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VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers

JC Dumville,[1] G Worthy,[1] MO Soares,[1] JM Bland,[1] N Cullum,[1*] C Dowson,[2] C Iglesias,[1] D McCaughan,[1] JL Mitchell,[3] EA Nelson[4] and DJ Torgerson[1] on behalf of the VenUS II team

[1]Department of Health Sciences, University of York, UK
[2]Biological Sciences, University of Warwick, UK
[3]Micropathology Ltd, Coventry, UK
[4]School of Healthcare, University of Leeds, UK

*Corresponding author

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Abstract

VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers

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[1]Department of Health Sciences, University of York, UK
[2]Biological Sciences, University of Warwick, UK
[3]Micropathology Ltd, Coventry, UK
[4]School of Healthcare, University of Leeds, UK

*Corresponding author

Objectives: To compare the clinical effectiveness and cost-effectiveness of larval therapy with a standard debridement technique (hydrogel).
Design: A pragmatic, three-arm, randomised controlled trial with an economic evaluation.
Setting: Community nursing services, community leg ulcer clinics and hospital outpatient leg ulcer clinics. A range of urban and rural settings.
Participants: Patients with venous or mixed venous/arterial ulcers (minimum ankle brachial pressure index of 0.6) where a minimum of 25% of ulcer area was covered by slough and/or necrotic material.
Interventions: Loose larval therapy and bagged larval therapy compared with hydrogel.
Main outcome measures: The primary end point was complete healing of the largest eligible ulcer. The primary outcome was time to complete healing of the reference ulcer. Secondary outcomes were: time to debridement, cost of treatments, health-related quality of life (including ulcer-related pain), bacterial load, presence of methicillin-resistant *Staphylococcus aureus* and staff and patient attitudes to and beliefs about larval therapy.
Results: Between July 2004 and May 2007 the trial recruited 267 people aged 20–94 years at trial entry. There were more female ($n = 158$) than male ($n = 109$) participants and most ulcers were classified by the nurse as having an area greater than 5 cm^2. The time to healing for the three treatment arms was compared using the log rank test. The difference in time to healing in the three treatments was not statistically significant at the 5% level. Adjustment was then made for stratification and prespecified prognostic factors (centre, baseline ulcer area, ulcer duration and type of ulcer) using a Cox proportional hazards model. No difference was found in healing rates between the loose and bagged larvae groups. Results for larvae (loose and bagged pooled) compared with hydrogel showed no evidence of a difference in time to healing. When the same analytical steps were used to investigate time to debridement, larvae-treated ulcers debrided significantly more rapidly than hydrogel-treated ulcers; however, the difference in time to debridement between loose and bagged larvae was not significant. The adjusted analysis reported the hazard of debriding at any time for those in loose and bagged larvae groups as approximately twice that of the hydrogel group. No differences in health-related quality of life or bacteriology were observed between trial arms. Larval therapy was associated with significantly more ulcer-related pain than hydrogel. Our base-case economic evaluation showed large decision uncertainty associated with the cost-effectiveness of larval therapy compared with hydrogel, suggesting that larval therapy and hydrogel therapy have similar costs and effects in the treatment of sloughy and/or necrotic leg ulcers.
Conclusions: Larval therapy significantly reduced the time to debridement of sloughy and/or necrotic, chronic venous and mixed venous/arterial leg ulcers, compared with hydrogel; however, larval therapy did not significantly increase the rate of healing of the ulcers. It was impossible to distinguish between larval therapy and hydrogel in terms of cost-effectiveness. Future research should investigate the association of

debridement and healing and the value of debridement as a clinical outcome for patients and clinicians. To inform decision-makers' selection of debriding agents where debridement is the treatment goal, decision analytic modelling of all alternative debridement treatments is required.

Trial registration: Current Controlled Trials ISCRTN55114812.

Contents

List of abbreviations

A	adenosine
ABPI	ankle brachial pressure index
AUC	area under the curve
BNF	*British National Formulary*
C	cytidine
CEAC	cost-effectiveness acceptability curve
CFUs	colony-forming units
CI	confidence interval
df	degree of freedom
DNA	deoxyribonucleic acid
EQ-5D	European Quality Of Life-5 Dimensions instrument
4LB	four-layer bandage
G	guanosine
GP	general practitioner
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IPW	inverse probability weighting
IQC	internal quality control
MCS	mental component summary
MREC	Main Research Ethics Committee
MRSA	methicillin-resistant *Staphylococcus aureus*
NE	north-east
NW	north-west
PCR	polymerase chain reaction
PCS	physical component summary
PCT	Primary Care Trust
PSS	personal social services
QALY	quality adjusted life-year
RCT	randomised controlled trial
SAUC	standardised area under the curve
SD	standard deviation
SE	south-east
SF-12	Short Form 12, Version 2, 4-week recall
SSB	short-stretch bandage
SW	south-west
T	thymidine
VAS	visual analogue scale
VenUS I	Venous Ulcer Study I
VenUS II	Venous Ulcer Study II

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.

In memory of Victor Beeston, one of our valued consumer advisors on this trial, who died in 2006

Executive summary

Objectives

The objectives of the trial were to compare the clinical effectiveness and cost-effectiveness of larval therapy with those of a standard debridement technique (hydrogel).

Design

This was a pragmatic, three-arm, randomised controlled trial with an economic evaluation.

Setting

The setting was in community nursing services, community leg ulcer clinics and hospital outpatient leg ulcer clinics in a range of urban and rural settings.

Participants

Patients with venous or mixed venous/arterial ulcers (minimum ankle brachial pressure index of 0.6) where a minimum 25% of ulcer area was covered by slough and/or necrotic material.

Interventions

The treatments comprised loose larval therapy and bagged larval therapy in comparison with hydrogel.

Main outcome measures

The primary end point was complete healing of the largest eligible (the reference) ulcer and the primary outcome was time to complete healing of the reference ulcer. Secondary outcomes were: time to debridement, treatment costs, health-related quality of life (including ulcer-related pain), bacterial load, presence of methicillin-resistant *Staphylococcus aureus* (MRSA) and staff and patient attitudes to and beliefs about larval therapy.

Results

Between July 2004 and May 2007 the trial recruited 267 people aged 20–94 years at trial entry. There were more female than male participants (59.2% compared with 40.8%) and most ulcers (75.7%) were classified by the nurses as having an area greater than 5 cm^2. Using the log rank test, there was no evidence of a difference between the three treatment arms in the time to healing of venous leg ulcers ($p = 0.62$). Using a Cox proportional hazards model to adjust for stratification and prespecified prognostic factors (centre, baseline ulcer area, ulcer duration and type of ulcer) there was no evidence of a difference between bagged and loose larvae in terms of healing [chi-squared test statistic 0.194, degrees of freedom (df) = 1, $p = 0.66$]. When results for loose and bagged larvae were pooled and compared with hydrogel there was no evidence of a difference in time to healing. The hazard ratio for healing was 1.13 [95% confidence interval (CI) 0.76 to 1.68], which indicated a slightly increased risk of healing for the larvae group although this was not statistically significant ($p = 0.54$). The difference in time to debridement between loose and bagged larvae was not significant when compared in the Cox proportional hazards model ($p = 0.22$). The hazard of debriding at any time for both loose and bagged larvae was approximately twice that for hydrogel (hazard ratio for loose larvae relative to hydrogel was 2.56 (95% CI 1.76 to 3.71) and 2.06 (95% CI 1.39 to 3.03) for bagged larvae relative to hydrogel).

There was no statistically significant difference between the larvae and hydrogel with respect to scores on the Physical Component Summary ($p = 0.81$) and Mental Component Summary ($p = 0.97$) scores of the Short Form-12 health-related quality of life assessment. There was no evidence of a difference between larvae and hydrogel in terms of bacterial load over time ($p = 0.75$). When swab data were analysed up to the point of debridement only, there was also no evidence of a difference between the larvae and hydrogel groups ($p = 0.86$). Only 6.7% of participants had MRSA detected, using molecular

techniques, in their ulcers at baseline. There was no statistically significant difference between the larval and hydrogel therapy groups in the proportions of people who experienced eradication of MRSA by the end of the debridement treatment phase ($p = 0.34$) although this analysis has low statistical power because of the small numbers. People treated with larval therapy reported significantly more pain ($p < 0.001$) in the previous 24 hours when asked at the removal of the first debridement treatment compared with patients in the hydrogel arm; mean pain scores for both loose and bagged larvae were approximately twice those of the hydrogel participants.

Our base-case economic evaluation suggested a large decision uncertainty associated with the cost-effectiveness of larval therapy when compared with hydrogel with a 50% probability of larval therapy being cost-effective. The nature of the uncertainty associated with our estimates of difference in costs and health benefit suggests that larval therapy and hydrogel are likely to have similar costs and effects in the treatment of sloughy leg ulcers.

Conclusions

Larval therapy significantly reduced the time to debridement of sloughy and/or necrotic chronic venous and mixed venous/arterial leg ulcers compared with hydrogel. However, larval therapy did not increase the rate of healing of the ulcers and was associated with significantly more ulcer pain. It was impossible on the basis of this evidence to distinguish between larval therapy and hydrogel in terms of cost-effectiveness.

Implications for health care

There is no evidence from this trial that larval therapy should be used routinely on sloughy or necrotic leg ulcers with the aim of speeding healing or reducing bacterial load.

If debridement *per se* is a treatment goal, e.g. before skin grafting or other surgery, then larval therapy should be considered; however, it is associated with significantly more pain than hydrogel.

Recommendations for future research

In the context of sloughy or necrotic venous and mixed aetiology leg ulcers, The Venous Ulcer Study II (VenUS II) did not find that use of an active debridement treatment resulted in more rapid wound healing. Further robust exploration of the relationship between debridement and healing is required, including in wounds of different aetiologies, to inform clinical wound-care practice, where debridement is commonly undertaken.

Relatively little is known about the outcomes that matter most to people with chronic wounds. Further research is required to explore of the value of debridement to patients and clinicians.

There are several wound debridement methods available. When making debridement treatment choices, decision-makers are faced with a more complex decision than that represented by a single trial. To ensure the most cost-effective treatments are used, decision analytic modelling of all alternative debridement treatments should be undertaken. Modelling should aim to resolve decision uncertainty where debridement is the treatment goal and where treatments aim to promote ulcer healing.

Trial registration

This trial is registered as ISRCTN55114812.

Chapter 1
Background

Leg ulcers

Venous leg ulcers have been defined as non-healing wounds occurring on the lower limb [mid-calf to one inch (2.5 cm) below the malleolus] of people who do not have significant arterial insufficiency in the affected limb.[1] Clinically significant arterial disease is usually ruled out by an ankle brachial pressure index (ABPI) equal to or greater than 0.8 whilst the signs and symptoms of venous disease include lipodermatosclerosis, ankle flare, oedema and eczema.[2] Venous ulcers are typically moist, shallow, irregular in shape and found in the gaiter area of the leg.[2] Leg ulcers frequently have a mixed aetiology which may involve both venous and arterial insufficiency. These ulcers are normally identified as having an ABPI of between 0.6–0.8, but other clinical factors are also important.[2] Such ulcers may develop in patients with a history of venous insufficiency who, over time develop arterial problems.[3,4] Depending on the extent of arterial insufficiency, the usual treatments (i.e. high compression) may not be suitable for such ulcers,[2] and healing rates are reportedly slower than those of uncomplicated venous ulcers.[5] Cornwell *et al*.[6] examined 100 patients with leg ulcers (193 legs; 117 active ulcers) and found ischaemia in the absence of venous insufficiency in 9% of patients and ischaemia combined with venous disease in 22% of patients. The proportion of people with ischaemic disease may increase with an ageing population.

Venous leg ulcers are one of the most common types of chronic wound in the UK, with an estimated point prevalence of 0.16%.[7] The prevalence of venous leg ulcers increases with age and the annual UK prevalence in those over 65 years is estimated at 1.7%.[1] Venous leg ulcers develop as the result of underlying venous disease and usually take months to heal. They can be painful, malodorous and have been shown to severely impact on patients' mobility and quality of life.[8–10] In severe cases, ulceration can lead to limb amputation.[11]

Leg ulcers are also costly. A trial comparing two alternative bandage treatments for venous ulceration estimated the mean annual cost of treating a leg ulcer patient as £1300 at 2001 prices.[12] In 2004, the Healthcare Commission estimated annual National Health Service (NHS) leg ulcer treatment costs of £300–600 million yet these figures may not reflect recent increases in the cost of dressings used to treat chronic wounds. The NHS (England) spend on wound management prescribing increased by 8.5% between 2004 and 2005 and the Wound Dressings section of the *British National Formulary* (BNF) is in the Top 20 in cost terms; accounting for 5 million community prescriptions in England during 2006 at a cost of £122 million.[13] However, the main cost-drivers in the UK remain the staff time required to manage and treat leg ulcers. The majority of leg ulcer patients are treated in the community,[14] and often make up a large proportion of community nursing caseloads.[15] Community nursing time, particularly that associated with frequent home visits, drives these high costs. The increasing proportion of elderly people in the population is likely to lead to an increase in the absolute numbers of leg ulcers and consequently costs.

Treating venous leg ulcers

The treatment of venous leg ulcers aims to improve venous return in the leg and provide a wound environment that supports healing, whilst managing symptoms such as exudate. Although there are many types of wound dressings available and used in the management of venous leg ulcers, there is little evidence to suggest that any dressing type is more effective in terms of promoting healing.[16] By contrast, there is evidence that graduated, multicomponent, high-compression (ankle sub-bandage pressures of 25–35 mmHg) bandaging, which aids venous return, is an effective treatment for venous leg ulcers,[12,17,18] and is advocated in major UK guidelines.[2,19] Compression bandaging can be applied as single layers of bandage, stockings and increasingly, as multicomponent bandage 'systems' – the most commonly used being the four-layer bandage (4LB) and the short stretch bandage (SSB). The Health Technology Assessment (HTA) -funded Venous Ulcer Study (VenUS) I trial[12] directly compared the 4LB and the SSB and found that the

4LB was more clinically effective and cost-effective than the SSB in terms of time to ulcer healing and value for money. This finding has been reinforced by a recent individual data patient meta-analysis of five trials which confirmed that the 4LB is significantly more effective than the short stretch system in terms of time to healing.[20]

Wound management is a complex process that aims to promote wound healing and manage symptoms (such as pain and exudate) whilst meeting patients' needs. An important aspect of this management is thought to be preparation of the wound bed for healing by the removal of devitalised tissue from the ulcer surface; a process called 'debridement'.[21,22]

Wound debridement

Whereas acute wounds such as surgical incisions usually heal quickly because the edges are sutured together (known as 'healing by primary intention'), chronic skin ulcers heal from the bottom up (secondary intention) and frequently contain dead tissue including sloughed material and exudate. For centuries it has been believed that removing this slough and dead tissue (debridement) is beneficial to wound healing and reduces the likelihood of infection.[23] However, although the removal of such tissue is considered important, previous systematic reviews and clinical guidelines highlight the lack of robust evidence demonstrating that debridement speeds healing or reduces the risk of infection in chronic wounds such as venous leg ulcers.[2,19,24]

Several different debridement techniques are used in practice; these can be broadly categorised as: autolytic, surgical/sharp, mechanical and enzymatic methods of debridement (*Table 1*). However, recently there has been renewed interest in a fifth category – biosurgery – involving the use of larval therapy as a debriding agent.[25]

Accounts from the sixteenth century describe how army physicians observed larvae as having a positive impact on the wounds of injured soldiers, which had become naturally infested.[26] Records from the American Civil War suggest that fly larvae were applied as a therapy and in the 1930s sterile larvae were produced and used to treat wounds in the USA.[27] After the explosion in antibiotic use the treatment became almost completely redundant. In the 1990s there was renewed interest in the use of larval therapy in wound care, this time in Europe,[28] where there are currently two major suppliers of medical-grade larval therapy. The larvae produced for medicinal purposes are those of the *Lucilia sericata* (green-bottle) fly. This species selectively feeds on necrotic tissue leaving live tissue intact. Since the 1990s, larval therapy has been widely promoted in the nursing literature to treat different types of chronic wounds.[28–31] Larval therapy is classed as a medicinal product in Europe and, although used in the NHS, it remains an unlicensed product in the UK. It has been reported that the most common indication for use of larval therapy is as a treatment for leg ulcers.[32]

Proposed mechanisms of action for larval therapy

It is suggested that larvae debride wounds more swiftly than wound dressings and avoid the problems of surgical and mechanical debridement (pain, requirement for anaesthesia and appropriately trained personnel). It has also been suggested that larvae may have an effect beyond debridement by having a direct effect on wound healing and bacterial load. Proponents of larval therapy list a number of potential mechanisms for these proposed effects including the following:

- debridement
  - secretion of proteolytic enzymes that liquefy necrotic tissue[26,33]
  - ingestion of necrotic tissue leaving healthy tissue untouched[34]
- antimicrobial activity
  - physical presence of the larvae increasing the natural production of wound exudate, which washes out the bacteria[26]
  - destruction of bacteria [including methicillin-resistant *Staphylococcus aureus* (MRSA)] in the larval alimentary tract by antibacterial substances[35]
  - larval secretions may have antibacterial properties [36–40]
- healing
  - movement of the larvae stimulating the production of granulation tissue[26,41]
  - secretions from the larvae altering wound pH to one that is more conducive to wound healing[42]
  - larval secretions possibly containing substances that promote healing.[43–46]

In Europe, larval therapy is currently available in two formulations: loose, or 'free-range' larvae placed directly into the wound, and bagged larvae (where the larvae are contained in a meshed polyvinylalcohol bag). The bagged formulation was

TABLE 1 *Summary of wound debridement techniques*

Debridement techniques	Methods
Autolytic	Use of moist dressings/hydrogels to create a suitable environment to facilitate debridement
Surgical/sharp	Slough and/or necrotic tissue is cut away from the wound
Mechanical	Slough and/or necrotic tissue is physically separated from the wound using approaches such as high-pressure irrigation and wet-to-dry dressings (not common in UK)
Enzymatic	Topical exogenous enzymes are applied to the wound surface
Biosurgery	Larval therapy

developed to make larval therapy more acceptable to patients and more easily handled by nurses; however, two studies assessing patients' views of bagged and loose larvae reported that patients showed no preference either way.[47,48] Additionally, one small laboratory study reported that loose larvae were more likely to survive and grow faster than bagged larvae; this finding was interpreted as evidence that loose larvae will be more effective debriding agents.[49] A second *in vitro* study conversely suggested that loose and bagged larvae demonstrated the same rates of debridement.[50] Steenvoorde *et al*.[51] report the outcome of 69 gangrenous or necrotic chronic wounds after 54 wounds were treated with loose larvae and 15 were treated with bagged larvae. The authors, using a composite outcome measure of total benefits, reported that wounds progressed significantly better when treated with the loose larval therapy. However, this was a small, unblinded, non-randomised study using multiple outcomes and is not robust evidence of the comparative clinical effectiveness of loose versus bagged larvae.

Existing evidence for the effects of larval therapy on debridement and healing

Non-randomised controlled trial evidence

Case series have reported good outcomes when treating chronic wounds (several different aetiologies),[52] foot ulcers[53] and leg ulcers[54,55] with loose larvae in terms of rapid debridement and improved healing. Studies have also compared larval therapy with conventional treatments in an *ad hoc* way. In an unblinded study, Sherman[56] reported the results of 43 pressure ulcers treated with loose larvae compared with 49 treated with conventional therapy. The study concluded that loose larvae promoted rapid debridement, although the method of assessing debridement was not reported. Each of these case studies has serious methodological flaws and is at risk of selection and assessment bias. As a result, their conclusions, although providing a foundation for further work, cannot be used as evidence that larval therapy speeds debridement or healing.

Randomised controlled trial evidence

A search of MEDLINE and the Cochrane Wounds Group Specialised Trials Register (28 February 2008) identified one published randomised controlled trial (RCT) of loose larval therapy involving only 12 patients, all with venous leg ulcers.[57] This small trial found that venous leg ulcers treated with larval therapy debrided more quickly than those treated with hydrogel. The study did not follow participants until complete healing; therefore the extent to which larval therapy speeds venous ulcer healing remained unknown. The trial also reported that larval therapy was a cost-effective treatment; however, this analysis was limited.

A search of the Register of Current Controlled Trials and the National Research Register (throughout the trial and finally in May 2008) identified two further completed trials and one ongoing trial investigating the impact of larval therapy on debridement and/or healing. One further trial (Dompmartin; *Table 2*) was identified via a personal communication. No results could be obtained for the completed trial, see *Table 2* for details.

Existing evidence for larval therapy: antimicrobial action

Open wounds, such as venous leg ulcers, are at risk of infection from pathogenic micro-organisms, which can cause adverse events for the patient and may also delay wound healing. There is no clear definition of bacterial load in the literature; however, the term is used here to describe the

TABLE 2 *Unpublished randomised controlled trials of larval therapy*

Contact name	Title	Progress	Details
Debridement and healing			
Maylor – Archive record M0050089573	Desloughing wounds: a randomised controlled trial comparing larval therapy and standard autolytic techniques	Completed 2001	Contacted second time 5 March 2008. E-mail returned undelivered
Davies – ISRCTN46226449	A study to assess the efficacy of maggots as a wound debridement agent for venous leg ulcers under graduated compression bandages	Ongoing. Anticipated start date recorded on database as 3 December 2007	Investigator contacted to confirm. Recruitment of 40 participants planned. Primary outcome % area debrided. Planned end date June 2008
Dompmartin	Use and interest of the maggot therapy in the treatment of fibrin and/or infected wounds. A randomised study. Study objectives: estimate the efficiency of the use of live maggots (larval or maggot therapy) in the treatment of pressure, venous and arteriovenous ulcers compared with the classic treatment commonly used for this pathology. Aims to recruit 120 participants	On-going	Investigator e-mailed that two-thirds of participants have been recruited
Anti-microbial action			
Lacey – ISRCTN03572121	A randomised controlled trial of larval therapy versus standard care in the management of necrotic wounds with and without methicillin-resistant *Staphylococcus aureus*	Completed 2005	Principal investigator not available. No response from second contact provided or from Research and Development department. E-mailed 25 February 2008 and provided a qualitative study

quantity of micro-organisms in a wound. It has been suggested that wounds containing at least 1×10^6 colony-forming units (CFUs)/gram of tissue are slower to heal than wounds with a lower bacterial load,[58–63] – it is important to note that the wounds in these papers included postsurgical pressure ulcers and burns. More recently authors in the field have identified a stage before wound infection that they have named 'critical colonisation', where, although a wound's bacterial load would not qualify it as an infection, the load is high and may impact on healing.[64] Others note that a relationship between bacterial load and healing mediated by levels of micro-organisms alone may be too simplistic,[65] and that the type of bacterial species present in a wound[66–68] and interactions between different species[69] may also be important; although a definitive body of work is lacking.

Existing research does not allow clear conclusions regarding a relationship between the bacteriology of chronic wounds and healing to be drawn.[70] In addition to general work in the field described above, more recent work has suggested either an association[66,68,71] or no association[72] between bacterial load and/or species and leg ulcer healing. All studies were prospective and involved the collection of bacterial samples using discs,[72] swabs[66,71], or swabs and biopsies[68] and healing assessment conducted at regular time points. Analyses assessed how differences in healing time varied in relation to wound bacteriology. However, future research in this area requires a more robust design to allow a causal relationship between micro-organisms and healing to be fully investigated. Any possible relationship between micro-organisms and healing could be confounded; that is to say that a wound better able to fight infection is also more likely to heal. From this viewpoint a reduction in bacterial load may be a symptom of healing rather than the cause.

A recent Cochrane review investigating the impact of systemic and topical antimicrobials on venous leg ulcer healing found that there is currently insufficient evidence to suggest that wound infection or colonisation was prognostic for healing.[73] Two RCTs are highlighted as having investigated a possible association between wound status (infected or colonised) and healing; both were subgroup analyses and involved very small

numbers. Alinovi *et al*.[74] reported a positive association between reduced bacterial load and healing rates whereas Huovinen *et al*.[75] reported that *S. aureus* did not appear to delay healing. Other RCTs[76] have also reported no relationship between bacteriology and healing, however, this body of work is far from conclusive about any potential relationship between the microbiology of chronic wounds and healing.

Moreover, chronic skin ulcers are prone to bacterial infection, including with MRSA, which has been isolated in community-dwelling people.[77,78] For example, a recent study in a UK diabetic foot ulcer clinic recorded MRSA in 13% of ulcers (where 65% of ulcers were classed as clinically infected)[79] and in France, the leg ulcers of 31% of patients admitted to hospital contained MRSA on admission.[80] A high community prevalence of MRSA in chronic wounds raises the potential for cross-infection, for example during hospitalisation.

Non-randomised controlled trial evidence

It has been proposed that whilst feeding, larvae also ingest and destroy bacteria and in doing so can alleviate symptoms associated with infection and also potentially reduce bacterial load.[26] Again, there has been very little recent research on this proposed antimicrobial action. Initial reports regarding the antimicrobial activity of larval secretions were *in vitro* findings published in the 1930s.[27] More recently Thomas *et al*.[39] reported that *L. sericata* larval secretions showed good antimicrobial activity against *Streptococcus* A and B and *S. aureus in vitro*, with some activity detected against *Pseudomonas* sp. and MRSA. A further *in vitro* study tested excretions/secretions from *L. sericata* larvae against MRSA and also reported antimicrobial activity.[36] A recent *in vitro* study also reported that whole body extractions of larvae were active against wound isolates of Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and MRSA.[37,38] However, there is relatively little *in vivo* work. Steenvoorde and Jukema[81] treated 16 wounds infected with Gram-positive and/or Gram-negative bacteria with loose ($n = 3$) and bagged ($n = 13$) larvae and monitored the impact on wound flora. They reported a greater reduction in Gram-positive than Gram-negative bacteria after larval treatment.

The potential action of larvae on MRSA is of great interest because it is difficult to treat, has detrimental effects on patient health and is extremely costly to the NHS. The *in vitro* work above is supported by limited *in vivo* evidence. A prospective case series used loose larvae to treated diabetic foot ulcers that had been colonised with MRSA for more than 3 weeks.[82] In total, 13 participants were recruited and treated with larval therapy. The study reports that MRSA was eliminated in all but one ulcer. However, this evidence is severely limited by the lack of a control group so it is impossible to say whether MRSA would have disappeared without larval therapy, or there may have been some false-positive MRSA detection in the initial analysis.

Evidence from randomised controlled trials

As with the effectiveness of larval therapy on debridement and healing, although the existing research provides interesting data, more research is required to investigate the antimicrobial activity of larval therapy using RCTs. A search of MEDLINE, the Cochrane Wounds Group Specialised Trials Register and national and international research registers identified only one completed relevant RCT. This has not been published (as of 1 May 2008) and no results could be obtained for the completed trial (*Table 2*).

Acceptability of larval therapy

In additional to clinical efficacy, to be an effective treatment larval therapy must be acceptable to both patients and nurses. Three studies have investigated the patient acceptability of larval therapy.[47,48,83] As part of the development of this study we used a questionnaire to assess leg ulcer patients' preferences for loose larvae (versus hydrogel) and bagged larvae (versus hydrogel) by measuring the improvement in healing time that the patients would require in order for them to prefer larval therapy over hydrogel.[47] In total, 41 patients completed a questionnaire (they were randomised to receive either a loose larvae or a bagged larvae questionnaire), with 25% stating they would never use larvae. On average, those patients who would consider larval therapy as a treatment option would do so even if the healing rate with larval therapy was equivalent to treatment with hydrogel. There was no difference in preference between loose and bagged larvae. Steenvoorde *et al*.[48] treated the non-healing wounds of 41 Dutch patients (further details not supplied) with larval therapy, noting that none refused the

treatment. The patients were asked to complete a questionnaire regarding their treatment. Of the 37 patients who returned the questionnaires, none reported adverse feelings about larval therapy and 89% would have it again.

Kitching[83] conducted in-depth interviews with six UK-based participants who had received larval therapy on a chronic wound or burn. The study reported that patients tended to feel initial repulsion towards the larval therapy but this changed to a more positive view after the treatment was received. Four of the six patients reported less pain when treated with the larval therapy. This study also discussed the importance of the treating nurse in helping patients make the decision to accept larval therapy; however, nurses' perceptions of larval therapy have not previously been formally assessed.

Summary of main points

Leg ulceration is a chronic and common condition that is highly prevalent in older people and impacts negatively on quality of life. Although there is good-quality evidence that compression bandaging that delivers sub-bandage pressures of 25–35 mmHg at the ankle helps to heal venous ulcers more than no compression, only approximately 50% of ulcers are healed by 16 weeks with best treatment,[12] therefore research to identify further effective interventions is warranted. Larval therapy, a traditional approach to wound management, is increasingly used on leg ulcers[32] and has been postulated to stimulate healing, reduce bacterial load and infection and eradicate MRSA, yet the only clinical evidence available to support claims of the effects on healing came from a small RCT which did not follow patients to healing. Evidence to support effects on microbiology was largely from laboratory studies. We therefore undertook an RCT to evaluate the effects of loose and bagged larvae on leg ulcer debridement, healing, microbiology, costs, and also to investigate nurse and patient attitudes to larval therapy. We identified the appropriate patient population for study as being people with leg ulceration of venous or mixed venous/arterial pathology; the latter because ulcers in the presence of some arterial insufficiency are likely to contain more slough and necrotic tissue than purely venous ulcers.

Research objectives

To compare the clinical effectiveness and cost-effectiveness of larval therapy with a standard debridement technique (hydrogel) in terms of its effect on time to complete healing of leg ulcers, time to debridement of leg ulcers, cost of treatment and health-related quality of life (HRQoL).

Primary objective

- To compare the effects of larval therapy and hydrogel on the time to complete healing of venous and mixed venous/arterial leg ulcers.

Secondary objectives

- To compare the cost-effectiveness of larval therapy with that of hydrogel.
- To compare the effects of larval therapy and of hydrogel on time to debridement of venous and mixed aetiology leg ulcers.
- To compare the effects of larval therapy and hydrogel on bacterial load and presence of MRSA.
- To assess staff and patient attitudes to and beliefs about larval therapy.

Chapter 2
Methods

Trial design

The Venous Ulcer Study II (VenUS II) was a pragmatic multicentre, randomised, controlled, open, fixed sample, parallel group trial with equal randomisation. Participants with sloughy or necrotic leg ulcers were allocated equally between three treatment groups: loose larvae, bagged larvae or hydrogel.

Approvals obtained

The study was approved by West Midlands Research Ethics Committee – details of site-specific approvals are given in Appendix 1. Approval was also obtained from the relevant Research and Development departments (see Appendix 1). Larval therapy is classified as a medicinal product, therefore clinical trial authorisation was obtained from the Medicines and Healthcare Products Regulatory Agency (22803/0001/001). The trial was registered at inception: ISRCTN55114812, National Research Register: N0484123692.

Duration of follow-up

All participants were followed up for a minimum of 6 months. Planned follow-up was 12 months; however, it became necessary to extend the recruitment phase into 6 months of the 12-month follow-up period. Participants recruited in the final 6 months of recruitment were therefore followed up for between 6 and 12 months.

Trial sites

There were 22 UK sites and one in Europe (Hungary). Sites were recruited throughout the duration of the trial.

Participant eligibility

Eligible participants were people with leg ulcers that were deemed to be either of venous or mixed venous/arterial aetiology and which contained slough and/or necrotic material. People were eligible for recruitment from hospital wards, outpatient departments (e.g. dermatology, surgery), community leg ulcer clinics and community nurse caseloads. Patients in nursing and residential homes were eligible for inclusion if they were identified as above. To identify potential participants, trial sites were encouraged to regularly screen all existing leg ulcer patients against the eligibility criteria (below) (Appendix 3.1). Where people were ineligible the reason(s) for exclusion were recorded.

Inclusion criteria

People for whom all of the following criteria applied:

- They had a sloughy and/or necrotic leg ulcer (slough and/or necrotic tissue assessed as covering at least 25% of the wound) of purely venous or mixed venous/arterial aetiology. The 25% cut-off point was determined by senior wound-care specialists who advised that larval therapy would not be regarded as an appropriate treatment for people with less slough coverage.
- They had an ABPI equal to or more than 0.6 determined using standard technique as described by Vowden *et al*.[84]
- They received their leg ulcer care either from community nurse domiciliary visits or at leg ulcer clinics held in a hospital or community setting.
- They had an ulcer with an area of more than 5 cm^2 or an ulcer equal to or less than 5 cm^2 and the ulcer was not healing ('not healing' defined as no measurable change in area over month preceding assessment).
- They were aged 18 years or above.
- They were willing and able to give written informed consent.

People with diabetes mellitus whose blood sugar was well controlled (HbA1c equal to or less than 10%) and who had venous or mixed aetiology ulcers were eligible to participate, as were people with rheumatoid arthritis whose ulcers were deemed to be venous in origin.

The trial reference ulcer was defined as the largest ulcer containing at least 25% slough and/or necrotic tissue. If the ulcer was small (area equal to or less than 5 cm^2) it had to be both non-healing and contain at least 25% slough and/or necrotic tissue.

Exclusion criteria

People who:

- were currently in a trial evaluating other therapies for their leg ulcer
- had previously been entered into the trial
- were women of child-bearing potential
- were pregnant or lactating
- were allergic to hydrogel dressings or any of their components
- had grossly oedematous legs, which in the opinion of the recruiting health care professional were unsuitable for treatment with larval therapy and/or hydrogel
- were on anticoagulants (e.g. warfarin) and could not be admitted to a health care facility while receiving larval therapy (this exclusion became necessary during recruitment when the manufacturers of larval therapy added anticoagulation as a contraindication unless patients were closely monitored).

Recruitment into the trial

All nurses participating in the study received training in all aspects of the trial including participant recruitment. Potential participants who met the inclusion criteria were given full trial details by a research nurse or their regular nurse during routine care (Appendix 2). Details were provided verbally and written information was given to the patient to take away. Patients were given a minimum of 24 hours to consider participation in the trial. Written consent was obtained from all patients who were willing to participate and their general practitioner (GP) was notified of their involvement in VenUS II.

Baseline assessment

Once participants had consented to trial participation several baseline measures were recorded by the nurse in the patient record form (Appendix 3.3).

Ulcer area

Previously, ulcer area together with ulcer duration were identified as the two main prognostic factors for healing venous leg ulcers treated with compression.[85] Margolis *et al*.[86] then dichotomised these continuous variables, and found that an area of 5 cm^2 and a duration 6 months were the cut-off points that maximised the differences between patients whose ulcers healed and those whose ulcers did not. In VenUS II baseline ulcer surface area was assessed using acetate tracings of ulcer perimeters (taken using a wound grid marked with 1 cm^2 squares and marker pen). An assessment was then made by the recruiting nurse of whether the reference ulcer area was equal to or less than 5 cm^2 or greater than 5 cm^2 for stratification purposes. The actual area was calculated at the York Trials Unit at a later date using the MOUSEYES computer program.[87]

Duration of reference ulcer

Longer ulcer duration is associated with longer time to healing and is an important prognostic variable;[9,47] we therefore recorded duration of reference ulcer at baseline based on participant report.

Number of ulcer episodes on leg with reference ulcer

Data from VenUS I[12] suggested that a greater number of ulcer episodes is prognostic of a longer healing time; we therefore recorded the number of ulcer episodes on the leg of the reference ulcer, based on participant report.

Sex

The sex of participants was recorded to allow comparison with the existing information on the population of people with ulcers in which women outnumber men.[88]

Date of birth

Date of birth was recorded at recruitment so that age at recruitment could be calculated. Increased age has been associated with slower healing rates in one study.[89]

Ulcer position and image

For monitoring purposes a record of the position of all ulcers on the trial leg including the reference

ulcer was made. Digital photographs were also taken of all leg ulcers present at recruitment, including the reference ulcer.

Health-related quality of life

Participants were given a quality-of-life questionnaire booklet to complete immediately after recruitment. The questionnaire comprised the Short Form 12-item Health Survey (SF-12, Version 2, 4-week recall)[90] and the European Quality Of Life-5 Dimensions (EQ-5D) instrument.[91]

Ulcer microbiology

A swab was taken at baseline (described below) so that bacterial load in the ulcer could be assessed and the presence of MRSA ascertained.

Other

VenUS I reported that ulcer area, ulcer duration, number of ulcer episodes, ankle mobility (classified as full range of ankle motion, reduced range of ankle motion or fixed ankle), and body weight were prognostic for healing. These data were all collected at baseline, also recorded was an ulcer type variable (ABPI greater than 0.8 and treated with high compression; ABPI greater than 0.8 and not treated with high compression, and ABPI 0.6–0.8). We also assessed ulcer-related pain over the previous 24 hours using a visual analogue scale (VAS) (no pain to worst pain imaginable). The minimum value on the scale was 0 mm and the maximum was 150 mm.

Randomisation

Randomisation was carried out with stratification by centre and ulcer area ($\leq 5\,cm^2$ or $> 5\,cm^2$) using varying block sizes of three and six. Participants were randomised equally between three arms: loose larvae, bagged larvae, or hydrogel. To maintain allocation concealment the generation of the randomisation sequence and subsequent treatment allocation were performed by an independent, secure, remote (telephone) randomisation service (York Trials Unit). The computerised randomisation system was checked periodically during the trial following standard operating procedures.

Sample size

The original sample size calculation was based on a comparison of three groups of 200 each using survival analysis to assess time to healing of the reference ulcer (primary outcome). This would have given us 89% power to detect a reduction in median healing time from 20 weeks to 14 weeks, whilst allowing for 15% attrition. Under-recruitment led us to apply for an 18-month extension for recruitment with a revised overall target of 370 participants (90% power to detect a reduction in median healing time from 20 to 12.7 weeks whilst allowing for 15% loss to follow-up), or 270 participants to detect the same difference with 80% power.

Trial interventions

VenUS II was divided into two phases. Phase 1 was a debridement phase during which participants received either larval therapy or hydrogel up to debridement (or up to cessation of the trial debridement treatment before debridement had occurred – classified as 'withdrawal from trial treatment'). Participants randomised to larval therapy did not receive compression during Phase 1 because compression potentially suffocates the larvae. Instead, patients receiving larvae wore a layer of orthopaedic wool and a simple, light crepe bandage as described in the manufacturers' specifications. Participants in the hydrogel group continued with their normal bandage regimen. If more than one application of larvae was required, the participants' usual trial bandages were applied between larval treatments. All nurses involved in the trial were trained in larval therapy application (hydrogel being a standard treatment).

Phase 2 comprised treatment of the wound (postdebridement or withdrawal from trial debridement treatment) with a standard knitted viscose dressing with or without compression (use of which was determined by ABPI and participant tolerance). Where compression was not contraindicated the protocol advocated the use of the 4LB.[12]

Loose larvae group (Phase 1)

Participants received sterile larvae (*L. sericata*), (Zoobiotic, Bridgend Wales, UK). The number of pots of larvae to be used at a single application was

determined by referring to a 'calculator' supplied by the manufacturer (Appendix 4.1). The calculator assesses ulcer size and percentage of ulcer covered with slough. The required number of larvae was then ordered from the manufacturer (*Table 3*). At the time of the trial it was not possible to order larvae for a Monday delivery.

