medical opinion rather than on patient preference studies.[146]

With the clinical outcomes showing no evidence of significant benefit in either healing rate or QoL, and the cost analysis showing the incremental cost of nearly £100 associated with the use of antimicrobial dressings, the economic analysis alongside the clinical trial shows a low probability that the intervention is cost-effective. The analysis of the data collected clearly showed that, compared with non-adherent dressings, antimicrobial dressings resulted in a significant increase in costs and a non-significant change in QALYs.

## Cost-effectiveness modelling

The modelling was carried out to allow a more detailed examination of the determinants of cost-effectiveness and the exploration of areas where there was significant uncertainty in the evidence that would benefit from further research. As with the economic analysis alongside the clinical trial, the base case of the modelling showed the antimicrobial dressings to be dominated by inert dressings, with there being no difference in clinical outcomes and a higher cost associated with the antimicrobial dressings.

In a sensitivity analysis, the dressing type was included in the model, even though it was not a statistically significant predictor of healing, and a small benefit in utility was assumed to occur at the point of healing, based upon the differences in changes of EQ-5D generated utilities. Although this resulted in a small average incremental benefit for the antimicrobial dressings, it was not sufficient to justify the additional cost and there remained a high probability that the treatment was not cost-effective.

It was only when further scenarios were examined which used maximum estimates of utility benefit from ulcer healing, based upon differences in utility that did not allow for the confounding effects of comorbidities, that some estimates of incremental cost-effectiveness were obtained that were within a generally accepted range of cost-effectiveness.

## Conclusions

This analysis demonstrates some of the difficulties that arise in appraising technologies for the treatment of venous leg ulcers. The overall cost-effectiveness of a new technology that is aimed to

improve the healing of leg ulcers depends upon four main drivers:

- the incremental cost of the new technology
- the incremental benefit in terms of earlier healing
- the improvement in utility associated with healing of the ulcer
- any differences in utility during the treatment period that are associated with the different treatments.

In this particular study there was no evidence of earlier healing or differences in utility between the groups in the treatment period. Both this study and earlier work[57] have failed to demonstrate clear evidence of a utility benefit associated with ulcer healing. While this study and previous work[144] have used generic measures to estimate a benefit of approximately 0.1 in utility for ulcer healing, there is considerable doubt about the validity of the scales used in assessing this utility and the methodology has not provided correction for possible confounding due to comorbidities. These issues may affect the estimate in opposite directions and further work is required to provide more valid estimates of the changing utility that can be used for future modelling.

If the alteration in utility were in the order of 0.1 and the net benefits of earlier healing in financial and health terms are added together, then even small alterations in time to healing may justify the cost of new treatments if the costs are a relatively small proportion of the overall cost of leg ulcer management. Under these circumstances a trial that was adequately powered to detect a difference in healing rate that might prove cost-effective would require a very large sample size that would be difficult to achieve. Before undertaking further large and expensive clinical studies in this area it would be beneficial to carry out utility studies to quantify the benefits of ulcer healing and guide the design and sample size estimation for such trials. Such work may require the development of new generic or disease-specific measures that have a better face validity in assessing the health impact of leg ulceration.

Antimicrobial dressings have been widely adopted without positive clinical evidence and our survey suggests that silver-donating antimicrobial dressings are currently used in approximately 40% of cases. If this reflects national practice, then the implication is that the NHS could be spending several million pounds on dressings each year with no evidence of clinical benefit.

While it is not possible to generalise the results of this particular study to all antimicrobial agents or other wound aetiologies, its findings are in tune with other evidence that shows no benefit from antimicrobials in the healing of ulcers. Two recent systematic literature reviews have failed to demonstrate any evidence to suggest that any particular class of antimicrobial agent has a significant benefit.[2,113] In addition, a recent major randomised study of another group of antimicrobial dressings, honey-impregnated dressings, has also shown no significant improvement in venous ulcer healing from the use of antimicrobial dressings.[109]

In the light of all this evidence there is little to support the use of antimicrobial dressings in the treatment of venous leg ulcers. It would therefore seem logical to use the least expensive, inert dressings beneath compression therapy as standard care.

## Implications for health care

1. Based on the results of this trial, there is no indication for the regular use of silver-donating dressings beneath compression in the treatment of venous ulcers: the evidence has shown no advantages over less expensive non-adherent dressings.
2. The trial supports the use of compression bandaging for the healing of venous ulcers, with application of non-adherent dressings (without any antimicrobial component) to the ulcerated areas.
3. Viewed in the light of trial data on other antimicrobial dressings, the results suggest that there is no indication for the regular use of antimicrobial dressings in general in promoting the healing of venous ulcers.
4. The finding of very widespread use of silver-donating dressings, shown by this trial not to be cost-effective, should stimulate the NHS to encourage and to facilitate recruitment of patients to large, well-designed studies of new technologies before they disseminate in an uncontrolled way.
5. This trial has demonstrated a number of the bureaucratic, organisational and cultural obstacles to research, which need to be addressed centrally for improved development of cost-effective services in the long term. In particular, effective mechanisms for engaging frontline clinical staff with the NHS research agenda are urgently required.

## Recommendations for future research

1. The differences in healing rates between the two geographical areas of this study have implications for future research. They emphasise the need for very clear descriptions of epidemiology, treatment methods and the experience of staff engaged in compression bandaging; and they suggest an advantage to multicentre studies in different geographical areas, to produce results which can reasonably be generalised to the population as a whole.
2. It is recommended that research into new treatments for leg ulcers includes mathematical modelling to establish the potential value of further clinical trials, and to assist in appropriate trial design prior to undertaking large and expensive clinical trials.
3. This study has not addressed the problems of ulcers that fail to heal after 12 weeks of compression, or the problem of patients who are unable to tolerate compression. It is uncertain whether antimicrobial dressings might have any advantages in either of those situations. Uncertainty also remains about the diagnosis of 'infection' in leg ulcers which might be relevant to the use of antimicrobials. These are complex areas for research, but more information would be useful to guide clinical practice.
4. Further work is required in order to identify and validate QoL measures for use in the venous ulcer population. The development of a disease-specific QoL measure for venous ulcer patients that can be used in economic evaluation may be an area for future studies. The currently available generic measures seem insufficiently sensitive to the impact on QoL associated with venous ulceration.
5. The choice of dressing applied within the silver-donating and control groups showed geographical variation even though there are comprehensive national and local guidelines available. Further studies are needed on how clinicians make decisions regarding dressing type and, in particular, the influence of sales representatives as sources of evidence and guidance.

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## Contribution of authors

Jonathan Michaels (Professor of Vascular Surgery) designed the study, obtained funding, analysed trial data and contributed to writing the final report. Bruce Campbell (Consultant Vascular Surgeon and Professor) helped in the design of the study and obtaining funding, developed and conducted the surveys, and contributed to the writing and editing of the final report. Brenda King (Tissue Viability Nurse Specialist) conducted the surveys and contributed to writing the final report. Jackie MacIntyre (Research Nurse) conducted the surveys, collected data, contributed to writing the final report and was responsible for the day to day running of the trial in the Exeter region. Simon Palfreyman (Senior Research Nurse) conducted the surveys, collected and analysed data, contributed to the writing and editing of the final report, and was Project Manager for the trial. Phil Shackley (Senior Lecturer Health Economics) undertook the economic evaluation, analysed data and contributed to the writing of the final report. Matt Stevenson (Senior Operational Research Analyst/Health Economics and Decision Science) undertook the economic and mathematical modelling and contributed to the writing of the final report.