Larvae were retained in the wound by securing a net mesh dressing with Sleek tape (Smith and Nephew, Hull, UK) onto strips of either hydrocolloid dressing or zinc paste bandage applied around the ulcer. Where wounds were dry and/or necrotic, the wound was kept moist by application of a saline-moistened gauze pad over the net mesh retention dressing. Larvae could be applied to an ulcer previously treated with Purilon hydrogel (because it does not contain propylene glycol which is toxic to larvae); however, the use of other dressings, including other hydrogels, between larval treatments was prohibited by the protocol.

Loose larvae were left on the ulcer for 3–4 days, although nurses could check the participant and larvae during this period (i.e. to rehydrate). The removal of larvae was a straightforward process. Once the mesh was removed the majority of larvae would fall out of the wound or move away from it and were caught in a suitable receptacle or retrieved with a forceps or a gloved hand. Any larvae remaining were gently removed manually or irrigated out of the wound with a jet of saline. Larvae were disposed of in accordance with the local guidelines for each site. Once the larvae were removed the treating nurse assessed the amount of slough/necrotic tissue remaining on the wound and decided whether a further application of larval therapy was required.

Where further application was required, Purilon hydrogel and the participant's usual bandage were applied and more larvae were ordered for reapplication as soon as possible. The timescales of treatment were recorded. Once debridement was deemed complete by the treating nurse, or a decision was made to cease trial treatment before debridement, participants moved into Phase 2.

Bagged larvae (Phase 1)

Participants received sterile larvae (*L. sericata*), (Biomonde, Barsbüttel, Germany) within a sealed dressing. The number of bags was calculated according to the manufacturer's specifications (Appendix 4.2) and ordered from the manufacturer (*Table 4*). At the time of the trial larvae could not be delivered for application on a Monday.

Bagged larvae were applied directly to the ulcer without the need for hydrocolloid/zinc paste retention strips. The bag was kept in place by a simple retention bandage, e.g. crepe. Bagged larvae remained in the ulcer for 3–4 days, although the nurses could check on the larvae during this period (i.e. to rehydrate). When ready for removal, the bag was simply lifted from the wound and disposed of intact. Larvae were disposed of in accordance with the local guidelines for each centre.

TABLE 3 *Timetable for the ordering, application and removal of loose larvae*

Order larval therapy	Friday or Monday	Tuesday or Wednesday	Thursday
Apply larval therapy	Tuesday	Wednesday or Thursday	Friday
Remove larval therapy	Friday/Saturday	Saturday, Sunday or Monday	Monday or Tuesday
If more larvae needed	Place order for delivery on Tuesday	Place order for delivery on Tuesday	Place order for delivery on Tuesday or Wednesday

TABLE 4 *Timetable for the ordering, application and removal of bagged larvae*

Order larval therapy	Friday or Monday	Tuesday or Wednesday	Thursday
Apply larval therapy	Tuesday	Wednesday or Thursday	Friday
Remove larval therapy	Friday/Saturday	Saturday, Sunday or Monday	Monday or Tuesday
If more larvae needed	Place order for delivery on Tuesday	Place order for delivery on Tuesday	Place order for delivery on Wednesday or Thursday

Where further application was required, Purilon hydrogel and the participant's usual bandage were applied and more larvae were ordered for reapplication as soon as possible. The timescales of treatment were recorded. Once debridement was deemed complete by the treating nurse, or a decision was made to cease trial treatment before debridement, participants moved into Phase 2.

Control group (Phase 1)

Participants in the control group received Purilon hydrogel dressing (Coloplast A/S, Humlebæk, Denmark) covered with a knitted viscose dressing. Nurses discontinued the hydrogel treatment when they regarded the ulcer as debrided and the date was recorded. Once debridement was deemed complete by the treating nurse, or a decision was made to cease trial treatment before debridement, participants moved into Phase 2.

Compression therapy – the 'trial bandage'
Participants received high or reduced compression depending on their ABPI and tolerance as described in *Tables 5* and *6*. *Table 7*, which contains general information about bandages and bandaging technique, was also supplied to trial nurses. Participants whose ABPI was equal to or more than 0.8 but who were unable or unwilling to tolerate compression were still eligible to participate in this trial and received reduced compression.

Participants with an ABPI equal to or more than 0.8 and suitable for high compression
Participants with a venous ulcer and an ABPI ≥ 0.8 were offered compression in the form of the 4LB either throughout the trial (hydrogel) or when not receiving larval therapy (see *Table 5*). This trial design therefore answers the pragmatic question of whether the benefits of larval therapy outweigh the disadvantages of going without compression during larval therapy.

Participants with an ABPI equal to or more than 0.6 but less than 0.8 or people not suitable for high compression
These participants were offered reduced compression in the form of a three-layer bandage comprising orthopaedic wool, crepe and a class 3A compression bandage (see *Tables 6* and 7).

Participant follow-up

Appendix 5 shows a summary of the VenUS II trial.

From baseline to withdrawal from trial (debridement) treatment (Phase 1)

Every nurse visit was recorded by the treating nurse along with location and reason for visit (Appendix 3.4–3.6, depending on trial arm). Nurses also recorded the number of applications of trial treatment. Visit information relating to trial debridement treatment was recorded until the reference ulcer debrided (as assessed by the treating nurse) or the participant was recorded as no longer receiving the trial treatment (both events resulting in the participant moving to Phase 2). During Phase 1, when the debridement treatment was removed participants were asked to complete a VAS (as completed at baseline) to assess how painful their ulcer had been over the last 24 hours (no pain to worse pain imaginable, where a higher score was worse).

We advised nursing staff that larval therapy and hydrogel should continue either until debridement or for a minimum of 6 weeks if debridement had not been achieved. Previous studies indicate that the median number of applications of hydrogel needed to achieve debridement is 15.[57]

TABLE 5 *Recommended high-compression four-layer system (40 mmHg compression at the ankle of 18 cm circumference)*

Ankle circumference	Layer 1	Layer 2	Layer 3	Layer 4
< 18 cm	Wool to make circumference a minimum of 18 cm	Crepe bandage	Class 3a bandage	Cohesive bandage
18–25 cm	Wool	Crepe bandage	Class 3a bandage	Cohesive bandage
25–30 cm	Wool	Class 3C bandage	Cohesive bandage	
> 30 cm	Wool	Class 3A bandage	Class 3c bandage	Cohesive bandage
Ankle circumference was measured at the narrowest point.				

TABLE 6 *Recommended reduced compression (23 mmHg at the ankle with 18 cm circumference)*

Ankle circumference	Layer 1	Layer 2	Layer 3
< 18 cm	Wool to make circumference a minimum of 18 cm	Crepe bandage	Cohesive bandage
18 cm or more	Wool	Crepe bandage	Cohesive bandage
There is no special form of a 'light' compression bandage for ankles of circumference greater than 25 cm.			

TABLE 7 *Bandages and their method of application*

Bandage	Application	Examples
Wool	Spiral to cover ulcer and shape leg to cone	Velband, Soffban, Ksoft, Softex, Sohfast, Surepress padding
Crepe	Spiral with 50% overlap and 50% extension	Hospicrepe, crepe, K lite, Soffcrepe, Setocrepe
Class 3A bandage	Figure of eight, 50% overlap and 50% extension	Elset, Profore#3
Class 3C bandage	Spiral with 50% overlap and 50% extension	Tensopress, Profore+, Setopress, Surepress
Cohesive bandage	Spiral with 50% overlap and 50% extension	Coban, Profore#4 Koflex, Co-plus, AAA-flex

The reasons for deciding to stop delivering (withdrawing from) the trial treatment were recorded as:

- deterioration in the ulcer evidenced by clinically significant increase in reference ulcer size observed over 2 consecutive weeks
- no change in ulcer size but a significant increase in slough and/or necrotic tissue
- allergic reaction to larval therapy or hydrogel
- participant hospitalised and trial treatment not adhered to

If a participant stopped receiving the trial treatment they moved into Phase 2 of the study and follow-up continued as per the protocol.

From reference ulcer debridement/withdrawal from trial debridement treatment to trial exit (Phase 2)

Following ulcer debridement the trial treatment specified was a knitted viscose dressing and compression if appropriate (determined by ABPI and participant tolerance). Every nurse visit was recorded, along with location of visits and compression treatment received in the Dressing Log Booklet (Appendix 3.7, same for all three arms). If during Phase 2, a clinical decision was made to change the treatment for a participant who was still following the trial treatment protocol, a withdrawal-from-treatment form was completed with the reason for this change recorded and the new treatment noted.

Trial completion

Participants exited the trial when:

- the participant had been in the trial for over 12 months (6–12 months in some cases)
- the participant wished to exit the trial
- the participant's doctor or nurse withdrew them from the trial
- the participant was lost to follow-up
- the participant had died
- other (details requested).

Participants whose reference ulcer healed ceased to have routine clinical data collected but were asked to continue completing HRQoL and resource-use questionnaires. If the reference ulcer was not the only leg ulcer the participant had, nurses were also asked to record if the participant became ulcer free.

Measurement and verification of primary measure

A variety of disease-specific and generic outcome measures were employed to ascertain clinical effectiveness.

Primary end point

The primary end point was defined as time to complete healing of the reference ulcer.

Ulcer healing was defined as complete epithelial cover in the absence of a scab (eschar). When nurses deemed the reference ulcer to be healed they were asked to seek independent verification from a nurse not involved in the care of the patient one week after the visit at which they regarded the ulcer as healed. If the two nurses did not agree that healing had occurred, the participant continued in the trial until they agreed that the reference ulcer had healed. Upon healing a 'reference ulcer healed form' was completed (Appendix 3.2).

Remote, blinded assessment of healing from photographs was also conducted. Nurses took a digital photograph of the reference ulcer every week until 6 months after recruitment and then monthly until healing or exit (Appendix 6). Before taking the photograph the nurses were requested to clean the skin surrounding the leg ulcer to reduce the risk of treatment detection in the photographs (e.g. remnants of zinc paste). The nurses were also asked to take an image 1 week after healing was regarded by them as having occurred.

Two blinded assessors independently assessed all photographs for each participant to determine a date for healing. This assessment process was piloted by two additional nurses before being undertaken for the main analysis. At the pilot stage it was noted that the trial nurses and clinical blinded outcome assessors viewed an ulcer as healed in the presence of a very small amount of eschar or scab. A revised definition for the blinded outcome assessment was agreed as:

> Clinically, extensive epithelialisation is judged to have occurred (possibly under a very small amount of eschar/dry skin), no further primary wound contact dressing is judged to be required (maintenance treatment may be started).

The assessors discussed any discrepancies with referral to a third assessor for a final decision if required. The primary outcome was calculated using the date of healing as decided by the blind assessors. However, if no photographs were available for a participant then the date of healing decided by the treating nurse was taken as the healed date.

Measurement and verification of secondary outcomes

Collection of resource use data

During Phase 1 information recorded (Appendix 3.3–3.6) included reason for nurse visit and whether each visit was ulcer related; treatment received (used to calculate number of applications); the location of the visit and the compression system used.

During Phase 2 the Dressing Log Booklet (Appendix 3.7) recorded the reason for and the location of the visit and the compression system used.

Nurses were also asked to record details of participant hospitalisation, including the reason for the hospitalisation and length of stay (Appendix 3.8).

At baseline and at 3-monthly intervals thereafter participants were posted a questionnaire asking about health and social-care resource use during the preceding three months (Appendix 3.9). The questionnaire was designed for participant completion and was returned to the trial office using a reply-paid envelope. Participants indicated how many times in the previous month they had used health services (for example, seen a GP or nurse; or received hospital care) and any health service use that was ulcer related. The collection of self-reported resource-use data was continued until trial completion.

Time to debridement

Debridement was defined as a 'cosmetically clean wound'. Nurses recorded whether a wound had debrided at the end of Phase 1; however, the main debridement outcome was assessed by remote, blinded outcome assessors from photographs of the reference ulcer using the definition: 'a cosmetically clean wound requiring no further treatment for debridement'. If no photographs were available for a participant then the date of debridement healing decided by the treating nurse was taken.

Bacterial load

Data were collected using microbiological swabs taken at baseline and after each Phase 1 treatment up to debridement or for a maximum of 1 month (if the ulcer debrided within 1 month then weekly)

and then monthly until healing or trial completion. A protocol for obtaining the swabs was provided for nurses. (Appendix 7) We used swabs, rather than biopsies, for sample collection. It was felt that the specialist skills required to take biopsies and the discomfort of this process for the participant (especially given the number of samples being taken) could not be justified based on existing data regarding the comparative quality of bacterial load data from each source.

Samples (dry swabs), identified by study number, participant's date of birth and date taken, were sent by First Class post at ambient temperature to Micropathology Ltd, Coventry, UK. Upon receipt, samples were stored at –70°C.

Bacterial load was assessed by measuring the amount of bacterial DNA present in wound samples. This molecular approach was able to provide a broad measure of bacterial load deemed suitable for this simple microbiological substudy. This approach was selected over other analytical methods that require specimen integrity, i.e. plating/culturing because of the logistical difficulties involved in processing a large numbers of viable samples from multiple centres across the UK. Because molecular analysis did not require sample preservation – swabs could be sent to a central location, stored and then analysed in batches. This batch analysis system and fact that bacterial load could be measured using a single assay, rather than requiring multiple cultures for subspecies growth, also meant that the molecular approach was much less resource intensive than qualitative analysis.

Bacterial DNA was released from swabs using a protocol adapted from Schabereiter-Gurtner *et al*.[92] Swabs were processed in batches that included negative and positive swabs to control for contamination and extraction efficacy (see 'Quality control'). Swabs were broken off into labelled 2-ml sample tubes containing 500 μl XB buffer (150 mM sodium ethylenediamine tetraacetic acid, 225 mM NaCl, pH 8.5), 60 μl lysozyme (100 mg/ml) and 25 μl lysostaphin (1 mg/ml). The swabs were incubated at 37°C for 30 minutes and then subjected to three cycles of freezing (–70°C) and thawing (72°C). Following this, 220 μl aliquots of each bacterial suspension were removed into a fresh tube and processed for nucleic acid extraction using the QIAamp DNA Blood Biorobot MDx kit combined with the Qiagen MDx Biorobot (Qiagen, Valencia, CA, USA) so that nucleic acids from 200 μl of sample were eluted into 200 μl TE buffer (10 mM Tris–HCl, 1 mM ethylenediamine tetraacetic acid, pH 8.0). The remainder of each sample containing the original swab was stored at –70°C.

Nucleic acids from each swab were subjected to real-time quantitative polymerase chain reaction (PCR) using the following universal 16S ribosomal RNA gene primers: forward, 5′-AGA GTT TGA TCA TGG CTC AG-3′,[93] reverse, 5′-ACC GCG GCT GCT GGC AC-3′.[94] The reaction mixture consisted of ReadyMix Taq PCR reaction mix (12 μl; Sigma-Aldrich, Poole, UK), combined primers (1 μl, 5 μM), $MgCl_2$ (1.5 μl, 25 mM), Evagreen fluorescent dye (1 μl; Biotium, Hayward, CA, USA) and template (10 μl, extracted nucleic acids). Real-time PCR was performed in a Rotorgene 3000 (Corbett Research UK Ltd, St Neots, UK) under the following parameters: 95°C for 40 seconds, followed by 30 cycles of 97°C for 20 seconds, 55°C for 20 seconds, and 72°C for 20 seconds (acquiring to the Sybr channel).

The bacterial load (10^x copies/ml) was calculated by comparison of extracted DNA levels with a standard curve, which was generated for each assay using 10-fold dilutions of DNA extracted from a culture of *S. aureus* that had been quantified by viable and particle-counting methods. Unknowns were calculated by interpolation and results were expressed as 16s ribosomal RNA gene copies per ml. The lowest limit of detection of the assay was 10^3 copies/ml.

Positive and negative extraction controls were included in each batch of swabs processed. Positive controls were prepared by absorbing 500 μl of a 4-hour broth culture of *S. aureus* onto sterile swabs, which were stored at –70°C until required. Negative controls were sterile swabs only. Extraction controls were processed using the same protocols as live samples and the extracted nucleic acids was analysed as described previously.

Positive extraction control swabs were expected to provide bacterial load results of at least 1×10^4 *S. aureus* genome equivalents/ml and negative control swabs were expected to have a bacterial load of less than 1×10^3 *S. aureus* genome equivalents for results from that batch of swabs to be accepted.

Each quantitative PCR assay also included a quality control sample that consisted of extracted nucleic acids of a known bacterial load [internal quality control (IQC)]. This IQC sample had to provide a result varying no more than 0.5 of a log from the

predicted value for the results of that PCR assay to be accepted.

MRSA assay

All baseline swabs were tested for MRSA. Those participants with a positive baseline swab then had all further weekly/monthly swabs analysed for the presence of MRSA. Participants with negative swabs at baseline had one further swab analysed at 2 months to see if MRSA was detectable at the time when debridement treatment would have ceased in most cases.

MRSA was detected using a single-round PCR assay specific for the 3′-terminal region of the Staphylococcal Chromosomal Cassette containing the *mecA* gene responsible for methicillin resistance (SCCmec) when specifically inserted into the *S. aureus* genome at *orfX*.

Nucleic acids were obtained from swabs as described for the bacterial load swabs and subjected to single-round PCR using the following primers: forward *rjmec* 5′-TAT GAT ATG CTT CTC C-3′ and reverse *orfX* 5′-AAC GTT TAG GCC CAT ACA CCA-3′.[95] The reaction mixture consisted of PCR buffer (5 μl; Labmaster, Sevenoaks, UK), dNTPs (5 μl; Web Scientific, Crewe, UK), combined primers (1.5 μl, 5 μM), water (18.5 μl; Sigma-Aldrich, Poole, UK), $MgCl_2$ (1 μl, 25 mM; Sigma-Aldrich), and Immolase DNA polymerase (0.5 μl, Bioline, London, UK). The cycling parameters were 95°C for 20 seconds, followed by 45 cycles of 97°C for 20 seconds, 57°C for 20 seconds, and 72°C for 20 seconds. PCR products were detected by ethidium bromide and agarose gel electrophoresis. Products were referenced to a positive control (MRSA, kindly provided by Prof. C. Dowson, University of Warwick, UK) and results were scored as either 'detected' or 'not detected'. The minimum detection threshold for MRSA was ascertained to be equivalent to 1×10^3 CFUs/ml.

Health-related quality of life

Generic instruments were used to measure participants' perceptions of health outcome in this trial; these have previously been shown to be sensitive to changes in venous ulcer healing status.[96] Generic instruments are also particularly useful for comparisons across groups of participants and have wide scope for use in economic evaluation. Their generic nature also makes them potentially responsive to side or unforeseen effects of treatment. The package of instruments was designed to be comprehensive yet brief and suitable and was administered at baseline and at 3, 6, 9 and 12 months' follow-up.

Participants received the instruments by postal questionnaire to be completed either in the clinic waiting room or at home. The booklet included the EQ-5D and the SF-12. We used a layout of the SF-12 shown in previous work to yield improved response rates and quality.[97]

A systematic review investigating ways of increasing questionnaire response rates reported that response to postal questionnaires was doubled [odds ratio = 2.02; 95% confidence interval (CI) 1.79 to 2.27] when a financial reward was included with the questionnaire, versus no incentive.[98] The response rate increased further when the incentive was not conditional on response, versus upon return of questionnaire (odds ratio = 1.71; 95% CI 1.29 to 2.26). Based on these data, we offered an incentive for participants to return their questionnaire. We notified participants in their 9-month questionnaires that once we received their final questionnaire they would receive £5 in recognition of their commitment to our study and the time they spent completing questionnaires.

Adverse events

An adverse event can be defined as 'any undesirable clinical occurrence in a subject, whether it is considered to be device related or not'.[99] Although it is normal to monitor adverse events within an RCT, we had a mandatory responsibility to collect these data as part of VenUS II, given that it was a trial of an investigational medicinal product that is unlicensed in the UK. Both treatment-related and unrelated adverse effects were reported to the trial office on an adverse-event reporting form. The reporting clinician indicated whether, in their opinion, the event was related to trial treatment, or not. Events were also classed as serious or non-serious. Some events were always classified as serious (death, life-threatening risk, hospitalisation, persistent or significant disability/incapacity). For other events the treating nurse made a clinical decision about the seriousness. Nurses were asked to report serious adverse events, such as admission to hospital, directly to the Trial Coordinator. Nurses were asked to report all adverse events on the adverse event form and state whether they considered them to be related to the trial treatment (possibly/probably/definitely or not). We established a list of possible treatment-related adverse events *a priori*, based on reports in the literature and the VenUS I trial. These are described as follows.

Pressure damage

Excessively high levels of compression or the inappropriate application of compression can lead to pressure damage and in a small number of cases, leg or foot amputation,[84] although frequently these adverse outcomes are not well described in research reports. Pressure damage presents on pressure areas (areas of small radius and/or little padding) such as the malleoli, Achilles tendon, or the front of the foot and is indicated by non-blanching erythema. Bands of high pressure on the leg can result in lines of skin damage along the lines of the bandage. Assessment of the skin of the leg after each bandage removal is a fundamental part of leg ulcer management.

Maceration, excoriation and infection

Compression bandages may keep wound exudate in contact with the skin surrounding the ulcer, leading to maceration of the periulcer skin. Occlusion of the ulcer and the skin provides a moist environment, which may encourage fungal and bacterial infections of the periulcer skin or the ulcer itself. Maceration presents as swollen, white, soggy skin. Excoriation is the appearance of red, inflamed skin around the ulcer, thought to be caused by wound exudate which contains enzymes. Infection presents usually with a combination of any or all of inflammation, pain, odour, heat and purulent discharge.

Ulcer-related pain

Research investigating the impact of a leg ulcer on HRQoL has demonstrated that pain is one of the most troublesome aspects of having a venous leg ulcer.[100–104] Larval therapy may increase[54,105] or decrease[83] ulcer pain, or have no effect.[52]

Ulcer deterioration

Assessment of ulcer healing progress is complex and includes assessment of the colour of the wound bed, e.g. a pink or red wound bed may indicate epithelialisation or granulation tissue, whereas yellow slough, or green/blue/black colours may indicate the presence of infection. Ulcer area was also assessed, although the trajectory of venous ulcer healing is not necessarily linear, and therefore assessment of progress can be difficult. If an ulcer has necrotic tissue edges then the autolysis of this dead matter, under compression, may lead to an apparent increase in the area of the ulcer. Ulcer deterioration included increase in ulcer area, malodour, apparent allergy and ulcer bleeding.

Qualitative study of nurses' and patients' perceptions of and attitudes towards larval therapy

A qualitative study was undertaken to look at the acceptability and experiences of participants and staff in relation to larval therapy. Purposive sampling was used to recruit patient and nurse participants who had and had not had experience of larval therapy.

Four groups were to be interviewed:

- up to eight people with venous or mixed venous/arterial leg ulcers who had experienced larval therapy (either bagged or loose larvae) (final number of interviewees to be decided depending on saturation of themes)
- up to eight people with venous or mixed venous/arterial leg ulcers who had not experienced larval therapy (final number of interviewees to be decided depending on saturation of themes)
- up to eight nurses currently caring for people with leg ulcers who had been involved in larval therapy previously (either bagged or loose larvae) (final number of interviewees to be decided depending on saturation of themes)
- up to eight nurses currently caring for people with leg ulcers who had not been involved in larval therapy previously (final number of interviewees to be decided depending on saturation of themes).

Recruitment to the qualitative study

Patients

Participants were recruited from three of the VenUS II trial centres, i.e. York, Bolton and Bradford (as these centres were readily accessible by the interviewer) using purposive sampling.[106] Health professionals involved in the care of people having treatment for a leg ulcer either at home or at a leg ulcer clinic were asked to give a leaflet about the study (Appendix 8) to potential interviewees. Potential participants considered whether they would like to be included and if they decided to participate and to give consent to be interviewed, an interview was scheduled at a convenient time and was conducted according to the Interview Schedule (Appendix 9).

Nurses

Nurses working in Huddersfield, York, Scarborough, Bolton and Bradford were recruited to the study (as these centres were readily accessible by the interviewer). The nurses worked either in the leg ulcer clinics or in the community. Nurses were given written and verbal information about the study at least 1 week before their recruitment into the study (Appendix 9). After giving written consent to take part in the study, nurses were interviewed at a time and in a location (usually their place of work) that was convenient.

Semi-structured interviews were conducted with each respondent to gain an insight into his/her health beliefs and views/experiences of larval therapy. The interviews aimed to yield naturalistic data concerning the experience of having larval therapy, attitudes, beliefs and the acceptability of receiving and giving the treatment. The interviews explored how these beliefs and attitudes were altered through experiencing the treatment (Appendix 9).

Statistical analyses

All analyses were conducted on an intention-to-treat basis, including all participants in the groups to which they were randomised, using two-sided significance tests at the 5% significance level. Analyses were conducted in SAS version 9.1 (SAS UK, Marlow, UK).

Baseline data

All baseline data were summarised by treatment group. Baseline data were summarised descriptively. No formal statistical comparisons were undertaken.

Primary analysis

Time to healing was derived as the number of days from randomisation until the date of healing as confirmed from the blinded photograph assessment (or the date recorded by the nurses if no photographs were available). Participants who did not heal were treated as censored and their date of trial exit, date of their last available assessment, or 365 days/trial cessation, as appropriate was used to calculate their duration in the trial.

An initial analysis of time to healing of the reference ulcer compared the three treatment groups using a log-rank test. Kaplan–Meier survival curves were constructed and the median time to healing and corresponding 95% CI for each group were calculated. A Cox proportional hazards model was used to adjust the analysis for the randomisation stratification factors (centre, baseline ulcer area) as well as duration, and ulcer type. Actual baseline area (as measured from the tracings) and duration of ulcer were used. A treatment contrast was included in the model to compare healing rates between loose and bagged larvae. It was decided *a priori* that if there was no evidence of any difference between the loose and bagged larval therapy then the hazard ratios and 95% CI would be presented for larval treatment overall (loose and bagged combined) compared with hydrogel. This strategy was not detailed explicitly in the original study protocol but was stipulated in the analysis plan, which was written before any data analysis. If there was a statistically significant difference ($p \leq 0.05$) in healing rates between loose and bagged larvae then the hazard ratio and 95% CI would be presented separately for each type of larval treatment compared with hydrogel. The assumption of proportional hazards was assessed graphically using log–log plots of the estimated survivor function and Schoenfeld residual plots. We also included interaction terms between each variable and log (time) in the Cox model. The results from the adjusted analysis are presented as the primary results.

As there were a number of centres that only recruited a small number of participants (fewer than 10), sensitivity analyses were conducted to assess the impact of different methods of handling these small centres. This was done by: combining small centres, stratifying by centre, and by excluding centre from the model.

Secondary analyses

Time to debridement

Time to debridement was derived as the number of days from randomisation until the date of debridement as confirmed from the blinded photograph assessment (or the date recorded by the nurses if no photographs were available). Participants who did not debride were treated as censored; the censoring date was date of healing or date of trial completion, date of their last available assessment, or 365 days/trial cessation, as appropriate.

The time to debridement was analysed in the same way as the primary outcome variable, with adjustment for the same covariates. The same

treatment contrasts were used and results were presented as hazard ratio and 95% CI for larval therapy compared with hydrogel, or each larval treatment separately compared with hydrogel dependent on the analysis results comparing loose and bagged larvae.

Health-related quality of life

The HRQoL was measured using the SF-12 questionnaire at baseline and 3, 6, 9 and 12 months. Descriptive statistics (mean; SD) for the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were calculated by treatment group and across all arms. The overall scores for the PCS and MCS were analysed in two ways. First, the area under the curve (AUC)[107] over all assessments was calculated for each participant and then this was standardised to produce a standardised area under the curve (SAUC), which divides the AUC by the length of follow-up for each participant. The overall SAUC was compared between larvae and hydrogel groups using a Wilcoxon rank sum test. We also used a multilevel regression model (SAS proc mixed) which allows for repeated observations within each participant. The total score at each follow-up assessment (3, 6, 9 and 12 months) was the outcome variable and the model included terms for treatment, time, baseline score, ulcer area, ulcer duration and ulcer type. The interaction between time and treatment arm was assessed for inclusion in the model. As the primary aim of the project was to compare larval therapy with hydrogel the primary comparison of this analysis was larval therapy compared with hydrogel.

Bacterial load

Bacterial load data were log transformed (using logs to base 10) and summarised over time using descriptive statistics. A linear random coefficients model was fitted to log bacterial count to compare changes in bacterial load over time between the larval therapy and hydrogel groups. Time of the ulcer swab (number of days from baseline) was treated as a continuous measure and a quadratic term for time ($time^2$) was included to test if the effects of time were non-linear. Treatment (larvae or hydrogel), time, baseline ulcer area, ulcer duration and ulcer type were treated as fixed effects and participants (to allow for a different intercept for each participant) and participant–time interactions [to allow for different effects of time (slopes) for each participant] were treated as random effects. The interaction between treatment and time (to test if changes in bacterial load over time differed between treatments) was also included in the model. Two analyses were performed: one assessed bacterial load until the end of the trial for each participant; and the other only analysed bacterial load data up to the end of Phase 1 (to debridement if the participant debrided during the trial, or to the end of the trial if the participant did not debride).

MRSA

All baseline swabs collected from the reference ulcer were tested for the presence of MRSA. This was a dichotomous outcome (presence or absence of infection). For MRSA-positive participants, the proportions of participants where MRSA was eradicated by the end of Phase 1 were compared between larvae and hydrogel groups using Fisher's exact test. This analysis was repeated for the proportions of MRSA-negative participants who tested positive for MRSA at any follow-up assessment.

Complete healing of all ulcers

The numbers of participants who healed completely by the end of their trial follow-up (i.e. all ulcers on both legs, not just the reference ulcer) were summarised by treatment group but no statistical analysis was performed.

Adverse events

The numbers of adverse events experienced by each participant were compared between treatment groups using a negative binomial model adjusting for the same covariates as the primary analyses (ulcer size, ulcer duration, type of ulcer). The number of participants experiencing an adverse event, the number of events recorded and their seriousness and suspected relationship to treatment were summarised for each treatment group.

Ulcer-related pain

The score from the VAS assessed at the first treatment removal visit (asking about ulcer pain over the previous 24 hours) was compared between treatment groups using linear regression, adjusting for baseline ulcer-related pain score, ulcer area, ulcer duration and ulcer type.

Economic analyses

A cost-effectiveness analysis and a cost–utility analysis were performed using patient-level data collected as part of VenUS II. Intention-to-treat analyses compared incremental costs with incremental ulcer-free days (cost-effectiveness analysis) and incremental quality-adjusted life-time (cost–utility analysis).

The perspective for the economic analysis was that of the UK NHS and Personal Social Services (PSS). Hence, benefits included clinical and health-related benefits valued from the perspective of society, and costing included use of NHS and PSS resources required to achieve those benefits.[108] The time horizon for the analysis was 12 months after recruitment, and consequently neither costs nor health benefits [quality-adjusted life-years (QALYs), ulcer-free days] were discounted. The analyses were conducted using STATA 10 (StataCorp 2007, College Station, TX, USA).

Health benefits

Mean time to healing estimation

To meet the needs of decision-makers, the focus of economic evaluations alongside RCTs is on estimating mean costs and health benefits (QALYs and ulcer-free days) associated with health technologies. Unlike in clinical evaluations where the median is often preferred, in economic evaluations the mean is the only statistic that provides useful information on the expected health benefits and costs associated with health technologies.

In VenUS II, healing was the event of interest, however, as well as being healed, individuals could be censored or die. Nearly all statistical methods for survival analysis are based on the assumption that the reason for censoring is independent of the outcome – non-informative censoring. Yet, when the event of interest is not death – as is the case in VenUS II – participants who do die are usually censored even though we know that healing cannot occur after death. As only nine people were reported to have died during VenUS II follow-up, it was decided not to consider death as an informative censoring event in the estimation of time to healing. Nonetheless, this issue may be explored in a future analysis using multistate models to estimate the transition probabilities of different events of interest (debridement, healing, amputation and/or death).[109]

If all participants were followed until the event of interest occurs (ulcer healing), mean time to event could be estimated by integrating the survival function over time. However, in VenUS II we know that censoring occurred as a result of loss to follow-up, death or study conclusion (participants were followed for a maximum of 1 year). In this case, conventional methods for the estimation of mean time to event (mean time to ulcer healing) are considered inappropriate. To estimate mean survival time over a specific study period, two options have been explored in the literature: (1) the restricted mean approach; (2) the weighted ordinary least squares regression or inverse probability weighting (IPW) approach.[110]

In the last 5 years the IPW method has been proposed as a robust method to estimate mean cost and QALYs.[111–113] Consequently, our base-case analysis was conducted using inverse probability weights in the estimation of mean time to healing, as well as mean costs and QALYs. In this approach only participants with observed time to healing data contribute with non-zero terms, but their contributions are inversely weighted by the respective probability of being observed. The weight is then zero if the participant is censored before or within an interval, corresponding to a missing observation. If the participant survives the interval or dies (heals), the weight is the inverse of the probability of not being censored at the end of the interval or at the time of death (healing) respectively.[114] Consequently, individuals who are less likely to be observed are weighted most heavily. The censoring distribution was estimated through the Kaplan–Meier estimator and CIs were evaluated through non-parametric bootstrap.

As the IPW estimation procedure has not yet been applied to non-absorbent events such as healing, the restricted mean estimate was also computed to validate the current results.[115] Mean time from randomisation to healing, restricted to an upper time limit, was calculated as the area under the survivor function from zero to the chosen finite time limit. The time point of restriction was evaluated in conformity to the statistical criterion proposed by Karrison,[116] who suggests that information should be used until the standard error of the survival probability estimate does not exceed a certain lower limit; in the present analysis assumed as 10%.[117] To account for stratification variables and prognostic factors, the survival function was estimated using the same Cox model defined in the clinical analysis.

The results of the estimation procedures returned mean time to healing for each trial arm. If larval therapy reduced time to healing, the difference in time to healing between the larval and hydrogel groups would have been negative, which can make interpretation more difficult for the reader. To simplify the interpretation of the cost-effectiveness analysis, the effectiveness outcome was reported as gains in ulcer-free days, which assume the same absolute value as difference in time to healing but have the opposite sign.

Utility scores

The health-state descriptor measure used was the EQ-5D, a widely recognised and validated descriptive system of HRQoL.[91] HRQoL data were collected at baseline and 3, 6, 9 and 12 months. The EQ-5D questionnaire has five questions, each relating to a different health dimension: mobility, self-care, ability to undertake usual activity, pain and anxiety/depression. Each question has three possible response levels: no problems, moderate problems and severe problems. Based on their combined answers to the EQ-5D questionnaire, participants can be classified as being in one of 243 possible health states. Each of these health states has an associated utility weight which denotes the impact this state will have on HRQoL. Responses to EQ-5D questionnaires were used to compute individual's utility scores, which were used to calculate QALYs. Utility scores were calculated using an independent predefined algorithm obtained by the elicitation of societal preferences for the health dimensions in a random population sample through a time trade-off technique.[118] Hence, perfect health has a weight of 1, which decreases as health becomes impaired. Quarterly QALYs were calculated by applying individual's utility weights to survival time using the AUC approach,[107,119] which is defined by linearly interpolating the utility scores measured over time.

Mean QALY estimation

Not all participants were followed up for a full year because of censoring. To account for the impact of censoring,[120] and so avoid bias, mean QALYs over the 12 months follow-up period were again estimated using the IPW method.[112,113,121] The study time horizon was partitioned in homogeneous subintervals (quarterly intervals) and mean QALYs were estimated in each interval. To ensure comparability with the clinical analysis, linear regression was used to adjust QALYs by the same covariates and also baseline utility.[119] QALYs were weighted by the inverse of the probability of an individual not being censored. If a participant died their utility values were recoded as 0. Mean total QALYs were then estimated as the sum of the estimated mean QALYs per period for each trial arm, considering the mean value of the rest of the covariates observed in the whole sample.

Resource use and unit costs

A cost for each trial participant was calculated as the product of resources used by their relevant unit cost. Resource-use data were collected in nurse questionnaires and self-reported participant questionnaires.

Analysis was carried out using 2006 costs in Pounds Sterling.

Three different elements were considered in the estimation of costs:

- trial debridement treatment
- health care provider time (visits to/from health care provider for leg-ulcer-related reasons)
- cost of compression therapy.

Other treatments, such as primary and secondary dressings or skin preparations, were assumed to be used equally across treatment arms: these resources were not included in the economic analyses.

Trial debridement treatments applied

Ulcer debridement data used in the analysis were collected by the treating nurse at each visit. Where data on the number of larvae pots/bags required were missing (31% for bagged larvae and 54% of loose larvae), these were estimated from the existing data using linear regression and the area of the reference ulcer at baseline. When costing the number of larvae bags or pots for each participant we assumed the cheapest combination of bags or pots of larvae possible. Unit costs were obtained from the larvae suppliers (*Table 8*).

Visits to/from health care providers

Data from two sources of information on visits to or from health care providers were available in VenUS II: nurse-reported and self-reported. Ulcer-related self-reported data were collected after healing of the reference ulcer while nurse-reported data were systematically collected only for the reference ulcer; however, some participants had multiple ulcers. To record ongoing resource use after healing of the reference ulcer, self-reported data were used in the base case, while the use of nurse-reported data was explored in a sensitivity analysis.

The cost per visit was calculated assuming different durations of home and clinic visits (*Table 9*). The self-reported data collected information about the visit setting (home or clinic); however, this was recorded for all nurse visits rather than for ulcer-related visits only. Consequently, we assumed that the setting of ulcer-related visits from self-reported data would follow the same pattern as that reported for all nurse visits, where data were available. Hospital visits were costed on an outpatient visit.

TABLE 8 *Description of unit costs of trial treatments for debridement*

Trial debridement treatments	Cost, £	Source
Loose larvae application kit, LarvE©		
One pot = 300 maggots	58.0	Zoobiotic
Half pot = 150 maggots[a]	35.0	Zoobiotic
Postage costs	16.5	
BG application kit, Biobag©		
50 units	59.26	Biomonde
100 units	67.17	Biomonde
200 units	79.03	Biomonde
300 units	98.79	Biomonde
Freight charge	20.89	
Purilon® Gel (Coloplast) (8 g)		
	1.55	BNF[122]

BNF, *British National Formulary*.
a No longer available.

Compression therapy

The costs of compression therapy were determined on a visit-by-visit basis. As no information on the size of the system brand was available, an arithmetic average cost for commercially available systems was used to cost the class recorded (High compression: 4LB, SSB, two-layer, three-layer high compression; Low compression: three layer reduced compression; light compression), assuming that the elements used to compose the compression system were as per protocol (*Table 10*). Where the use of more than one compression system was reported in a single visit, the more costly system was considered.