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# Appendix 1

## CONSORT statement checklist

| Paper section and topic | Item | Descriptor | Reported on page no. |
|---|---|---|---|
| ***Title and abstract*** | | | |
| | 1 | How participants were allocated to interventions (e.g. 'random allocation', 'randomised' or 'randomly assigned') | iii |
| ***Introduction*** | | | |
| Background | 2 | Scientific background and explanation of rationale | 1–8 |
| ***Methods*** | | | |
| Participants | 3 | Eligibility criteria for participants and the settings and locations where the data were collected | 18 |
| Interventions | 4 | Precise details of the interventions intended for each group and how and when they were actually administered | 19–20 |
| Objectives | 5 | Specific objectives and hypotheses | 18 |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors) | 20 |
| Sample size | 7 | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules | 18–19 |
| Randomization – sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restrictions (e.g. blocking, stratification) | 19 |
| Randomisation – allocation concealment | 9 | Method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned | 19 |
| Randomisation – implementation | 10 | Who generated the allocation sequence, who enrolled participants and who assigned participants to their groups | 19 |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated | 19 |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses | 23 |

*continued*

| Paper section and topic | Item | Descriptor | Reported on page no. |
|---|---|---|---|
| ***Results*** | | | |
| Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons | 25 |
| Recruitment | 14 | Dates defining the periods of recruitment and follow-up | 25 |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group | 26 |
| Numbers analysed | 16 | Number of participants (denominator) in each group included in each analysis and whether the analysis was by 'intention-to-treat'. State the results in absolute numbers when feasible (e.g. 10/20, not 50%) | 27 |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% confidence interval) | 28–42 |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory | 26–36 |
| Adverse events | 19 | All important adverse events or side effects in each intervention group | 26 |
| ***Discussion*** | | | |
| Interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes | 57 |
| Generalisability | 21 | Generalisability (external validity) of the trial findings | 59 |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence | 57–61 |

# Appendix 2
## STROBE checklist

| | Item | Recommendation | Reported on page no. |
|---|---|---|---|
| ***Title and abstract*** | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | iii |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | iii |
| ***Introduction*** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 1–8 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 18 |
| ***Methods*** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 17–23 |
| Setting | 5 | Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection | 17 and 23 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 18 |
| | | (b) For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable | 20–21 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 28–42 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 19 |
| Study size | 10 | Explain how the study size was arrived at | 18–19 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 23 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | 23 |
| | | (b) Describe any methods used to examine subgroups and interactions | 21 |
| | | (c) Explain how missing data were addressed | 22–23 |
| | | (d) If applicable, explain how loss to follow-up was addressed | 27 |
| | | (e) Describe any sensitivity analyses | 29–36 |

*continued*

| | Item | Recommendation | Reported on page no. |
|---|---|---|---|
| ***Results*** | | | |
| Participants | 13 | (a) Report numbers of individuals at each stage of study (e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) | 36/37 |
| | | (b) Give reasons for non-participation at each stage | n/a |
| | | (c) Consider use of a flow diagram | n/a |
| Descriptive data | 14 | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders) | 37 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 36–42 |
| | | (c) Summarise follow-up time (e.g. average and total amount) | 36–42 |
| Outcome data | 15 | Report numbers of outcome events or summary measures over time | 36–42 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 36–42 |
| | | (b) Report category boundaries when continuous variables were categorised | 36–42 |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n/a |
| Other analyses | 17 | Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses) | n/a |
| ***Discussion*** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 57 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 57–59 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence | 57–59 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 59 |
| ***Other information*** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | n/a |

n/a, not applicable.

# Appendix 3
## Assessment forms

## Baseline assessment form

# LEG ULCER ASSESSMENT FORM

**TRIAL ID:** **VISIT: Initial/3 months/6 months**

**NEW REFERRALS & PRIOR TO COMPRESSION THERAPY**

(CIRCLE APPROPRIATE RESPONSES)

**PERSONAL DETAILS**
**TRIAL ID:** _____
NAME _____
ADDRESS _____
_____
_____POSTCODE _____
DOB _____ TEL NO. _____
MALE/FEMALE_____
**MEDICAL HISTORY**

| | | |
|---|---|---|
| ANAEMIA | YES | NO |
| DIABETES MELLITUS | YES | NO |
| OSTEOARTHRITIS | YES | NO |
| RHEUMATOID ARTHRITIS | YES | NO |
| HYPERTENSION | YES | NO |
| CARDIAC FAILURE/MI | YES | NO |
| STROKE/TIA | YES | NO |

OTHER/ILLNESSES/OPERATIONS_____
_____

DATE _____
GP _____
SURGERY _____
_____
_____ POSTCODE _____
ASSESSOR:
_____DN/PN/CNS
CONTACT NO: _____
_____
__

| | | | |
|---|---|---|---|
| PREVIOUS ULCERATION | R | L | NO |
| VARICOSE VEINS | R | L | NO |
| DEEP VEIN THROMBOSIS | R | L | NO |
| VEIN SURGERY/INJECTION | R | L | NO |
| PHLEBITIS/CELLULITIS | R | L | NO |

FAMILY HISTORY YES/NO
**MEDICATION** _____
_____
_____
_____

ALLERGIES/SENSITIVITIES_____
_____
MOBILITY: HOUSEBOUND/50 MTRS/1 MILE/NOT RESTRICTED
**ULCER PAIN :** CONTINUOUS/INTERMITTENT/ONLY AT DRESSING TIME

SMOKER YES/NO
(If yes amount per day) _____
EX SMOKER YES/NO
SLEEP CHAIR BED

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| HISTORY OF SWOLLEN LEG | R | L | NO | ACHING LEGS | R | L | NO |
| INTERMITTENT CLAUDICATION | R | L | NO | REST PAIN | R | L | NO |

**SIGNS**

| | | | |
|---|---|---|---|
| OBVIOUS VARICOSITIES | R | L | NO |
| OEDEMA | R | L | NO |
| ECZEMA (VENOUS) | R | L | NO |
| STAINING | R | L | NO |
| INDURATION | R | L | NO |
| ATROPHIE BLANCHE | R | L | NO |
| ANKLE FLARE | R | L | NO |
| SHINY TAUT SKIN | R | L | NO |
| FOOT WHITE ON ELEVATION | R | L | NO |
| FOOT DUSKY ON DEPENDENCY | R | L | NO |
| PRESENCE OF GANGRENE | R | L | NO |
| ANKLE FIXED | R | L | NO |
| HIP FIXED | R | L | NO |

_____
DIET: NORMAL/POOR/INADEQUATE/SPECIAL
WEIGHT: LOSING/STATIC/GAINING
BLOOD SUGAR _____ MMOLS
ANKLE CIRCUMFERENCE: R_____L_____ CM

**ULCER DETAILS** R L
DURATION OF ULCER(S) _____
CURRENT SITE(S) _____
_____

| | | |
|---|---|---|
| SLOUGH | R | L |
| NONE | | |
| NECROSIS | R | L |
| NONE | | |
| GRANULATION | R | L |
| NONE | | |
| EPITHELIALIZING | R | L |
| NONE | | |
| EXUDATE | R | L |
| NONE | | |

AMOUNT/COLOUR
_____

| | | |
|---|---|---|
| ODOUR | R | L |
| NONE | | |

SWAB TAKEN YES

CALF CIRCUMFERENCE: R_____L_____ CM

**ULCER SIZE** (select largest ulcer)
MAXIMUM WIDTH: R_____ L _____CM
MAXIMUM HEIGHT: R _____ L _____ CM

**VISITRAK MEASUREMENT**:-
RIGHT: Area _____Width _____ Height _____
LEFT: Area _____ Width _____ Height _____

DRESSING CHOSEN R _____
L _____

**STORE THIS COPY WITH TREATMENT CARE PLAN**

NO
**BLOOD PRESSURE** _____
**DOPPLER ASSESSMENT**
(Divide ankle by highest brachial systolic pressure)
BRACHIAL SYSTOLIC PRESSURE R _____ L _____

ANKLE SYSTOLIC PRESSURE
**Right**: Dorsalis Pedis _____ Posterior Tibial _____
Signal M / B / T Signal M / B / T
**Left**: Dorsalis Pedis _____ Posterior Tibial _____
Signal M / B / T Signal M / B / T
(Signal: M=Monophasic B= Bi-phasic T=Tri-phasic)

ANKLE PRESS. INDEX R _____ L _____
**DIAGNOSIS: R _____ L _____**
REFERRAL TO:-GP/Consultant/Tissue Viability
PATIENT INFO LEAFLET GIVEN YES NO
BANDAGE COMBINATION: R _____
L _____
**HEAL DATE: RIGHT _____ LEFT _____**

## Weekly assessment form

**LEG ULCER EVALUATION FORM**

**PATIENT NAME:** **TRIAL ID:** **LEG:**
**LEFT/RIGHT**

**Trace wound every 4 weeks.** ***Note:*** **Condition of skin, plot area of granulation, slough and necrotic tissue on the tracing.**

| **Date:**<br>**Visit Number:** | | | | |
|---|---|---|---|---|
| **Has bandage slipped** | **YES / NO** | **YES / NO** | **YES / NO** | **YES / NO** |
| **Previous Dressing:**<br>**BATCH NO.**<br><br>**Dressing:**<br>**Primary**<br>**Frequency of change** | | | | |
| **Nature of Wound bed:**<br>Healthy granulation<br>Epithelialisation<br>Slough<br>Necrotic tissue over granulation | *(Circle all that apply)*<br>Healthy granulation<br>Epithelialisation<br>Slough<br>Necrotic tissue over granulation | *(Circle all that apply)*<br>Healthy granulation<br>Epithelialisation<br>Slough<br>Necrotic tissue over granulation | *(Circle all that apply)*<br>Healthy granulation<br>Epithelialisation<br>Slough<br>Necrotic tissue over granulation | *(Circle all that apply)*<br>Healthy granulation<br>Epithelialisation<br>Slough<br>Necrotic tissue over granulation |
| **Exudate**<br>Colour<br>Strike through | **YES / NO** | **YES / NO** | **YES / NO** | **YES / NO** |
| **Odour YES / NO** | **YES / NO** | **YES / NO** | **YES / NO** | **YES / NO** |
| **Pain:**<br>Continuous/intermittent /only at dressing time<br>Scale 0 - 10 = | *Please circle*<br>continuous/intermittent /only at dressing time<br>Scale 0 - 10 = | *Please circle*<br>continuous/intermittent /only at dressing time<br>Scale 0 - 10 = | *Please circle*<br>continuous/intermittent<br>/only at dressing time<br>Scale 0 - 10 = | *Please circle*<br>continuous/intermittent/ only at dressing time<br>Scale 0 - 10 = |
| **Condition of Surrounding Skin:**<br>Wet eczema<br>Dry eczema<br>Healthy<br>Maceration<br>Oedema/oozing serous fluid | *Please circle*<br><br>Wet eczema<br>Dry eczema<br>Healthy<br>Maceration<br>Oedema/oozing serous fluid | *Please circle*<br><br>Wet eczema<br>Dry eczema<br>Healthy<br>Maceration<br>Oedema/oozing serous fluid | *Please circle*<br><br>Wet eczema<br>Dry eczema<br>Healthy<br>Maceration<br>Oedema/oozing serous fluid | *Please circle*<br><br>Wet eczema<br>Dry eczema<br>Healthy<br>Maceration<br>Oedema/oozing serous fluid |
| **Leg Re-shaping** | *please circle*<br>**Ankle/Calf/Shin** | *please circle*<br>**Ankle/Calf/Shin** | *please circle*<br>**Ankle/Calf/Shin** | *please circle*<br>**Ankle/Calf/Shin** |
| **Bandage regime** | Standard 4-layer<br>Short stretch<br>Other | Standard 4-layer<br>Short stretch<br>Other | Standard 4-layer<br>Short stretch<br>Other | Standard 4-layer<br>Short stretch<br>Other |
| **Visitrak tracing taken** ***(Take 4-weekly)*** | **YES/NO** | **YES/NO** | **YES/NO** | **YES/NO** |
| **New medication**<br><br>**<u>Adverse Events</u>**<br>**Describe** | **YES/NO** | **YES/NO** | **YES/NO** | **YES/NO** |
| **Referral to CNS/GP**<br><br>**Referral to Consultant** | **YES/NO (Date)**<br><br>**YES/NO (Date)** | **YES/NO (Date)**<br><br>**YES/NO (Date)** | **YES/NO (Date)**<br><br>**YES/NO (Date)** | **YES/NO (Date)**<br><br>**YES/NO (Date)** |

| | | | | |
|---|---|---|---|---|
| **In Patient Stay (Reason)** | | | | |
| **Dressing Management Rationale for change** | **Changed / continued** | **Changed / continued** | **Changed / continued** | **Changed / continued** |
| **Heal Date** | | | | |
| **Wound Assessed by** | **CNS / DN / Res N** | **CNS / DN / Res N** | **CNS / DN / Res N** | **CNS / DN / Res N** |

# Appendix 4

## Survey questionnaires

**Survey questionnaire on leg ulcer services in the UK**

**Is there a dedicated leg ulcer service in your locality?** Yes ☐ No ☐

**If Yes,** Is it based in hospital or in the community?

And who supervises it? ***Name:***
***(Details of whom to contact, please)*** ***Address:***

Is it "shared" by any other Acute Trust Yes ☐ No ☐

If Yes, which?

**If there is <u>NO</u> dedicated leg ulcer service in your locality**, how are leg ulcers dealt with? Please write overleaf or in a separate letter.
**THANK YOU.**

**Questionnaire about venous ulcer services**

**1. Is there any specially organised service for treating venous ulcers in your area?**

**Yes** ☐ **No** ☐

***If Yes**, please go to <u>question 2</u> and complete the rest of this questionnaire.*

***If No**, please could you let us know on a separate sheet how venous ulcers are dealt with in your area. There is no need to complete any other questions. Thank you.*

**2. Is the venous ulcer service a single, integrated service, or is there more than one** different service in operation?

**a)** Single integrated service ☐

**b)** More than one service ☐

***If*** more than one service: How many?

Who supervises each? (Please give contact details)

We would welcome as much information as you are prepared to give about the different services; how and where they operate; and the degree of coordination/collaboration between them.

**For the remainder of the questions, please give details of the service with which you are personally involved.**

| **3. Is your venous ulcer service based in:** (mark one box only) | | **Do you have "out-reach" services in….** (mark as many boxes as apply) |
|---|---|---|
| **a)** Acute hospital (which department?) | ☐ | ☐ |
| **b)** Community hospitals | ☐ | ☐ |
| **c)** General practice surgeries | ☐ | ☐ |
| **d)** Other (please state) | ☐ | ☐ |

**4. What population (number of people) does your venous ulcer service serve?** Is it based on acute Trust catchment areas, PCTs, other ?