TABLE 9 *Description of parameters used to calculate unit costs related to consultations with health care providers*

Parameter description	Value	Source
Nurse consultations		
Duration of clinic visits, minutes	22	VenUS I[12]
Home vs clinic visit duration ratio	40/22	VenUS I[12]
Cost per minute depending on location		
Clinic visits, £	0.6667	PSSRU[123]
Home visits, £	1.0852	PSSRU[123]
Travelling fixed cost for home visits, £	1.3	PSSRU[123]
Hospital consultations		
Hospital visits (outpatient visit), £	113	PSSRU[123]
Doctor consultations		
Cost per visit, £ (based on general practitioner) depending on location		
Surgery consultation, £	25	PSSRU[123]
Home visits (includes travel time), £	69	PSSRU[123]

PSSRU, Personal Social Services Research Unit

TABLE 10 *Description of unit costs of compression bandaging systems*

Bandaging system	Cost (£ Sterling)	Source
High-compression bandaging: 4LB		
K-Four®	6.26	BNF[122]
Profore	8.21	BNF[122]
System 4	7.77	BNF[122]
Ultra Four®	5.67	BNF[122]
Mean cost	6.98	
High-compression bandaging: SSB		
Actiban	3.18	BNF[122]
Actico	3.21	BNF[122]
Comprilan	3.12	BNF[122]
Rosidal K®	3.36	BNF[122]
Silkolan	3.39	BNF[122]
Mean cost	3.25	BNF[122]
High-compression: two-layer kits		
ProGuide	8.49	BNF[122]
Coban®	8.08	BNF[122]
Mean cost	8.29	
Class 1		
Advasoft® (Advancis)	0.39	BNF[122]
Cellona® Undercast Padding(Vernon-Carus)	0.42	BNF[122]
Flexi-Ban® (Activa)	0.44	BNF[122]
K-Soft® (Urgo)	0.40	BNF[122]
Ortho-Band Plus® (Bailey, Robert)	0.37	BNF[122]
Softexe® (Medlock)	0.58	BNF[122]
Ultra Soft® (Robinsons)	0.42	BNF[122]
Velband® (J&J)	0.66	BNF[122]
Profore® #1 (S&N Hlth)	0.62	BNF[122]
Mean cost	0.48	

Mean cost estimation

Resource use data collected are also subject to censoring and estimating the mean total cost based on complete case analysis will underestimate the true expected costs. An IPW regression (as described above) was used to account for censoring, possible baseline imbalances and randomisation stratification variables. Mean cost estimation was made by partitioning the study period into multiple time intervals (quarterly periods) and the IPW regression per period estimates were then summed to obtain total expected costs.

Cost-effectiveness

As in the clinical analysis, in the incremental cost-effectiveness analysis estimates of total cost and health benefit (ulcer-free days and QALYs) were reported for larval treatment (pooling data from the loose and bagged larvae groups) and hydrogel treatment. Nonetheless, for completeness descriptive measures on costs and health benefits were described for each of three trial arms.

To assess cost-effectiveness, we compared the mean difference in costs between trial arms with

TABLE 10 *Description of unit costs of compression bandaging systems (continued)*

Bandaging system	Cost (£ Sterling)	Source
Class 2		
Neosport® (Neomedic)	0.99	BNF[122]
Soffcrepe® (BSN Medical)	1.14	BNF[122]
Setocrepe® (Medlock)	1.18	BNF[122]
Profore® #2 (S&N Hlth)	1.16	BNF[122]
K-lite	0.89	BNF[122]
Mean cost	1.07	
Class 3A		
Elset®	3.06	BNF[122]
Elset® S	5.13	BNF[122]
K-Plus®	2.17	BNF[122]
Profore® #3	3.46	BNF[122]
Mean cost	3.46	
Cohesive		
Coban® (3M)	3.61	BNF[122]
Ko-Flex®	2.90	BNF[122]
Profore® #4	2.86	BNF[122]
Hospifour® # 4	1.93	BNF[122]
Mean cost	2.83	
Class 3C		
Setopress (Medlock)	3.46	BNF[122]
Tensopress® (S&N Hlth)	3.47	BNF[122]
Profore+	3.18	BNF[122]
Mean cost	3.37	
Compression systems (using mean costs for each class, presented below)		
Three-layer high compression: 1, 3C cohesive	6.67	
Three-layer reduced compression: 1, 2 cohesive	4.34	
Light compression: 1 cohesive	3.30	

BNF, *British National Formulary*.

the mean difference in number of ulcer-free days and QALYs. The results of economic evaluation studies can be graphically represented in what is known as a cost-effectiveness plane where results are characterised in one of four potential scenarios (*Figure 1*).

Alternative scenarios on the cost-effectiveness plane:

- If the results from the economic evaluation analyses of VenUS II fall in the north-west (NW) quadrant of the cost-effectiveness plane it implies that larval therapy is dominated by hydrogel, in other words, larval therapy is more expensive and is associated with fewer health benefits than hydrogel. In this case, the decision regarding adoption of larval therapy is straightforward and one should not adopt it.
- Similarly a straightforward decision can be made when the cost-effectiveness measure is positioned in the south-east (SE) quadrant. In this situation, larval therapy would be dominant, i.e. estimated to be less costly and more beneficial than hydrogel and should therefore be implemented.

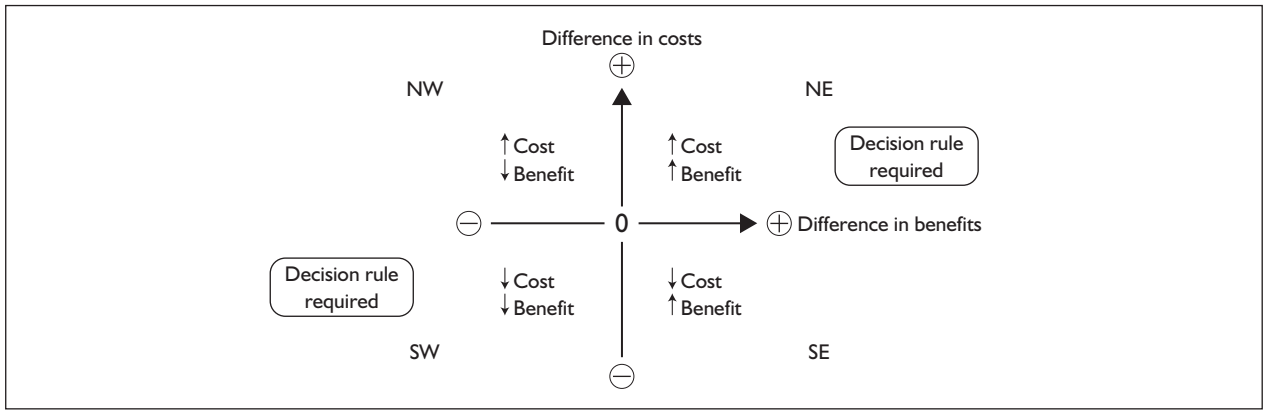

FIGURE 1 *Cost-effectiveness plane showing cost and benefit differences between alternative treatments (NW, north-west; NE, north-east; SW, south-west; SE, south-east).*

- In the NE or SW quadrants, decisions are more difficult to make. Here one must evaluate whether the increased cost of the new intervention is worth the increased benefit (NE scenario), or if the reduced benefit conferred by the new treatment is justified by the reduced costs (SW).

To ascertain the cost-effectiveness of a health care intervention relative to another in the absence of dominance, one needs to conduct an incremental analysis of cost-effectiveness. The incremental cost-effectiveness ratio (ICER) is the most commonly used cost-effectiveness measure and combines costs and health in a single measure to which a decision rule for cost-effectiveness can be applied. It combines costs and benefits in a ratio of the mean difference in cost between the alternative treatments being compared with the mean difference in health benefits such that:

$$\text{ICER} = (C1 - C0)/(B1 - B0)$$

where: $C1$ is the mean cost associated with the technology under evaluation (larvae); $C0$ is the mean cost associated with the technology of comparison (hydrogel); $B1$ is the mean health benefit associated with the technology under evaluation (larvae); and $B0$ is the mean health benefit associated with the technology of comparison (hydrogel).

The decision rule for cost-effectiveness on the basis of the ICER indicates that a treatment strategy can be considered cost-effective only if the decision-maker's willingness to pay for an additional unit of health benefit (QALYs, ulcer-free days) is greater (or equal) to the ICER. In this context, the decision-maker is responsible for establishing the willingness to pay.

Uncertainty assessment

The treatment decision is uncertain because the expected cost-effectiveness outcomes are assumed to be stochastic (in a Bayesian approach to parameter probability). Nevertheless, decision-makers have to decide on the provision of services, even in the presence of uncertainty. It has been argued that, irrespective of whether the cost-effectiveness estimate is statistically significant at conventional (arbitrary) levels, the expected cost-effectiveness can be used to decide on the adoption of the new technology.[124]

Confidence intervals

Uncertainty around the decision to adopt the treatment under evaluation was assessed through a non-parametric bootstrap resampling technique.[125] This is a common methodology used to construct confidence intervals around the incremental costs and health benefits from sampled cost and effectiveness random variables.[126–128] First, the bootstrap technique was used to sample (with replacement) from the observed cost and effectiveness pairs, maintaining the correlation structure. For each bootstrap resample, an IPW estimate of expected total costs, expected QALYs and expected time to healing was calculated, which allowed computation of cost-effectiveness and cost–utility outcome replicates. The 95% CIs for the differential costs and QALYs were then calculated using bias-corrected non-parametric bootstrapping.[125]

Cost-effectiveness acceptability curves

To explore the decision uncertainty regarding the cost-effectiveness of larval therapy, cost-effectiveness acceptability curves (CEAC) were estimated. The CEAC expresses the likelihood that the cost-effectiveness estimate reflects a cost-effective intervention, based on the existing evidence.[129] The CEAC summarises, for every value of willingness-to-pay thresholds, the evidence in favour of the intervention being cost-effective. In this case, given the trial data, the CEAC for larval therapy represents the probability of this therapy being cost-effective compared with hydrogel for a range of willingness-to-pay values for an ulcer-free day/QALY. This represents a Bayesian interpretation of cost-effectiveness uncertainty, although a full Bayesian analysis was not undertaken.

Sensitivity analysis

Total costs of treating venous leg ulcers are driven by nursing costs and hospitalisation costs.[12] As information on nurse and hospital visits was also collected by nurses (as well as self report), the use of this information source to estimate total costs was explored in sensitivity analysis. Nurse-reported costs of health care provider visits were calculated distinguishing the visit location. Clinic, home or GP surgery visit costs were estimated assuming differential visit duration, see *Table 11*. Ulcer-related hospitalisations were costed based on the duration of hospitalisation through a bed day cost. Nevertheless, if a participant was hospitalised for a non-ulcer-related reason and received ulcer treatment while in hospital, this ulcer-related cost was calculated considering only the hospital nurse time.

To explore the impact of using nurse-reported data on visits and hospitalisations, the cost-effectiveness of larval therapy was re-estimated using these data and including the cost of trial treatments, nurse visits and hospitalisations. Two scenarios were implemented:

TABLE 11 *Description of parameters used to calculate unit costs related to visits to health care providers and hospitalisations in the sensitivity analysis*

Parameter description	Value	Source
Nurse consultations		
Duration of clinic visits, minutes		
Loose larvae application	37	survey
Bagged larvae application	22.5	survey
Dressing application (compression or no compression)	22	VenUS I[12]
Home vs clinic visit duration ratio	40/22	VenUS I[12]
Cost per minute depending on location		
Clinic visits, £	0.6667	PSSRU[123]
Home visits, £	1.0852	PSSRU[123]
Travelling fixed cost for home visit, £	1.3	PSSRU[123]
GP surgery visits, £	0.4667	PSSRU[123]
Hospital visits, £	0.6667	PSSRU[123]
Doctor consultations		
Cost per visit (based on general practitioner) depending on location		
Surgery consultation, £	25	PSSRU[123]
Home visits (includes travel time), £	69	PSSRU[123]
Hospitalisations		
Ulcer-related hospitalisation day (outpatient visit), £	113	PSSRU[123]
Amputation, £	8201	UK ref costs[130]

PSSRU, Personal Social Services Research Unit

- Scenario 1: Ignoring amputation costs in the calculation of hospitalisation costs.
- Scenario 2: Considering amputation costs in the calculation of hospitalisation costs.

Amputation is an expensive procedure and a small number of events may change the total costs estimates. As information on amputation was not systematically collected, the inclusion of amputation costs was assessed in a sensitivity analysis, recalling that this analysis may be biased. As described in *Table 11*, amputation costs (scenario 2) were considered as a one-off cost.

One-way sensitivity analysis was also carried out in an attempt to disentangle the influence of the duration of nurse visits in total treatment cost. The base-case analysis (considering self-reported visits to/from health care providers) was reproduced for a range of sensible values of the following parameters:

- duration of nurse visits
- ratio of home versus clinic visit duration (to explore whether changing site of visit affects cost-effectiveness).

Qualitative data analysis

Interviews were recorded onto tapes and transcribed verbatim. Analysis of the interview had five stages: reading the text and coding for descriptive labels; sorting for patterns within the data; identifying outliers or negative cases and revising theory accordingly; generalising and refining constructs and theories; more detailed reflection and revision. Analysis was conducted with the assistance of the computer software package ATLAS.TI (Atlas.ti, Berlin, Germany). The data were analysed using an iterative, comparative approach to elicit similarities and differences across the data set.[131]

At the coding stage, reliability of coding was assessed by asking another researcher to independently code some of the raw data, using previously agreed coding criteria. This is close to the concept of inter-rater reliability which is familiar in quantitative research.[131] The 'independent researcher' had no connection with the study of larval therapy, but had wide experience of analysing and interpreting qualitative data. Codes had been derived by the primary analyst after close reading of the total data set to identify all the key issues, concepts and themes by which the data could be examined and referenced. Four patient and nurse interview transcripts (representing 10% of the data set) were randomly selected and subjected to examination by the independent researcher for adequacy of the coding framework and accuracy of coding. Subsequent discussion between the independent researcher and the primary analyst led to further refinement of the coding framework, which was then applied across the total data set.

Chapter 3
Changes to protocol

Participating centres

The original proposal contained eight recruiting sites and planned to recruit participants over 18 months with all participants being followed up for 12 months. As the trial progressed, recruitment fell below expected levels and further sites were recruited. Details regarding the recruitment duration of each site can be found in Appendix 1. An extension in time and funding was obtained from the funder and the recruitment period was extended to 35 months (June 2004 to May 2007). The recruitment period was also extended into 6 months of the 12-month follow-up period.

Inclusion/exclusion criteria

In the original protocol inpatients, patients with bilateral leg ulcers and patients with more than four leg ulcers were excluded from the trial. Low rates of recruitment at an early stage led us to request Main Research Ethics Committee (MREC) approval to remove these exclusions: inpatients were eligible for inclusion from August 2004; people with bilateral leg ulcers were eligible for inclusion from November 2004; and people with more than four leg ulcers were eligible for inclusion from November 2004.

During the trial the manufacturers of the loose larvae added a contraindication to the use of larvae for those receiving anticoagulants when they were not under constant medical supervision. As a result, this was added as an exclusion criterion (May 2005).

Sample size

A recruitment rate that was substantially under target led us to apply to the funder for an extension to the recruitment period. To calculate the most appropriate duration for the extension we estimated the difference in median time to healing detectable with 90% power with different sample size scenarios (and allowing for a 15% loss to follow-up) (*Table 12*).

We requested an 18-month extension to recruitment with a revised recruitment target of 370 participants (90% power to detect a reduction in median healing time from 20 to 12.7 weeks while allowing for 15% loss to follow-up), or 270 participants to detect the same difference with 80% power.

Digital images

The reference ulcer was originally photographed weekly throughout the study until healing. During the trial it became apparent that this requirement created an amount of work for nurses working on the trial that was difficult to justify and was probably reducing recruitment of new participants; furthermore, the requirement for weekly photographs was causing some inconvenience to participants. This was especially the case where participants were coming back to clinics specifically for a digital image to be taken or where nurses were travelling long distances to take images in participants' homes. The trial statistician (Professor Martin Bland) undertook a simulation using data

TABLE 12 *Simulated sample size scenarios*

Duration of extension (months)	Revised sample size	Treatment effect (median time to healing with larval therapy) (weeks)
6	170	10.2
12	260	11.6
18	370	12.7
24	480	13.4
30	600	14.0

from a previous study (VenUS I). He explored the effect that monthly rather than weekly follow-up would have had on the precision of the estimate of the treatment effect for the VenUS I trial and found that it would have almost no impact (but the benefit to this trial would be potentially greater recruitment because centres were less likely to reach capacity). MREC approval was gained to reduce the frequency of collection of digital images from weekly to monthly after 6 months of follow-up.

Recruitment into other trials

Our initial protocol precluded participants in this trial from participating in other trials during follow-up. One of our main recruiting centres voiced strong concerns that they were unable to recruit clinic patients into other leg ulcer clinical trials because of the extended duration of follow-up of patients in VenUS II. The trial statistician, Professor Bland, simulated the effect on the VenUS I end point estimate of 50% of participants being randomised into other trials and found no discernable impact on power so we obtained MREC approval for VenUS II participants, randomised more than 6 months previously, to be recruited to other trials while still being followed up for VenUS II

Questionnaire response rate

As discussed in Chapter 2, a systematic review investigating ways of increasing questionnaire response rates reported that the response rate to postal questionnaires was doubled (odds ratio = 2.02; 95% CI 1.79 to 2.27) when a financial reward was included with the questionnaire, compared with no incentive. Based on these data we obtained MREC approval to include £5 with the final questionnaire sent to participants at 12 months; however, participants were only informed of this unconditional token of our appreciation in their 9-month letter.

Interim analysis

Before the trial commenced we were concerned that it might be difficult to recruit sufficient numbers of participants to a three-arm trial and we therefore sought mechanisms by which we might be able to close one arm to recruitment early without losing valuable information. We therefore planned to undertake an interim analysis after 200 participants had been followed for 92 days at which point:

- If there was a treatment difference between the two larvae formulations in favour of loose larvae then we would continue with the three-arm trial because bagged larvae may still be more acceptable or cost-effective than loose larvae. We calculated that, after 15% attrition, we would end up with approximately 160 participants in each group. This would give us 78% power to detect an absolute difference in proportions healed of 15% (from 50% to 65% ulcers healed at 16 weeks).
- If there was no discernible difference between the two larvae formulations then we would close the loose larval therapy arm down (because bagged larvae would always be likely to be more acceptable). If the loose larvae arm had closed at the interim analysis we would have changed the randomisation ratio. We had then planned to randomise 276 participants to the control arm and only a further 209 to the larval therapy arm giving a total of 276 in larval therapy including the original 67 participants receiving loose larvae (assuming 15% attrition). This would have given us 90% power to detect an absolute difference in proportions healed of 15% between the two arms.
- If bagged larvae seemed slightly less effective we would have continued with the three arms;
- If bagged larvae seemed ineffective at the interim analysis we were to close the bagged larvae arm down. We would have changed the randomisation ratio at this point to 1 : 1 (two arms). We would have randomised 243 participants to each of the continuing arms; leaving 206 after 15% attrition. This would have given us 84% power to detect an absolute difference in proportions healed of 14% between the two arms.

These steps were agreed with the funder before finalising the research contract. However, after the start of the trial a number of arguments were presented against conducting an interim analysis. It was suggested that the analysis seemed unnecessarily complicated, inefficient and quite likely to mislead. In practice, if the results of an interim analysis had meant it was possible to close either larval therapy arm, we would have already recruited more than 200 participants (because of the time taken to do the analysis, consult stakeholders and make decisions). Additional

participants would also have been recruited in the 92 days while the 200th participant was being followed up. In practice, there would have been fewer than 250 participants per group after closure of one group. The standard error of a difference between two groups of 250 would be 87% of that for two groups of 189, hence the detectable difference for given power is 87% of that for three groups. So there would not be much difference and delays would make this closer to 100%. For these reasons, we sought and received approval from MREC and the funder to not conduct the interim analysis and we retained three treatment arms until trial closure.

Chapter 4
Clinical results

Recruitment

Recruitment began in July 2004 and ceased in May 2007. In total, 1712 participants with leg ulcers were screened as potential participants and of these, 267 (15.6%) were randomised. Over the course of the trial there was a total of 22 participating centres in the UK plus one in Hungary. Recruitment was staggered with centres joining and leaving the trial over its course. Recruitment of at least one trial participant took place in 18 of the 22 sites (participants per centre ranged from 1 to 52; *Figure 2*). The rate of recruitment is shown in *Figure 3*. Further details of the recruiting sites are presented in Appendix 1.

Of the 267 participants, 94 received loose larvae, 86 received bagged larvae and 87 received hydrogel. *Figure 4* shows the flow of participants through the trial.

Baseline demographics and clinical characteristics of participants by treatment arm

The baseline characteristics of participants are summarised in *Tables 13–16*. *Table 15* summarises the participants by the prespecified prognostic factors. Most ulcers (75.7%) were classified by the nurses as having an area greater than 5 cm^2, although the actual areas measured from baseline tracings were used in the statistical analyses. There was some imbalance between the treatment groups with respect to ulcer duration (at least 6 months or more than 6 months) with fewer 'older' ulcers (more than 6 months) in the bagged larvae group (46.5%) compared with the loose larvae (64.9%) or hydrogel (59.8%) groups. Similarly, there was some imbalance in ulcer type; with more participants with an ABPI of 0.8 or more treated with high compression in the hydrogel group (70.1%) compared with the larvae groups (loose and bagged were similar at 53.2% and 53.5%).

As expected, there were more female than male participants (59.2% compared with 40.8%) and a greater proportion of men in the hydrogel group (50.6%) compared with the loose (38.3%) or bagged (33.7%) larvae groups. However, as there is no evidence that gender is a prognostic factor for ulcer healing, this imbalance is unlikely to affect healing outcomes and gender was not included in any analyses.

The mean age of participants was 74 years, with a range from 20.9 to 94.9 years. The mean participant weight was 81.1 kg and 50.9% of

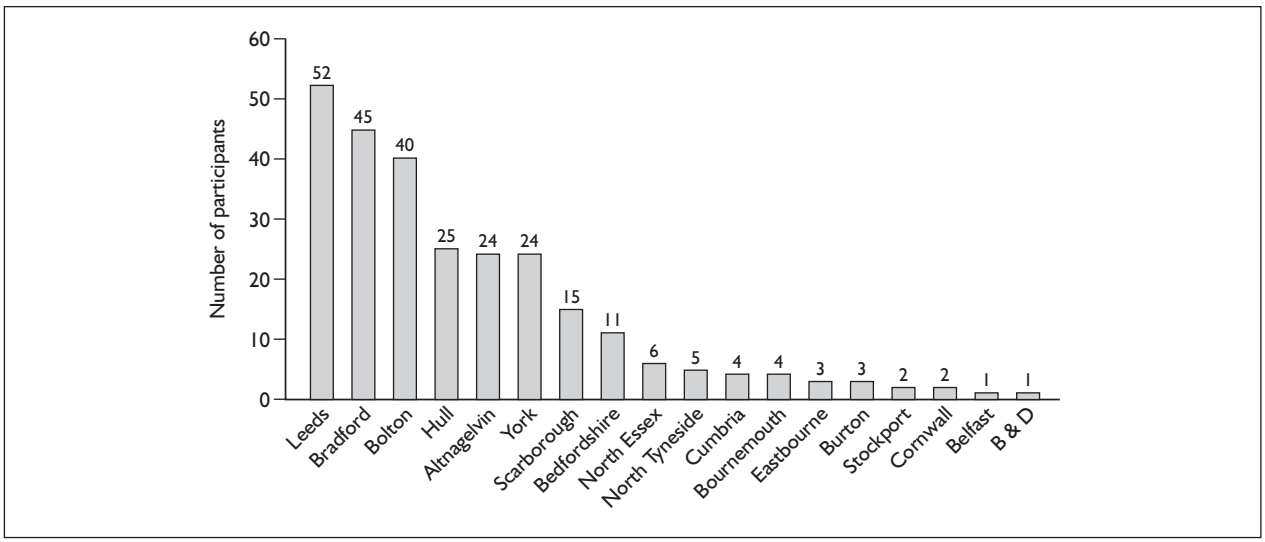

FIGURE 2 *Participant recruitment by site (four sites, including the site in Hungary, did not recruit).*

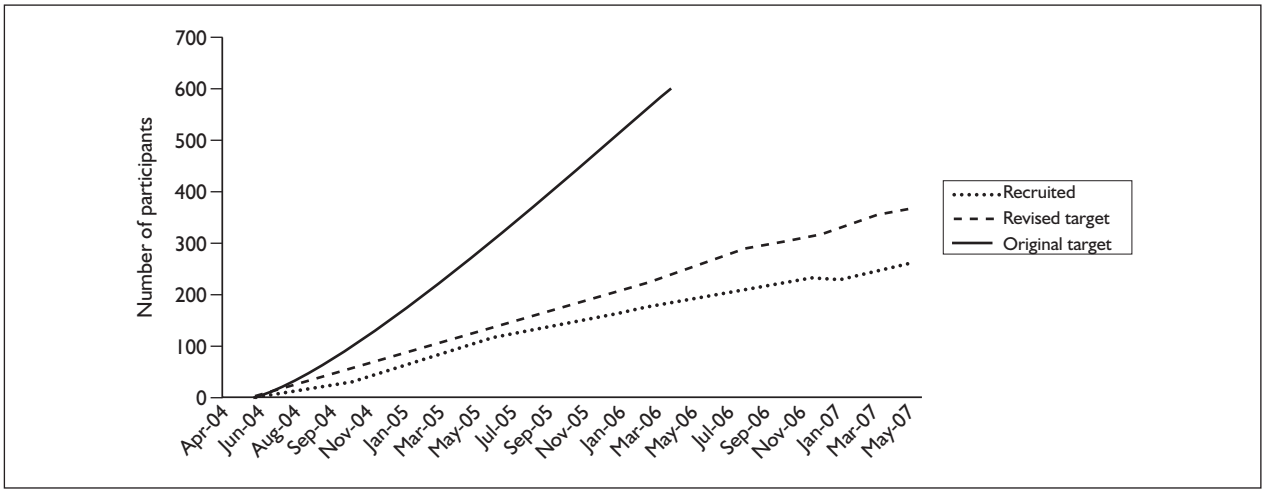

FIGURE 3 *Trial recruitment rate.*

participants had no mobility problems. The mean ABPI of the reference limb (the leg with the reference ulcer) was 1.0 with a range from 0.6 to 2.1 and 53.4% of participants had full ankle mobility. The mean ankle circumference was 25 cm, ranging from 18 to 51 cm. These factors were fairly well balanced between the three treatment groups.

With respect to the reference ulcer, ulcer duration was positively skewed; 50% of ulcers had been present for less than 7 months. The median duration of the current reference ulcer was 7 months (range 1 to 372) overall; 9 months for the loose larvae group, 6 months for the bagged larvae group and 8 months for the hydrogel group. The median time since the first ulcer was 25 months [range 1–720 months (i.e. 60 years)] and there was some imbalance with the hydrogel group having a median duration of 37.5 months compared with 21 and 24 months for the loose and bagged larvae groups respectively. The number of ulcer episodes since the first occurrence was similar between groups with an overall median of 1 (range 0 to 25) indicating that for at least 50% of participants this was their second episode of leg ulceration. The data for baseline ulcer area (as measured from the tracings) was also skewed with a median ulcer area of 13.2 cm^2 (range 0.6–197.9 cm^2). The ulcers in the bagged larvae group were slightly larger (median 17.3 cm^2) compared with the loose larvae and hydrogel groups (both medians of 12.2 cm^2). Although there was an observed baseline imbalance between treatment groups for ulcer duration and surface area, as these were identified at the design stage as important prognostic factors for ulcer healing, these were prespecified as factors to be included in the primary analyses.

Trial withdrawal from treatment and trial completion

The numbers withdrawing from trial treatment were similar in each group, with 41.4% of loose larvae, 41.9% of bagged larvae and 39.1% of hydrogel participants withdrawing from treatment, but only six (6.4%), three (3.5%) and four (4.6%) participants, respectively, withdrawing their consent to further follow-up assessments. A total of nine participants (four loose larvae, four bagged and one hydrogel) died during the trial.

The reasons given for trial completion are shown in *Table 17*. In total, 14.2% of participants requested trial withdrawal and 9.7% of participants were either withdrawn by their doctor or nurse or admitted to hospital. There were 45.3% of participants whose ulcers all healed completely during the trial (clinical data collection stopped but HRQoL data was still requested).

Primary outcome: ulcer healing

The initial analysis of time to healing used a log-rank test to compare the survivor functions of the three treatment groups (loose larvae, bagged larvae and hydrogel). There was no evidence of a difference between the three treatment groups in time to ulcer healing [log rank test statistic 0.995, degrees of freedom (df) = 2, $p = 0.62$] (*Table 18*). We then used a Cox proportional hazards model to adjust for stratification and prespecified prognostic factors [centre, baseline ulcer area, ulcer

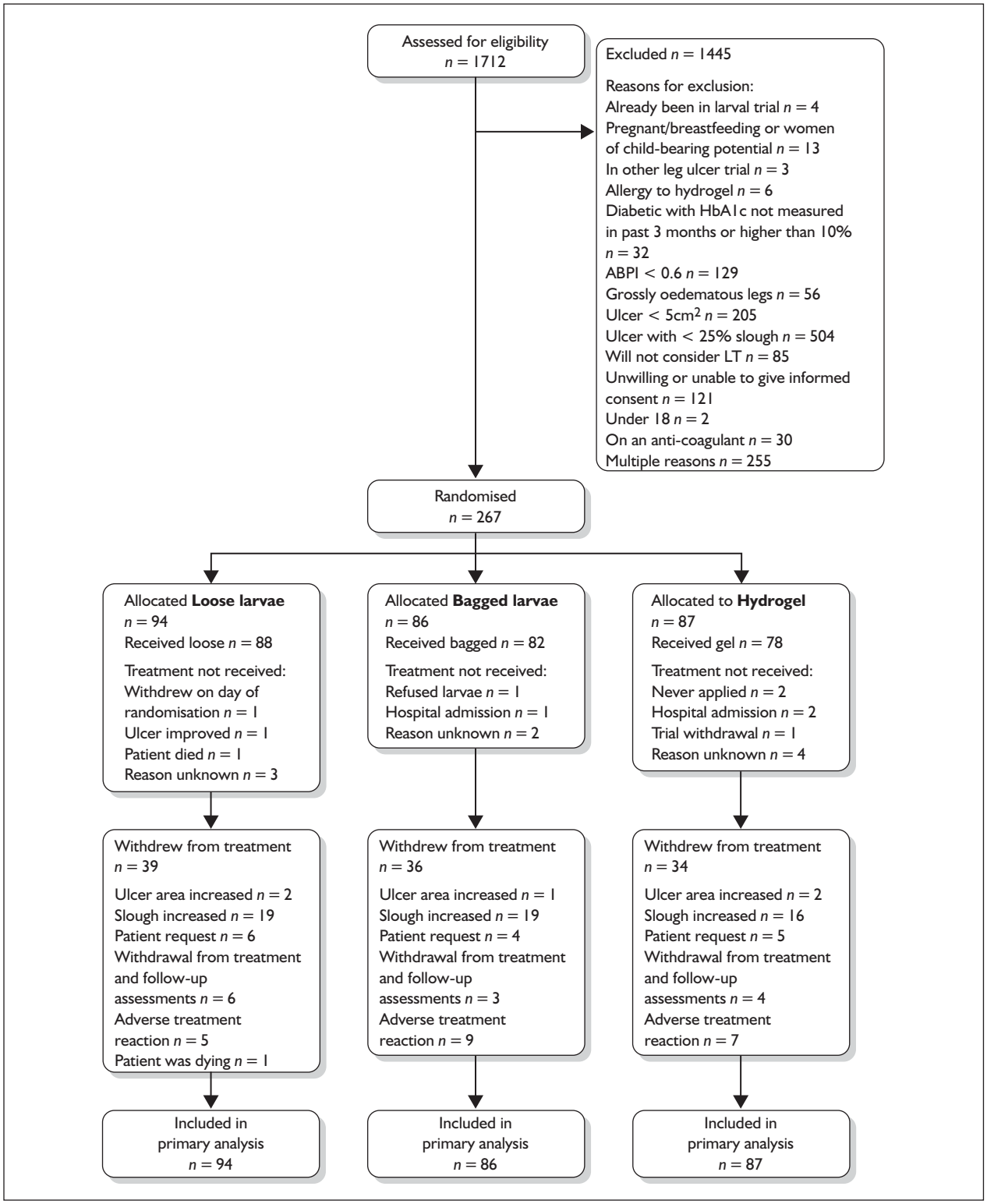

FIGURE 4 *CONSORT diagram. ABPI, ankle brachial pressure index; LT, larval therapy.*

duration and type of ulcer (ABPI ≥ 0.8 and high compression; ABPI ≥ 0.8 and low compression; ABPI 0.6 to 0.8)]. We compared the healing rates between the loose and bagged larvae arms in this model and found no evidence of a difference between them (chi-squared test statistic 0.194, df = 1, $p = 0.66$). Results are therefore presented for larvae overall (pooling data from the loose

TABLE 13 *Baseline data by prespecified prognostic factors*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
Ulcer area				
≤ 5 cm^2	23 (24.5%)	20 (23.3%)	22 (25.3%)	65 (24.3%)
> 5 cm^2	71 (75.5%)	66 (76.7%)	65 (74.7%)	202 (75.7%)
Ulcer duration				
≤ 6 months	33 (35.1%)	46 (53.5%)	35 (40.2%)	114 (42.7%)
> 6 months	61 (64.9%)	40 (46.5%)	52 (59.8%)	153 (57.3%)
Ulcer type/treatment				
ABPI ≥ 0.8 and high compression	50 (53.2%)	46 (53.5%)	61 (70.1%)	157 (58.8%)
ABPI ≥ 0.8 and low compression	31 (33.0%)	30 (34.9%)	17 (19.5%)	78 (29.2%)
ABPI 0.6–0.8	13 (13.8%)	10 (11.6%)	9 (10.3%)	32 (12.0%)

ABPI, ankle brachial pressure index.

TABLE 14 *Baseline participant data*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
Gender				
Male	36 (38.3%)	29 (33.7%)	44 (50.6%)	109 (40.8%)
Female	58 (61.7%)	57 (66.3%)	43 (49.4%)	158 (59.2%)
Participant age (years)				
Mean (SD)	74.1 (12.9)	73.5 (12.2)	74.3 (12.8)	74.0 (12.6)
Median (range)	76.6 (20.9–94.2)	76.5 (32.7–94.9)	75.4 (35.8–93.5)	76.0 (20.9–94.9)
Missing	0	0	0	0
Weight (kg)				
Mean (SD)	79.7 (24.3)	76.7 (21.4)	87.0 (27.6)	81.1 (24.9)
Median (range)	73.6 (38.0–158.0)	73.1 (44.5–164.0)	82.7 (42.7–172.0)	76.4 (38.0–172.0)
Missing	4	6	4	14
Mobility				
Walks freely	48 (51.1%)	42 (48.8%)	46 (52.9%)	136 (50.9%)
Walks with difficulty	42 (44.7%)	36 (41.9%)	33 (37.9%)	111 (41.6%)
Immobile	3 (3.2%)	7 (8.1%)	6 (6.9%)	16 (6.0%)
Missing	1 (1.1%)	1 (1.2%)	2 (2.3%)	4 (1.5%)

TABLE 15 *Baseline reference limb data*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
ABPI[a]				
Mean (SD)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	1.0 (0.2)
Median (range)	1.0 (0.6–2.0)	1.1 (0.6–2.1)	1.0 (0.6–1.4)	1.0 (0.6–2.1)
Missing	4	2	2	8
Ankle circumference(cm)[a]				
Mean (SD)	24.3 (3.2)	25.0 (4.0)	25.6 (3.8)	25.0 (3.7)
Median (range)	24.0 (18.0–34.0)	25.0 (18.0–51.0)	25.0 (19.0–39.0)	24.5 (18.0–51.0)
Missing	8	7	3	18
Ankle mobility[a]				
Full ankle motion	49 (52.1%)	43 (50.0%)	48 (55.2%)	140 (52.4%)
Reduced ankle motion	39 (41.5%)	33 (38.4%)	31 (35.6%)	103 (38.6%)
Fixed	4 (4.3%)	6 (7.0%)	5 (5.7%)	15 (5.6%)
Missing	2 (2.1%)	4 (4.7%)	3 (3.4%)	9 (3.4%)

ABPI, ankle brachial pressure index; SD, standard deviation.
a Of the limb with the reference ulcer (received trial treatment).

TABLE 16 *Baseline ulcer data*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
Duration of ulcer (months)				
Mean (SD)	24.5 (40.6)	17.9 (32.6)	27.1 (57.5)	23.2 (44.8)
Median (range)	9.0 (1.0–240.0)	6.0 (1.0–204.0)	8.0 (1.0–372.0)	7.0 (1.0–372.0)
Missing	2	3	1	6
n	92	83	86	261
Time since first ulcer (months)				
Mean (SD)	85.7 (127)	80.6 (123)	116 (174)	94.0 (143)
Median (range)	21.0 (1.0–618.0)	24.0 (1.0–600.0)	37.5 (1.0–720.0)	25.0 (1.0–720.0)
Missing	4	3	1	8
n	90	83	86	259
Number of ulcer episodes[a]				
Mean (SD)	2.5 (3.5)	2.3 (3.4)	2.7 (3.4)	2.5 (3.4)
Median (range)	1.0 (0.0–22.0)	1.0 (0.0–25.0)	1.0 (0.0–20.0)	1.0 (0.0–25.0)
Missing	7	7	8	22
n	87	79	79	245
Ulcer area (cm2)				
Mean (SD)	23.2 (31.1)	29.4 (34.2)	19.8 (22.3)	24.2 (29.9)
Median (range)	12.2 (0.6–174.9)	17.3 (1.8–197.9)	12.2 (1.0–116.8)	13.2 (0.6–197.9)
Missing	2	2	6	10
n	92	84	81	257

SD, standard deviation.
a Since first episode of ulceration.