**5. Is your service managed by an acute Trust or PCTs?** Which one?

**6. Staffing:**

**a) Who is the clinician in overall charge of your venous ulcer service (probably you)?** (Name and specialty)

**b) What other medical and nuring staff are involved?** (Their discipline, grade and how many full time equivalents?)

**7. Do you use written guidelines for management of venous leg ulcers?**

Yes ☐ No ☐

***If Yes:*** **PLEASE SEND A COPY OF YOUR GUIDELINES**

**a)** Were these guidelines developed locally? **Yes** ☐ **No** ☐

***If Yes***: Were they based on existing guidelines from elsewhere?

**Which one?**

**8. How are patients referred to the service?** (Mark as many boxes as apply)

**a)** From practice/community nurses ☐
**b)** From general practitioners ☐
**c)** From hospital consultants ☐
**d)** Other ☐

***If other,*** who?_____

**9. How are patients selected for referral to vascular surgeons?**

**10. <u>Measurement of ankle Doppler systolic pressure indices</u>:**

**In primary care:** Who undertakes measurement of Doppler ankle pressures?

How are they trained?

**11. <u>Multi-layer compression bandaging:</u>**

**In primary care:** Who undertakes multi-layer compression bandaging?

How are they trained?

12. We are particularly interested in the use of topical antimicrobial agents used in the treatment of venous ulcers:

**a) How often are topical antimicrobial agents used in your service?**

(Mark one box only, please)

Never ☐
Rarely ☐
About half the ulcers ☐
Frequently (>50%) ☐
Always ☐

Please name the ones you use? (In rank order of use, as best you can):

| |
|---|
| |

**b) How often have patients referred to your service been treated with topical antimicrobials before seeing you?** (Mark one box only, please)

Never ☐
Rarely ☐
About half the ulcers ☐
Frequently (>50%) ☐
Always ☐

Please name the ones used? (In rank order of use, as best you can):

| |
|---|
| |

**13. <u>Audit</u>:**

**a) Have you a database of the patients treated by your service?**

**Yes** ☐ **No** ☐

b) How many patients are seen in your service:

As new referrals each week?

As follow-up attendances each week?

In total each year (patients, not attendances)?

Are these figures: **An estimate?** ☐ **Based on audit?** ☐

**THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.**
**PLEASE DO INCLUDE ANY OTHER COMMENTS OR INFORMATION ON SEPARATE SHEETS.**
***PLEASE REMEMBER TO ATTACH ANY GUIDELINES YOU USE (see Question 7)***

*Survey of Venous ulcer services in the UK.*
*Bruce Campbell (09.09.03)*

## Survey questionnaire on use of silver and other antimicrobial products

**TISSUE VIABILITY SERVICE**

**Use of Silver Products**

[Introduction]

1. Do you use dressings that contain silver? ❑ Yes ❑ No

2. Please tick all the dressings you have heard of that contain silver:

❑ Acticote Range ❑ Contreet Range ❑ Other (please state)

❑ Urgutol SSD ❑ Silver Cell

……

❑ Aquacel AG ❑ Actisorb Silver

……

3. Do you use any other antimicrobial/antiseptic dressing? ❑ Yes ❑ No

4. Can you list any other type of antimicrobial/antiseptic dressing?

.....

.....

5a. Which is your favourite dressing that contains silver?

.....

5b. Does this product donate silver to the wound? ❑ Yes ❑ No ❑ Unsure

5c. Why would you choose this particular product?

.....

.....

6. Please indicate how many patients you have used a silver dressing on within the last month?

❑ 0 - 3 Patients ❑ 7 - 10 Patients ❑ 16+ Patients

❑ 4 - 6 Patients ❑ 11 - 15 Patients

7. Please indicate the type of wound you would use silver products on:

❑ Venous Ulcer ❑ Diabetic Foot Ulcer ❑ Other (please state)

❑ Arterial Ulcer ❑ Post Operative Surgical

……

8. Thinking about the last patient you used a silver product on, please list the reasons for using it:

.....

.....

9a. Have you seen/read any research/evidence/information about this particular product?

❑ Yes ❑ No

9b. Please state the source of this information:

❑ Journal ❑ Colleague ❑ Other (please state)

❑ Company Literature ❑ Conference

……

9c. If you have ticked 'Journal' to question 9b, please state which:

.....

10a. Have you received any education on the use of topical antimicrobials/antiseptics?

❑ Yes ❑ No

10b. What education have you received?

❑ Company Rep ❑ In-Service Training ❑ Other (please state)

❑ Course ❑ Accredited

……

11a. Have you been approached by a pharmaceutical company representative in the last 6 months, promoting silver based products? ❑ Yes ❑ No

11b. Please list the products and/or companies:

.....

.....

11c. Did the representative leave any samples for you to look at? ❑ Yes ❑ No

11d. Were you asked to trial/evaluate any products? ❑ Yes ❑ No

11e. If yes, how did you evaluate it?

.....

.....

11f. Did the representative:

❑ book to arrange a meeting?

❑ call without an appointment?

11g. How many nurses were they able to see in that one visit?

.....

12. Are you a nurse prescriber? ❑ Yes ❑ No

13. Please indicate your area of practice:

❑ District Nurse ❑ Practice Nurse ❑ Other (please state)

❑ Community Nurse ❑ Private Care

……

14. Please indicate your Agenda for Change Banding:

.....

15. Please indicate length of time in your current post:

❑ 0 - 1 Years ❑ 6+ Years

❑ 2 - 5 Years

16. Please rate your experience of wound care:

❑ Beginner ❑ Competent

❑ Novice ❑ Expert

Thank you for taking the time to complete this questionnaire. Please return to:

# Appendix 5

## Quality of life questionnaire

**Trial ID Number.**

**VULCAN PROJECT – Antimicrobial Dressings for Venous Leg Ulcers.**

**Patient Questionnaire.**

**Baseline**

PLEASE COMPLETE AND RETURN IN THE PRE-PAID ENVELOPE.

***Please tick one***

**a) Mobility**

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

**b) Self-care**

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

**c) Usual Activities**

I have no problems with performing my usual activities ☐
*(e.g. work, study, housework, family or leisure activities)*

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

**d) Pain/Discomfort**

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

**e) Anxiety/Depression**

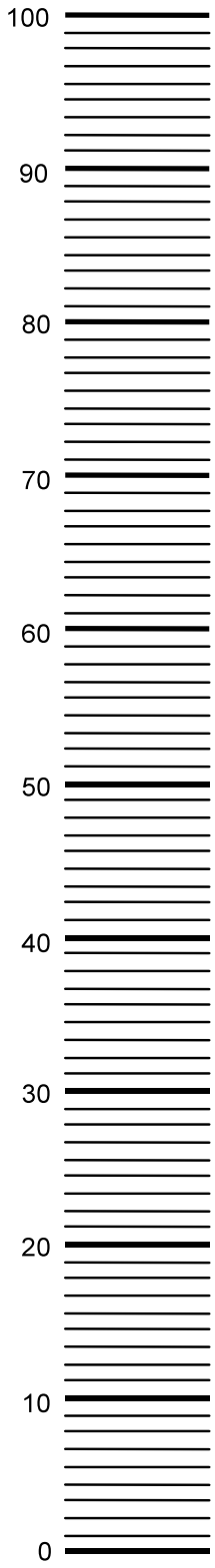
I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

**Please mark the scale on this page to show how you feel your overall health is today**

**Best imaginable health State**




**Worst imaginable health state**

PART ONE.

The following questions ask for your views about your health and how well you are able to do your usual activities.

If you are unsure about how to answer any question, please give the best answer you can and make any comments in the space available after the questionnaire

1 In general would you say your health is:

*Please tick one*

Excellent ☐
Very good ☐
Good ☐
Fair ☐
Poor ☐

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

*Please tick one*

Much better now than one year ago ☐
Somewhat better now than one year ago ☐
About the same ☐
Somewhat worse now than one year ago ☐
Much worse now than one year ago ☐

**HEALTH AND DAILY ACTIVITIES**

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

*Please tick one box on each line*

| | Yes, limited a lot | Yes, limited a little | No, not limited at all | For office use |
|---|---|---|---|---|
| a. *Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports. | ☐ | ☐ | ☐ | ☐ |
| b. *Moderate activities*, such as moving a table, pushing a vacuum cleaner, bowling or playing golf | ☐ | ☐ | ☐ | ☐ |
| c. Lifting or carrying groceries | ☐ | ☐ | ☐ | ☐ |
| d. Climbing *several* flights of stairs | ☐ | ☐ | ☐ | ☐ |
| e. Climbing *one* flight of stairs | ☐ | ☐ | ☐ | ☐ |
| f. Bending, kneeling or stooping | ☐ | ☐ | ☐ | ☐ |
| g. Walking *more than a mile* | ☐ | ☐ | ☐ | ☐ |
| h. Walking *half a mile* | ☐ | ☐ | ☐ | ☐ |
| i. Walking *100 yards* | ☐ | ☐ | ☐ | ☐ |
| j. Bathing and dressing yourself | ☐ | ☐ | ☐ | ☐ |

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

*Answer Yes or No to each question*

| | | YES | NO | For office use |
|---|---|---|---|---|
| a. | Cut down on the *amount of time* you spent on work or other activities | ☐ | ☐ | ☐ |
| b. | *Accomplished less* than you would like | ☐ | ☐ | ☐ |
| c. | Were limited in the *kind* of work or other activities | ☐ | ☐ | ☐ |
| d. | Had *difficulty* performing the work or other activities (e.g. it took extra effort) | ☐ | ☐ | ☐ |

5 During the *past four weeks*, have you had any or the following problems with your work or other daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

*Answer Yes or No to each question*

| | | YES | NO | For office use |
|---|---|---|---|---|
| a. | Cut down on the *amount of time* you spent on work or other activities | ☐ | ☐ | ☐ |
| b. | *Accomplished less* than you would like | ☐ | ☐ | ☐ |
| c. | Didn't do work or other activities as *carefully* as usual | ☐ | ☐ | ☐ |

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

*Please tick one*

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

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

*Please tick one*

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very severe ☐

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

*Please tick one*

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

**YOUR FEELINGS**

9 These questions are about how you feel and how things have been with you during the past month. For each question, please indicate the one answer that comes closest to the way you have been feeling.

*Please tick one box on each line*

How much time during *the past month*

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time | For office use |
|---|---|---|---|---|---|---|---|
| a. Did you feel full of life? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Have you been a very nervous person? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Have you felt so down in the dumps that nothing could cheer you up? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Have you felt calm and peaceful? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. Did you have a lot of energy? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| f. Have you felt downhearted and low? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| g. Did you feel worn out? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| h. Have you been a happy person? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| i. Did you ever feel tired? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

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 friends or close relatives)?

*Please tick one*

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

## HEALTH IN GENERAL

11 Please choose the answer that best describes how *true* or *false* each of the following statements is for you.

*Please tick one box on each line*

| | | Definitely true | Mostly true | Not sure | Mostly false | Definitely false | |
|---|---|---|---|---|---|---|---|
| a. | I seem to get ill more easily than other people | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. | I am as healthy as anybody I know | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. | I expect my health to get worse | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. | My health is excellent | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**THE FOLLOWING QUESTIONS ASK ABOUT OTHER WAYS IN WHICH THE TROUBLE WITH YOUR ULCER HAS AFFECTED YOU**

12 Has your performance of daily activities or your job been limited?

*Please tick one*

a lot ☐

moderately ☐

a little ☐

not at all ☐

13 How long has your ulcer been causing you problems? _____

# Appendix 6

## Resource use questionnaire

**Venous Ulcers: VULCAN trial**

Health Events Questionnaire Patient number _____

Instructions

**In order that future provision of the services being studied can be improved, we need to know about your use of health services. If you could answer the questions below, it would help us greatly.**

If you are unsure of any of your answers, write down your best guess.

**Hospital and outpatient services:**

Q1. In the last **three months**, have you had to attend a hospital's Casualty or Accident and Emergency Department because of your leg ulcers?

Please tick correct box: Yes ☐ No ☐

If ***YES***, how many times have you attended A&E? ☐

Q2. In the last **three months**, have you been admitted to hospital?

Please tick correct box: Yes ☐ No ☐

If ***YES***, please indicate the specialities you were admitted to, how long you spent in hospital, and whether these trips were related to your leg ulcers.

| Speciality | How many days? | Ulcer related? |
|---|---|---|
| | | |
| | | |
| | | |

Q3. In the last **three months**, have you attended a hospital or community-based clinic **for your leg ulcers**?

Please tick correct box: Yes ☐ No ☐

If ***YES***, how many times have you visited a **hospital** clinic? ☐

If ***YES***, how many times have you visited a **community** clinic? ☐

If you travel to a **hospital** clinic, how do you normally get there?

- Using NHS-provided transportation ☐
- Privately, using money provided by NHS ☐
- In any another way ☐

If you travel to a **community** clinic, how do you normally get there?

- Using NHS-provided transportation ☐
- Privately, using money provided by NHS ☐
- In any another way ☐

How far do you normally have to travel to a clinic? (A rough estimate is fine.)

hospital ☐

community ☐ miles.

**Other services:**

Q4. In the last **three months**, have you been to see a GP about your leg ulcers, or has a GP been to see you at your home?

Please tick correct box: Yes ☐ No ☐

If ***YES***, how many times have you been to see a GP? ☐

If ***YES***, how many times has a GP been to see you at your home? ☐

Q5. In the last **three months**, have you been to see a chiropodist?

Please tick correct box: Yes ☐ No ☐

If ***YES***, how many times? ☐

**Compression hosiery**

Q6. In the last **three months**, have you been prescribed any compression hosiery by a nurse or doctor?

Please tick correct box: Yes ☐ No ☐

If ***YES***, what types of hosiery (if any) were you prescribed?

| Compression hosiery | How many times? |
|---|---|
| | |
| | |
| | |

**Antibiotics**

Q7. In the last **three months**, have you been prescribed any antibiotics **for your leg ulcer**?

Please tick correct box: Yes ☐ No ☐

If ***YES***, what antibiotics (if any) were you prescribed?

| Name of antibiotic | How often did you have to take them? | For how many days or weeks? |
|---|---|---|
| | | |
| | | |
| | | |

(Examples of "how often", could be once a day, twice a day, once a week.)

**Other medicines**

Q8. In the last **three months**, have you been prescribed any other medicines **for your leg ulcer**?

Please tick correct box: Yes ☐ No ☐

If ***YES***, what other medicines (if any) were you prescribed?

| Name of medicine | How often did you have to take it? | For how many days or weeks? |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |

(Examples of "how often", could be once a day, twice a day, once a week.)

# Appendix 7

# Original trial protocol

## Randomised controlled trial and economic modelling to evaluate the place of anti-microbial agents in the management of venous leg ulcers

***Planned investigation***

**Aim**

The overall aim of the project is to develop and populate a cost-effectiveness model, using data from a RCT, for the management of venous leg ulceration and to use this to:

a) assess the specific case of an anti-microbial topical dressing currently used in the management of leg ulcers
b) extend the model to provide generalised conclusions about the potential costs and effectiveness of other interventions in this condition.

**Objectives**

1. To carry out a randomised controlled trial to compare the most commonly used anti-microbial local treatment with standard care.
2. To establish current practice with regard to the use of topical anti-microbial dressings and systemic antibiotics in the treatment of leg ulceration.
3. To develop a cost-effectiveness model for the management of leg ulceration.
4. To collect observational data regarding the treatment, clinical outcome, and cost of the management of venous leg ulcers.
5. To obtain societal utilities for health states relating to venous ulceration.
6. To populate the model with data from the RCT, observational trial, published literature and utility valuation and to carry out cost-effectiveness analysis and sensitivity analysis regarding a range of options for the management of venous leg ulceration.