TABLE 17 *Reasons for trial completion*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
Completion reason				
Participant wishes	13 (13.8%)	12 (14.0%)	13 (14.9%)	38 (14.2%)
Withdrawn by nurse/doctor/admitted to hospital	9 (9.6%)	7 (8.1%)	10 (11.5%)	26 (9.7%)
All ulcers healed (HRQoL still required)	45 (47.9%)	41 (47.7%)	36 (41.4%)	122 (45.7%)
Participant died	4 (4.3%)	4 (4.7%)	1 (1.2%)	9 (3.4%)
Lost to follow-up (unable to be contacted by nurse)	3 (3.2%)	3 (3.5%)	3 (3.5%)	9 (3.4%)
Unhealed after 12 months of follow-up (6–12 months for some participants)	10 (10.6%)	11 (12.8%)	14 (16.1%)	35 (13.1%)
Trial closed (cessation of data collection 30 November 2007)	4 (4.3%)	5 (5.8%)	8 (9.2%)	17 (6.4%)
Exit form not returned	6 (6.4%)	3 (3.5%)	2 (2.3%)	11 (4.1%)

HRQoL, health-related quality of life.

and bagged arms) compared with hydrogel. The median times to healing were 236 days (95% CI 147 to 292) for participants receiving larvae and 245 days (95% CI 166, upper limit not estimable) for those receiving hydrogel (*Table 19*). *Figures 5* and *6* show the Kaplan–Meier survival curves for all three treatment groups and larvae compared with hydrogel respectively.

The adjusted analysis results are presented in *Table 20*. The hazard ratio was 1.13 (95% CI 0.76 to 1.68), which indicated a slightly increased risk of healing for the larvae group although this was not statistically significant ($p = 0.54$). Plots of Martingale residuals were used to check the linearity assumption of terms in the model and these indicated that using the logarithm of both baseline ulcer area and duration provided a better fit therefore the model presented includes the logged terms. However, using the log-transformed data did not alter any conclusions. Both baseline ulcer area and ulcer duration were statistically significant predictors of time to healing ($p < 0.0001$) with larger ulcers and those of a longer duration having a reduced risk of healing. There was no evidence that healing rates differed between trial centres ($p = 0.31$).

The proportional hazards assumption was checked using log–log plots of the estimated survivor function and by including interaction terms between each variable and time in the model. Visual inspection of the survival function and log–log plots indicated potential non-proportionality of hazards for the treatment groups; however, further investigation using statistical testing of the time–treatment interaction indicated no evidence of non-proportionality ($p = 0.25$) and this was confirmed by plotting scaled Schoenfeld residuals. The only variable which did appear to violate the proportional hazards assumption was ulcer type (ABPI ≥ 0.8 and high compression; ABPI ≥ 0.8 and low compression; ABPI 0.6–0.8). Two sensitivity analyses were performed which included removing ulcer type from the model, and stratifying by ulcer type. Neither altered the conclusions; the hazard ratio for larvae versus hydrogel from the stratified model was 1.15 (95% CI 0.77 to 1.71). We also undertook sensitivity analyses to investigate the effect of centre, as several centres only recruited small numbers of participants. The sensitivity analyses included stratifying the model by centre, treating centre as a random effect in a frailty model and removing centre from the model. None of these approaches altered the conclusions about the treatment effect. We also repeated the time-to-healing analysis using the date of healing as recorded by the nurses on the patient record forms (as opposed to the date from the blinded assessment of photographs), and this did not alter any of the conclusions.

TABLE 18 *Healing estimates by trial arm*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Number healing	48 (51.1%)	43 (50.0%)	38 (43.7%)
Kaplan–Meier estimate of median time to healing (days) (95% CI)	236 (147 to 292)	234 (138 to 322)	245 (166, not estimable)
Log-rank test statistic; *p*-value	0.995 (2 df); $p = 0.608$		
Wilcoxon test statistic; *p*-value	0.940 (2 df); $p = 0.940$		

TABLE 19 *Healing estimates by larvae vs hydrogel arm*

	Larvae (*n* = 180)	Hydrogel (*n* = 87)
Number healing	91 (50.6%)	38 (43.7%)
Kaplan–Meier estimate of median time to healing (days) (95% CI)	236 (161 to 278)	245 (166, not estimable)
Log-rank test statistic; *p*-value	0.946 (1 df); $p = 0.331$	
Wilcoxon test statistic; *p*-value	0.124 (1 df); $p = 0.725$	

TABLE 20 *Adjusted analysis of time to ulcer healing*

	Parameter estimate	Standard error	Hazard ratio (95% CI)	*p*-value
Larvae: hydrogel	0.123	0.202	1.131 (0.761 to 1.682)	0.542
Log ulcer area	−0.521	0.102	0.594 (0.486 to 0.726)	< 0.0001
Log ulcer duration	−0.568	0.092	0.567 (0.473 to 0.678)	< 0.0001
Ulcer type				
ABPI ≥ 0.8 high compression: ABPI 0.6 to 0.8	0.086	0.223	1.090 (0.703 to 1.688)	0.701
ABPI ≥ 0.8 low compression: ABPI 0.6 to 0.8	−0.111	0.301	0.894 (0.495 to 1.615)	0.711
Centre				0.308

ABPI, ankle brachial pressure index.

Complete healing

Participants with multiple ulcers at randomisation remained in the trial after healing of the reference ulcer. At the end of follow-up, all ulcers of 124 participants (46.4%) were completely healed; representing 48.9% (46/94) in the loose larvae group, 47.7% (41/86) in the bagged larvae group and 42.5% (37/87) of hydrogel participants.

Ulcer debridement

There was a statistically significant difference in the time to debridement between the three treatment groups (log-rank test $p < 0.0001$) (*Table 21*), and also when the two larvae groups were combined and compared with hydrogel (*Table 22*; *Figures 7* and *8*). The median time to debridement was shorter for the loose larvae (14 days, 95% CI 10 to 17 days) compared with 28 days (95% CI 13 to 55 days) for bagged larvae and 72 days (95% CI 56

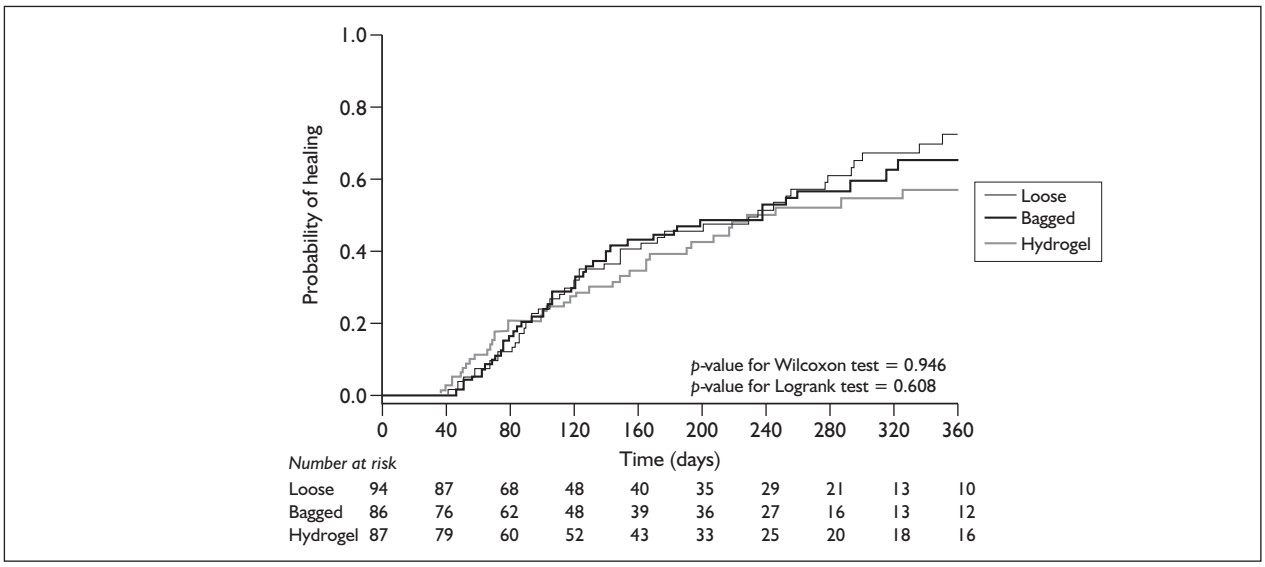

FIGURE 5 *Kaplan–Meier plot of time to healing by treatment group.*

to 131 days) for hydrogel. However, the difference in time to debridement between loose and bagged larvae was not significant when compared in the Cox proportional hazards model ($p = 0.22$). As larvae had a statistically significant effect on debridement, compared with hydrogel, the results from the Cox model are presented for each type of larvae separately.

Table 23 shows the results from the adjusted analysis of time to debridement after adjustment for the same factors used in the time to healing analysis. The hazard of debriding at any time in the loose and bagged larvae groups was approximately twice that of the hydrogel group with the hazard ratios for loose larvae compared with hydrogel being 2.56 (95% CI 1.76 to 3.71) and 2.06 (95% CI 1.39 to 3.03) for bagged larvae compared with hydrogel. The only other factor that was significantly related to time to debridement was baseline ulcer area ($p = 0.02$) with larger ulcers at baseline having a reduced risk of debriding. There was no evidence that debridement rates differed between trial centres ($p = 0.17$). Model assumptions were checked using the same methods as for the time-to-healing analysis and there was no evidence of any departures from the proportional hazards assumption for any of the factors in the model.

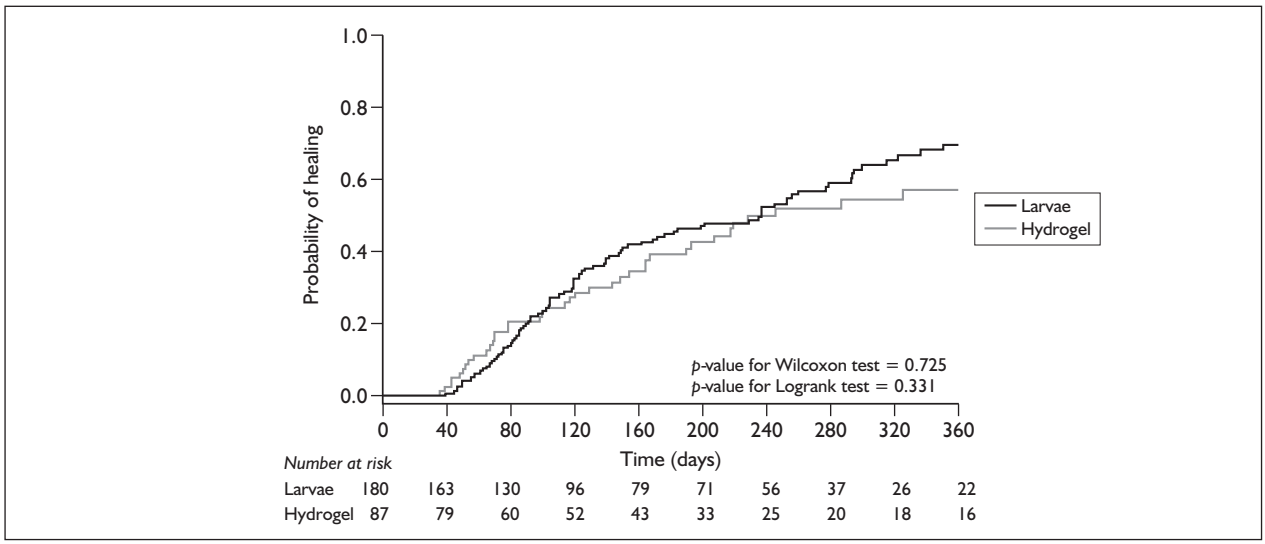

FIGURE 6 *Kaplan–Meier plot of time to healing by larvae vs hydrogel.*

TABLE 21 *Debridement estimates by trial arm*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Number debriding	75 (79.8%)	66 (76.7%)	55 (63.2%)
Kaplan–Meier estimates of median time to debridement (days) (95% CI)	14 (10 to 17)	28 (13 to 55)	72 (56 to 131)
Log-rank test statistic; *p*-value	25.38 (2 df); $p < 0.0001$		
Wilcoxon test statistic; *p*-value	34.96 (2 df); $p < 0.0001$		

TABLE 22 *Debridement estimates by larvae vs hydrogel arm*

	Larvae (*n* = 180)	Hydrogel (*n* = 87)
Number debriding	141 (78.3%)	55 (63.2%)
Kaplan–Meier estimates of median time to debridement (days) (95% CI)	17 (12 to 23)	72 (56 to 131)
Log-rank test statistic; *p*-value	23.06 (1 df); $p < 0.0001$	
Wilcoxon test statistic; *p*-value	29.57 (1 df); $p < 0.0001$	

TABLE 23 *Adjusted analysis of time to ulcer debridement*

	Parameter estimate	Standard error	Hazard ratio (95% CI)	*p*-value
Loose larvae: hydrogel	0.939	0.189	2.556 (1.764 to 3.705)	< 0.0001
Bagged larvae: hydrogel	0.721	0.198	2.055 (1.394 to 3.031)	0.0003
Log ulcer area	−0.187	0.078	0.829 (0.711 to 0.967)	0.017
Log ulcer duration	−0.067	0.062	0.936 (0.828 to 1.057)	0.286
Ulcer type				
ABPI ≥ 0.8 high compression: ABPI 0.6 to 0.8	−0.169	0.181	0.845 (0.593 to 1.203)	0.350
ABPI ≥ 0.8 low compression: ABPI 0.6–0.8	−0.114	0.239	0.892 (0.558 to 1.426)	0.634
Centre				0.172

ABPI, ankle brachial pressure index.

Sensitivity analyses investigating the effect of centre also did not alter any of the conclusions.

Health-related quality of life

The SF-12 questionnaire was used to assess self-reported HRQoL at baseline, and 3, 6, 9 and 12 months. Descriptive statistics of the PCS and MCS scores are presented in *Tables 24–26* and *Figures 9* and *10*. Descriptive statistics of the other component scores are presented in *Table 27*. Only the PCS and MCS have been analysed, all other components are presented descriptively. In all cases the minimum, and worst, score possible was 0 and the maximum was 100.

The mean PCS and MCS for the trial population at baseline were both lower than the mean values for the general US population. The median age of the VenUS II population was 76 years so we have compared the mean baseline scores of the participants with the US norm-based scores for individuals aged 75 and above.[132] For the PCS the means (SD) were 33.3 (11.4) for the larvae group and 35.9 (11.5) for the hydrogel group, compared

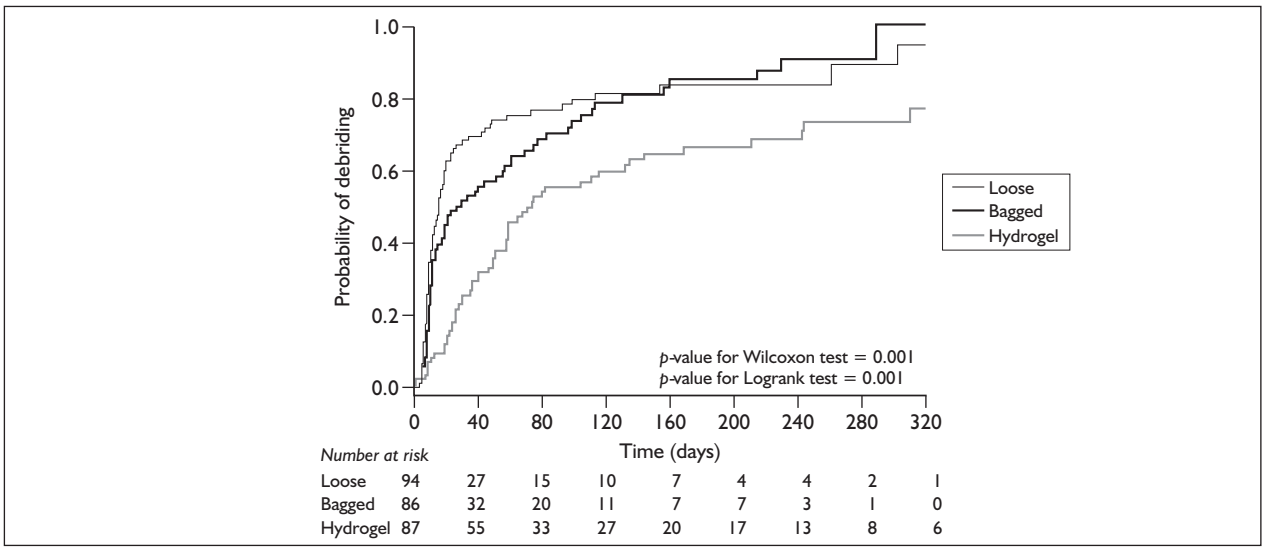

FIGURE 7 *Kaplan–Meier plot of time to debridement by treatment group.*

with 37.9 (11.16) for the general US population. For the MCS the baseline means were 46.9 (12.3) for the larvae group and 47.2 (11.0) for the hydrogel group, compared with 50.4 (11.66) for the general US population. This implies that the trial population had a low overall quality of life in terms of physical and mental health compared with a similar age group in the USA. *Figure 9* shows the mean PCS (and 95% CI) by larvae or hydrogel group, over time. This shows that there was little difference between the treatment groups at any time and no clear pattern of improvements over time.

For the MCS the mean scores for the larvae group increased slightly and then remained constant whereas the hydrogel group scores were more variable but differences over time for both groups were very small (*Figure 10*). Each of the PCS and MCS scores were compared between the larvae and hydrogel groups using two analysis methods. Firstly an overall measurement was computed for each participant; the SAUC, and compared between the groups using a Wilcoxon rank sum test (*Table 26*). There was no evidence of a difference between the treatment groups for PCS (median values of 0.4 for larvae and –0.5 for hydrogel indicating a small average deterioration in the hydrogel group but no evidence of a difference between groups; $p = 0.25$). The result for the MCS was similar ($p = 0.95$, with median values of –0.8 for larvae and –0.7 for hydrogel).

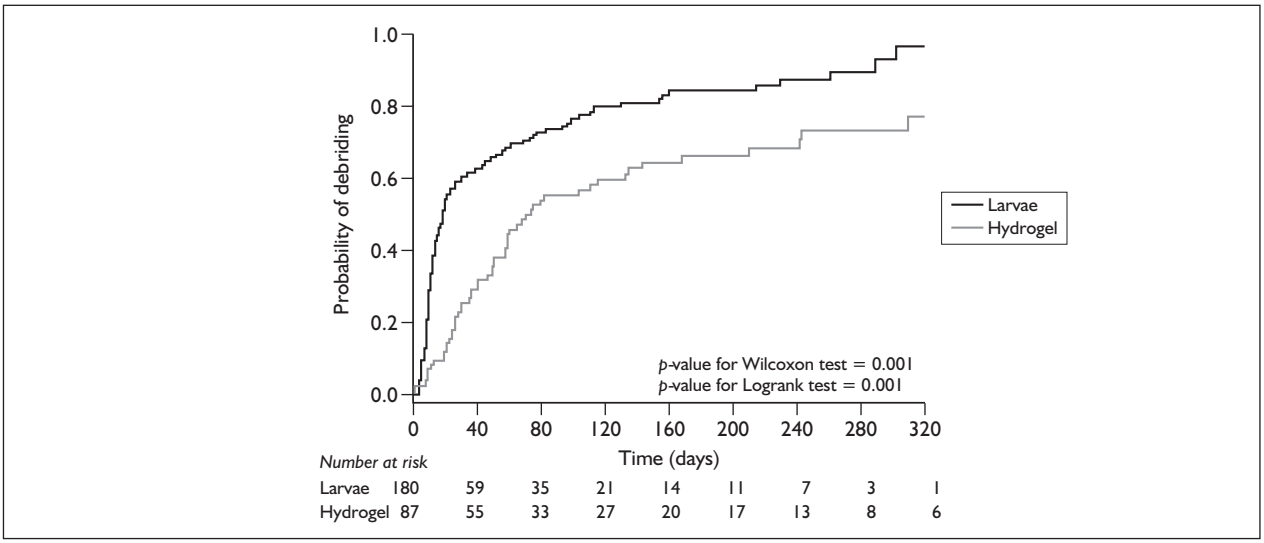

FIGURE 8 *Kaplan–Meier plot of time to debridement for larvae compared with hydrogel.*

TABLE 24 *SF-12 physical component summary scores*

	Larvae (*n* = 180)	Hydrogel (*n* = 87)	Overall (*n* = 267)
Baseline	***153***	***73***	***226***
Mean (SD)	33.3 (11.4)	35.9 (11.5)	34.2 (11.5)
Median (range)	31.6 (13.3 to 61.5)	33.7 (13.0 to 61.8)	32.4 (13.0 to 61.8)
Missing, *n* (%)	27 (15.0%)	14 (16.1%)	41 (15.4%)
3 months	***136***	***69***	***205***
Mean (SD)	33.9 (11.4)	34.9 (10.0)	34.2 (10.9)
Median (range)	32.2 (8.8 to 60.3)	33.2 (13.2 to 56.0)	32.4 (8.8 to 60.3)
Missing, *n* (%)	44 (24.4%)	18 (20.7%)	62 (23.2%)
6 months	***124***	***63***	***187***
Mean (SD)	34.9 (12.5)	35.1 (9.1)	34.9 (11.4)
Median (range)	34.0 (13.0 to 58.0)	33.3 (20.3 to 55.0)	33.4 (13.0 to 58.0)
Missing, *n* (%)	56 (31.1%)	24 (27.6%)	80 (30.0%)
9 months	***105***	***52***	***157***
Mean (SD)	35.5 (12.0)	36.2 (9.6)	35.7 (11.3)
Median (range)	33.6 (8.5 to 59.3)	35.7 (19.1 to 54.8)	35.1 (8.5 to 59.3)
Missing, *n* (%)	75 (41.7%)	35 (40.2%)	110 (41.1%)
12 months	***95***	***49***	***144***
Mean (SD)	35.0 (12.8)	35.7 (11.2)	35.3 (12.3)
Median (range)	31.8 (10.4 to 57.5)	35.9 (11.9 to 57.5)	32.3 (10.4 to 57.5)
Missing, *n* (%)	85 (47.2%)	38 (43.7%)	133 (49.8%)

SD, standard deviation.

We also fitted a repeated measures multilevel regression model to the PCS and MCS scores. The values at 3, 6, 9 and 12 months were the outcome measures, and the baseline value, treatment group and time were included as fixed effects. The interaction between treatment and time was assessed for inclusion but was not significant in either model. Different covariance patterns were assessed for the repeated measurements within participants but the results were similar so an unstructured covariance matrix was used. For the PCS, there was no evidence of an overall difference between larvae and hydrogel ($p = 0.75$) and the mean PCS score (over all follow-up assessments) was 34.4 (95% CI 32.95 to 35.84) for larvae and 34.0 (32.14 to 35.98) for hydrogel. Similar results were obtained for the MCS where there was also no evidence of a difference between larvae and hydrogel ($p = 0.82$). The mean MCS score (over all follow-up assessments) was 46.56 (95% CI 44.79 to 48.34) for larvae and 46.88 (44.83 to 49.27) for hydrogel.

In terms of missing HRQoL data, of the participants that healed 25% (loose larvae), 25.6% (bagged larvae) and 15.8% (hydrogel) did not return forms subsequent to healing. In contrast, for those participants who did not heal 60.9% (loose larvae), 62.8% (bagged larvae) and 63.3% (hydrogel) had HRQoL forms missing at trial exit. Most participants with missing HRQoL data had all data missing after a particular assessment, and these numbers suggest that those participants with more severe ulcers or worse general health were less likely to return questionnaires. However, summary statistics of PCS and MCS scores by healing status (data not shown) showed similar scores at baseline for those participants who later healed or did not heal and these were similar to the mean values by group. Repeating the repeated measures modelling to compare healed and non-healed patients showed no evidence of any differences in overall PCS between healed and unhealed patients ($p = 0.80$) but that healing status had an effect on the MCS ($p = 0.004$) with

TABLE 25 *SF-12 mental component summary scores*

	Larvae (*n* = 180)	**Hydrogel (*n* = 87)**	**Overall ((*n* = 267)**
Baseline	***153***	***73***	***226***
Mean (SD)	46.9 (12.3)	47.2 (11.0)	47.0 (11.8)
Median (range)	46.9 (15.2 to 67.8)	48.8 (24.0 to 65.9)	47.8 (15.2 to 67.8)
Missing	27	14	41
3 months	***136***	***69***	***205***
Mean (SD)	47.5 (12.8)	46.7(11.2)	47.3 (12.3)
Median (range)	51.0 (16.2 to 67.7)	47.9 (15.6 to 74.8)	48.9 (15.6 to 74.8)
Missing	44	18	62
6 months	***124***	***63***	***187***
Mean (SD)	48.4 (11.4)	48.3 (10.7)	48.3 (11.1)
Median (range)	49.3 (16.2 to 64.4)	50.2 (20.0 to 69.6)	49.3 (16.2 to 69.6)
Missing	56	24	80
9 months			
Mean (SD)	48.3 (11.3)	47.9 (11.9)	48.2 (11.5)
Median (range)	49.8 (16.2 to 67.3)	44.9 (20.6 to 67.0)	49.3 (16.2 to 67.3)
Missing	75	35	110
12 months	95	49	144
Mean (SD)	48.6 (12.1)	47.2 (12.5)	48.1 (12.2)
Median (range)	52.6(16.2 to 68.6)	48.5 (16.3 to 68.4)	49.8 (16.2 to 68.6)
Missing	85	38	133

SD, standard deviation.

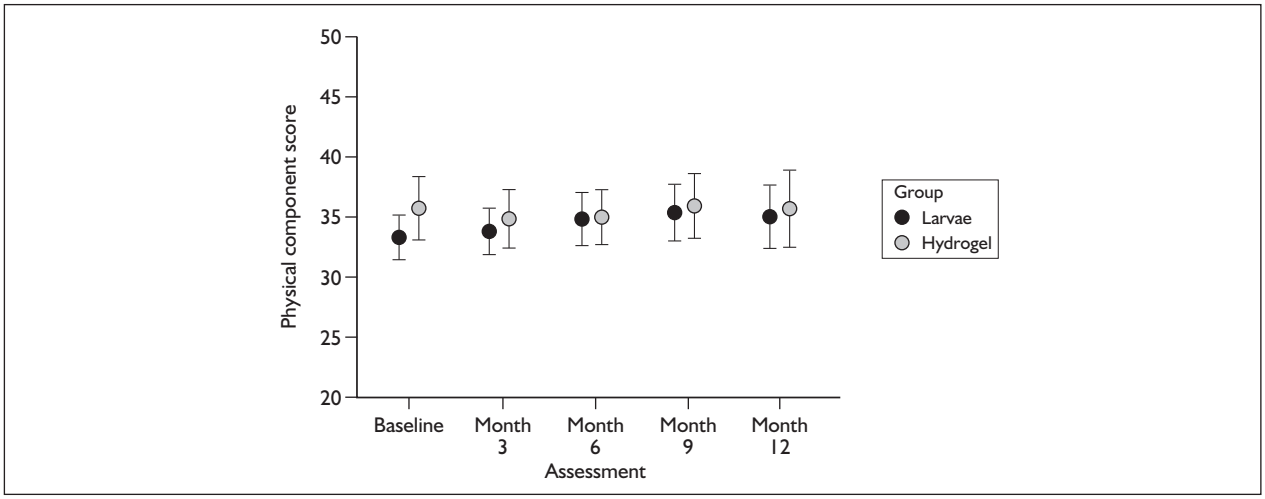

FIGURE 9 *Short Form-12 physical component scores over time (mean and 95% CI).*

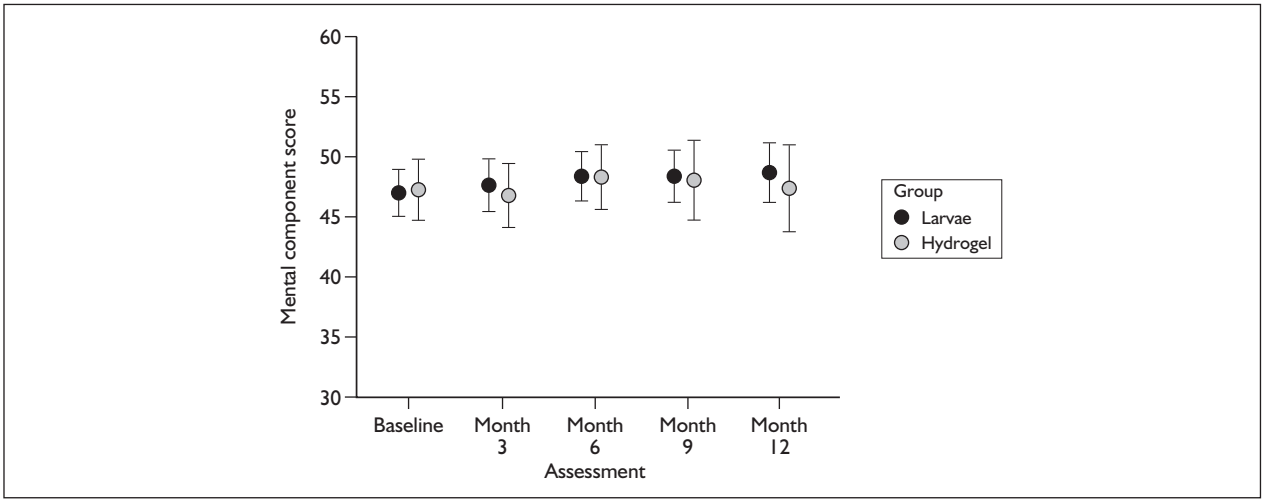

FIGURE 10 *Short Form-12 mental component scores over time (mean and 95% CI).*

TABLE 26 *Summary statistics of SAUC scores for SF-12 physical and mental components*

	Larvae	Hydrogel	*p*-value from Wilcoxon test
Physical component			
Mean (SD)	0.3 (6.5)	−0.7 (5.8)	
Median (range)	0.4 (−26.0 to 26.4)	−0.5 (−19.6 to 10.6)	0.2515
n	133	67	
Mental component			
Mean (SD)	0.0 (8.8)	0.0 (8.3)	
Median (range)	−0.8 (−22.1 to 30.3)	−0.7 (−19.4 to 27.2)	0.9525

SD, standard deviation.
A negative value indicates an decrease in score (deterioration) from baseline and a positive value indicates an increase (improvement) in score from baseline

TABLE 27 *Other SF-12 scores [mean (SD)]: physical and mental*

	Larvae	Hydrogel	Overall
Physical scores			
Physical functioning			
Baseline	34.4 (12.2)	36.4 (11.1)	35.0 (11.9)
3 months	34.1 (12.2)	33.9 (11.0)	34.0 (11.8)
6 months	34.8 (12.7)	33.8 (10.3)	34.5 (11.9)
9 months	35.5 (12.3)	35.2 (10.6)	35.4 (11.7)
12 months	35.8 (13.1)	35.3 (10.9)	35.6 (12.4)
Role physical			
Baseline	36.9 (10.9)	38.0 (10.6)	37.2 (10.8)
3 months	38.0 (11.7)	37.4 (10.9)	37.8 (11.4)
6 months	38.9 (11.3)	38.8 (10.1)	38.8 (10.9)
9 months	38.4 (11.5)	39.7 (9.9)	38.9 (11.0)
12 months	39.0 (12.7)	39.0 (9.9)	39.0 (11.8)

continued

TABLE 27 *Other SF-12 scores [mean (SD)]: physical and mental (continued)*

	Larvae	Hydrogel	Overall
Pain			
Baseline	36.3 (13.3)	39.2 (12.8)	37.2 (13.2)
3 months	39.3 (13.7)	39.7 (13.0)	39.4 (13.5)
6 months	40.1 (13.3)	40.8 (11.9)	40.3 (12.8)
9 months	41.4 (13.6)	41.2 (12.2)	41.3 (13.1)
12 months	40.1 (14.0)	40.2 (13.2)	40.1 (13.7)
General health			
Baseline	38.0 (12.2)	41.1 (11.1)	39.0 (11.9)
3 months	37.0 (11.4)	39.9 (11.7)	38.0 (11.5)
6 months	38.1 (11.8)	39.7 (10.3)	38.6 (11.3)
9 months	38.1 (11.2)	39.0 (10.7)	38.4 (11.0)
12 months	38.0 (11.4)	39.1 (11.4)	38.4 (11.4)
Mental scores			
Vitality			
Baseline	41.3 (11.2)	42.0 (10.6)	41.5 (11.0)
3 months	41.5 (11.2)	42.4 (10.7)	41.8 (11.0)
6 months	42.4 (11.4)	42.5 (10.0)	42.4 (11.0)
9 months	42.7 (11.3)	42.7 (11.4)	42.7 (11.3)
12 months	41.8 (12.1)	42.0 (9.9)	41.9 (11.3)
Role emotional			
Baseline	44.2 (13.2)	44.7 (12.3)	44.4 (12.9)
3 months	44.5 (14.0)	42.8 (13.1)	43.9 (13.7)
6 months	44.7 (12.1)	43.8 (11.2)	44.4 (11.8)
9 months	44.4 (13.0)	44.9 (11.8)	44.6 (12.6)
12 months	45.4 (12.7)	44.0 (13.1)	45.0 (12.8)
Social functioning			
Baseline	38.2 (14.3)	39.4 (14.0)	38.6 (14.2)
3 months	38.2 (15.2)	37.5 (14.3)	38.0 (14.9)
6 months	40.5 (14.0)	40.2 (13.5)	40.4 (13.8)
9 months	41.0 (15.0)	41.8 (15.3)	41.3 (15.1)
12 months	40.6 (15.1)	40.1 (14.8)	40.4 (14.9)
Mental health			
Baseline	45.7 (12.5)	46.8 (11.8)	46.1 (12.2)
3 months	47.4 (12.4)	47.1 (11.1)	47.3 (12.0)
6 months	47.9 (11.2)	48.4 (11.7)	48.1 (11.3)
9 months	48.1 (10.7)	46.6 (11.8)	47.6 (11.0)
12 months	48.4 (11.3)	46.9 (11.3)	47.9 (11.3)

healed patients having a better mental health score (difference in means 4.30, 95% CI 1.42 to 7.18). We are planning to undertake further analyses using these data and data from the ongoing HTA-funded VenUS III trial to explore the impact of ulcer healing on patient quality of life.

Microbiology

Bacterial load

Table 28 shows summary statistics of the baseline bacterial count (logs to base 10) and the within-participant change over time (baseline to final)

TABLE 28 *Ulcer bacterial load (log bacterial count; copies/ml)*

	Loose larvae	Bagged larvae	Hydrogel	Overall
Baseline (initial wound swab)				
Mean (SD)	6.5 (1.3)	6.4 (1.2)	6.5 (1.2)	6.5 (1.2)
Median (range)	6.5 (3.4 to 8.9)	6.5 (3.2 to 9.3)	6.6 (3.3 to 8.8)	6.5 (3.2 to 9.3)
n	92	84	84	260
Within-participant change for all participants (baseline to final)				
Mean (SD)	0.2 (1.6)	0.1 (1.5)	0.2 (1.5)	0.2 (1.5)
Median (range)	0.2 (−3.7 to 3.4)	0.1 (−3.7 to 4.5)	0.2 (−2.9 to 3.6)	0.2 (−3.7 to 4.5)
n	92	84	84	260
For patients who debrided, within-participant change from baseline to debridement				
Mean (SD)	−0.2 (1.3)	−0.5 (1.5)	0.3 (1.5)	−0.1 (1.4)
Median (range)	0.0 (−3.2 to 2.8)	−0.5 (−3.7 to 3.5)	0.3 (−3.5 to 3.8)	0.0 (−3.7 to 4.8)
n	74	65	55	194
For patients who did not debride, within-participant change from baseline to final swab				
Mean (SD)	0.3 (1.6)	−0.2 (1.2)	−0.3 (1.5)	−0.1 (1.4)
Median (range)	0.0 (−3.7 to 2.9)	−0.1 (−2.1 to 2.4)	−0.4 (−2.5 to 3.6)	0.0 (−3.7 to 3.6)
n	17	18	29	64

SD, standard deviation.
A negative value indicates an increase in bacterial count from baseline and a positive value is a decrease in bacterial count.

for three different groups of participants: (1) all participants (to last available swab); (2) only those participants who debrided (to last available swab during the debridement treatment phase); (3) participants who did not debride (change from baseline to last available swab). The average log bacterial count at baseline was 6.5 (approximately 3.1×10^6 copies/ml) and the three treatment groups were similar. The summaries of the within-participant change from baseline show that on average, most participants, regardless of whether or not they debrided, had very little change in the bacterial load of their ulcer over time with median log differences in the range of −0.5 to 0.2 copies/ml.

To investigate whether there were any differences between the larvae and hydrogel treatments in reducing the bacterial load of the ulcer, a repeated measures analysis (linear random coefficients model) was used. Two models were used; one analysed data from all available swabs for each participant; the other used only swab data up to the point of debridement for those participants who debrided and to the end of the trial for any participants who did not debride. The results for the model using all data and for the model using only data up to debridement are in *Table 29*. When using all swab data there was no evidence of a difference in bacterial load over time between larvae and hydrogel [$p = 0.75$, estimate of the mean log bacterial count (standard error) for larvae was 6.59 copies/ml (0.06) and for hydrogel it was 6.64 copies/ml (0.08)]. Time had a significant effect ($p = 0.01$) indicating that overall ulcer bacterial load decreased over time, but the interaction between treatment and time was not significant ($p = 0.63$) indicating that decreases in bacterial load over time did not differ between the larvae and hydrogel groups.

When analysing only swab data up to the point of debridement, there was also no evidence of a difference between the larvae and hydrogel groups [$p = 0.86$, estimate of the mean log bacterial count (standard error) for larvae was 6.72 copies/ml (0.07) and for hydrogel it was 6.73 copies/ml (0.09)]. Furthermore, there was no evidence of a time effect and bacterial load appeared to remain constant over time ($p = 0.91$), and again there was no evidence that the effect of time differed between the larvae and hydrogel groups ($p = 0.65$).

TABLE 29 *Analysis of bacterial load (all swabs and only swabs up to debridement)*

	Estimate (standard error)	*t*-statistic	*p*-value
All swabs			
Log baseline ulcer area	0.185 (0.042)	4.37	< 0.001
Log ulcer duration	0.125 (0.034)	3.70	< 0.001
Ulcer type			
ABPI ≥ 0.8 high compression: 0.6–0.8	−0.237 (0.135)	−1.76	0.080
ABPI ≥ 0.8 low compression: 0.6–0.8	−0.263 (0.146)	−1.81	0.072
Time	−0.0027 (0.001)	−2.60	0.011
Time^2	7.46×10^6 (3.17×10^6)	2.36	0.019
Larvae vs hydrogel	−0.032 (0.101)	−0.31	0.754
Larvae × time interaction	−0.0004 (0.0007)	−0.48	0.629
Log baseline ulcer area	0.170 (0.049)	3.46	< 0.001
Only swabs up to debridement			
Log ulcer duration	0.112 (0.039)	2.91	0.004
Ulcer type			
ABPI ≥ 0.8 high compression: 0.6–0.8	−0.316 (0.212)	−2.05	0.042
ABPI ≥ 0.8 low compression: 0.6–0.8	−0.360 (0.166)	−2.17	0.031
Time	0.0002 (0.002)	0.11	0.914
Time^2	2.05×10^6 (6.57×10^6)	0.31	0.755
Larvae vs hydrogel	0.019 (0.113)	0.17	0.864
Treatment × time interaction	−0.0007 (0.0001)	−0.47	0.646

ABPI, ankle brachial pressure index.