## Existing research

***The use of anti-microbial agents***

There have been a large number of trials, including many randomised controlled trials, of a variety of potential agents that have been used in the management of leg ulcers. A number of systematic reviews have considered the data from randomised controlled trials in this area. In particular, high quality reviews have previously been commissioned by the HTA (1) and have also been published in the Cochrane Database of Systematic Reviews (2) (3). The recent HTA report (1) identified 30 trials, of which 21 considered topical agents, and 9 evaluated systemic antibiotics. The conclusion in the case of venous leg ulcers was that existing evidence was equivocal and generally of poor quality, and there was no strong evidence to support an individual agent, for either topical or systemic use.

Other systematic reviews have come to similar conclusions, the most recent one being the Cochrane review, which is currently going through the editorial process with the wound group at the Cochrane collaboration, with some of the authors being members of the proposed research team (4).

***Other treatments for venous ulceration***

Venous ulceration is a common disease, and there are a large number of treatment modalities that have been used in its management. Many of these have been assessed through clinical trials, and there is a considerable body of secondary research, with a number of large systemic reviews looking at the results of these trials. The most convincing evidence is in favour of compression, with evidence that multi-layer compression bandaging and other techniques producing a high compression result in improved healing (5) (6). A systematic review of the use of Pentoxifylline suggested that this may have some added benefit (7), although the cost-effectiveness of this treatment is not proven, and patients on the treatment suffered some additional side effects. Other modalities, including the use of oral zinc (8), intermittent pneumatic compression (9), skin grafting (10), therapeutic ultrasound (11), laser therapy (12), and electromagnetic therapy (13), have not provided clear evidence of benefit of any of these treatments. One recent randomised controlled trial of surgical treatment for superficial venous incompetence in suitable patients suggested a benefit from surgery in reducing ulcer recurrence rates (14).

***Research into outcomes***

The majority of trials considering the treatment of venous leg ulcers have used time to complete ulcer healing or recurrence rate at one year as

the main measures of outcome. Some attempts have been made to look at quality of life following leg ulceration. The SF-36 (15) (16), Nottingham Health Profile (17), and Freiburg Life Quality Assessment (18) have all been used in this respect (15).

In general the results have shown that most of the generic health related quality of life scales are not very responsive to the presence or absence of leg ulceration. In particular a recent randomised controlled trial, which showed significant differences in healing rates between two groups, failed to show any significant difference in the health status measured by the SF-36 and Euroqol (EQ-5D)(19). There are no high quality published data relating to utilities in patients with leg ulceration that would be appropriate for the calculation of quality-adjusted life expectancy.

### *Cost-effectiveness*

There have been a number of trials that have considered the cost-effectiveness of particular aspects of the management of venous ulcers. A recent trial from Sheffield considered the cost-effectiveness of community leg ulcer clinics (19). Other studies have considered cost-effectiveness of particular dressings (20), the use of pentoxifylline (7), and the effect of using care pathways and guidelines (21). These studies were carried out in several different countries and in different settings.

### *Implications of existing evidence*

There are a number of aspects of the existing evidence that have been taken into account in planning the proposed trial. Firstly there are a very large number of potential anti-microbial agents for either topical or systemic use, with conflicting evidence regarding potential benefit. This raises the question of the most appropriate agents for further study. A pragmatic approach has been taken to this, in that the most widely used current anti-microbial dressings have been chosen on the basis that these are the ones most favoured by practitioners, and that any changes in the use of these is likely to have the biggest overall effect on the cost-effectiveness of service provision. Another implication of this finding is the need to collect appropriate data and to produce a model that will allow generalisation to a wider range of potential treatments. This can then be used to determine the parameters under which other untested or new agents are likely to be cost-effective.

Existing research has identified multi-layer compression bandaging as current best practice for the healing of venous ulcers (6) (5).

The lack of high quality evidence regarding outcomes and costs suggests that the identification of suitable outcome measures and cost analysis will need to be an integral part of the proposed trial.

## Method

A cost-effectiveness model will be developed and used to assess the specific case of an anti-microbial dressing, using data from a randomised controlled trial. The modelling will be extended to produce generalisable conclusions regarding the potential costs and effectiveness of other interventions for venous leg ulceration. There are three main aspects to this work: the collection of probability, cost and outcome data; the development of a cost-effectiveness model; and modelling and sensitivity analysis to produce both specific and generalisable conclusions about the cost-effectiveness of alternative management policies for venous leg ulcers.

### *1. Collection of data*

#### Randomised control trial data collection

All eligible patients will be invited to participate in a randomised controlled trial of anti-microbial dressings. A preliminarily survey has been carried out of 31 specialist vascular nurses working in 25 different districts within the UK. The results of this suggested that the most commonly used anti-microbial agents are silver sulphadiazine (Flamazine, Smith & Nephew) and povidone-iodine fabric dressing (e.g. Inadine, Johnson & Johnson) followed by cadexomer-iodine paste dressing (e.g. Iodoflex, Smith & Nephew). These are preliminary results and an initial part of the trial will be a survey to discover the most commonly used anti-microbial agents in the UK. The results of this survey will be used to inform the final choice of agent for the randomised controlled trial. The number of patients available for recruitment to the trial offer the possibility of a three-way randomisation between a non-adherent dressing and two anti-microbial treatments.

#### *Planned interventions*

The anti-microbial dressing will be used in conjunction with best medical treatment, which will be standardised between the two centres, and based on existing evidence-based care pathways.

The standard intervention will be the application of a low adherence knitted viscose dressing to the ulcer, with multi-layer compression bandaging. The dressings and bandage will be revised weekly unless more frequent dressings are required on clinical

grounds due to pain, discharge, or loosening of the bandage. Multi-layer compression bandaging will be continued until the ulcer is fully healed, with Grade II below-knee fitted compression hosiery applied following complete healing. If this is not tolerated then a Grade I stocking will be applied.

In the trial group the appropriate anti-microbial dressing will be applied at each dressing change until the ulcer is fully healed. Dressings will be reviewed at each change and the active treatment discontinued if there is evidence of sensitivity to the dressing.

***Planned inclusion/exclusion criteria***
All patients with active ulceration of the lower leg that has been present for a period of greater than six weeks will be considered for inclusion in the randomised control trial.

The following are specific exclusion criteria:

- Refusal to give of informed consent to participate in a randomised controlled trial
- Ankle brachial pressure index of less than 0.8 in the affected leg
- Diabetes Mellitus
- Pregnancy
- Atypical ulcers, including those where there is suspicion of malignancy, co-existing skin conditions or vasculitis
- Sensitivity to the anti-microbial treatment agent or specific contraindications to that agent.

***Proposed outcome measures***
The primary outcome measure will be complete ulcer healing at three months. Other secondary outcome measures that will be included in the analysis are healing at six months and one year, recurrence at six months and one year, EQ-5D (22) and SF-36 (23) health related quality of life questionnaires, and the McGill pain questionnaire (24). In addition, information will be collected at the time of each dressing change regarding clinical symptoms, ulcer size (maximum axial and circumferential ulcer diameter), adverse events and co-morbidity.

In those patients with bilateral ulceration, the treatment for the chosen arm of the trial will apply to the dressings to both limbs. For the purpose of the primary outcome measure of complete ulcer healing, the index limb will be that with the greatest ulcer size at the time of randomisation. Where there is more than one site of ulceration on a single limb the primary end-point will be complete healing of all ulcers on that limb.

***Recruitment and randomisation***
Patients fitting the inclusion criteria will be identified following assessment of their leg ulceration. They will be provided with written information regarding the trial, and invited to participate. Those giving informed consent will be stratified on the basis of initial ulcer size and randomised through a telephone randomisation process.

**Observational data collection**
In the areas served by both participating centres there are already well-developed leg ulcer services, with existing evidence-based guidelines and computer databases. As might be expected the exact organisation of the service differs between the centres to reflect local circumstances, priorities and needs.

In Sheffield the service is based around community leg ulcer clinics, which provide support and training for community nurses in the assessment, management, and bandaging techniques for patients with leg ulceration. Leg ulcer management is carried out in accordance with locally developed evidence-based guidelines that were recently revised as a collaborative venture between community nursing experts in leg ulceration, the vascular surgical service at The Northern General Hospital, and the dermatology service at The Royal Hallamshire Hospital. All patients are assessed using a common protocol and data are entered onto an initial assessment form, which is recorded on a computer database and updated by communication with community nurses at regular intervals. The main support for leg ulcer services from secondary care is provided by leg ulcer clinics, which are nurse-led clinics running in parallel to the vascular surgical clinics. The database currently contains information on approximately 350 patients with active leg ulceration.

In Exeter there is a similar service, which is configured as a 'hub & spoke' arrangement through a central clinic at Franklyn House. There are 2.5 Whole Time Equivalent (WTE) nurses employed in this clinic who collaborate with nurses from the community to provide regular community clinics. There are reciprocal arrangements with nurses from the community attending the clinic at Franklyn House for support and training. Support from secondary care is provided by a dermatologist (Dr Bower – co-applicant), who attends the clinic at

Franklyn House, with referrals being made to other services as necessary. The service in Exeter has also developed local evidence-based guidelines and assessment protocols, and data of all newly assessed patients are entered onto a computer database. In the past year 801 new patients have been identified and recorded on the database, of whom approximately 450 have active ulceration.

**Cost data collection**
Data will be collected regarding the major cost drivers for all patients entered into the randomised control trial and in the observational cohort. These data will include the frequency and type of dressings used; number of contacts with community nurses, general practitioner and hospital clinical staff; periods of hospitalisation; and any interventions carried out relating to the leg ulceration and prescribed medications. Data regarding the use of hospital services (inpatient stay, outpatient visits and A&E attendance) will be obtained from the patient administration system at the NGH and Exeter DGH; frequency and type of dressing use and contacts by district nurses (from District nurse records and diaries); primary and other community care service use will be obtained from patients. All resources will be costed using national average unit costs. In addition to this, common procedures and interventions will be identified from the database and randomised controlled trial, and detailed specific costs for these will be calculated through observation and timing of a sample of the interventions.

**Utility data collection**
Societal utilities for the various health states identified in the model will be obtained through a separate evaluation exercise. For each of the defined health states a scenario will be developed describing the symptoms experienced by patients in that health state. This will be based upon the data collected in the randomised controlled trial and additional patient interviews, if required. The scenarios will be brief descriptions of less than a single page of text and will describe the current health state, including the symptoms, concerns, and the need for ongoing treatments. A general population sample will be selected and each of the scenarios evaluated using a standard time trade off method (25) in which the health state was compared to a state of full health to obtain a utility evaluation for that state. This process will be carried out through direct interview, with a trained interviewer, and previous experience suggests that 4–5 health states can be valued in this way in an interview lasting approximately ½ hour. A sample of 100 general population subjects will be identified through a local agency that has been used to identify such samples in the past.

**Data collection procedures**
The first stage of the project will develop existing systems to allow detailed observational data to be collected on as many patients as possible. Information will be provided to all registered patients about the proposed study and they will be asked for informed consent to participate in the observational arm of the trial and be contacted at a later date if they are suitable for the RCT. All data from consenting patients will be consolidated in a single database for the purposes of analysis. A joint group will be set up to identify and implement modifications to the data assessments to ensure that identical fields and coding systems are implemented at both centres. Additional fields will be added to the database to include data collection about major cost drivers and other aspects of care or outcome measures that are required for the cost-effectiveness analysis.

Additional follow up data, including ulcer healing; nature of dressings; use of systemic and local anti-microbial agents, and other interventions; and co-morbidity, will be collected on the database. These will be submitted as a summary on a standard, machine readable form by community nursing staff. Where updated information regarding a patient with active ulceration is not received for a period of 8 weeks this will trigger direct contact from the research staff to ensure completeness of data collection. Three-monthly reports will be requested on all those with healed ulceration to record recurrent ulceration and other clinical events (e.g. surgical treatments).

***2. Cost-effectiveness modelling***
The model will be developed by an iterative process in which a group of clinical experts in the field (the trial participants plus other invited experts), will develop a schematic model for the process of care and potential outcomes of treatment for patients with venous leg ulceration. The process will be modelled from the time of clinical presentation, using a Markov process. The definition of clinical states for the model will be based upon expert opinion and information from existing databases. Discreet, clinically relevant states will be identified for which specific costs, transition probabilities, and outcomes will be ascertained.

The cost-effectiveness model will be developed using standard decision analysis software (DATA, Treeage Software Inc. CA) using a Markov process to model the clinical management and outcome of

venous ulceration. Initial probabilities outcomes, costs and utilities will be derived from the patients enrolled in the randomised controlled trial of topical anti-microbial agents. Where there is significant uncertainty regarding specific variables the data from the trial will be supplemented by the observational data and literature review, and estimates of the range of uncertainty will be made. The outcome of the model will be assessed both in terms of the cost-effectiveness in terms of cost per ulcer free patient month, and cost per quality adjusted life year (QALY) based upon utilities derived from the EQ-5D, values identified from published literature and a separate exercise to generate societal utilities for the health states identified in the model.

#### *3. Sensitivity analysis*

Major areas of uncertainty will be addressed through sensitivity analysis. Where individual variables have been identified for which there is uncertainty a one-way sensitivity analysis will be carried out over the range of likely values. If several variables are identified which are shown by this analysis to have significant implications for the conclusions a multi-way sensitivity analysis will be carried out using a second order Monte Carlo simulation.

The model will be generalised in order to allow the evaluation of other possible changes in practice, including changes in antibiotic prescribing and other potential interventions that may improve the rate of healing or reduce recurrence rates following initial healing. Through sensitivity analysis a number of different potential scenarios will be evaluated in order to assess the cost-effectiveness of other possible treatments. Calculations will be made regarding the improvement in outcome that would be required for novel treatments of a specific cost in order for them to fall below generally accepted thresholds for cost per quality adjusted life year gained.

## Ethical arrangements

Ethical approval will be sought from the local Research Ethics Committees (LRECs) of the lead applicant and approval for local issues will be sought from other relevant LRECs. Both the control and treatment arms of the randomised controlled trial of topical anti-microbial agents involve commonly accepted treatments, and as such there are not anticipated to be any additional risks to the patients. The additional data collected as part of the trial are all non-invasive, and the only potential risks to patients are inconvenience or possible distress caused by completing the questionnaires. All questionnaires and interview protocols will be designed to take this into account and will be approved by local Research Ethics Committees.