MRSA

Overall only 18 out of 267 participants (6.7%) had MRSA detected in their baseline ulcer swab, of whom seven were in the loose larvae group, five in the bagged larvae group and six in the hydrogel group (*Table 30*). MRSA was absent from swabs taken at the end of the debridement phase [to debridement if they debrided, or the end of the trial period if they did not debride (one loose and one hydrogel)] in 100% (5/5) of participants in the bagged larvae group, 57.1% (4/7) of participants in the loose larvae group and 50% (3/6) of the hydrogel participants. Three participants in the loose larvae group but none in the other groups had a recurrence of MRSA after debridement.

TABLE 30 *Detection of methicillin-resistant* Staphylococcus aureus *(MRSA)*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
MRSA detected at baseline	7/94 (7.4%)	5/98 (5.8%)	6/87 (6.9%)	18/267 (6.7%)
Eradicated by end of debridement treatment phase (% of those with MRSA)	4/7 (57.1%)	5/5 (100.0%)	3/6 (50.0%)	12/18 (66.7%)
MRSA recurred postdebridement (% of those with baseline MRSA)	3/4 (75%)	0/5	0/3	0/12
No MRSA at baseline	87	81	81	249
MRSA detected at follow-up (% of those MRSA negative at baseline)	5/87 (5.7%)	7/81 (8.6%)	2/81 (2.5%)	14/249 (5.2%)

We compared the proportions of participants with MRSA detected at baseline who were free from MRSA by the end of the debridement treatment (Phase 1) – there was no evidence of a difference between the larvae and hydrogel groups (75% or 9/12) compared with the hydrogel group (50% or 3/6), Fisher's exact test $p = 0.34$). This analysis was repeated for the proportion of participants testing negative for MRSA who were found to have MRSA at one or more follow-up assessments and again there was no evidence of a difference between the larvae and hydrogel groups (7.1% or 12/168) compared with 2.5% (2/81), Fisher's exact test $p = 0.16$.

Ulcer-related pain

Using the SF-12 we collected data about general, bodily pain, at 3-monthly intervals. We also collected data about ulcer-related pain and enquired about the intensity of pain experienced over the previous 24 hours both at baseline and when the debridement treatment was first removed. Participants indicated the intensity of pain they had experienced on a VAS, the scale of which ranged from no pain (0 mm) to worst pain imaginable (150 mm), midpoint 75 mm. Mean 24-hour ulcer-related pain scores at the first dressing removal during the debridement treatment were twice as high in the larvae group compared with the hydrogel group (*Table 31*). The difference in the ulcer-related pain score over the previous 24 hours was compared between larvae and hydrogel after adjusting for baseline pain score, log ulcer duration and log ulcer area (*Table 32*). There was significantly more pain experienced by both larvae groups ($p < 0.001$) compared with hydrogel, with a difference in pain score for loose larvae compared with hydrogel of 46.74 (95% CI 32.44 to 61.04) and for bagged larvae compared with hydrogel of 38.58 (95% CI 23.46 to 53.70).

TABLE 31 *Mean ulcer-related pain scores at first removal of debridement treatment*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
Mean (SD)	88.3 (47.2)	86.2 (51.3)	41.8 (43.9)	72.8 (51.9)
Median (range)	95 (0 to 150)	100 (0 to 150)	25 (0 to 150)	66 (0 to 150)
Missing	12	13	14	39
n	82	73	73	228

SD, standard deviation.
Visual analogue pain scale (0 represents no pain, 150 represents maximum pain.

TABLE 32 *Difference in ulcer-related pain score at first removal (larvae – hydrogel)*

	Estimate (standard error)	*p*-value	95% CI
Treatment group[a]			
Loose larvae: hydrogel	46.74 (7.25)	< 0.001	32.44 to 61.04
Bagged larvae: hydrogel	38.58 (7.67)	< 0.001	23.46 to 53.70
Ulcer type			
ABPI ≥ 0.8 high compression: ABPI 0.6–0.8	16.98 (10.07)	0.09	−2.86 to 36.82
ABPI ≥ 0.8 low compression: ABPI 0.6–0.8	15.12 (10.70)	0.16	−5.97 to 36.21
Baseline pain score	0.41 (0.07)	<0.001	0.26 to 0.55
Area (log)	1.34 (2.94)	0.65	−4.41 to 7.10
Ulcer duration (log)	−4.23 (2.36)	0.07	−8.86 to 0.40

ABPI, ankle brachial pressure index.
a Loose larvae *n* = 82; bagged larvae *n* = 70; hydrogel *n* = 71.

TABLE 33 *Adverse events*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)	Overall (*n* = 267)
Number of participants with one or more adverse events	49 (52.1%)	44 (51.2%)	38 (43.7%)	131 (49.1%)
Total number of adverse events	110	126	104	340
Events per participant				
1	18 (36.7%)	19 (43.2%)	18 (20.7%)	55 (42.0%)
2	17 (35.7%)	5 (11.4%)	4 (10.5%)	26 (19.8%)
3	7 (14.3%)	8 (18.2%)	6 (15.8%)	21 (16.0%)
4	1 (2.0%)	4 (9.1%)	4 (10.5%)	9 (6.9%)
5	3 (6.1%)	2 (4.5%)	0 (0.0%)	5 (3.8%)
6 or more	3 (6.1%)	6 (13.6%)	6 (15.8%)	15 (11.5%)
Event classed as serious	16 (14.6%)	17 (13.5%)	14 (13.5%)	47 (13.8%)
Relationship to treatment				
Unrelated/unlikely	82 (74.6%)	96 (76.2%)	90 (86.5%)	268 (78.8%)
Possibly related	14 (12.7%)	16 (12.7%)	6 (5.8%)	36 (10.6%)
Probably related	4 (3.6%)	6 (4.8%)	5 (4.8%)	15 (4.4%)
Definitely related	10 (9.1%)	6 (4.8%)	3 (2.9%)	19 (5.6%)
Unable to assess	0 (0.0%)	2 (1.6%)	0 (0.0%)	2 (0.6%)
Event details (all)				
Admitted to hospital	15 (13.6%)	14 (11.1%)	13 (12.5%)	42 (12.4%)
Ulcer infection	27 (24.6%)	22 (17.5%)	27 (26.0%)	76 (22.4%)
Ulcer deterioration	20 (18.2%)	27 (21.4%)	20 (19.2%)	67 (19.7%)
Pain	16 (14.6%)	21 (16.7%)	13 (12.5%)	50 (14.7%)
Other	29 (26.4%)	41 (32.5%)	31 (35.6%)	99 (29.1%)
Problem with larvae	3 (2.7%)	1 (0.8%)	0	4 (1.2%)

Adverse events

Adverse event data were collected by the treating nursing staff. Nurses classified events as non-serious or serious and treatment-related or non-treatment-related. In total, 131 participants had 340 adverse events. Of these 13.8% were classed as serious. More participants receiving larval therapy experienced one or more adverse events compared with hydrogel participants (51.7% compared with 43.7%) However, this difference was not statistically significant [chi-squared test statistic 1.50 (1 df), $p = 0.22$]. We also compared the total number of events experienced by each participant (larvae versus hydrogel) using a negative binomial model, adjusting for the prognostic factors used in the randomisation (ulcer type, baseline ulcer area and duration) and again there was no evidence of a difference [chi-squared test statistic 2.65 (1 df), $p = 0.10$]. Details of all adverse events reported are shown in *Table 33*.

Summary of clinical findings

- Median times to healing were 236 days (95% CI 147 to 292 days) for larval therapy and 245 days (95% CI 166, not estimable) for hydrogel therapy. In an adjusted analysis there was no evidence of a difference between larval and hydrogel therapy in the time to healing of venous and mixed venous/arterial leg ulcers ($p = 0.54$) or between loose and bagged larvae ($p = 0.66$).
- Larval therapy debrided ulcers significantly faster than hydrogel ($p < 0.0001$). Loose larvae debrided most quickly with a median time to debridement of 14 days (95% CI 10 to 17 days) compared with 28 days (95% CI 13 to 55 days) for bagged larvae and 72 days (95% CI 56 to 131 days) for hydrogel. However, in an adjusted analysis the difference between loose and bagged larvae in debridement times was not statistically significant ($p = 0.22$).

- Initial ulcer area and ulcer duration were both statistically significant predictors of time to healing, but only area was significantly related to time to debridement.
- There was no statistically significant difference between the larval and hydrogel groups with respect to scores on the PCS ($p = 0.81$) and MCS ($p = 0.97$) of the SF-12 HRQoL assessment. Other SF-12 components showed similar results between treatment groups and little change within treatment groups over time.
- Only 6.7% of participants had MRSA detected in their ulcers at baseline. There was no statistically significant difference between larval and hydrogel therapy in the proportions with MRSA eradicated by the end of the debridement phase ($p = 0.34$) although the numbers were very small. There was also no statistically significant difference between treatments in the reduction of bacterial load during debridement treatment.
- Recipients of larval therapy reported significantly more pain ($p < 0.001$) in the previous 24 hours at the removal of the first debridement treatment compared with hydrogel recipients. Mean pain scores (measured using a VAS scale) for each of loose and bagged larvae being around twice those of the hydrogel participants.
- Slightly more larval therapy recipients reported one or more adverse events, but the numbers of events classed as serious and the overall numbers of events were similar between treatment groups.

Chapter 5
Economic analyses

A total of 267 people were recruited into VenUS II: 94 were allocated to receive loose larvae, 86 to receive bagged larvae and 87 to receive hydrogel. There were eight participants for whom we were unable to report any resource use data (recorded as missing values throughout).

Resource use and costs

Trial debridement treatment

The number and duration of trial debridement treatments are described in *Table 34*. Participants receiving larval therapy obtained their first treatment application approximately 3 days later than participants allocated to hydrogel (because of the need for ordering and delivery). Those allocated to one of the larval therapy arms had, on average, 1.45 trial treatment applications before the debridement treatment was discontinued (i.e. participant was moved to Phase 2) or data were censored. Participants in the hydrogel arm received, on average, 9.2 applications of Phase 1 treatment before being moved onto Phase 2 or data were censored.

Nineteen participants never received the trial debridement therapy (see *Figure 4*). Data regarding nurse visits were missing for 14 participants, while five people received a treatment other than the trial treatment (one in the loose larvae arm and four in the hydrogel arm). The duration of Phase 1 (debridement) treatment was, on average, 30 days longer in the hydrogel arm (mean days of treatment 43 days) than the larval therapy arms (mean days of treatment 12 to 13 days).

The average estimated cost of the trial debridement treatment, per application was: loose larvae £71.70 (SD £13.40; minimum to maximum £51.50 to £132.50); bagged larvae £111.90 (SD 33.6; minimum to maximum £80.10 to £218.50) and hydrogel £1.50 (SD 0).

Visits to/from health care providers

Visits to and from health care providers were recorded by participants and used for the base-case analysis. These self-reported data suggested that the number of consultations with health care

TABLE 34 *Characterisation of trial debridement treatment application (Phase 1) for participants who reported any resource use*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Time until first treatment application (days)			
Mean (SD)	5.09 (3.86)	5.61 (4.46)	2.49 (3.99)
Median (min to max)	4 (0 to 16)	5 (0 to 27)	0 (0 to 22)
Missing (%)	7 (7)	7 (8)	8 (9)
Number of applications of trial treatment			
Mean (SD)	1.44 (1.22)	1.46 (1.06)	9.2 (27.78)
Median (min to max)	1 (0 to 8)	1 (1 to 8)	3 (0 to 244)
Missing (%)	5 (5)	4 (5)	5 (6)
Duration of trial treatment (days)			
Mean (SD)	11.95 (9.11)	12.84 (11.47)	43.17 (51.76)
Median (min to max)	9 (2 to 48)	10 (1 to 93)	25 (3 to 364)
Missing (%)	6 (6)	4 (5)	9 (10)

SD, standard deviation; min to max, minimum to maximum.

professionals was similar in each trial arm (*Table 35*) with the majority of nurse and hospital visits being related to ulcer treatment.

The proportion of visits that took place at home was similar between all arms (63% for the loose larvae arm and 64% for bagged larvae arm; 67% for hydrogel). A summary of the unadjusted ulcer-related costs of health care provider visits for each of the trial treatments is presented in *Table 36*.

Compression therapy

The use of high-compression bandaging through the trial was similar across all arms (*Table 37*).

Total costs

The cost of nurse visits was the major driver of total costs. In the base-case analysis, patient-reported data on ulcer-related visits to and from health care providers were combined with trial debridement treatment costs and compression therapy. Quarterly estimates are presented in *Table 38*.

To account for the censored nature of cost data, mean differences in ulcer-related costs between treatments were estimated using inverse probability weighted regression estimates of time to survival. The results of the base-case analysis show that larval therapy costs, on average, £96.70 more per participant per year (95% bias corrected

TABLE 35 *Number of consultations with health care providers (resource use is presented for participants who reported at least one category of resource use)*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Total number of nurse visits			
Mean (SD)	42 (43)	40 (42)	45 (46)
Median (min to max)	30 (0 to 171)	28 (0 to 172)	31 (0 to 269)
n (%)	88 (94)	82 (95)	82 (94)
Number of nurse visits related to ulcers			
Mean (SD)	37 (40)	36 (41)	39 (45)
Median (min to max)	27 (0 to 171)	24 (0 to 172)	27 (0 to 269)
n (%)	88 (94)	82 (95)	82 (94)
Total number of doctor visits			
Mean (SD)	6 (7)	7 (7)	9 (12)
Median (min to max)	3 (0 to 36)	4 (0 to 36)	6 (0 to 62)
n (%)	88 (94)	82 (95)	82 (94)
Number of doctor visits related to ulcers			
Mean (SD)	2 (4)	3 (5)	4 (9)
Median (min to max)	1 (0 to 19)	1 (0 to 33)	1 (0 to 62)
n (%)	88 (94)	82 (95)	82 (94)
Total number of hospital visits			
Mean (SD)	11 (20)	9 (17)	7 (13)
Median (min to max)	4 (0 to 107)	3 (0 to 100)	3 (0 to 80)
n (%)	88 (94)	82 (95)	82 (94)
Number of hospital visits related to ulcers			
Mean (SD)	10 (20)	7 (15)	5 (12)
Median (min to max)	1 (0 to 109)	1 (0 to 88)	1 (0 to 74)
n (%)	88 (94)	82 (95)	82 (94)

SD, standard deviation; min to max, minimum to maximum.

TABLE 36 *Unadjusted costs of leg-ulcer-related health care provider costs (participant reported data)*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Ulcer-related doctor visits			
Mean, £ (SD)	32 (75)	34 (68)	75 (230)
Median, £ (min to max)	0 (0 to 414)	0 (0 to 325)	0 (0 to 1683)
n (%)	78 (83)	71 (83)	75 (86)
Ulcer-related nurse visits			
Mean, £ (SD)	702 (1084)	691 (1145)	854 (1379)
Median, £ (min to max)	191 (0 to 4292)	59 (0 to 6438)	279 (0 to 8047)
n (%)	78 (83)	71 (83)	75 (86)
Ulcer-related visits to hospital			
Mean, £ (SD)	848 (1712)	621 (1337)	446 (1186)
Median, £ (min to max)	0 (0 to 9379)	0 (0 to 6554)	0 (0 to 7006)
n (%)	78 (83)	71 (83)	75 (86)

SD, standard deviation; min to max, minimum to maximum.

TABLE 37 *Resource use (data from nurses)*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Use of compression on first phase II visit for larvae and on first visit for hydrogel, number (%)			
No compression	7 (7.5)	5 (5.8)	4 (4.6)
Low compression	33 (35.1)	34 (39.5)	29 (33.3)
High compression	41 (43.6)	39 (45.4)	49 (56.3)
Missing	13 (13.8)	8 (9.3)	5 (5.8)
Highest compression levels used, number (%)			
No compression	7 (7.5)	4 (4.7)	1 (1.2)
Low compression	18 (19.2)	22 (25.6)	20 (23.0)
High compression	64 (68.1)	56 (65.1)	61 (70.1)
Missing	5 (5.3)	4 (4.7)	5 (5.8)

CI –£491.90 to £685.80) (*Table 39*). This difference was not statistically significant.

Health benefits

Mean time to healing

The difference in estimated mean time to healing (over 12 months) favoured larval therapy. On average, participants treated with larval therapy healed 2.42 days before those in the hydrogel arm. However, this difference was not statistically significant (95% bias corrected CI of the difference was from –40.95 days to 31.91 days) (see *Table 40*). Estimation through the restricted mean approach (see Chapter 2) returned 2.74 additional ulcer-free days for larval therapy users, confirming the appropriateness of the IPW regression.

Utility and QALYs

Quarterly utility scores per participant by trial arm are presented in *Table 41* and unadjusted average QALYs per group are described in *Table 42*. The results show that, after adjustment for original imbalances in utility scores at baseline, stratification covariates and after accounting for the censored nature of data, individuals in the larval therapy arms had, on average, a better quality of life than individuals in the hydrogel arm [the annual difference in QALYs was 0.011 (95% CI –0.067 to 0.071), see *Table 43*].

TABLE 38 *Base case: total and quarterly unadjusted costs*

Quarterly costs (£ Sterling)	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Months 0–3			
Mean (SD)	922 (964)	786 (943)	740 (939)
Median (min to max)	470 (127 to 3741)	458 (15 to 4564)	368 (0 to 5114)
n (%)	78 (83)	71 (83)	74 (85)
Months 3–6			
Mean (SD)	543 (995)	500 (674)	577 (789)
Median (min to max)	176 (0 to 5580)	185 (0 to 2804)	278 (0 to 4875)
n (%)	61 (65)	66 (77)	66 (76)
Months 6–9			
Mean (SD)	476 (853)	399 (725)	301 (524)
Median (min to max)	98 (0 to 3718)	69 (0 to 2831)	53 (0 to 2579)
n (%)	53 (56)	54 (63)	52 (60)
Months 9–12			
Mean (SD)	264 (429)	210 (420)	245 (466)
Median (min to max)	113 (0 to 1857)	14 (0 to 1700)	63 (0 to 1927)
n (%)	48 (51)	48 (56)	46 (53)
Total costs			
Mean (SD)	1833 (1978)	1696 (1948)	1596 (1861)
Median (min to max)	1195 (139 to 9821)	868 (29 to 10,135)	1123 (0 to 9989)
n (%)	78 (83)	71 (83)	75 (86)

SD, standard deviation; min to max, minimum to maximum.

TABLE 39 *Adjusted annual costs (base-case analysis): adjustment for type of ulcer, ulcer duration (logarithmic), ulcer area (logarithmic), centre (aggregating centres with fewer than 10 elements)*

Arm	Mean (£)	95% bias corrected CI (£)
Hydrogel	1976.4	1521.4 to 2500.2
Larval therapy	2073.1	1724.4 to 2433.4
Difference	96.7	−491.9 to 685.8

TABLE 40 *Adjusted mean time to healing (base-case analysis): adjustment for baseline utility, type of ulcer, ulcer duration (logarithmic), ulcer area (logarithmic), centre (aggregating centres with fewer than 10 elements)*

Arm	Mean (days)	95% bias corrected CI (days)
Hydrogel	206.5	202.7 to 260.2
Larval therapy	204.1	207.9 to 248.3
Difference	−2.42	−41.0 to 31.9

TABLE 41 *Unadjusted utility weights (EQ-5D) by arm and by time*

Time/statistic	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Baseline			
Mean (SD)	0.534 (0.301)	0.434 (0.342)	0.539 (0.313)
Median (min to max)	0.648 (–0.239 to 1)	0.587 (–0.349 to 1)	0.62 (–0.239 to 1)
Missing (%)	8 (9)	5 (6)	6 (7)
3 months			
Mean (SD)	0.551 (0.343)	0.562 (0.33)	0.559 (0.317)
Median (min to max)	0.620 (–0.594 to 1)	0.620 (–0.349 to 1)	0.620 (–0.181 to 1)
Missing (%)	23 (24)	18 (21)	16 (18)
6 months			
Mean (SD)	0.596 (0.334)	0.588 (0.339)	0.566 (0.301)
Median (min to max)	0.691 (–0.594 to 1)	0.587 (–0.349 to 1)	0.689 (–0.181 to 1)
Missing (%)	33 (35)	25 (29)	26 (30)
9 months			
Mean (SD)	0.608 (0.345)	0.561 (0.381)	0.628 (0.315)
Median (min to max)	0.691 (–0.594 to 1)	0.620 (–0.239 to 1)	0.691 (–0.349 to 1)
Missing (%)	41 (44)	33 (38)	38 (44)
12 months			
Mean (SD)	0.630 (0.329)	0.565 (0.382)	0.615 (0.322)
Median (min to max)	0.691 (–0.594 to 1)	0.620 (–0.181 to 1)	0.674 (–0.239 to 1)
Missing (%)	47 (50)	41 (48)	43 (49)

SD, standard deviation; min to max, minimum to maximum.

Cost-effectiveness and uncertainty

Our base-case analysis showed that participants randomised to receive larval therapy for debridement had slightly greater health benefits at 12 months but also incurred higher costs than hydrogel users, though none of these differences were statistically significant. In these circumstances we use a decision rule to assess whether the treatments are cost-effective; we do this by combining our estimates of differential costs and health benefits as a ratio, the ICER. That is the ratio of the mean difference in cost between the alternative treatments and the mean difference in health benefits between the alternative treatments. The ICER associated with larval therapy use was estimated at £8826 per QALY gained and £40 per ulcer-free day. The point estimates of cost and effect differences were small relative to their standard error, indicating that the uncertainty around the decision to adopt larval therapy is high.

To investigate the uncertainty of the mean difference in costs and health benefits between trial arms we used the incremental cost-effectiveness plane, where we graphically plotted the results of 4000 replicates of the non-parametric bootstrap of the mean difference in cost and health benefits (QALYs, ulcer-free days).

As *Figure 11* shows, the cost and effectiveness pair replicates fall in all the quadrants of the plane in a fairly symmetrical way, suggesting that differential costs and health benefits can go in any possible direction. This suggests that there is considerable uncertainty associated with the mean differential cost and mean differential effectiveness between the larval therapy and hydrogel arms. In turn, this implies that there is considerable uncertainty associated with the cost-effectiveness of larval therapy when compared with hydrogel.

Although in 24% of the simulations our point estimates of cost–utility suggested a better

TABLE 42 *Quarterly and annual unadjusted QALYs by arm and by time*

Time/statistic	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
0–3 months			
Mean (SD)	0.136 (0.069)	0.123 (0.075)	0.138 (0.071)
Median (min to max)	0.157 (–0.025 to 0.25)	0.147 (–0.067 to 0.25)	0.155 (–0.052 to 0.25)
Missing (%)	24 (26)	19 (22)	16 (18)
3–6 months			
Mean (SD)	0.145 (0.079)	0.146 (0.077)	0.141 (0.071)
Median (min to max)	0.167 (–0.148 to 0.25)	0.155 (–0.087 to 0.25)	0.161 (–0.041 to 0.25)
Missing (%)	36 (38)	25 (29)	29 (33)
6–9 months			
Mean (SD)	0.152 (0.079)	0.149 (0.082)	0.159 (0.065)
Median (min to max)	0.173 (–0.148 to 0.25)	0.16 (–0.06 to 0.25)	0.173 (–0.053 to 0.25)
Missing (%)	43 (46)	37 (43)	42 (48)
9–12 months			
Mean (SD)	0.157 (0.081)	0.14 (0.091)	0.155 (0.073)
Median (min to max)	0.173 (–0.148 to 0.25)	0.151 (–0.045 to 0.25)	0.173 (–0.004 to 0.25)
Missing (%)	48 (51)	41 (48)	44 (51)
Annual (complete case analysis)			
Mean (SD)	0.597 (0.28)	0.574 (0.3)	0.636 (0.241)
Median (min to max)	0.665 (–0.455 to 0.25)	0.635 (–0.092 to 0.975)	0.661 (0.032 to 1)
Missing (%)	54 (57)	44 (51)	47 (54)

QALYs, quality-adjusted life-years; SD, standard deviation; min to max, minimum to maximum.

TABLE 43 *Adjusted annual QALYs: adjustment for baseline utility, type of ulcer, ulcer duration (logarithmic), ulcer area (logarithmic), centre (aggregating centres with fewer than 10 elements)*

Arm	Mean QALYs (years)	95% bias corrected CI (years)
Hydrogel	0.540	0.489 to 0.589
Larval therapy	0.551	0.505 to 0.591
Difference	0.011	–0.067 to 0.071

QALYs, quality-adjusted life-years.

performance of the comparator treatment (larval therapy was dominated, NW quadrant), in a non-negligible proportion of cases (27%) the results favoured larval use for debridement (larval therapy dominated, SE quadrant).

The CEAC (*Figure 12*) indicates that the probability of larval therapy being cost-effective when compared with hydrogel is almost constant at 50% for a range of willingness-to-pay values. This result is a direct consequence of the distribution of the cost-effectiveness cloud, where the joint density for costs and effects is almost evenly spread through the four quadrants of the cost-effectiveness plane (*Figure 11*); suggesting that larval therapy and hydrogel have similar costs and effects in the treatment of sloughy leg ulcers. As expected, the decision uncertainty evaluated at a willingness-to-pay value equal to the ICER indicates that when compared with hydrogel, larval therapy has

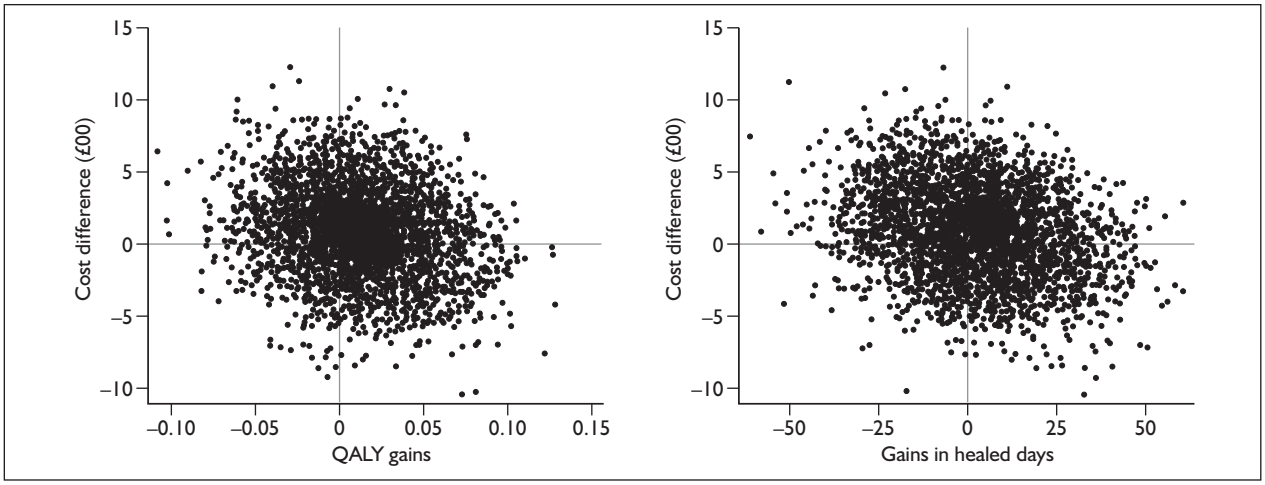

FIGURE 11 *Cost-effectiveness plane, base-case analysis. QALY, quality-adjusted life-year.*

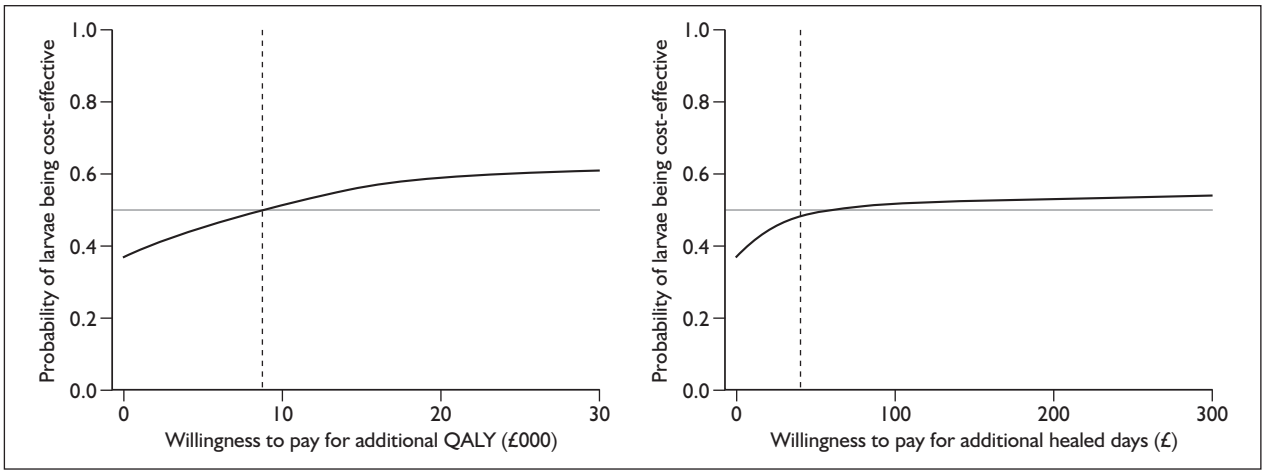

FIGURE 12 *Cost-effectiveness acceptability curve (CEAC), base-case analysis. The horizontal line represents a probability of cost-effectiveness of 0.5, whereas the dashed line represents the incremental cost-effectiveness ratio (ICER) values. CE, cost-effectiveness; QALY, quality-adjusted life-year.*

approximately a 50% probability of being cost-effective in the treatment of sloughy leg ulcers.

Sensitivity analyses

Sensitivity analyses were conducted focusing on resource-use estimates and cost parameters. Firstly, the use of nurse-reported data on nurse visits and hospitalisations was evaluated. The number of visits (calculated from data collected by nurses) was slightly lower than that recorded by patients, but again was similar for all arms. This difference may be related to the fact that nurses did not collect data after healing (*Table 44*). The use of nurse-reported data allowed us to distinguish between hospital visits and inpatient stays and cost them appropriately.

Amputation was identified as influential for adjusted cost differences between arms, and consequently two scenarios were evaluated, one not considering costs associated with amputations and the other including amputation costs.

Scenario 1: nurse-reported data excluding amputation

Unadjusted costs estimated using nurse-reported visit data indicated that bagged larvae were more costly (*Table 45*). Conversely, patient-reported costs data indicated that loose larvae were more costly. The adjusted analysis of costs estimated smaller

TABLE 44 *Number of ulcer-related nurse visits and hospitalisations evaluated through nurse data*

	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Number of nurse visits			
Mean (SD)	37.9 (35.4)	38.3 (35.7)	37.6 (38.1)
Median (min to max)	25 (2 to 221)	27 (1 to 220)	25.5 (0 to 207)
Missing (%)	5 (5)	4 (5)	5 (6)
Number of nurse visits during trial treatment for debridement (phase I)			
Mean (SD)	4.5 (3.4)	4.7 (3.9)	12.1 (22.7)
Median (min to max)	4 (0 to 23)	4 (1 to 32)	7 (0 to 184)
Missing (%)	5 (5)	4 (5)	5 (6)
Ulcer-related hospitalisations			
n	7	4	2
Ulcer-related amputations			
n	1	0	2

SD, standard deviation; min to max, minimum to maximum.

costs for larvae users (–£31.30); however, this was not statistically significant (*Table 46*). As only costs are subjected to sensitivity analysis, the cost-effectiveness/utility was based on the health benefits estimates of the base-case analysis (*Tables 40* and *43*). The decision to adopt larval therapy was associated with considerable uncertainty (*Figures 13* and *14*).

Scenario 2: nurse-reported data including amputation costs

The cost estimates for this scenario show that unadjusted total costs incurred by participants in the hydrogel group are higher than for the larval therapy groups (*Table 47*). Adjusted cost estimates (*Table 46*, scenario 2) confirm this result, suggesting that the use of larval therapy may reduce costs by £227 per patient per year. The CEAC and cost-effectiveness plane show that the probability of larval therapy being cost-effective varies between 55% and 75% for a willingness-to-pay range between 0 and £30,000 (*Figures 15* and *16*). The scenarios further explained the uncertainty surrounding the decision of adopting larval therapy. Although the number of participants who had an amputation is very low (three participants), the high costs incurred shifted the estimate of cost difference. As information on this event was not collected systematically but only through 'reason for hospitalisation' data, we might be underestimating the event rate and consequently biasing the cost estimates. Nevertheless, amputation is revealed to be an important cost driver for leg ulcer participants.

One-way sensitivity analysis

As identified across other studies in wound care, both the setting and the duration of nurse visits

TABLE 45 *Sensitivity analysis – scenario 1. Total unadjusted costs using nurse-reported nurse visits and hospitalisations (excluding amputations)*

Total unadjusted costs (£ Sterling)	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Mean (SD)	1508 (1746)	1643 (2010)	1451 (1991)
Median (min to max)	1028 (91 to 12,560)	1019 (130 to 14,007)	727 (19 to 11,136)
n (%)	89 (95)	82 (95)	82 (94)

SD, standard deviation; min to max, minimum to maximum.

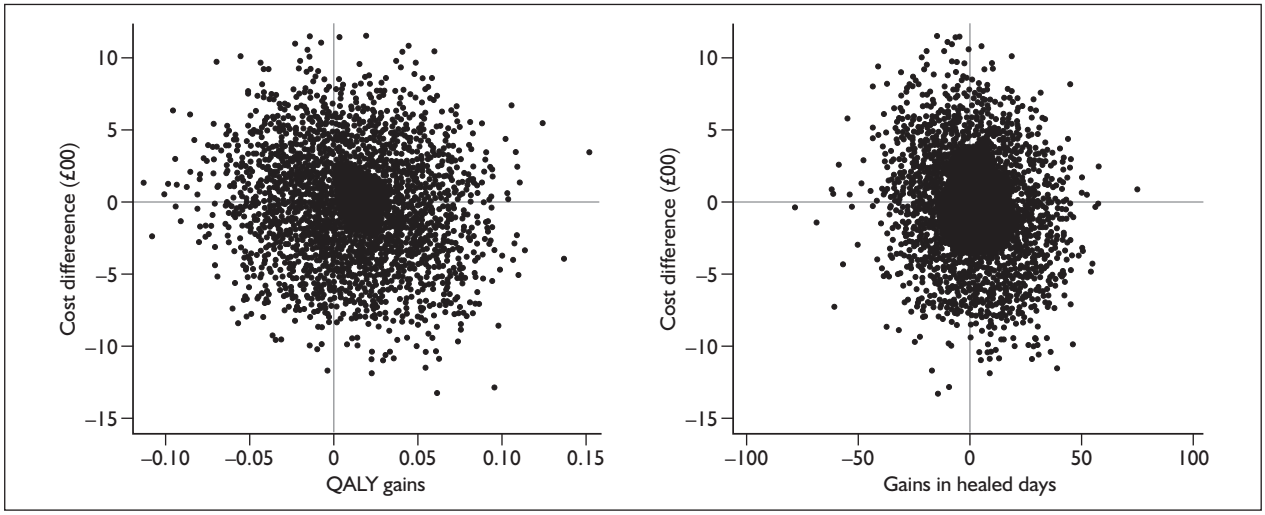

FIGURE 13 *Cost-effectiveness plane, scenario 1. QALY, quality-adjusted life-year.*

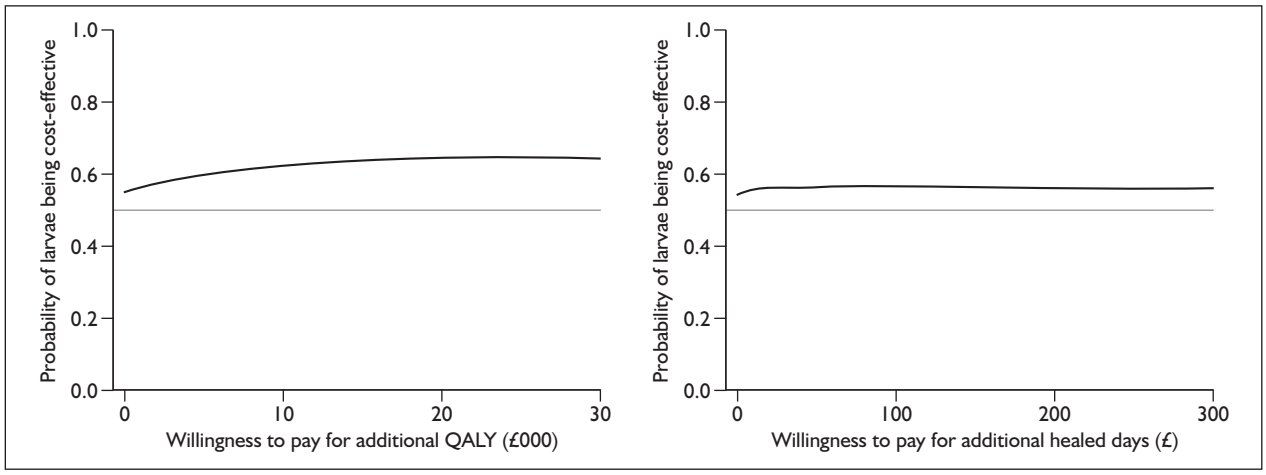

FIGURE 14 *Cost-effectiveness acceptability curve, scenario 1. CE, cost-effectiveness; QALY, quality-adjusted life-year.*

TABLE 46 *Sensitivity analysis. Adjusted annual costs using nurse reported nurse visits and hospitalisations, excluding amputation costs (scenario 1) and including amputation costs (scenario 2): adjustment for type of ulcer, ulcer duration (logarithmic), ulcer area (logarithmic), centre (aggregating centres with fewer than ten elements)*

	Scenario 1		Scenario 2	
Arm	**Annual costs (£)**	**95% bias corrected CI**	**Annual costs (£)**	**95% bias corrected CI**
Hydrogel	2369.9	1773.6 to 3004.7	2534.6	1928.6 to 3218.1
Larval therapy	2338.7	1964.5 to 2719.1	2307.9	1927.1 to 2703.3
Difference	−31.3	−726 to 707.9	−226.7	−988.8 to 511.8

TABLE 47 *Sensitivity analysis – scenario 2. Total unadjusted costs using nurse-reported nurse visits and hospitalisations (including amputations)*

Total unadjusted costs (£ Sterling)	Loose larvae (*n* = 94)	Bagged larvae (*n* = 86)	Hydrogel (*n* = 87)
Mean (SD)	1598 (1999)	1643 (2010)	1648 (2262)
Median (min to max)	1028 (91 to 12,560)	1019 (130 to 14,007)	819 (19 to 11,136)
n (%)	89 (95)	82 (95)	82 (94)

SD, standard deviation; min to max, minimum to maximum.

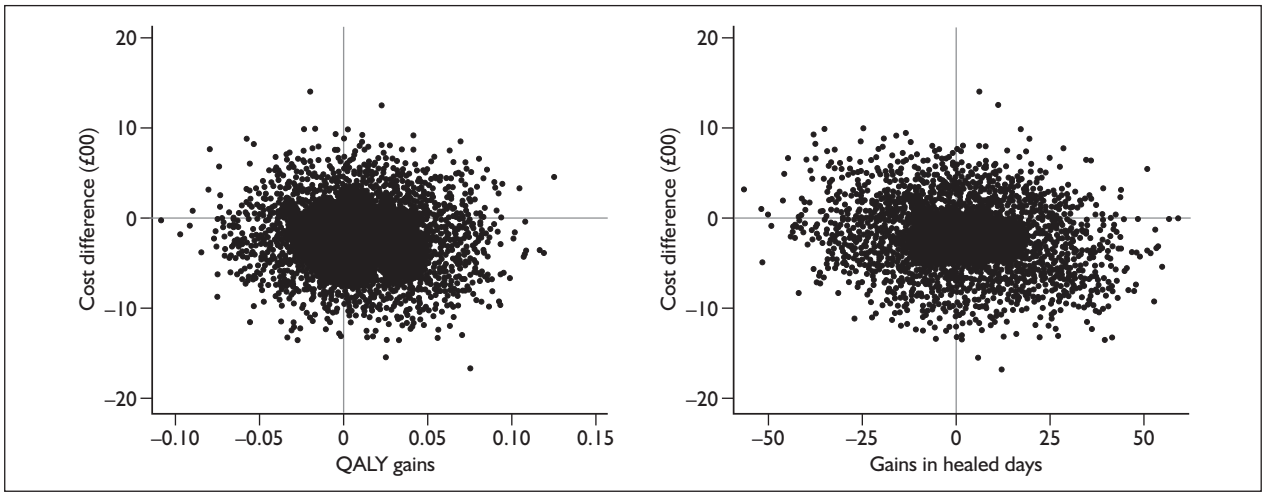

FIGURE 15 *Cost-effectiveness plane, scenario 2. QALY, quality-adjusted life-year.*

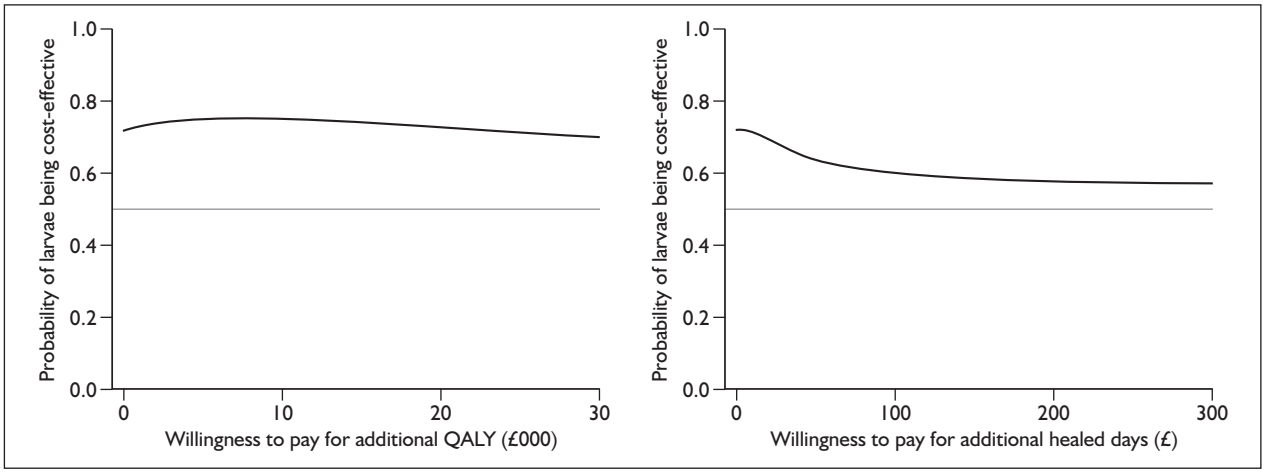

FIGURE 16 *Cost-effectiveness acceptability curve (CEAC), scenario 2. CE, cost-effectiveness; QALY, quality-adjusted life-year.*

are important in the evaluation of cost differences. A one-way sensitivity analysis was conducted to evaluate the influence of nurse visit costs on the cost difference. To this end, duration of nurse visits was increased/reduced by up to 13 minutes, i.e. the maximum reduction evaluated was 13 minutes and the maximum increase was 13 minutes from base-case values. As a consequence, a 5-minute reduction in clinic visit duration from the base-case analysis resulted in values of 31 minutes for a home visit and 17 minutes for a clinic visit (see *Table 9* in Chapter 2).

The sensitivity analysis shows that homogeneously reducing visit duration increases the cost difference (*Figure 17*). A 5-minute reduction in each visit increases the cost difference to £132 [bias corrected 95% CI (£–408.90 to £652.10)]. While the differences were not statistically significant, the uncertainty surrounding the cost difference reduces as the visit duration reduces.

The ratio of clinic to nurse home visit duration was subjected to sensitivity analysis. In the base-case analysis this ratio was 40 : 22, and in the sensitivity analysis it varied between 30 : 22 and 60 : 22.

As the duration of home visits increases in relation to clinic visits, the cost difference reduces and the uncertainty increases, i.e. confidence intervals are wider (*Figure 18*). None of the scenarios considered in the sensitivity analysis revealed a statistically significant difference in costs at conventional levels of significance.

Summary of cost-effectiveness data

- The estimated mean cost per application (£) of trial debridement treatments was higher for larvae than hydrogel. Both the use of high-compression bandaging and the number of visits to and from health care professionals were similar across all groups.
- Nurse visits were the major cost driver. The adjusted annual cost difference between larval

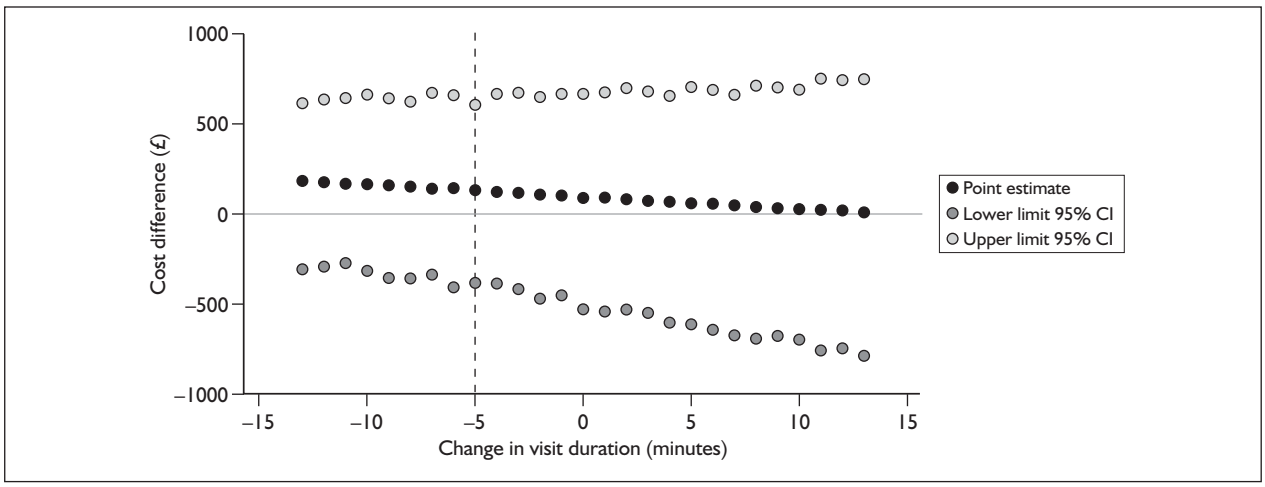

FIGURE 17 *Influence of nurse visit duration on adjusted cost difference, one-way sensitivity analysis. Bias corrected 95% CI based on 2000 bootstrap replicates.*

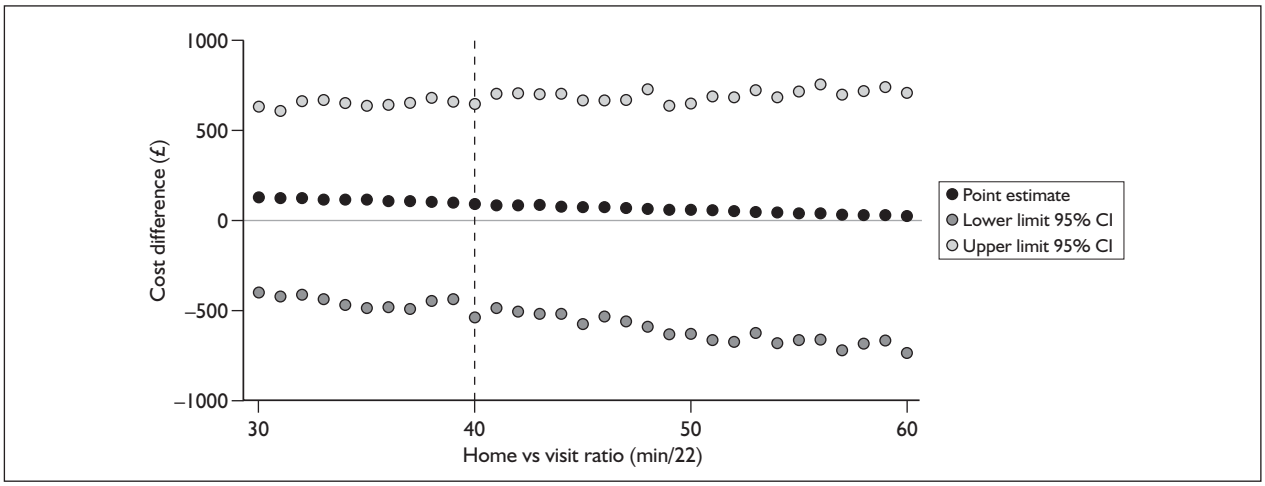

FIGURE 18 *Influence of home vs clinic nurse visit duration ratio on adjusted cost difference, one-way sensitivity analysis. Bias corrected 95% CI based on 2000 bootstrap replicates. The dashed line indicates the base-case analysis.*

therapy and hydrogel was estimated as £96.70 (larvae more expensive), but this difference was not statistically significant (95% bias corrected CI varied from £–491.90 to £685.80)

- On average, participants treated with larval therapy healed 2.42 days before those in the hydrogel arm and had more QALYs (annual difference was 0.011). However, these differences were not statistically significant (95% bias corrected CI –40.95 to 31.91 gains in healed days and –0.067 to 0.071 QALYs gained).
- The ICER associated with larval therapy use was estimated at £8826 per QALY gained and £40 per ulcer-free day. The nature of the uncertainty associated with our estimates of mean costs and health benefit suggests that larval therapy and hydrogel are likely to have similar costs and effects in the treatment of sloughy leg ulcers.
- Using nurse-reported data as an alternative information source for resource use returned smaller but non-significant adjusted costs for larval therapy compared with hydrogel (–£31.30). When amputation costs were included, this cost difference decreased to –£227. While larvae are dominant in these scenarios, these results are associated with high levels of uncertainty.
- One-way sensitivity analyses did not show any effect of altering the duration of nurse visits on the overall conclusions of the cost-effectiveness and cost–utility assessments.

Chapter 6

Results from the qualitative study of participant and staff attitudes and experiences of larval therapy

Patient interviewees

Participants were recruited from three clinical sites involved in VenUS II. Purposive sampling was used to ensure representation from patients who received their leg ulcer treatment in different clinical settings (at home and in clinics), to ensure inclusion of people of minority ethnic origin and of people who both had and had not experienced larval therapy as treatment for their leg ulcer.

In total, 18 participants were recruited to this qualitative study. Fourteen participants with leg ulcers were recruited into the study from those attending vascular clinics; one attached to a hospital (Bradford) and one in a community setting (Bolton) during April and July 2007. On arrival for their appointment at the clinic in Bolton, potential participants were informed about the study by the clinic nurse, and provided with an information sheet. A member of the research team (J.D.) was on hand to give a full explanation of the study and answer any questions or concerns. Participants who consented to take part in the study were then interviewed after their clinical consultation had taken place by the nurse researcher (D.M.). At the Bradford clinic, patients were given written information and a verbal explanation of the study (using the services of interpreters where necessary) at least one week in advance of the interviewer attending the clinic. Subsequently, interpreters assisted in gaining the consent of, and conducting interviews with two participants (P12 and P14).

A further four patients, who were receiving treatment for leg ulcers in their own homes were recruited through referral from a team of community nurses (based in York) in March and June 2007. These patients were told about the study by the community nurse involved in their care, and those who wished to hear more agreed to being contacted by the researcher (D.M.), who provided them with a full verbal explanation and written information about the study, before their deciding whether they wished to participate. One patient referred by a nurse declined to take part in the study, because he said he doubted its value.

Patient participant characteristics

Details of the study participants are given in *Tables 48* and *49*, based on their previous experience of larval therapy. In summary, 12 study participants were male, with ages ranging from 29 to 93 years (median age 64 years). The ages of the six female participants ranged from 62 to 76 years (median age 69.5 years). Fifteen participants were White British, one (male) was Asian (Pakistani), one (male) was Iraqi and one (female) was Black Caribbean. Duration of participants' current ulcer ranged from 1 month to 108 months (median 36 months; mean 44 months).

Five of the 18 participants had experience of being treated with larval therapy. Of these five participants, three were male and two were female; one female participant had experienced loose larvae, and one bagged larvae; two male participants had experienced bagged larvae and one loose larvae. Of the 13 participants who had never been treated with larval therapy, 10 were male and three were female.

Patient experiences of living with a leg ulcer

Many of the participants described lives that were disrupted or diminished because of their leg ulcers, which they associated with pain, restricted mobility, weight gain, odour, disturbed sleep (their own and their partners'), loss of physical and economic independence, reliance on medication, social embarrassment and low mood.

TABLE 48 *Participants who had not previously had leg ulcers treated with larval therapy*

Patient ID	Sex	Age	Ethnic origin	Lives with family (yes/no)	Duration of ulcer (months)
P1	M	67	White British	Yes	12
P2	M	61	White British	Yes	6
P3	M	65	White British	Yes	18
P4	F	62	White British	Yes	72
P5	M	31	White British	Yes	36
P6	M	69	White British	Yes	108
P7	M	63	White British	No	1
P8	M	70	White British	Yes	96
P10	F	71	White British	Yes	12
P12	M	45	Asian (Pakistani)	No	72
P13	F	76	Black Caribbean	Yes	60
P14	M	29	Iraqi	No	60
P16	F	76	White British	Yes	6

M, male; F, female.

TABLE 49 *Participants who had previously had leg ulcers treated with larval therapy*

Patient ID	Sex	Age	Country of origin	Lives with family (yes/no)	Duration of ulcer (months)	larval therapy (loose)	Larval therapy (bagged)
P9	F	68	White British	Yes	30	No	Yes
P11	M	52	White British	Yes	36	No	Yes
P15	M	82	White British	Yes	72	Yes	No
P17	M	93	White British	No	84	No	Yes
P18	F	66	White British	Yes	12	Yes	No

M, male; F, female.

Pain

While some participants said they were able to *'shrug off'* or tolerate pain from their ulcers, others described excruciating pain which kept them awake at night, or led them to depend on medication to enable them to sleep.

Varying levels of pain were attributed to the stage of healing of their ulcer, to external factors, such as hot weather, and to the application of compression bandaging.

> *they don't hurt me, I'm one of those people who can suffer pain I think.* (P17)

> *you get quite depressed, the pain is obnoxious, absolutely obnoxious.* (P10)

> *you're just going to sleep and then it 'whoa, what the hell?, and it wakes you up. It's only the ulcer telling you 'I'm here', isn't it? The pain of it wakes you up…* (P7)

> *it's a lot better, at the beginning I was taking a lot of pain killers, but I don't take any now.* (P18)

> *I was having to keep the leg outside the covers because the heat was making it worse.* (P18)

> *the pain sometimes goes, like after a day or two on your tablets it will subside and it'll be okay, but then you come to get it redressed and you know you are going to get pain after the redressing of the bandages.* (P11)

Mobility

The majority of the participants interviewed attributed lack of mobility to comorbidities such as osteoarthritis (resulting in stiff knees and hips) rather than to pain from their ulcer. However, the two youngest male respondents (P5 and P14) said that their leg ulcers restricted how far and for how long they could walk, which had a negative effect on their ability to work.

Although some participants were determined that they would not let their ulcer *'slow them down'*, others highlighted some of the physical and psychological consequences of immobility because of their ulcer pain. Reduced mobility was perceived as linked to social isolation and a dependence on others (P16). The importance of being able to drive to keep up social contact with his family and friends was stressed by P15.

> *I don't let it slow me down, I mean I struggle with my walking anyway because I am waiting for an operation on my left hip…so my movement is relatively slow and limited.* (P2)

> *I was avoiding walking, you know, I need to do more walking to get back some level of physical fitness and get rid of that… [pats his stomach]* (P1)

> *I can't walk, I can't really walk more than 100 metres without feeling, well not severe, but average pain and I have to stop.* (P5)

> *I can move and walk for one hour, two hours, but more than that, no…it hurts me a lot and sometimes makes me fed up with life.* (P14)

> *it means that I can't walk, I can't go out, I can't go into [name] or on the bus to [name] where I used to…so I do miss going out, yes I do…walking down to the post office to get my pension… but I haven't been able to, so my daughter-in-law does a lot for me…* (P16)

> *I can drive, once I get into my car, not far, but I can drive, yes…* (P15)

Social embarrassment

Having to wear special clothes or shoes to accommodate compression bandaging was associated with social stigma by three (male) respondents. Asked about the effect of his leg ulcer on his life, P11 responded that it was:

> *Terrible…when I am in the bandages, the compression bandages…this is the only pair of shoes I can get in. I take 12s or 13s anyway, so when I've got the compression bandages, these are the only pair of 14s I've seen in my life, and I have had to take the laces out, so it means unless I go out in these shoes, I don't go out for a meal or anything.* (P11)

P6 felt similarly socially curtailed because of difficulties in finding shoes to fit:

> *because you can't get your shoes on when they put all these bandages on, you can't get your shoes on and you can't get dressed up or anything to go out…* (P6)

P3 described attracting unwanted glances due to his wearing shorts rather than full length trousers for comfort with his compression bandages.

> *if you can get over the embarrassment because you are walking around with a bandage on your leg, I could wear the pants and then my legs get very hot which is bad for them, so I tend to wear shorts, so people are always looking at me.* (P3)

The pervasive odour emanating from leg ulcers was regarded as a further potential source of social embarrassment:

> *it's like rotten cabbage…it's like a stinky cabbage… when it's really on its bad side, it does not smell very nice.* (P6)

Nuisance factor

Having a leg ulcer was perceived as time-consuming (P3), activity restricting (P5, P6, P7, P11, P12, P14, P16) and a general nuisance (P10, P13, P15, P18) because of having to attend regular clinic appointments, spending time (and sometimes money) in consultations with doctors and nurses, and running into difficulties pertaining to care of the ulcer when travelling away from home.

> *it is time-consuming, it does restrict you to go anywhere, you've got to allow time for it.* (P3)

> *within a fortnight I saw a specialist, if you pay, you'll get in that much earlier…* (P15)

> *when I went to see the Dermatologist at the hospital, she did suggest the pressure bandage…but that created its own problems, particularly as we go away*

in our motor home and each time we were going away, I was having to contact local surgeries in the area we were travelling to… (P18)

'Everything under the sun': leg ulcer treatments (other than larval therapy) cited by participants

The majority of participants reported having tried more than one type of treatment for their ulcer (see *Table 50*), in the form of compression bandaging, gels and dressings, creams and ointments. One participant, P15, said he had been treated with gentian violet and potassium permanganate on the respective recommendations of a doctor abroad and one in the UK. P9 simply said that she had tried *'everything under the sun'*.

Participants' descriptions of the treatments they received for their leg ulcers were couched in terms that suggested little or no real involvement on their part in the decision-making process about choice of treatment.

they tried honey at first but it was too painful… they're using like an iodine ointment now, which seems to be doing the trick…it started healing, so they said, well, let's carry on… (P1)

While some participants appeared to have complete faith in professional expertise, others voiced concern about the effectiveness or side effects of the various treatments used on them, or about the ways in which they were administered.

he is not sure of what they are actually using, but they are doing their best they can for him and he is grateful for the help that he is getting, he says what ever they feel is appropriate that they are using, dressings and bandages and so on.
(P12 via interpreter)

then they suggested the up and coming thing is the honey treatment…and I were getting shocking nights, they were burning and I kept complaining about it, my leg was terribly raw and they said, 'well, it could be it's doing it's job, so I said 'Okay', and I ploughed on… (P15)

each time the bandage was being put on, by different people, sometimes it was too tight, sometimes it was not tight enough… (P18)

P15 expressed concern about the lack of consistency of approach to the application of treatments by members of community nursing teams:

the trouble is, you never see the same person every day, or every visit, I suppose I've got about five or six different nurses that will come and attend to my leg, and none of them do it the same way…they all do it slightly differently... (P15)

P7 was more pointed in his criticism of *'district nurses'* (community nurses) and drew an unfavourable comparison between them and the nurses working in the vascular clinic.

I thought, I want to be getting to that ulcer centre at [name], they look after you here…they look after you better than the district nurses…I mean they assess you…and they know what they are doing. I have great faith in these people. (P7)

Patient attitudes to and experiences of larval therapy: overview

A brief overview of data relating to acceptability of larval therapy, preferences for loose or bagged larvae, and participants' previous experience of handling maggots is presented here, followed by a more detailed analysis of the qualitative interview data.

Acceptability of larval therapy

The majority of the participants interviewed stated that they would be prepared to have larval therapy as a treatment for their leg ulcer. Five out of the 18 participants had tried larval therapy, and a further 10 participants said that they would be willing to try it.

Two respondents (P13 and P16; both female and aged 76 years) stated categorically that they would not find larval therapy acceptable under any circumstances. However, interestingly, one of these participants, (P16) revised her opinion during the course of the interview when she learnt that larvae were obtainable in 'bagged' form; this prompted her to say that she might be prepared to consider having larval therapy.

One respondent (P8) was equivocal about whether or not he would accept larval therapy. He said he

TABLE 50 *Leg ulcer treatments (other than larval therapy) cited by patient participants*

Patient ID	Compression Bandaging	Honey	Hydrogel	Ointment	Dressings	'Zip sock'	Other
P1		✓					
P2	✓		✓				
P3	✓			✓			
P4		✓		✓			
P5	✓						
P6	✓				✓		
P7	✓				✓		
P8	✓		✓				
P9							
P10	✓				✓	✓	
P11	✓				✓		
P12	✓	✓					
P13	✓				✓	✓	
P14	✓			✓			
P15	✓	✓		✓	✓		✓
P16	✓	✓					
P17		✓			✓		
P18	✓			✓		✓	

would need to be convinced of its effectiveness before he could make a decision. *Figure 19* summarises participants' responses to the question posed during interview concerning acceptability of larval therapy.

Of the 15 respondents who said that they would be prepared to accept, or had accepted, larval therapy as treatment, 13 said that they would be prepared to accept either loose or bagged larvae. Of the two remaining participants, one said he was unsure about whether he would prefer to have loose or bagged larvae, stating that he would wish to know more about the effectiveness of the different types and to be shown them before he could express a preference, while P18 had been recruited to VenUS II and had been randomised to receive loose larvae. Given a choice, she said she *'might have preferred'* to have had bagged larvae, but she emphasised that this was not a strong preference as she *'didn't mind having the loose'*.

Prior experience of larvae generally

Male participants were more likely than female participants to have handled *'maggots'*. Of the 12 male participants, seven had handled maggots, in connection with fishing as a hobby as a child, two of whom (P5 and P11) mentioned that they

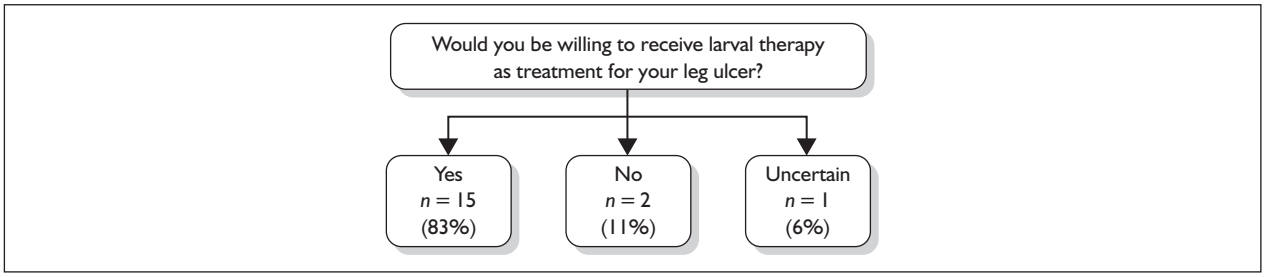

FIGURE 19 *Patient willingness to try larval therapy.*

had held or *'rolled maggots'* in their mouths when fishing. Neither of the male participants who were born outside the UK (P12 and P14) had had any experience of handling maggots as a child.

None of the female participants mentioned that they had handled larvae. P9 said she had seen them as a child *'in a tin'* belonging to her brother when he had been going fishing. P16 could not recollect if she had actually ever seen larvae, though she remembered that her son had used them when he went fishing when he was young.

Of the five participants who had received larval therapy (three male and two female), two of the males (P11 and P17) said that they had had experience of handling maggots, while the other three participants (one male and two females) (P15, P9, P18) had not.

Attitudes to larval therapy: detailed findings from participant interviews

A range of factors, either alone or in combination, appeared to influence participants' views and decision-making about the acceptability of larval therapy. The majority of participants who had already accepted, or who said they would be willing to try, larval therapy ($n = 15$) displayed:

- a strong desire to try any treatment that might ameliorate or hold out the hope of a cure for their leg ulcer
- prior knowledge of, or contact with, 'maggots'
- an open-minded approach towards new or 'alternative' therapies
- positive health beliefs about the effectiveness of larval therapy
- an absence of, or willingness to overcome, any feelings of squeamishness about *'creepy-crawlies'* on the part of the participant or their family members.

Participants who appeared less willing (P8), or unwilling, (P13, P16) to accept larval therapy exhibited squeamishness or strong feelings of aversion to the idea of larval therapy; had had little, or no, prior knowledge or contact with 'maggots'; were sceptical about whether larval therapy would be beneficial, or believed that it could cause harm; and were supported in their views by their family members (with the exception of P16, whose son, she said, had actively encouraged her to try larval therapy).

Factors associated with a willingness to accept larval therapy

'I'll try anything'

Participants' willingness to try any kind of treatment that might hold hope for the amelioration or cure of their ulcer was encapsulated in the phrase *'I'll try anything'*, which was recurrent in a majority of their accounts of living with their leg ulcer. For these people, larval therapy was viewed as a last resort, a treatment to try when everything else had failed to rid them of their ulcer and its associated pain.

> *basically, I would do anything that would do my leg good.* (P1)

> *when you get into a strait with leg ulcers they are painful and you can't find a cure for them, you'll do anything.* (P6)

> *we just felt it was worth trying anything, because I didn't feel I was getting anywhere very much really, and you know, it was worth trying various things and seeing if that helped.* (P18)

Prior knowledge of, or contact with, 'maggots'

Television, newspapers, books about the First World War, magazines, nurses, friends and fellow patients at the leg ulcer clinic that they attended, were all quoted by participants as sources of knowledge about larval therapy, which contributed to them developing positive views of how it might be beneficial in treating their ulcer.

> *I've seen on the television they've used them – was it about Florence Nightingale, and it eats only dead tissue, not live tissue. It's not like it's going to bore into your leg and finish up at your heart or your head or somewhere, no, it only eats dead tissue.* (P2)

> *they found this in 1916 with the chaps laid in trenches for days…they were full of maggots, but the wound was clean…* (P17)

P7 recounted an article in a magazine reporting the case of a young girl whose foot was apparently saved by the application of larval therapy:

> *she reckoned that she would have to have her foot off, but they put the maggots on and the maggots must have ate all the badness or whatever…* (P7)

About half the participants who said they would be willing to accept larval therapy had handled

maggots, usually as a child when they had gone fishing. P7 said he had handled them when working on a farm:

> *I'm not frightened of maggots, I can pick a big handful in my hand and it wouldn't bother me one bit, the maggots wouldn't bother me at all.* (P7)

P5 and P11 mentioned *'rolling'* maggots in their mouths during fishing trips, while P6 said he had bred them specifically for fishing when he had observed them closely:

> *I used to breed maggots myself for fishing and they only eat bad stuff. If you put good stuff there they won't touch it…* (P6)

Two participants (P12 and P14), born in Pakistan and Iraq respectively, constituted 'negative cases'[133] in that they were willing to try larval therapy, although they had never seen or handled maggots, or heard of them being used to treat wounds. Their expressed willingness to accept larval therapy appeared to be based largely in their trust in the expertise of health care professionals to do their best for them:

> *they are doctors, they know more than me…so I listen to them whatever they say…* (P14)

> *he is saying that if they [health care professionals] felt that it would benefit him and would improve his health, his ulcer, he wouldn't have a problem with it, no…* (P12 via an interpreter)

An open-minded approach to new or 'alternative' therapies

Participants who were readily accepting of larval therapy appeared to have an interest in, and were open to, trying new health care technologies, to adopt a proactive approach to seeking treatment options, and to be prepared to take the risk of having new treatments for which there was no established evidence base. When asked if she would be interested in taking part in a trial of treatments for leg ulcers, P10 agreed to participate, even before she knew the details of the trial.

> *at Christmas, when this [her ulcer] was really going bad [name] said 'why don't you come on one of our trials?' So I said, well, I have nothing to lose, so they picked this one, the ultrasound.* (P10)

> *for the majority of people, it is an unknown quantity.* (P17)

> *stick them on, by all means!* (P7)

P11 was the instigator of his receiving larval therapy after hearing about it from the media. Disappointed by the lack of interest that he encountered initially in his GP and other health care professionals, he persevered and finally got the treatment he wanted:

> *They didn't suggest it. I told them I wanted it…I'd heard on radio, television programmes about it so I tried at the GP, but they didn't seem interested in it... and I tried the clinic I was going to at [name] and they didn't do 'owt...and when I came to [name] … the doctor agreed there…* (P11)

P18 also tried larval therapy as a result of information found in the media. Her husband had seen an advert in the local paper about larval therapy, and suggested to her that it was *'worth a try'*. P18 mentioned that she had used the Internet to search for treatments for leg ulcers, especially when she first developed her ulcer, and that she was willing to try 'alternative' or complementary therapies as well as more established treatments.

> *I've tried homeopathic and acupuncture and I go to an osteopath, yeah, I tend to look down that route to see what there is, rather than down the traditional route…* (P18)

P1 expressed a general interest in alternative approaches to health care, particularly those that have been used in the past, but which have not always received support from the medical profession.

> *I find it interesting that medicine in general is going back to methods that we used 150 years ago…leeches used for the anticoagulant and so many herbal remedies that are actually the source of the drugs they give in tablet form. I'm just pleased that the medical professions are getting a more open mind than it had 50 years ago, apparently.* (P1)

Positive beliefs about the effectiveness of larval therapy

Participants who were willing to accept larval therapy appeared to hold strong beliefs that 'maggots' would work as well as, or better than, other treatments, such as surgical debridement.

These beliefs were grounded in their own experience of observing or handling maggots, anecdotes and media coverage.

P3 had seen a television programme about the use of maggots, which had made a strong impression on him that they could be extremely effective in removing dead or infected tissue and from an article that he had read, he assumed they were safe.

> *years ago I had an accident and I got my leg partly run over…there was dead tissue, and they had to cut it away…but maggots would probably have got rid of that just as easily as the knife…because to get to the dead tissue, they had to cut into the good tissue…* (P3)

> *when it was explained that they only eat the dead tissue and don't go into the live tissue, there's no problem.* (P3)

P5 was the only participant willing to have larval therapy who raised significant concerns about the possibility that they might harm him in some way, for example, by causing infection.

> *I would be open to using maggots, why not?....if it's clean and by putting maggots a wound cannot cause any infection…if it can't cause me any infection, it can only be good…if I've got proof that it can't cause me any harm…* (P5)

Absence of, or willingness to overcome, feelings of squeamishness on the part of the participant or their family

All but two of the male participants who were predisposed to accepting larval therapy remarked that they did not experience any feelings of squeamishness or distaste in relation to larvae, perhaps because most of them had handled maggots at some stage in their lives.

> *I've had them in my hands and everything, I've put them in my mouth…* (P5)

P1 had not been *'keen'* on handling maggots as a child, but said he would be prepared to have larval therapy if he thought it would be beneficial for his ulcer; (P2) said his feelings were not strong enough to deter him from having treatment:

> *I'm not very keen, you know, sticking worms on the end of a hook to go fishing…I'm not sort of one of the celebrities in the jungle types, you know stick my head in a bag of them!* (P1)

> *I mean, it makes you feel a little squeamish, but no, it's fine, I wouldn't object.* (P2)

None of the female participants interviewed had ever handled maggots but of those willing to have larval therapy, only one (P4) expressed feelings of distaste, related to the thought of maggots *'eating your flesh away'*. However, she too believed she would be able to overcome these feelings if she could be sure that her leg ulcer would be helped by larval therapy.

In several cases, the attitudes and feelings of family members appeared to play a potentially supportive role in participants' decision-making about whether to have larval therapy; in other cases, the fact that they were unlikely to object seemed to be taken into account in participants' decision-making. P18 pointed out that her husband had been the one to tell her about larval therapy in the first instance, and that he was *'quite happy with the idea'* (P18), while P2 said his wife was as interested in it as he was. Participant 15 had already made the decision to accept larval therapy when he was interviewed. His wife was present at the interview also, and described her initial reaction to the suggestion of larval therapy as *'Yuuuuk'!* Nevertheless, she said she was willing to try anything to help her husband, and referred to the decision they made for him to have larval therapy as a joint one. P15's wife then described how she had watched as the loose larvae were applied and removed by the community nurses in their home.

P6 thought his wife would not object to his having larval therapy because both he and her father had bred maggots for fishing:

> *I don't think she would bother because she used to go fishing and I was breeding my own maggots, so she wouldn't bother, and her dad used to go fishing.* (P6)

Factors associated with a reluctance or unwillingness to accept larval therapy

Factors associated with reluctance or unwillingness to accept larval therapy were evident in the accounts of three participants (P8, P13 and P16). These included: feelings of squeamishness or

strong feelings of aversion to larval therapy; little or no previous contact with maggots; scepticism about the benefits of larval therapy; negative views of larval therapy shared by family members.

The accounts of the three participants, derived from their interviews, are presented here in the form of case studies or summary descriptions[106] to illustrate how the interplay of these factors could lead the participants to say that they would be likely to reject larval therapy as a form of treatment for their leg ulcer (*Boxes 1–3*). During the course of her interview, P16 appeared to revise her attitudes towards larval therapy, as she learnt more about it, and as she reflected on a discussion she had had with her son just before the interview. P8 implied that he might be willing to accept larval therapy if there was strong enough evidence to support its effectiveness in healing ulcers, and if its application could be effected in a manner that did not distress his wife or cause any domestic upset. P13 seemed adamant that she would never consider larval therapy an acceptable form of treatment.

Patients' experiences of larval therapy as a treatment for leg ulcers: detailed findings from participant interviews

Three male (P11, P15 and P17) and two female (P9 and P18) participants recruited to the study experienced larval therapy as a treatment for their leg ulcer. Three of the five (P9, P11 and P17) had experienced bagged larvae and two (P15 and P18) had experienced loose larvae.

Participants frequently adopted a narrative style to recount details concerning their experiences of *'having maggots'*, and used vivid words and phrases that conveyed a strong message of what the experience meant to the individuals concerned. These experiences will be discussed under the subheadings below in an attempt to portray those aspects which appeared to be of most significance to the participants and, where appropriate, their exact words will be reproduced at length in quotation.

BOX 1 *Case study A*

Participant 8 was 70 years old and had had his ulcer for a period of 8 years. He attributed its cause to an occasion when he caught his leg on a bench and broke the skin. Compression bandaging was his mainstay treatment.

P8 said that he had not gone fishing or handled maggots in his youth:

> *I suppose the closest I've come to anything is picking up a worm occasionally.*

He described his distaste for 'creepy-crawlies' as a family trait that he had inherited from his mother and shared with his wife:

> *I think probably the initial starting point was probably with my mother, she didn't like what she called creepy-crawlies… maggots, worms and things like that, I've never particularly enjoyed them. My mother was very much against anything that wriggled. My wife has been the same, we've been married 30 odd years and creepy-crawlies send her really wobbly. I think, being honest, I've always had this…*

P8 put forward three reasons as explanations for his reluctance to accept larval therapy. First, he suggested that the treatment would be inappropriate for the type of ulcer he had; second, he said the odds of his ulcer being healed would have to be high to convince him; and, third, he said he knew that his wife would not tolerate maggots in the house.

> *I associate maggots and wounds where you've got a sort of crater, and at the moment I've no crater…if they turned round and said would you have it on your leg now, I'd say no. If I had the wound and they said, the chances are 50/50, I'd say no. So it would have to be at least 75/25 success rate.*
>
> *the big problem, as I say, is getting it over to my wife. It's not just the question of 'I don't want to touch them, I don't want to see them.' It's a question of 'I don't want maggots in the house', and I think if she turned around and said if you do that you'll have to go into a hotel or something until it's sorted…then I would say no.*

P8 summed up his feelings about larval therapy at the end of the interview:

> *they're not something I would particularly want to be involved in, but if I was very bad, and I had, as I say, a 75/25 chance of recovering with the use of them, I would personally be prepared to go along with it, but not at the expense of any of my family.*

BOX 2 *Case Study B*

Participant 13, aged 76 years, originated from the West Indies, and had come to the UK with her husband about 30 years ago. Her husband had died recently, though she had other family members who had settled in the UK. P13 wished to return to live in her birthplace, but she said that when she had gone for a visit her ulcer had become much worse, so she had come back to the UK for further treatment.

Apparently a doctor had suggested to P13 3 or 4 years previously that she try larval therapy, a suggestion that had provoked strong feelings of fear and revulsion. P13 told how profoundly disturbing she found the notion of having maggots applied to her own flesh because of associations with dirt, and images of meat rotting in the sun, overrun with maggots. She feared that they would consume her own flesh, and make her ulcer worse, not better.

> *I am worrying that the maggot will be feeding on my flesh, and then when you think it is curing, it's making it worse or it is getting bigger, you know, because maggots is worms, and I know this is why, if you have a meat and it spoil, this is what make maggots, it is dirty.*

She expressed a deep rooted fear of 'all creeping things'; particularly those such as earthworms, which she perceived as dirty and repellent, so that she would avoid contact with them. She had never handled maggots or worms to go fishing when she was a child.