## Proposed sample size

It is estimated that the existing databases in Sheffield and Exeter contain a total of approximately 800 patients with current active ulceration. Previous experience suggests that the majority of these patients would be prepared to be enrolled in the observational arm of the trial, and that approximately 40–50% would agree to randomisation. Allowing for the exclusion criteria, it is anticipated that a minimum of 300 patients (150 for each group) will be randomised in the trial of topical anti-microbial dressings. This will allow for a loss to follow-up or withdrawal rate of 25%. A cost-effectiveness study by Morrell et al (19) undertaken within the Trent region leg ulcer study gave a 3 month ulcer healing rates of 34% and 24% in the intervention and control groups respectively. Basing the sample size calculation on these figures: a two group continuity corrected chi-squared test with a 0.050 two-sided significance level will have 80% power to detect the difference between a Group 1 proportion healed, of 24% at 3 months and a Group 2 proportion healed, of 44% (odds ratio of 2.488) when the sample size in each group is 97. A two group continuity corrected chi-squared test with a 0.050 two-sided significance level will have 80% power to detect the difference between a Group 1 proportion, of 34% and a Group 2 proportion, of 54% (odds ratio of 2.279) when the sample size in each group is 106.

It is likely that it would be possible to recruit considerably larger numbers of patients and this would allow the potential to carry out a three-way randomisation with similar power if the initial work suggested that this was appropriate. A three-arm trial, the simplest strategy is to adopt, in terms of analysis, will be the approach which regards a three-treatment comparison as little different from carrying out a series of three independent trials, and to use conventional significance tests without adjustment as argued by Saville (26). As a consequence, the sample size will be estimated as if three independent comparisons are to be made and as a consequence the trial would need to recruit approximately 450 patients (i.e. 150 into each arm).

The sample size for the Time Trade-Off study will be based on the tables produced by Furlong et al

(26) which indicate that a sample size of between 100 and 110 participants would have an 80% power and 5% significance to detect a mean difference of ± 0.06 in utility values for the health-state scenario descriptions.

## Consumer involvement

A consumer panel of patients who have a healed ulcer, and who are attending outpatients for follow-up, will be recruited to provide guidance on the conduct of the trial. Recruitment will be via an invitation letter and an informal interview. Examples of areas the consumer panel will be asked to comment on include patient information sheets, questionnaires, recruitment issues and dissemination. The panel will consist approximately five members and will meet initially every two months but meet more frequently if the panel feels it would be appropriate. One of the members of the panel will be invited to be on the Trial Steering Committee.

## Independent supervision of trials

In accordance with the MRC Guidelines for Good Clinical Practice, a Trial Steering Committee and a separate Data Monitoring & Ethics Committee (DMEC) will be set up to supervise the trial. The Trial Steering Committee will be chaired by an expert in vascular surgery who has not been involved in the development of the trial and who has no association with either participating centre. It will include one additional member of the clinical team in each of the participating centres who is not directly involved in the trial along with the co-applicants, staff employed for the trial and a consumer representative. The DMEC will be made up of experts in the field from outside the participating centres, and will include at least one consultant vascular surgeon, one experienced health economist, and a district nurse with experience of the management of leg ulceration. The DMEC will have access to all on-going data collection, will receive copies of 6 monthly progress reports, and will be notified immediately of any adverse events occurring during the trial and of any complaints from trial participants.

## Project timetable and milestones

**0–6 Months** Validation and standardisation of existing databases. Identification of all patients with active ulceration and provision of information regarding the trial, with requests to participate.

**6–18 Months**
Retrospective review of past history of participants, including identification of duration of ulceration, prior treatments, and antibiotic prescribing (topical and systemic). Recruitment of eligible patients to the randomised controlled trial of topical anti-microbial agents.

**18–30 Months**
Follow up period for patients in randomised controlled trial of topical anti-microbial agents.

**6–30 Months**
Continuing data collection for all patients in the RCT and observational arms of the trial.

**12–24 Months**
Development of cost-effectiveness model.

**18–24 Months**
Development of scenarios describing health states

**24–30 Months**
Societal utility valuation through TTO interviews.

**24–30 Months**
Collation and analysis of collected results to provide data for economic model.

**30–36 Months**
Finalisation of economic model analysis, sensitivityanalysis and report preparation.

## Expertise

The project team is based upon an existing collaboration between Sheffield and Exeter, which has been responsible for a large randomised controlled trial of varicose vein treatment, which has been funded by the HTA and has successfully recruited 1000 patients to a similar project with both randomised and observational arms associated with cost-effectiveness analysis. In addition both Sheffield and Exeter have well established community programmes for the management of leg ulcers, and the leaders of these programmes in both centres are joining the trial team as participants. The research team includes nurses, medical staff and academics; and also collaboration between primary and secondary care.

Jonathan Michaels has experience in undertaking large multi-centre research trials and will be involved in the economic modelling, analysis and presentation of results.

Bruce Campbell has published widely in the area of venous disease and has participated in large multi-centre research trials. He will be responsible for the protocol development. He will also be involved in data collection and analysis and writing up aspects of the final report. He will oversee the management of the project in Exeter, including direct and regular supervision of the Exeter research nurse, liaising with the community leg ulcer service, and dealing with clinical problems and surgical referrals of trial patients.

John Brazier has published widely in the area of quality of life assessment and has undertaken a significant number of economic research projects. He will be involved in the supervision of the health economics research assistant and will oversee the utility study, costing and modelling.

Mike Campbell holds a Professorship in medical statistics and will be involved in the analysis, supervision of the research assistant and provide statistical expertise and advice.

Moyez Jiwa is a GP and researcher will provide day-to-day advice on clinical aspects of the study (particularly those relevant to primary care) and provide support in identifying study participants from the Trent Region and in maximising co-operation with primary care in Sheffield.

Simon Palfreyman has several publications in the area of venous ulceration and is also undertaking a PhD which will derive a condition specific measure of outcome for patients with leg ulcers and information from this may be included within the project. He will be involved in the literature searching and reviewing, quality of life assessment, data collection and analysis.

Brenda King has expertise in leg ulceration. She was also part of a recently completed cost-effectiveness study, in collaboration with ScHARR, examining leg ulcer clinics.

Chris Bower is a Consultant Dermatologist with extensive experience in the management of leg ulceration. He is the lead Consultant for the leg ulcer service in Exeter and will supervise the recruitment and follow-up of patients in the Exeter arm of the trial.

Pauline Hooper manages patients with leg ulceration and has expertise in their care. She will be involved in recruitment and supervision of patients in the Exeter arm of the trial.

## Justification of support required

- Research Nurses. Two research nurses, one mid point G Grade and one mid point F grade WTE for 3 years. This is based upon 1 WTE nurse each in Sheffield and Exeter. The complexity of the trial, the need for supervision and co-ordination, and the ability to recruit a nurse of sufficient experience justifies the recruitment of a G grade nurse. The research nurses would be responsible for co-ordinating recruitment and randomisation, chasing up clinical outcomes, supervising the database (with clerical support), managing ethics applications, co-ordinating steering group, literature review, development of clinical scenarios and utility evaluations.
- Health economist. Research Associate Grade 2 0.5 WTE for 3 years. This person would be responsible for development of model and advice on the collection of cost data under supervision of Professor Brazier.
- Clerical support 1 WTE. The post would fund 0.5 WTE in Sheffield and 0.5 WTE in Exeter for database development, data entry and secretarial duties.
- Trial Management. 1 session per week for 3 years (Mr Michaels) for overall trial management, development of the project, analysis, dissemination and writing of trial reports.
- GP Research Fellow 0.5 session per week for 3 years. To provide advice on issues related to General Practice and assist with community recruitment
- Research Associate Grade 3. To assist with statistical support and analysis.
- Consumables expenses will include questionnaire printing, correspondence.
- Travelling expenses for the research nurses visiting the leg ulcer clinics patient visits, steering group and DMEC meetings.
- Cost for telephone randomisation procedure.
- Cost will also be incurred for the collection of data by General Practices and ulcer clinics, and to identify the general public sample for the TTO survey.

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***We look forward to hearing from you.***

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