> *All creeping things I do not like, I am scared of them, all what is creeping, spiders, snakes, lizards, all them things…I know them worms, I know the millipede, all these are dirty, creeping things…*
>
> *the boys, not me, the boys were getting the worms, all sorts of things to go fishing in the sea…*

Her husband had supported her decision to refuse to have larval therapy; like her, he was apparently unconvinced that they could help heal her ulcer, believing they could only make it worse.

> *there is a long time that they have been talking about these maggots and I would just like to know, how many people have they cured from them?... My husband, he did not agree, he tell me, how can they put worms on a sore foot? I don't think it can heal this sore while the worms are feeding on the sore, it will just be making it wider, so I decided not to do it, the doctor called me in the room and I tell her 'No'.*

BOX 3 *Case Study C*

Participant 16, also aged 76 years, lived with her son and his wife, who took a close interest in her welfare. She had suffered recurrent ulcers, the most recent being of about 6 months' duration, which was being treated with applications of honey and dressings. She described her affected leg as swollen and painful, with constant leakage into the bandages.

Initially, when asked if she would be prepared to consider larval therapy, she expressed her revulsion by twisting her face into a grimace, saying, 'Oh, God, no, no, no way maggots!' signalling her disgust at the thought of maggots crawling freely over her leg, and her fear that they might burrow into her flesh in some way.

> *they are going to be creepy-crawly things and where do they go? And do they go inside your leg, or do they…you don't know, do you, you don't know?*

P16 was not sure if she had ever actually seen any maggots, though she had memories of her son storing them in a box in the fridge when he used to go fishing. In preparation for the interview, she said she had talked to her son about the possibility of having maggots to heal ulcers, and that he had encouraged her to think about trying them because he knew that they had helped soldiers' wounds during the First World War.

As the interview progressed, and she learned that larval therapy could be applied in bagged form, P16 began to reconsider her initial reaction to refuse treatment: 'Does anybody say 'yes' straightaway?'

Thinking about how long she had suffered from ulcers, and worrying about the burden of care on her son and daughter-in-law, she thought that she might consider having bagged larvae on her ulcer, though she did wonder if they would be less effective in bagged form.

> *Ah, that would make a difference to me, because then I would know where they were…but how would they do any good if they were in a little bag?*

Setting where patients received larval therapy

Four of the five patients experienced larval therapy in their own homes, applied by nurses who were members of the community nursing team, generally well-known to participants, who referred to them by their first name and spoke highly of them and their dedicated approach to care.

P11 was the only participant in hospital on account of his leg ulcer when the larvae were applied, and his experience was in marked contrast to the others. He complained that he had been made to feel like a *'peep show'* during his stay in hospital as nurses whom he did not know came to take a quick 'peep' at the larvae when they were being rehydrated, their use being something of a novelty on the ward.

A major potential drawback of receiving larval therapy in a community setting was highlighted by one the two participants who suffered intense pain soon after the larvae were applied. P18 described seeking advice, in vain, during a pain-filled and sleepless night, and how she had had to wait for the nurse to return the following day to have the larvae removed and the pain relieved.

> *I mean, I couldn't take them off myself, I had to wait until the next day, if it had been happening during the day, I would have contacted the Sister and asked her to come round, but because it happened overnight I couldn't do anything about it, and I didn't get any sleep, I was just sitting watching the clock go round until the time that she was due to come, and just kept taking the painkillers…I rang [the out of hours service] at about half past three in the morning, and left a message and he [the emergency doctor] rang me back but you see, a lot of people don't know anything about the larval therapy, so when I told him about it, it was something he had not come across before, and all he could suggest was keep taking the painkillers…* (P18)

Perceived competence of staff

Participants who received larval therapy in their home were pleased with the experience and praised the nurses who applied it. The manner in which the nurse broached the topic of using larval therapy was perceived as important by P17, who was pleased that the nurse had *'asked'* his permission to use it, so that he felt drawn in to the decision-making process, though in fact he happily deferred to her expertise saying that he would try anything she recommended: *'whatever you want, I'll try'* (P17).

By contrast, P11 judged his experience of receiving larvae in hospital as a disappointment; his stay coincided with a Bank Holiday, the Tissue Viability Nurse was apparently unavailable, and he was critical of the nurses who had applied the larvae to his ulcer.

> *I was just a bit disappointed that they were actually put on by someone who really hadn't done it before and wasn't one of the Tissue Viability Nurses…it were people who had to read the instructions on the packet…and they were like feeling their way, and to me, something like that is a specialist thing and someone like a main person from, a district nurse type, I think should have been [there], and then as they got on, the seniority got less and less…they weren't at the top of their game on that front…* (P11)

Expectations versus experience

Pain

Descriptions of pain, unanticipated and intense, dominated the accounts of the two female participants (P9 and P18). The male participants (P15 and P17) had not expected to feel any pain, and neither did they report any, just a little *'irritability'* just before the larvae were removed (P15).

> *it didn't affect me during the day and it didn't affect me at night. No, the last day you get a bit irritable, you wanted them off, because you knew they were coming off, but other than that, no…* (P15)

P11 observed little change in the level of pain he experienced while the larvae were in situ – he described the pain as no more or less than usual with his leg ulcer. P9 and P18 both appeared shocked by the intensity of the pain they suffered within a short period of the larval therapy being applied; P18 had not expected to feel any pain; P9 had anticipated that she might feel a low level of pain while the larvae were *'crawling around and cleaning up the slough'*. Both participants believed that they had a high pain threshold, but both sought to have the larvae removed earlier than planned because they found the pain unbearable. P9 said she had experienced constant pain *'from the moment they* [the larvae] *went on'* and was concerned because the pain exacerbated her angina:

> *I really wasn't so bothered about the pain of the maggots, I was more bothered about the angina… because every attack I have makes it [her heart] weaker, and I couldn't afford that you know...* (P9)

P18's pain was attributed to a reaction to the larval enzymes by the nurse who had applied the therapy, an explanation repeated by P18 during her interview:

> I seemed to have a reaction, I couldn't sleep *at all…I went to bed for about an hour, and I was in so much pain, I just sat in the chair all night…it was like shooting pains really, coming up my leg, almost like knives going into it…it was the sort of pain where I just didn't know what to do with myself…* (P18)

> *when I spoke to Sister about it afterwards, she said that there are a few people that get a reaction to the enzymes from the larvae, not the larvae itself, but from the enzymes, and I may have been one of the people that did…* (P18)

Although she did not make any connection between the pain she experienced and vascular impairment, P18 did refer to a forthcoming operation in the near future:

> *he [a Vascular Surgeon] said that I really need an operation on my vein, on the vein in my leg, because without that operation I will probably keep getting ulcers.* (P18)

Appearance of larvae: 'the thought is worse than the act'

Two participants (P15 and P18) commented on how they were pleasantly surprised when they first saw the larvae. The 'maggots' appeared much smaller than they had expected, like *'wisps of hair'* or an *'eyelash'*, which made the process of having them applied much more pleasant, and less disturbing.

> *I think a lot of people, as well as myself, tend to think of maggots as the sort fishermen use, you know, these big fat things that you see wriggling around, and I think if I had had those on my leg, perhaps I would not have been so happy about it, but [name] had told me they are very thin, they are sort of almost like an eyelash, and I think because of the size of them, they weren't these fat maggots that most people know about, I think that made a difference.* (P18)

P15 described the maggots as 'little wisps of hair so small you can hardly see them…'

Asked if they had watched the larvae being removed, they replied that they had, P15 saying that *'they had grown…yes, they jolly well had grown'* and P18 remarking that while they had grown, it was not as upsetting to look at them as she had thought it might be: *'the thought is worse than the act'*.

As P15 pointed out, *'you are not obliged to watch* [the larvae being removed] *you can leave it to the nurses'*, which is what P15's wife did when she was in the room when the nurse removed some of *'the hundred plus'* that she had put on, and some rolled onto the carpet.

Perceived effectiveness of larval therapy

With the exception of P11, participants felt that the larval therapy had done a good job of cleaning slough from their ulcer, but they also thought that their ulcers had deteriorated again, sometimes quite quickly. Effectiveness was initially measured by how clean the ulcer looked on removal of the maggots – participants looked to see if there was a visible improvement.

> *I was happy with the maggot treatment and I felt at the end of the time, my leg was feeling quite clean, but at the moment, if you took that bandage off now, there is a big …[indicates size and depth of ulcer with his fingers]…we have had it down as low as that…[indicates depth again] and now it's gone back to that [indicates size again], the area is not healing…it's growing, yeah, you can see it growing…* (P15)

P15's strong belief in 'maggots' as an effective therapy did not seem to be shaken by the fact that his ulcer remained unhealed, or the fact that apparently, according to his wife, the nursing staff had commented that they could see little change after applying the larvae.

> *but they said they didn't do you any good…* (P15's wife)

> *well, they said they didn't do me any good…I just felt my leg was cleaner, not as clean as it was way back, but cleaner than it is now…I have no problems with the maggots treatment, if that is the ideal way of curing an ulcer, go ahead full steam…* (P15)

P17 reported that in his case, the larvae had efficiently removed all the dead flesh, to leave a clean wound:

> *they eat all the dead, dead everything, dead flesh, skin, everything that is dead they clear away, and you are left with a clean wound…* (P17)

The two female participants (P9 and P18) who had their larvae removed 'early' due to pain,

reported improvements in their ulcer, that seemed to indicate a belief in the power of larval therapy to achieve a beneficial effect in even a very short period of time. Despite the pain that they had suffered, and the fact that their therapy was terminated after a brief application, they seemed satisfied with the results:

> *I truly believe in them. I think they are wonderful…I believe in them thoroughly but the only trouble is I couldn't keep them on a third night, but they did do a marvellous job, they did clear a lot of the slough away, but with me having angina, I'm afraid it was too painful…I couldn't have stood it any longer…they had done their job by then, and then it deteriorated again…* (P9)

P18 relied on the judgment of the nurse for her opinion that her ulcer had been improved by the application of the larvae, though she herself was disappointed that she had not been able to tolerate them for a second day, because she assumed there would have been an even better effect:

> *she said it did look cleaner after they took them away, so she said she could see the difference, because she had obviously seen the ulcer the day before when she was putting it on, so she said it had cleaned them up, yeah…* (P18)

P11 was unsure about the effect of the larval therapy on his ulcer. He had described his ulcer as having a *'terrible'* effect on his daily life, due to constant pain, disturbed sleep and feelings of social isolation. He had sought to have larval therapy as a treatment after hearing about it in the media. He appeared to have high expectations of its effectiveness. Until his admission to hospital, his ulcer had been treated mainly with compression bandaging. Once in hospital, larvae (bagged) had been applied to a large, necrotic, ulcerated area on his right leg. He revealed that he had not wanted to look at his ulcer when the larvae were removed for fear there had been little improvement. Neither did he seem willing to trust the judgment of the nursing staff, whose competence he had questioned elsewhere in his interview.

> *I had necrotic parts of the ulcer, so they had the larvae treatment on them, but it seems that…when they covered the ulcers, it [the bagged larvae] wasn't big enough, it was only big enough to go round the necrotic area. But I had it done, and it was taken off every day and rearranged and rehydrated and put back and redressed, but every time, people used to say, 'Oh, yes, that's a bit better, but you don't know whether they are just saying that, I really didn't want to look to be honest…not because of the maggots, I wasn't bothered about those. I just thought that perhaps if I looked at it and found out that it wasn't improving as much as I'd want it to improve I'd be upset about it.* (P11)

Only one participant (P18) commented that they thought loose maggots might be more effective than bagged ones. As a trial participant, P18 had been randomised to receive loose larvae, though, given a choice, she said she might have opted for bagged. However, she did speculate that perhaps the loose maggots might be able to work more effectively as they would not be constrained:

> *I didn't mind having them loose, but I think in a way there was this feeling of them being a bit more contained, rather than having sight of it, but then I thought maybe if they are in a bag, maybe they aren't doing their job so well, so I suppose there are two ways of looking at it.* (P18)

Reflections on the experience of having larval therapy

Asked about their understanding of how larval therapy works, two of the male participants referred to larvae eating dead cells, and then eating each other. None of the participants seemed particularly well informed at a detailed level about how the larvae actually functioned; mostly, they referred to bits of information they had picked up from newspaper or magazine articles, or books they had read.

> *apparently, they devour the cells do they not, I think [name of nurse] said one eats the other one, and one eats the other one, and one eats the other one that's eaten the bad skin…* (P15)

> *I knew alright about them, from reading books.* (P17)

Only participant (P18) referred to larval enzymes, in relation to the reaction she experienced at the outset of her treatment, the causal explanation offered by the nurse:

> *she said that there are a few people who get a reaction to the enzymes from the larvae, not the larvae itself, but from the enzymes…* (P18)

Participants believed that the views of people in general about larval therapy would be characterised by *'fear of the unknown'* (P17) and distaste because of

possible connotations of uncleanliness, leading to a degree of social stigma about having larval therapy:

> *for the majority of people, it is an unknown quantity…I am convinced that it's people's fear of them rather than anything else, you see the mere mention of maggots puts them off…* (P15)

P9 referred to people talking about maggots in a hushed tone, or preferring to refer to them euphemistically as *'that new treatment'*. P18 contrasted her attitudes towards larval therapy with those of her friends: *'I know some people when I mentioned it to them seemed quite shocked at the idea, but it didn't bother me…'* (P18)

With one exception (P11), participants seemed to retain their prior positive attitudes towards larval therapy, whether they had a 'good' or 'negative' experience of using them. Where the experience was deemed 'good', by the participant, their views of the beneficial effects were reinforced. Participants who seemed to have reported a 'negative' experience (P9 and P18), because of the pain they felt, still believed that they had benefitted from the treatment during the short time that they experienced it.

> *I would have maggots again tomorrow if necessary.* (P17)

> *I just think if they are the right thing for ulcers, then so be it…if they are going to help people…* (P15)

> *I don't regret being in the trial, even though there was a reaction…* (P18)

> *I've had maggots which I thought were a wonderful, wonderful thing. I believe in them thoroughly…* (P9)

P11, who had had bagged larvae applied to his large necrotic ulcer in hospital, was the only participant who appeared disillusioned by his experience. Holding high expectations at the outset, he appeared disappointed in the small improvement he discerned in his ulcer. P11 implied that he thought the ulcer might have improved more markedly if more larvae had been applied: *'I probably could have done with two bags* bigger *than what was there, or another bag…'* (P11). During his stay in hospital, P11 felt that the treatment had been mismanaged for a variety of reasons; in particular, he had been unhappy that the treatment was not applied by the Tissue Viability Nurse Specialist, as he had hoped.

Summary of main findings from patients' interview data

- The patient interview data revealed that the majority of participants were willing to try larval therapy either in bagged or loose form.
- Of the five participants who had experienced larval therapy, the four who had received it from community nurses were satisfied with the experience and believed they had seen an improvement in their ulcer.
- Only one participant (P11) had received larval therapy in hospital, and was disappointed with the experience and found little sign of improvement in his ulcer.

Nurse interviewees

Nurse participants ($n = 22$; *Tables 51* and *52*) were purposely selected to include some working in the community and some working in clinics, to reflect a broad age range, and to reflect nurses both with and without experience of using larval therapy for leg ulcers. The total number of nurse participants ($n = 22$) included two nurses working in a site not involved in the main study, who agreed to pilot the Nurse Interview Schedule. These nurses are identified as N(P)1 and N(P)2.

Four of the nurse participants (N17, N18, N19 and N20) were selected from a group of clinicians attending an academic course at the University of York. These were nurses with extensive experience of caring for patients with leg ulcers, who held senior clinical or combined clinical and academic posts.

Six participants (N1–N6) were based in Vascular Clinics in sites involved in VenUS II, one attached to the Outpatients' department of a hospital and the other in a community setting. Eleven participants (N7–N17 and N19) worked primarily in a community setting, while N18 worked in a hospital setting, and N20 was moving from a clinical to an academic role.

Although we had hoped to include a number of nurses of minority ethnic origin in the study, we found that the majority of nurses working in the sites where recruitment took place were White British, with the result that only two nurses from minority ethnic groups were recruited; N4 was

Black Caribbean and N16 was South East Asian in origin.

Nurse participant characteristics

All nurse participants were female and their ages ranged from 30 years to 62 years; the median age was 45 years (*Tables 51* and *52*). Participating nurses had between 1 and 27 years' experience of caring for people with leg ulcers (median was 9.8 years, mean was 11.3 years). Three participants (N8, N12 and N16) had no experience and three participants (N15, N18 and N20) had used larvae on only one or two occasions. Those nurses without any experience of using larval therapy were community nurses; all of the clinic nurses had experience of using larval therapy. Sixteen nurse participants had more extensive experience of using larval therapy. Of the 19 nurses who had used larval therapy, 17 (89%) had used loose larvae, 13 had used bagged larvae (68%) and 11 nurses had used both (58%).

Attitudes, beliefs and acceptability of larval therapy: findings from nurse interviews

Of the 22 nurse participants interviewed in the qualitative study, all but three (N8, N12, N16) had experience of using larval therapy. Nurses varied in the number of times they had used larval therapy, depending on individual factors, for example, relative seniority in the nursing team and the setting in which they worked. Within the community nursing team, it tended to be senior nurses or those with a particular interest in larval therapy who had most experience; experience of larval use was more evenly spread amongst clinic-based nurses, some of whom said they were using it as often as *'a couple of times per week'* (N2). Three nurses, (N15, N18 and N20) had limited experience, having used larvae on only one or two occasions.

Perceived utility, benefits and effectiveness of larval therapy

Nurse participants were unanimous in the belief that larval therapy was best suited to cleaning 'dirty' or 'sloughy' wounds to achieve a speedy debridement, and a dramatic, visible improvement in the condition of an ulcer, providing a morale booster for both patients and the staff caring for them:

> *I mean you can see the improvement…the area that they have cleaned up, it's been dramatic really in most of them, it's so good.* (N12)

> *it was quick, it was extremely quick, say if we put them on a Monday, by the time we got back, two to three days later, maybe 60–70% of the slough was gone, so fast, so quick fast….it did us all good, we thought, ahhh, right, we are getting somewhere after all these weeks and months something has finally happened…so from that point of view, the speed with which they can make a difference is significant I would say…* (N13, community nurse with 27 years' experience of wound care)

> *you put them on and you can see instant results… all the slough is gone when you take them off, it is so good because it is so visual.* (N14)

The role of larval therapy in the 'palliative' care of wounds that were malodorous and offensive, and deeply unpleasant for patients and their families was valued:

> *if you've got an ulcer that full of slough, it smells, and the quickest way to get rid of that is to use maggots.* (N11)

The use of larval therapy following, or instead of, surgical debridement was described as a cost-effective and safe means of cleaning a 'dirty' wound quickly:

> *I'll get them to come in and sharp debride the worse of it and then we'll use maggots to finish off, and that's probably my favourite way of using them, because otherwise I've got to use two or three applications and that's expensive.* (N11, Tissue Viability Specialist Nurse)

> *sometimes the other option is the surgeon will say, we'll debride it, and people don't want to go and have surgery…and they [the patient] said, I don't want it, and I say, well, let's try maggots…it's got to be cost-effective, and we don't want MRSA, that's another thing…* (N14)

The major perceived drawback of using larval therapy was that the results achieved in a short space of time were not maintained. Nurses described wounds as *'going in a backwards direction'* (N3) soon after the removal of larvae; *'after you take them off, the wound tends to go back to being sloughy'* (N1).

TABLE 51 *Nurses with experience of using larval therapy*

Nurse ID	Sex	Age	Position	Clinic/ community	Experience of ulcers (years)	Used larval therapy (yes/no)	Used larval therapy (loose)	Used larval therapy (bagged)
N(P)1	F	30	Tissue Viability Nurse	–	8	Yes	Yes	No
N(P)2	F	54	Tissue Viability Advisor	–	13	Yes	Yes	Yes
N1	F	33	Tissue Viability/ Research Nurse	Clinic	2	Yes	Yes	Yes
N2	F	52	Tissue Viability Nurse	Clinic	7	Yes	Yes	Yes
N3	F	62	Junior Sister	Clinic	13	Yes	Yes	Yes
N4	F	54	Clinic Nurse	Clinic	6	Yes	Yes	No
N5	F	34	Research Nurse	Clinic	1	Yes	Yes	No
N6	F	49	Research Nurse	Clinic	5	Yes	Yes	Yes
N7	F	38	Staff Nurse	Community	10	Yes (limited)	No	Yes
N9	F	48	District Nursing Sister	Community	25	Yes	Yes	Yes
N10	F	43	Staff Nurse	Community	4	Yes	Yes	Yes
N11	F	43	Tissue Viability Nurse	Community	13	Yes	Yes	Yes
N13	F	45	District Nursing Sister	Community	27	Yes	Yes	Yes
N14	F	47	District Nursing Sister	Community	7	Yes	Yes	Yes
N15	F	48	District Nursing Sister	Community	22	Yes (limited)	Yes	No
N17	F	48	District Nursing Sister	Community	25	Yes	Yes	Yes
N18	F	43	Clinical Research Nurse	–	12	Yes (limited)	No	Yes
N19	F	30	Clinical Research Nurse	–	9.5	Yes	Yes	No
N20	F	40	Teaching/ research	–	16	Yes (limited)	Yes	No

F, female.

TABLE 52 *Nurses without experience of using larval therapy*

Nurse ID	Sex	Age	Position	Clinic/ community	Experience of ulcers (years)	Used larval therapy (yes/no)	Used larval therapy (loose)	Used larval therapy (bagged)
N8	F	45	Staff Nurse	Community	1	No	No	No
N12	F	59	Health care Assistant	Community	20	No	No	No
N16	F	34	Staff nurse	Community	2	No	No	No

F, female.

> *we're not keeping it clean with an NA dressing, it is not enough…10 days down the line they've got a sloughy wound again.* (N2, clinic nurse)

> *I think they are right for the job that they do, but there is always a need once you take the larvae off, to have a different dressing that will keep the wound clean, because putting nothing on, just an NA Ultra, does not keep the wound clean.* (N1, Tissue Viability Nurse)

A further perceived limitation of larval therapy was that certain wounds, or certain types of patient, were deemed not suitable for treatment. Wounds with a thick eschar, or where the bottom of the wound bed could not be viewed clearly, and patients with vascular impairment, or those taking warfarin, were viewed as unsuitable for larval therapy:

> *I wouldn't use it if I couldn't see the bottom of the wound bed…if they've got a cavity…where that cavity was tracking…I would make sure that I would know where the base of the wound was, so you know what is going in and what is coming out…or is it a big thick eschar that you wouldn't use maggots on because they can't chew away at that…* (NP1)

> *if you put them on a leg that's got vascular problems, they're only going to reslough, so there is no point.* (N9)

> *I checked their drugs and they were on warfarin, and it's a contraindication you see…* (N9)

Amongst the nurses, opinion was divided as to whether debridement with larval therapy promoted the healing of leg ulcers:

> *I don't know whether they heal faster, I have no idea about that.* (N11)

> *they have, in my experience, enhanced the wound-care healing rates of wounds once they've been cleaned.* (N10)

> *they did a good job, but not completely, it was only partial, so I think expectation was a bit too high then, and the patient was pleased, but a little bit disappointed because they hoped that everything would be clean and ready for the healing process to take place.* (N13)

For a majority of nurses, larval therapy was considered a treatment to try when all else had failed, as a last resort:

> *traditionally, it has always been a last resort…if we've come up against a brick wall, then we try the larval therapy…* (N13)

A number of nurses appeared to work within a personal 'hierarchy' of tried and tested approaches to ulcer care, and larval therapy seemed to sit between first-line treatments, such as dressings and gels, and surgical debridement:

> *I would go for the simple choice first, and then move on to that [larval therapy], I wouldn't use it as the first choice to debride, but I would definitely put it on a par instead of allowing the surgeon to come and play with a scalpel.* (N19)

Cost-effectiveness of larval therapy emerged as an important consideration in some nurses' thinking about the value of the treatment. The current lack of evidence regarding its effectiveness meant that nurses were unsure whether or not it represented a cost-effective option:

> *the only reason I hesitate is the cost. If you're using maggots because you believe that debriding a wound faster makes it heal faster, that's one economic argument. If you're using them as a palliative measure to reduce smell, that is a different argument. I find it much easier to justify the palliative one because I know they work, I don't even need a trial, I know they work…* (N11)

> *sixty odd pounds per application, but then some dressings are very dear, desloughing can take so long…in the long run I think it is a matter of writing down how much you spent on using say a gel or some other method and gave it to a GP…it's taken X weeks at that cost…and compare it, I am sure that in the long run it is cost-effective.* (N17)

Concerns were raised by two senior, experienced nurses, working in the community, that larval therapy was currently being overused, as the latest 'fad' in wound care:

> *we seem to have maggots fans [laugh]…there are some nurses will always leap on the latest idea…I have nurses who will want to use maggots on nearly everything, and I've got doubts about that frankly… if there is a bit of slough, and we must debride it, I'm saying, why don't you put them into compression and see what happens, because in my experience that usually gives a satisfactory result…* (N11)

I have concerns that there's people thinking 'I'll put maggots on', that haven't got enough knowledge or have had any training. (N9)

Nurses' perceptions of patients' willingness to try larval therapy

In general, nurses believed that patients were open to the idea of trying larval therapy, as long as they could be reassured that the larvae could not escape from the dressing:

I am quite amazed at how accepting patients are of them. (N17)

most of them are fine about maggots as long as they feel confident that they are not going to get out. (N11)

Some patients were perceived as particularly enthusiastic about trying larval therapy as an innovative form of treatment, and likely to be disappointed if their request to try 'maggots' was not met:

I think they are keen to try things that are so called 'new' because they are cutting edge…they feel special when they are having them. (NP2)

patients might approach you and say, 'Can I have maggots?' and then you have to say to them your ulcer does not meet the requirements for it, and they say, 'what do you mean?' and you say, 'well if you put the maggots on they will die, there will be nothing for them to suck', and they will be right disappointed, you know. [patients, not maggots] (N4, clinic nurse)

Of the patients who appeared initially reluctant to try larvae, nurses believed that some might be open to persuasion, but not all:

some of them 'Oh no, I couldn't possibly have that,' but you know, you talk to some of them and they could change their mind, and they'll have them, but others are adamant… (N3)

One group of patients considered highly likely to try larval therapy were those described as *'willing to try anything'* because of their desperation to try any form of treatment that might offer hope of improvement for their ulcer, even one as *'extreme'* as larval therapy. Nurses believed that these patients could, or would, overcome any feelings of fear or distaste in their desire to find a cure:

a lot of our patients have got to the point where they will try anything because they are absolutely fed up of having a chronic wound because it has such a great impact on their life. (N6)

I think by the time they get to the stage of needing some fairly extreme therapy like that, they just don't care, they just want to try anything and they will agree to it. (N3)

ones that have had them have come to the end of the road…it's sort of like desperation and so I think they would try anything, even if they had some sort of fear about them. (N9)

Patients considered extremely unlikely to accept larval therapy were a small minority characterised as exhibiting strong feelings of fear or revulsion. Nurses attributed these feelings to: a lack of knowledge about larvae and how they function; associations of larvae with fishing maggots, dirt and death; worries about larvae emerging from the wound as full-blown flies; anxiety about experiencing an unpleasant *'wiggling'* sensation; and the notion of 'maggots' being able to escape from the dressing to crawl over their leg, burrow into their flesh, or escape into their bedding.

you ask them why they are squeamish, and they say, can you imagine putting those things on to me, nibbling, and then you say, well, they don't nibble, they suck…because I think they think it is something that is going to do more damage than good, because they don't understand how they work. (N4)

I think it is before they see them, because I think they think they are going to be big, like fishing maggots… (N7)

occasionally, people say to me, they won't turn into flies will they? (N11)

what the patients worry about is, can they escape, can they get out? (N18)

what they worry about is them escaping, or that they are going to eat into the skin and track through. (N14)

others are just adamant, 'Oh, the thought of it'… flies and maggots and things they think they are dirty although they are specially bred for it.' (N12)

The fear identified by nurses as lying uppermost in patients' minds, that larvae might escape, seemed

to lead to an assumption that patients would prefer to have bagged rather than loose larvae:

> *they get it into their head that they are going to escape, so it constantly plays on their mind, whereas I think if you put bagged maggots on they would feel a lot safer…* (N5)

Referring to a patient recruited into VenUS II, N18 commented:

> *luckily, she got teabag maggots…I am sure we would have had a lot more discussion if she had got the loose ones, which she really didn't want…it was the thought of them escaping, which they shouldn't have done, because I would have taped them in well…* (N18)

Other factors which nurses believed might affect the likelihood of patients accepting to try larval therapy were the views of partners and other family members, and the approach nurses take when they initially raise the possibility of using larval therapy. Data relating to these factors are summarised in *Boxes 4* and *5*.

Acceptability of larval therapy

Overall, nurse participants expressed the general view that larval therapy was a beneficial form of treatment (in terms of debridement) for the treatment of leg ulcers, and one that was acceptable to the majority of nurses and patients.

Nurse participants classified themselves and nurses that they knew into three groups with regard to acceptability of larval therapy: *'real converts'* (NP2) who thought *'maggots are marvellous'* (N4); nurses who attempted to overcome their own feelings of squeamishness to benefit patients (see N17 below); and a minority of nurses who would not *'entertain the idea'* of using larval therapy under any circumstances (N14).

At the point in time when they were interviewed, 19 of the 22 study participants had had experience of applying larval therapy, either in a clinic or community setting. Two participants (N8 and N16) had chosen not to apply larval therapy, because of their dislike of 'creepy-crawlies'. A further nurse (N12) said that the relatively 'junior' position that she occupied on the community nursing team meant that she was not required to apply larval therapy as *'the Sisters do them…'*.

During interview, nurses discussed acceptability of larval therapy with reference to:

- feelings of squeamishness, distaste or disgust
- perceived potential side effects of larval therapy: pain and bleeding
- practical issues.

Innate squeamishness

Half of the nurses interviewed said that they had *'no qualms'* about using larval therapy, or that it *'never bothered'* them (NP1, NP2, N1, N2, N3, N5, N6, N9, N10, N13, N14).

The remainder expressed varying degrees of squeamishness, linked to anxieties that larvae might escape from dressings, a general dislike of creepy-crawly creatures, and particular distaste for the wriggly movements of larvae.

Two (N8 and N16) of the three nurse participants who had never applied larval therapy attributed their reluctance to use it to their own squeamishness:

BOX 4 *Nurses' perceptions of the influence of family members in patient decision-making concerning acceptance of larval therapy*

Patients' relatives, in particular their partner or spouse, were thought by nurses to play an influential role in the decision-making process about whether or not a patient might be willing to try larval therapy. N17, a community nurse with 25 years' experience of looking after patients with leg ulcers, viewed a chronic ulcer as a family rather than individual affliction, and suggested that patients might be persuaded by family members to 'go for' larval therapy.

> *Patients are concerned, you know, 'I'll have to ask my husband', or 'I'll have to ask my wife, because I am not sure they will want that', but I think by the time you have a chronic ulcer it affects the whole family, it affects the people around them, so they are quite pleased to have a go, I had one lady and her husband persuaded her, go on, have a go, because she wasn't keen and I think it helped her to have somebody in the family saying, go on, go for it, I will support you, we'll get through it together really.* (N17)

BOX 5 *Nurses' perceptions of their role in promoting patients' acceptance of larval therapy*

Nurses believed the way in which they broached the subject of larval therapy with patients could influence their decision as to whether to accept or reject it, as could their endorsement of the treatment:

> *How you raise the subject with the patient…you're aware that you are suggesting something that some people would find deeply distasteful.* (N11)

> *you've got to approach patients in the right way. As soon as you say maggots, they are like 'Ooooooohhhhhh!' but you've got to explain, sort of pre-empt them, and sort of say, you know, 'I know a lovely treatment that we've tried', and you've got to reassure them that they are not going to escape.* (N14)

> *I've got an information booklet…that explains why we use them, when it started, you know, from the First World War times, and patients generally get very excited and can't wait…I've never had one resisted.* (N20)

> *my concern was that they would get out of the dressing, would you wake up the next morning and find them in the bed and things…* (N8)

> *I come from the Philippines, for me you see they are dirty, even though I know it is clean…I never like any worm at all, and to think about maggots, putting maggots onto the skin of a client, it just make my head big.* (N16)

Several nurses indicated that they would try to set aside or overcome their innate feelings of squeamishness in order to offer patients a potentially beneficial treatment for their ulcer.

> *I mean we do a lot of things in nursing that you don't particularly like doing, but you do them, you just get on…* (N15)

Actual 'hands-on' experience of applying larval therapy, and observing benefits for patients, resulted in some nurses reporting that their feelings of squeamishness diminished and their confidence in using larval therapy increased:

> *I was wondering how would I cope with these little live creatures…I was a bit apprehensive…I was hoping not to show any disdain, or you know, cock this up in front of the patient…I was pleasantly surprised to find that actually I had no concern about using them, usually I don't like creepy-crawly things, and then it just becomes another treatment, I have no qualms now I have had a go at them…* (N17)

> *I remember the first time I saw maggots I were like, Oooohhhhh, but I saw the condition of the patient's ulcer prior to the maggots being used, and obviously when they went on I was a little squeamish, and when they came out, I were like 'WOW', because they were so big and juicy and the ulcer was so clean!* (N4)

A minority of nurses reported that the transformation undergone by the larvae during the time they had been applied to the wound had shocked or disturbed them; an extreme case was N20, who described having a nightmare after applying larvae for the first time.

> *I did have nightmares subsequent [to using larval therapy]. I dreamt one night that I was in a room… and the maggots were falling down from the ceiling…it's a bit like, you're using it and you know you are using it, you're blocking out everything else, and then I suppose you have no control over when you might have a flashback about it…* (N20)

In two cases, (N11, N19) feelings of squeamishness were only experienced when the nurses came to remove larvae, after the wound had been debrided. At this stage, the larvae could no longer be considered clean or sterile, though they could potentially escape from the wound area to their surroundings, and the nurse would have to retrieve them:

> *it's not something that I feel completely comfortable with maggots, because when you put them on, they are very clean, and it's not until you come to take them off, and I suppose that is with any dressing you take off, you want to put them in the bin as soon as possible…* (N19)

> *sterile maggots and the maggots that have been on a filthy floor or rotting leg, you know, there is a difference, and I think once you start using them clinically, you start to differentiate between the two types…and some used maggots I still find repulsive.* (N11)

Four of the study participants (NP1, N1, N3, N5) attributed their lack of squeamishness to the fact that they had seen or handled fishing maggots at some stage in their lives. N10 believed she was not squeamish about maggots because of her upbringing on a farm, where maggots would have been a common sight. The three nurses who had not applied larval therapy prior to their interview reported that they had neither seen nor handled maggots.

Perceived potential side effects of larval therapy: pain and bleeding

Pain and bleeding in association with larval therapy were reported by nurses as leading to the early removal of larvae on occasion, but these occurrences did not seem to lead the nurses involved to question its acceptability. Only N15 mentioned that she might *'think twice'* about using larval therapy after a patient bled profusely subsequent to application of larvae. Of the 22 nurses interviewed, nine reported that patients had complained of pain, sometimes severe, during the period that they had received larval therapy. Pain did not seem to be considered by the nurses as an untoward event during larval therapy, particularly where an ulcer had been judged to be small, or not very 'sloughy'. Patients were usually advised by nurses to carry on with larval therapy, while taking analgesia.

A minority of patients were said to suffer pain so severe that nurses had had to remove larvae prematurely. In these cases, the cause of patients' pain was not necessarily linked by nurses directly to their having larval therapy. Nurses' suggested explanations for these patients' pain included the possibility of different pain thresholds amongst patients; the presence of arterial disease; and one suggestion that pain was psychosomatic in origin.

> *I wonder if the slough has gone and what the maggots are excreting is irritating the wound bed, sort of like a stinging pain…one gentleman asked for them to be taken off, it [his ulcer] was about 5 cm square…he couldn't tolerate the pain.* (N9)

> *two out of four patients I have looked after said it was quite painful, and they asked to come in a little bit earlier and have them taken off, and the other two were OK with it, and said it wasn't that bad, and just dealt with it.* (N5)

> *we had one lady had larvae put on during the day, actually admitted [to hospital] that night because she couldn't stand the pain…but she did have some arterial disease in the end…* (N6)

> *I went to see her and she said, just take them off, just take them off…I don't know if it whether it was a psychological pain because…she said she could feel them [the larvae] digging into her leg, you know, like a pin prick sort of thing…* (N7)

Bleeding in association with larval therapy was not considered unusual either, unless profuse, and did not appear to be a reason for considering the rejection of the use of larval therapy. A commonly suggested cause of bleeding was that the larvae had eaten their way down to the wound bed:

> *a little bit of bleeding, but nothing excessive, nothing that I haven't dealt with with other dressings…* (N5)

> *I think there wasn't much slough left for them to eat, so they were just having a chomp, but it wasn't a massive bleed, so we took the larvae off because it was clean.* (N1)

Two of the most experienced nurses interviewed, (N15 and N17), mentioned instances where patients who had received larvae had bled through their dressings so as to cause concern, but only (N15) commented that she might be less willing to consider using larval therapy in future.

> *she had an ulcer developing at the back of her leg that was beginning to get quite sloughy and we put maggots on that, when we took the dressing down, not the first time, but the second time, it actually bled, it haemorrhaged, we sent her up to A&E, she came back with a pressure bandage on…whether it was related to the maggots I don't know, but it has made me think twice about using maggots, and when I would use them…I know they are only supposed to eat the necrotic flesh…* (N15)

Practical issues

Practical issues linked to nurses' views of acceptability of larval therapy included the form of larvae available to them (bagged or loose); nurses' inability to prescribe larval therapy despite holding a nurse independent-prescribing qualification (larvae are currently an unlicensed medicinal product); training issues; cost of larvae; and occasional problems in the supply or delivery of larvae.

Where nurses expressed a preference for bagged or loose larvae, they were more likely to favour

bagged larvae, partly because they believed they were easier to apply, and less time consuming for senior nurses who would be expected to apply the larvae themselves, or supervise others. Nurses also deemed bagged larvae more acceptable to themselves and patients because the larvae were contained in the bag, which might provoke less anxiety about them escaping:

> *the majority of the ones I have treated have expressed a preference for bagged, just simply because they are contained.* (N17)

> *it's time-consuming when you've got free-range ones on because of putting them on. Putting the bagged ones on is far easier…bagged it's literally just a couple of seconds. Free-range you've got to make a framework and then I would say about 5–10 minutes putting them on. It's just an added complication and a fiddle…* (N9)

Lacking prescribing powers to prescribe larval therapy themselves meant that nurses were forced to rely on GPs and other doctors to generate the prescription necessary to obtain larval therapy. This was perceived as potentially problematic because doctors were said to lack interest in wound care, and to retain a tight control on the prescribing budget, and the cost of larval therapy could seem high in comparison with usual dressings.

> *GPs are very tight with the purse strings, so it's getting them on board as well I think actually.* (N17)

> *I don't think that doctors get as involved as they should do…* (N14)

Increased training for nurses was highlighted by many respondents as a means of promoting acceptability of larval therapy more widely. Clinic-based nurses believed that nurses working in general hospital wards and community nurses would benefit from a systematic approach to training and education aimed at increasing awareness and use of larval therapy by nurses other than those directly involved in tissue viability. NP2, a Tissue Viability Advisor, commented on some of the components of a pack she was using for training purposes.

> *I just think it would be a good idea for people to be taught on a more widespread basis, out on the wards…so they are not so concerned about using maggots…* (N6, Bradford clinic)

> *[they] watch and go through a systematic process of what they need and we have a pack, an information pack with patient information about maggots, and there is also a maggot care plan as well, so it is very systematic and easy to follow.* (NP2)

Generally, supply and delivery of larval therapy were considered good, though nurses highlighted a number of teething problems or hiccups that had occurred in the service:

> *we had some that were delivered elsewhere and went to the wrong depot, so we had to cancel a treatment and then reorder…* (N13)

> *the bagged ones from Germany hadn't arrived because of fog which is fair enough.* (N1)

> *I got to the patient's house, opened the pack, there was no maggots…they had sent everything but the maggots, I couldn't believe it, I was looking everywhere!* (NP2)

Not being able to able to obtain larval therapy on a Monday was not usually viewed as a problem because nurses could plan around that restriction:

> *we know we are not supposed to get them delivered on a Monday...as long as we plan ahead that is not a problem.* (N5)

However, for clinic nurses, finding community nurses to look after patients having larval therapy, for instance to carry out rehydration, over weekends posed a substantial problem:

> *on the ward it is different, they can put them on any day…because there is always somebody to take them off, but we are not here at weekends…* (N6)

Summary of main findings from nurse interviews

- The majority of the nurses interviewed considered larval therapy an efficient treatment for the debridement of dirty or 'sloughy' leg ulcers, which achieved visible results in a short period of time. The main drawback of larval therapy was perceived as the tendency of wounds to 'reslough', often quite quickly. Nurses believed that most patients were willing to accept the option of having larvae applied to their ulcer, though a small minority would always be resistant.

- Acceptability of larval therapy amongst the nurse participants was high. Nurses who imagined they would find the application of larvae difficult because of feelings of squeamishness on their part, found that they were able to carry out the procedure without becoming overly anxious.
- Pain was commonly, and bleeding less commonly, reported among patients receiving larval therapy, sometimes necessitating the removal of larvae.
- There was general satisfaction with the supply and delivery of larval therapy, despite occasional shortfalls. Nurses were less satisfied with having to rely on doctors to obtain prescriptions for larvae, and with the level of education and training available for hospital and community nurses about larval therapy.

Chapter 7
Discussion

This is the first randomised trial of larval therapy as a leg ulcer treatment that follows patients to healing and currently the only RCT of larval therapy that measures impact on MRSA. The findings of this RCT are therefore important and hugely relevant for decision-makers. This discussion will consider the clinical, cost and qualitative findings in turn, followed by an objective overview of the internal and external validity of the trial.

Clinical effectiveness

Ulcer healing

We did not find any evidence that a phase of treatment with either loose or bagged larvae reduced the time to leg ulcer healing compared with hydrogel. Loose and bagged larvae showed very similar results for healing and were considered as one group in the main analysis. The hazard ratio for healing for leg ulcers treated with larval therapy relative to hydrogel was 1.13 (95% CI 0.76 to 1.68) indicating that whilst larvae-treated participants were 13% more likely to heal, this difference was not statistically significant ($p = 0.54$). The CI around the hazard ratio means that the true value may range between a 68% increase in the chance of healing with larvae and a 24% reduction in the chance of healing with larvae.

The median healing times (236 days for the participants receiving larvae and 245 days for the hydrogel group) were longer than in our previous trial where the median healing time with 4LB was 92 days and 126 days with SSB.[12] The most likely explanation for the increased healing time in VenUS II is that inclusion was restricted to sloughy and necrotic leg ulcers and those associated with more arterial disease than in the previous study.

As previously,[12,85,86] we found that baseline ulcer area and ulcer duration were statistically significant predictors of time to healing ($p < 0.0001$) with larger ulcers and those of a longer duration taking longer to heal.

Ulcer debridement

We found good evidence that larval therapy does debride leg ulcers more quickly than hydrogel. The hazard ratio for debridement of 2.56 (95% CI 1.76 to 3.71) indicates that the ulcers of participants receiving loose larvae were more than twice as likely to debride at any time during the trial than those of participants receiving hydrogel. The hazard ratio for bagged larvae relative to hydrogel was 2.05 (95% CI 1.39 to 3.03), again suggesting that this treatment was a more effective debriding agent than hydrogel. Whereas a previous RCT[57] and a number of non-RCT studies[53,54,56,134] have concluded that larval therapy is an effective debriding agent; these are the first data from a large, robust RCT to confirm these findings.

Although the median time to debridement was longer in the bagged larvae group than the loose larvae group (28 days versus 14 days) this difference was not statistically significant in the adjusted analysis. Hence, although there was a trend for loose larvae to debride more quickly than bagged larvae, this difference may have occurred by chance and our trial was not powered to detect a difference in debridement between the two larvae formulations, only a difference in time to healing between larvae and hydrogel.

In this trial there was a delay of approximately 5 days between randomisation and first application of larval therapy, because larvae had to be ordered from either Wales or Germany, and delivered for use (as is the case in normal clinical practice). After this initial delay, debridement in the larval therapy groups was rapid up to day 20. At day 20 approximately 10% of those treated with hydrogel were debrided compared with approximately 58% of people receiving larval therapy. After day 20 the rate of debridement seemed to slow in the larval therapy group and then plateau at approximately day 80, whereas in the hydrogel group debridement occurred at a steady rate between days 0 and 80. Although larval therapy was observed to be an effective debriding agent, data suggest that not all ulcers receiving this treatment will debride (20% of reference ulcers did

not debride in the loose larvae group, 23% did not debride in the bagged larvae group). Reasons for this could include participant intolerance of larval therapy because of pain. Ulcer-related pain scores at the removal of the first debridement treatment were significantly higher for both loose and bagged larvae compared with hydrogel.

This trial did not investigate debridement as a longer term outcome so we do not know how many ulcers that did debride remained debrided. We do know that a number of participants were withdrawn from trial treatment in the larval therapy and hydrogel arms (trial treatment being debridement treatment in Phase 1 and knitted viscose dressings plus bandage in Phase 2) because of increased slough, suggesting that some ulcers resloughed after initial debridement. This is also supported by data from the qualitative interviews.

Bacterial load

Larval therapy has been proposed as an antimicrobial treatment for chronic wounds. Suggested mechanisms for its action are via secretions and digestive processes,[37–40,135] and via debridement of bacteria-rich tissue which is thought to be important in controlling infection.[35,37,38]

Data from VenUS II did not find evidence of an impact of larval therapy on the bacterial load of leg ulcers. Although bacterial load decreased over the duration of the trial – this decrease was not related to treatment group. Our aim was to investigate the antimicrobial action of larval therapy, so we have not yet conducted analyses to investigate the association between bacterial load and ulcer healing. These analyses will be reported separately.

Most previous research investigating the antimicrobial activity of larvae has been *in vitro*, using whole body extraction and isolated secretions.[37,38,44] Whereas this work is important, in VenUS II we assessed the impact of larvae on leg ulcers *in vivo* where the environment is very different to that of the Petri dish. Previously, Steenvoorde and Jukema[81] investigated the antimicrobial action of bagged larvae in 16 patients, the majority with osteomyelitis, fasciitis necroticans or gangrene. A varying number of wound swabs were taken from patients one month before larval treatment, during the treatment and after the larval treatment. The swabs were cultured to assess the growth of Gram-positive or Gram-negative bacteria. Bacterial load was not quantified further. The study concluded that larvae may have an impact on Gram positive bacteria but have less effect on Gram-negative bacteria. However, as this study had no comparison control group, attributing microbiological changes to larvae is difficult. Additionally, because a number of swabs were taken from each individual during the study, special analysis is required to account for correlation within participants.

VenUS II is the first RCT we have identified to investigate and publish data on the antimicrobial action of larval therapy but we also recognise the limitations of the methodology employed. We only investigated an association between larval therapy and total bacterial load. Beyond identification of MRSA we did not have the resources to conduct qualitative investigation of bacterial wound flora so cannot draw any conclusions about the impact of larval therapy on other species.

We assessed bacterial load using quantitative surface swabs, where the sample was taken from viable tissue at the wound surface with light pressure to extract wound fluid. Nurses were instructed to use a standardised protocol for sample collection (Appendix 7). We did not collect wound biopsies, which are commonly cited as the gold standard for measurement of bacterial load because they remove deeper tissue for analyses.[68,136] However, the collection of wound biopsies requires specialist skills and is more painful for the patient: their use could only be justified if they offered significantly better bacterial load data than swabs and we found this difficult to justify based on existing data. Studies have compared swab techniques with wound biopsies in terms of quantifying bacterial load, however the focus has typically been on identifying wound infection (defined as at least 1×10^6 CFUs/g tissue).[62,63] Bill *et al.*[136] took surface swabs using Levine's technique – swabbing a small area of the wound free from slough/necrotic tissue for five seconds with enough pressure applied to obtain fluid from the wound tissue – and wound biopsies from 38 patients with diabetic foot ulcers, venous leg ulcers and arterial leg ulcers. Wound biopsies identified 74% of wounds as having a bacterial load $> 10^5$ organisms/g tissue, compared with 58% of swabs. Sensitivity was reported as 79% and specificity 60%. Gardener *et al.*[137] compared the measurement of bacterial load in non-arterial chronic wounds using (1) swabbing wound exudate from the wound surface, (2) zigzagging a rotating swab over the whole wound area, and (3) Levine's technique (the swabbing approach used in VenUS II was a hybrid

of the Levine and the zigzagging approaches). The diagnostic value of each swabbing technique was assessed by comparing values with the result of a tissue biopsy (reference standard) where ulcers were classed as being either infected ($\geq 1 \times 10^6$) or non-infected (1×10^6). All samples were cultured. The Levine technique performed best – at 90% sensitivity, specificity was 57% (critical threshold 3.7×10^4 organisms per swab) and the authors conclude that the Levine swabbing technique is an acceptable alternative to tissue biopsy in identifying clinical infection. Davies *et al*.[68] investigated the microbiology of venous leg ulcers again by culturing quantitative surface swabs and biopsies taken from the same 66 patients. The authors report an association between increased bacterial load and delayed healing whether bacterial load was measured by swab or biopsy, with no difference in prognostic value.

Existing data suggest therefore that swabs are a viable alternative to biopsies in clinical practice when diagnosing infection. Unfortunately, there are no published data reporting the agreement of bacterial load estimates from tissue biopsies and swabs, for example using the Bland–Altman method.[138] It is possible that swabbing could have underestimated the bacterial load assessment in VenUS II, although there should be no systematic differences between the trial arms. Arguably, if larval therapy did impact on bacterial load we would have expected to see this with the use of swabs.

A more serious limitation which offers an alternative explanation as to why no difference in bacterial load was observed between trial groups is that, unlike most studies investigating bacterial load and chronic wounds, the samples in VenUS II were analysed using molecular techniques.[139] These measured the presence of bacterial DNA in samples, rather than culturing samples or employing fluid microscopy or fluorescent live–dead staining (the cost of and practicalities of using these techniques were prohibitive in this study, which collected thousands of samples from mainly community-dwelling people across the UK). Molecular techniques have the advantage that bacterial load can be quantified from a single sample, though they do not differentiate between live and dead organisms. For this reason, the measure of bacterial load may not have been sensitive to treatment-related changes if bacterial DNA from dead organisms was detected. Despite this limitation, however, if larval therapy has a clinically important impact on bacterial load we would have expected to see an impact of this over time using the molecular techniques and we did not.

MRSA

To determine the approximate prevalence of MRSA in venous and mixed venous/arterial leg ulcers, a pilot study was conducted on the first 75 baseline swabs collected for VenUS II. MRSA was present in 16% of participants. We obtained funds to analyse all swabs at baseline and to follow-up all MRSA-positive participants. However, data for our pilot were obtained using molecular techniques that detected *S. aureus* and the gene for methicillin resistance in two separate tests (the duplex assay) so the methicillin-resistance gene could be detected in the absence of *S. aureus*. This method potentially overestimated the prevalence of MRSA. Following the pilot we employed a new method that detected methicillin resistance in *S. aureus* only (the single primer set or SPS assay; all previous sample were reanalysed). Using this new, more accurate approach to measure MRSA for all baseline samples, only 6.7% of participants had MRSA present in their leg ulcer at baseline. We are not aware of any other figures for community leg ulcer patients in the UK. This figure is lower than previously reported figures for a UK diabetic foot clinic (13%)[79] (a study in which MRSA was assessed using MRSA-specific cultures). Other prevalence estimates of MRSA in ulcer patients are 31% for diabetic foot ulcers in patients admitted to a specialised diabetic foot unit in France[80] and 30% in a retrospective analysis of the medical records of patients with chronic ulcers admitted to secondary care;[140] in both cases it is unclear how MRSA was assessed.

Concern has been expressed over an apparent increase in the presence of MRSA in the community, and it has been suggested that larval therapy may remove localised MRSA from chronic wounds. We assessed the impact of larval therapy on MRSA after the debridement phase. Of the 18 participants with MRSA at baseline, 12 (66.7%) were MRSA-free following debridement; however, the small numbers involved mean that no conclusions can be made regarding difference between the treatment arms. One previous study conducted *in vivo* also investigated the impact of loose larvae on the presence of MRSA in 13 patients with diabetic foot ulcers where MRSA was detected using MRSA-specific culturing techniques.[82] The study reports that MRSA was eliminated in 12 of the 13 wounds (92%) treated

with loose larvae. However, the conclusions drawn from this study are limited because there was no control group. We therefore do not know what would have happened to similar wounds over the same period had they received standard care. The VenUS II data highlight the importance of a comparison group since MRSA was eradicated in nine of 12 cases (75%) in the combined larvae group. However, MRSA was also eradicated in three of six (50%) of the hydrogel group.

Health-related quality of life

Changes in HRQoL from baseline were investigated using the SF-12. The poor physical health of people with leg ulcers is, as in other studies,[12] emphasised by the low PCS. There was little change in the PCS score during the trial in both larvae and hydrogel groups. The MCS scores were higher than the PCS but again there was no evidence of a statistically significant change over time. We cannot conclude that larval therapy has any impact on participant HRQoL even though it increases the likelihood of debridement. The HRQoL measures in this study were generic rather than disease specific and so arguably may have missed changes in ulcer-specific dimensions. However, our previous work demonstrated that the SF-12 and EQ-5D are sensitive to, and thus able to measure, change in venous leg ulcer patients.[96]

Adverse events

Overall there were no significant differences in the numbers and types of adverse events between trial treatments. Interestingly, however, more of the adverse events reported for patients receiving larval therapy were classified by the treating nurse as possibly, probably or definitely related to the treatment (though the actual numbers were small). It must be emphasised that this was an open trial and therefore nurses were probably more likely to attribute adverse events (such as ulcer deterioration) to a treatment with which they were relatively unfamiliar.

Analysis of ulcer-related pain scores suggests that participants had more pain when treated with larvae compared with hydrogel. This is the first report of pain associated with larval therapy in a large number of leg ulcer patients, with a control group for comparison. Previous reports regarding the association between pain and larval therapy have come from small qualitative studies suggesting that some patients have a reduction in pain when treated with larval therapy[83] while some have increased pain.[54] As with the reporting of adverse events because participants were not blinded to treatment there is the possibility of some bias against the larvae. However, because this is a pragmatic trial and if larval therapy causes a perception of increased pain this remains an important finding. These data combined with data from the qualitative interviews (discussed below) suggest that there are some participants for whom larval therapy may lead to a substantial increase in pain which they attribute to the treatment. Reasons suggested in the literature as to why larval therapy may increase ulcer pain include a change in wound pH and participants with neuropathy having increased sensitivity to the movement of the larvae or to chemicals secreted by the larvae.[41,42]

Ulcer deterioration was defined as either an increase in ulcer area, malodour, apparent allergy and ulcer bleeding. Some ulcer deterioration in the larval therapy arms was reported. It is not clear if this was related to ulcer bleeding, which has been discussed as a side effect of larval therapy. Deterioration in the hydrogel group may have been related to a lack of response to the treatment and subsequent withdrawal from trial treatment.

Cost-effectiveness

In a field where there is a plethora of treatment options available to treat leg ulcers it is important that, in addition to clinical effectiveness, the value for money a treatment offers in terms of cost versus benefits is explored. In VenUS II this was assessed in both a cost–utility and a cost-effectiveness analysis. In both cases trial data suggest that larval therapy and hydrogel have similar costs and effects. In the base-case analysis the mean cost of larval therapy was £97 greater than the hydrogel treatment per participant per year and slightly more effective (mean difference in time to healing 2.4 days, mean difference in QALYs 0.01 both favouring larval therapy). Yet, there was a significant amount of uncertainty around the parameter point estimates and the corresponding ICERs, to the extent that the spread of points on the cost-effectiveness plane was almost uniform over the four quadrants. The decision uncertainty associated with the cost-effectiveness of larval therapy when compared with hydrogel indicated that there was approximately 50% probability of the larval therapy being cost-effective. The uncertainty associated with the distribution of differential cost and health benefits suggests that the costs and effects of larval therapy and hydrogel

are likely to be similar in the treatment of sloughy leg ulcers. Based on this result it could be argued that health care decision-makers should then be indifferent when choosing between these two therapies; however, given the higher levels of pain associated with larval therapy and the requirement for advance ordering and appropriate storage, decisions about whether to use larval therapy are likely to be greatly influenced by specific treatment goals (e.g. where rapid debridement is required) and patient wishes.

A number of sensitivity analyses were conducted to assess the impact of altering the base-case analysis. Although the use of nurse-reported visits (rather than participant-reported) suggested that larval therapy was a dominant therapy when compared with hydrogel, the decision uncertainty associated with the dominance of larval therapy was considerable. The probability of larval therapy being cost-saving (i.e. dominant) was 50%. There was a small number of amputations recorded in the trial and twice as many in the hydrogel group ($n = 2$) than the larval therapy groups ($n = 1$) but given that amputations were not reported in a systematic way we cannot discard the possibility of this difference being the result of chance. The number of events is small but the costs associated with amputations are high and unsurprisingly their inclusion had a significant effect on both our base-case estimate of mean difference in cost and the associated uncertainty. In this scenario larval therapy is associated with a 75% chance of being cost-saving (i.e. dominant). These data must be interpreted with caution, however, because *a priori* there is no reason to believe that rates of amputation would differ between trial arms, rather what we are observing is likely to be a chance imbalance (amputation is relatively rare even in this population). What this sensitivity analysis highlights is the importance of assessing amputation as an outcome in future wound-care trials.

Carrying out one-way sensitivity analyses where the setting and duration of nurse visits were both decreased and increased to assess the impact on cost-effectiveness did not impact on the cost-effectiveness conclusions.

It is important to note that the economic evaluation in VenUS II has only compared larval therapy with hydrogel and found them likely to have similar cost and health benefits, i.e. indistinguishable cost-effectiveness. In practice there are several other methods available for debriding wounds, so when making debridement treatment choices decision-makers are faced with a more complex decision than that represented by this trial. In terms of assessing cost-effectiveness, RCTs are limited by the number of comparisons they can make.[141] In this case we do not know how larval therapy or hydrogel relate to other debridement treatments in terms of cost-effectiveness. To make an informed decision from this wide selection of treatment options to ensure the most cost-effective treatments are used, data from this RCT and other studies should be incorporated into further decision analytic modelling work. This approach allows the synthesis of data on the costs and effects from relevant studies in a suitably structured model. The value of this approach is that, data permitting, the cost-effectiveness of several treatment options can be compared simultaneously.

Qualitative study: patient and staff acceptability and experiences of larval therapy

Acceptability

People with leg ulcers who had not received larval therapy were interviewed to assess their views about the acceptability of larval therapy with most stating that they would accept larval therapy as a treatment. Most of the participants had strong beliefs about the effectiveness of the treatment that stemmed from the media or anecdotal report. What was perhaps surprising is how generally acceptable larval therapy is to the relevant patient population; there were only two cases where interviewees would not consider larval therapy under any circumstance. In one case where a participant found the idea of larval therapy unacceptable the news that a bagged larvae formulation was available made larvae more acceptable; however, overall strong preferences were not expressed for bagged larvae. In one case a participant required effectiveness information to make an informed decision about whether to have loose of bagged larvae.

The findings from these patient interviews agree with previous work in which 35 UK patients with leg ulcers were asked about their preference for different types of larval therapy and their thoughts regarding the treatment.[142] In this study, larval therapy was acceptable to a majority (77%) of interviewees. As with data from our study, patients expressed a strong desire to heal their

ulcers – expressed as a willingness to try different treatments. In this previous study 23% (8/35) of participants would not consider larvae to treat their leg ulcer – of these eight, seven were women.[142] In VenUS II, two participants who stated initially that they would not accept larvae were also women.

The nurse data mirrored the participant data. Most nurses were happy to use larval therapy, especially after seeing positive debridement results in practice. Some nurses had previously successfully overcome some squeamishness. However, there were a small number of nurses who would not consider the use of larval therapy at all because of the nature of the therapy. Although there have been previous studies on the acceptability of larval therapy to participants, this is the first that highlights how important it is that nurses are happy to deliver the treatment.

The role of the nurse seems important in reassuring the patient about the treatment, especially explaining how the larvae were secured into place so that they could not escape. The importance of the treating health professional in helping to inform patients to make a decision about having larval therapy have also been highlighted elsewhere.[83,142] The nurses interviewed for VenUS II recognised that there are a number of leg ulcer patients who would try anything in the treatment of their ulcer, whereas there are others who would never consider larval therapy. Unlike patient participants, nurses appeared to have a preference for bagged larvae because they were viewed as easier and quicker to apply. The nurses believed that the bagged larvae would be more acceptable to participants, but this was not borne out in the participant interviews. It remains possible that some nurse antipathy to larval therapy partly explains our poor recruitment to the trial.

It is interesting to note that several of the nurses interviewed anticipated the results of VenUS II in that their clinical experience was of larvae leading to rapid debridement, although they did note that this debridement was often only temporary. There was less certainty expressed about the impact of larval therapy on healing.

Patient experience

Of the five interviewees who had received larval therapy two reported associated pain, which was severe in one case. Nurses also recognised that larval therapy may be associated with pain, although the nature and severity of this pain may have been underestimated. When nurses had treated patients who had reported extreme pain resulting in early termination of larval therapy, the nurses outlined potential underlying reasons for the pain, including arterial disease.

Interestingly, participants who had received larval therapy and nurses who had used it seemed to recognise that the treatment cleaned wounds – there was little discussion about healing, apart from the uncertainty about the impact of larval therapy on healing by nurses. The anecdotal reports of both the patients and the nurses suggest that debrided wounds are liable to reslough after the removal of larval therapy.

Consideration of the mechanisms and exploration of key findings

Although VenUS II demonstrates convincingly that larval therapy is a more effective debriding agent than hydrogel, healing and debridement are not linked in a straightforward manner as is often suggested.[23,143] In fact there are no high-quality data demonstrating a causal link between debridement and increased healing[2,24,144] and although there appears to be a strong clinical belief in the importance of debridement. For example, the most widely cited evidence that debridement is directly linked to faster healing is a trial of a growth factor in diabetic foot ulcers[145] in which a *post hoc* analysis of centre effects identified a correlation between 'high debriding' centres and better healing. Clearly this is circumstantial evidence that requires further experimental investigation; however, we have been unable to identify an RCT of sharp or surgical debridement (because such a trial would be the most direct evaluation of debridement *per se* without the extraneous effects of dressings and other procedures). A more recent study in non-healing chronic venous leg ulcers compared sharp debridement of sloughy ulcers with the usual care of non-sloughy, non-healing ulcers because the authors claimed it was not ethical to randomise.[144] This small evaluation ($n = 55$), although showing greater rates of healing in the debrided group, suffers from huge selection bias and never compared ulcers with similar prognosis (and there are few or no data available on the value of slough as a prognostic variable).

We cannot claim that VenUS II is a trial of debridement; it is a trial of larval therapy, which has been claimed to have wide and varying effects from debridement through antibacterial to direct healing effects. Nevertheless, our trial analysis has found no impact of larvae on healing even with the effective early debridement obtained using larvae. We plan a more detailed analysis of the relationship between debridement and healing using the trial data, but such a piece of work was outside the scope of this final report. Finally, it may be that successful debridement (i.e. a clean wound) has value to patients irrespective of any perceived link with healing; however, we have been unable to find any data in the literature regarding this and our HRQoL data showed no such effect. Additionally the importance patients place on debridement is likely to be influenced by nurses' attitudes.

We anticipate some criticism from strong advocates of larval therapy that time to complete healing was an inappropriate end point for the evaluation of a debridement treatment. They may feel that because larval therapy (and its comparator treatment) ceased often months before healing, then an effect on healing should not be investigated. There are important reasons, however, why it was essential to examine healing; first larval therapy is promoted as having an effect on healing and second there is no evidence (see above) of the link between debridement and healing. Our trial was pragmatic and reflects routine leg ulcer care in the UK in which patients have short bursts of debridement treatments in the hope of preparing the wound bed for healing.[143] For such an intervention to be worthwhile from a clinical and economic perspective one would expect to see an impact on the most important outcome, namely healing.

Contribution of this trial to the evidence

This is the first RCT that we have identified to investigate the effectiveness of larval therapy on the healing of venous and mixed venous/arterial ulcers. The only other published RCT of larval therapy was small and had debridement as a main outcome measure, hence a limited follow-up period. Although RCT evidence is limited, there are several non-RCT studies that advocate the use of larval therapy as a clinically effective treatment[26,30,31,34,146] – with 'effective' variously defined as: the promotion of healing,[41,44–46,147] promotion of debridement,[33] reduction of micro-organisms in the wound[37–39] and reduction of MRSA specifically.[39]

VenUS II supports the view that larval therapy is an effective debriding agent. However, it also raises an important question regarding the role of debridement in leg ulcer care. Further research is required to explore the relationship between debridement and healing and debridement and wound microbiology. Some of this we plan to undertake with the data collected in this trial but more clinical research in conjunction with laboratory studies is probably merited. It is clear that healing can (and did in this study) occur in the presence of what experienced clinical nurses regarded as 'slough'. It may be that clinicians are currently unable to discriminate between slough and other forms of exudate which may be conducive to healing. If this is the case then a debridement strategy could be beneficial in some situations and harmful to healing in others.

A piece of good news arising from this trial is the relatively low rate of MRSA identified in leg ulcers in community-dwelling individuals. This finding contrasts with other reports[79,80] but used the latest, more sensitive, molecular techniques for identifying MRSA. We have also demonstrated that MRSA can disappear from leg ulcers irrespective of whether or not patients received larval therapy.

Strength and limitations of the study

Study size

Recruitment of sufficient numbers of eligible patients was a huge challenge for this trial and we did not reach our initial sample size despite an extension in time and funding. The reasons for this are probably complex. Anecdotally, nurses reported that there were fewer leg ulcer patients 'on their books' than 5 years previously, attributing this to increased use of compression bandaging. Second, fewer ulcers than we originally anticipated were 'sloughy'. Indeed the main single reason for participant exclusion was ulcers not containing sufficient slough to be eligible. Because this is a prerequisite for using larval therapy, our experience in VenUS II suggests that performing a larger trial in the UK would be challenging. Information on these recruitment issues before the conduct of this full study would have been invaluable. This highlights the value of conducting pilot trials where feasibility data can be used to

assess recruitment rates and issues and plan in advance for these when designing a full trial.

Blinded outcome assessment

Like most trials of wound treatment in a community setting, we were unable to conduct in person, blinded outcome assessment for reasons of logistics and resourcing. Although blinded outcome assessment is fairly easy to achieve in a clinic or hospital setting, most of our participants were seen in their own homes. To conduct blinded outcome assessment for people treated at home we would need blinded assessors to lurk outside patients' homes while the treating nurse took away all evidence of current treatment, cleaned up the ulcer and then called the assessor in. Given the dispersed nature of leg ulcer patients through the community and the many nurses involved this was not logistically possible and would have doubled the cost of the trial. We are satisfied that our approach of remote, blinded assessment of serial photographs is robust and we would emphasise the importance of clinically active nurses making the assessments because ultimately whether a wound is regarded as clean, or healed, is a clinical judgement.

Although we did not find a difference in our primary outcome whether we used blinded or unblinded healing data, other wound trials have observed such as difference.[148] In a study of a dressing to treat exuding wounds the statistically significant effect in favour of the intervention seen using non-blinded data disappeared when blinded outcome assessment was used.[147] It is important to note that this study's outcome was wound improvement rather than healing, which is arguably a more objective outcome.

The use of blinded outcome assessment means that we have more confidence in our primary outcome but it is important to note that undertaking such assessment is not easy. In some cases we did not receive photographs (e.g. where a camera was stolen or camera data cards were lost) and we had to fall back on unblinded data. Using real-time assessment of photographs would also help to ensure as complete a data set as possible was available for blinded assessment. In future trials we would investigate the e-mailing or texting of images to allow closer, contemporaneous monitoring of images. During our pilot phase of the blinded outcome assessment process we noted that the clinical definition of healing that nurses had used was slightly different from the definition that was in the protocol. Nurses were classifying ulcers as healed in the presence of small amounts of dry skin and eschar, and this did not agree with our protocol. Had we not undertaken the blinded outcome assessment we would not have detected this discrepancy. It is unclear if the interpretation of healing is an issue for other studies. If we had followed the protocol definition we may have underestimated healing and compromised the pragmatic nature of the trial. We consulted with senior tissue viability nurses who agreed with the trial nurses in that an ulcer could be classed as healed in the presence of small amounts of eschar as long as a dressing was not required. As a consequence we changed our definition for the assessment process. We did not change our protocol because the assessment occurred after all data had been collected. This change represents a limitation of the study. However, we do not anticipate that this change will have influenced our results.

Attrition

As with VenUS I, we observed a marked reduction in the patient questionnaire response rate over time. At 12 months from baseline almost 50% of HRQoL data were missing. This was in spite of our efforts to ensure the return of questionnaires (reminders and a financial incentive). Preliminary analysis suggests that those participants who healed were more likely to return data so we may have overestimated HRQoL scores. It is important to highlight that, overall, there was no evidence of differential attrition within trial group.

Generalisability of the results

The data from VenUS II were collected from 18 centres across England and Northern Ireland. However, *Figure 2* highlights that most recruitment took place in clinical sites in the North of England. Different sites had different models of practice including outpatient clinics, community tissue viability services and district nursing teams, encompassing the different practices common to the UK and enhancing the generalisability of the study.

Conclusions

Larval therapy significantly reduced the time to debridement of slough and/or necrotic, chronic venous and mixed venous/arterial leg ulcers, compared with hydrogel. However, larval therapy

did not increase the rate of healing of the ulcers nor did it reduce bacterial load and larval therapy was associated with significantly more pain in the 24 hours before removal of the first application than hydrogel. Larval therapy was broadly acceptable to both patients who had and had not received it previously. It was impossible on the basis of this evidence to distinguish between larval therapy and hydrogel in terms of cost-effectiveness.

Implications for health care

There is no evidence from this trial that larval therapy should be used routinely on sloughy or necrotic leg ulcers with the aim of speeding healing or reducing bacterial load. If debridement *per se* is a treatment goal, e.g. before skin grafting or other surgery, then larval therapy should be considered; however, it is associated with significantly more pain than hydrogel. Most patients we interviewed were happy to consider larval therapy. However, future treatment decisions should be fully informed by the finding that there is no evidence of an impact on healing time.

Recommendations for future research

Although this study did not find any evidence that the use of an active debriding agent such as larval therapy results in more rapid healing of venous and mixed aetiology leg ulcers compared with a more passive debriding agent such as hydrogel, this trial does not directly answer the question of whether debriding sloughy and necrotic wounds speeds their healing. There is a variety of ways by which the bigger debridement question could be tackled; one could compare sharp (surgical) debridement with no active debridement for example, or, more pragmatically, one could compare the effect of having a policy of active debridement with a policy of no debridement. Such studies are likely to be focused on specific wound types, because the advantages of debridement may vary for different aetiologies. In reality it may be very difficult to garner sufficient enthusiasm for a debridement trial among clinicians, many of whom are unlikely to be in equipoise regarding the value of debridement.

Relatively little is known about the nature of the outcomes that matter most to the people with chronic wounds themselves and more research is needed on this topic, including an exploration of the value of debridement to patients and clinicians. It may be that a clean wound is perceived as having a value beyond that accruing from the association with a shorter healing time.

To inform health care professionals' selection of debriding agents where debridement is the treatment goal, decision analytic modelling of all alternative debridement treatments is required.

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Statement of independence of researchers

The larvae manufacturers had no role in the design of VenUS II, nor in the collection, analysis, and interpretation of data.

Collaborations and contributions of the authors

The VenUS II collaborators (current and past) are: Una Adderley, Jacqui Ashton, Gill Bennett, JMB, Anne Marie Brown, Sue Collins, Ben Cross, NC, Val Douglas, CD, JCD, Andrea Ellis, Caroline Graham, Christine Hodgson, Gemma Hancock, Shervanthi Homer-Vanniasinkam, CI, June Jones, Nicky Kimpton, Dorothy McCaughan, Elizabeth McGinnis, Jeremy Miles, JLM, Veronica Morton, EAN, Sue O'Meara, Angie Oswald, Emily Petherick, Ann Potter, Pauline Raynor, Linda Russell, Jane Stevens, MS, Nikki Stubbs, DJT, Kath Vowden, Peter Vowden, Michael Walker, Shernaz Walton, Val Wadsworth, Margaret Wallace Judith Watson, Anne Witherow, and GW.

JD and PR were trial managers (PR between 2003 and 2005; JD 2005 and 2008). GW and MB designed and conducted the clinical analysis. MS and CI designed and conducted the economic analyses. NAC was the chief investigator, led the design of the trial, chaired the Trial Management Group, edited and approved the final draft of the report. CD advised on the collection and analysis of microbiological data. DMM conducted the qualitative work and analysis. JM performed the microbiological analysis. EAN and DJT contributed to the study design and co-ordination.

TSC members

Dr Su Mason: Principal Research Fellow (Independent Chair), Clinical Trials Research Unit, University of Leeds.

Professor Francine Cheater: Professor of Public Health Nursing, School of Healthcare, University of Leeds.

Professor Mike Campbell: Professor in Medical Statistics, School of Health and Related Research, University of Sheffield.

Consumer representatives

Mrs Joyce Golton

Mr Victor Beeston (deceased)

DMEC members

Professor Keith Abrams: Professor of Medical Statistics, Department of Health Sciences, University of Leicester (Chair).

Dr Michelle Briggs: Senior Research Fellow, School of Healthcare, University of Leeds.

Mr Alun Davies: Consultant General and Vascular Surgeon, Imperial College, London.

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Appendix 1

Details of recruiting sites

TABLE 53 *Multicentred ethics committee approval was received from West Midlands Research Ethics Committee on 31 July 2003: MREC/03/7/049; only sites in which at least one patient was recruited are included in this table. Approvals were obtained and training given for five further sites, which did not recruit any participants.*

Trust	Service	SSI	R & D approval	Trained
Burton Hospitals NHS Trust	Outpatient leg ulcer clinics	10/02/2004; SE Staffordshire Local Research Ethics Committee	13/11/2003	26/05/2004; 01/11/2004
Bolton PCT	Outpatient leg ulcer clinics	24/05/2004; Bolton Local Ethics Committee	27/04/2004	23/07/2004
Bradford Teaching Hospitals NHS Trust	Outpatient leg ulcer clinic	21/11/2003; Bradford Local Ethics Committee	12/11/2003	07/06/2004
Western Trust	Outpatient leg ulcer clinic/ community tissue viability service	16/12/2003; Altnagelvin Hospital Research Ethics Committee	Not required at time	16/07/2004
North Cumbria Acute Hospitals NHS Trust	Outpatient leg ulcer clinics/ community tissue viability service	05/01/2004; North Cumbria Local Ethics Committee	07/01/2004	22/06/2004
Hull PCT	Outpatient leg ulcer clinics	03/11/2003; Hull and East Ridings Local Ethics Committee	17/11/2003 (East); 31/08/2004 (West)	
Leeds PCT	Community tissue viability service	02/12/2003; Leeds Local Research Ethics Committee	01/03/2004	09/07/2004; 19/07/2004
North Yorkshire and York PCT (two sites)	Leg ulcer clinics/community tissue viability service/district nurse teams	5/12/2003; York Research Ethics Committee	04/03/2004	08/09/2004; 21/09/2004; 08/10/2004
		16/07/2004; Scarborough and NE York Local Ethics committee	07/08/2004	27/09/2004; 02/11/2004; 19/01/2005
Belfast Health and Social Care Trust	Leg ulcer clinics/community tissue viability service	20/10/2004; HPSS Research Ethics Committee	Not required at time	16/07/2004; 06/02/2005
Stockport PCT	Leg ulcer clinics/community tissue viability service	08/12/2004; Stockport Local Research Ethics Committee	29/04/2005	14/03/2005; 27/05/2006
North Tyneside PCT	Community tissue viability service	18/03/2005; Newcastle and North Tyneside Local Research Ethics Committee	30/03/2005	11/05/2005
Bedfordshire Heartlands PCT		18/03/2005; Bedfordshire Local Research Ethics Committee	11/04/2005	22/04/2005; 18/05/2005
Eastbourne Downs PCT	Community tissue viability service	09/02/2006; East Sussex Local Research Ethics Committee	24/01/2006	13/03/2006
Bournemouth Teaching PCT	Community tissue viability service	09/02/2006; Dorset Local Research Ethics Committee	24/02/2006	13/03/2006
Havering PCT and Barking & Dagenham PCT	Outpatient leg ulcer clinics/ Community tissue viability service	09/02/2006; Barking and Havering Local Research Ethics Committee	27/02/2006; Barking and Dagenham PCT	20/03/2006
			09/03/2006; Havering PCT	
North and East Cornwall PCT, West of Cornwall PCT, Central Cornwall PCT.	Outpatient leg ulcer clinics/ Community tissue viability service	04/08/2006; Cornwall Research Ethics Committee	23/06/2006; (joint for all three Trusts)	14/08/2006
North East Essex PCT	Outpatient leg ulcer clinics/ Community tissue viability service	17/112006; Essex 2 Research Ethics Committee	06/03/2007	15/03/2007

NE, north-east; PCT, Primary-Care Trust; R&D, Research and Development; SE, south-east; SSI, site-specific information.

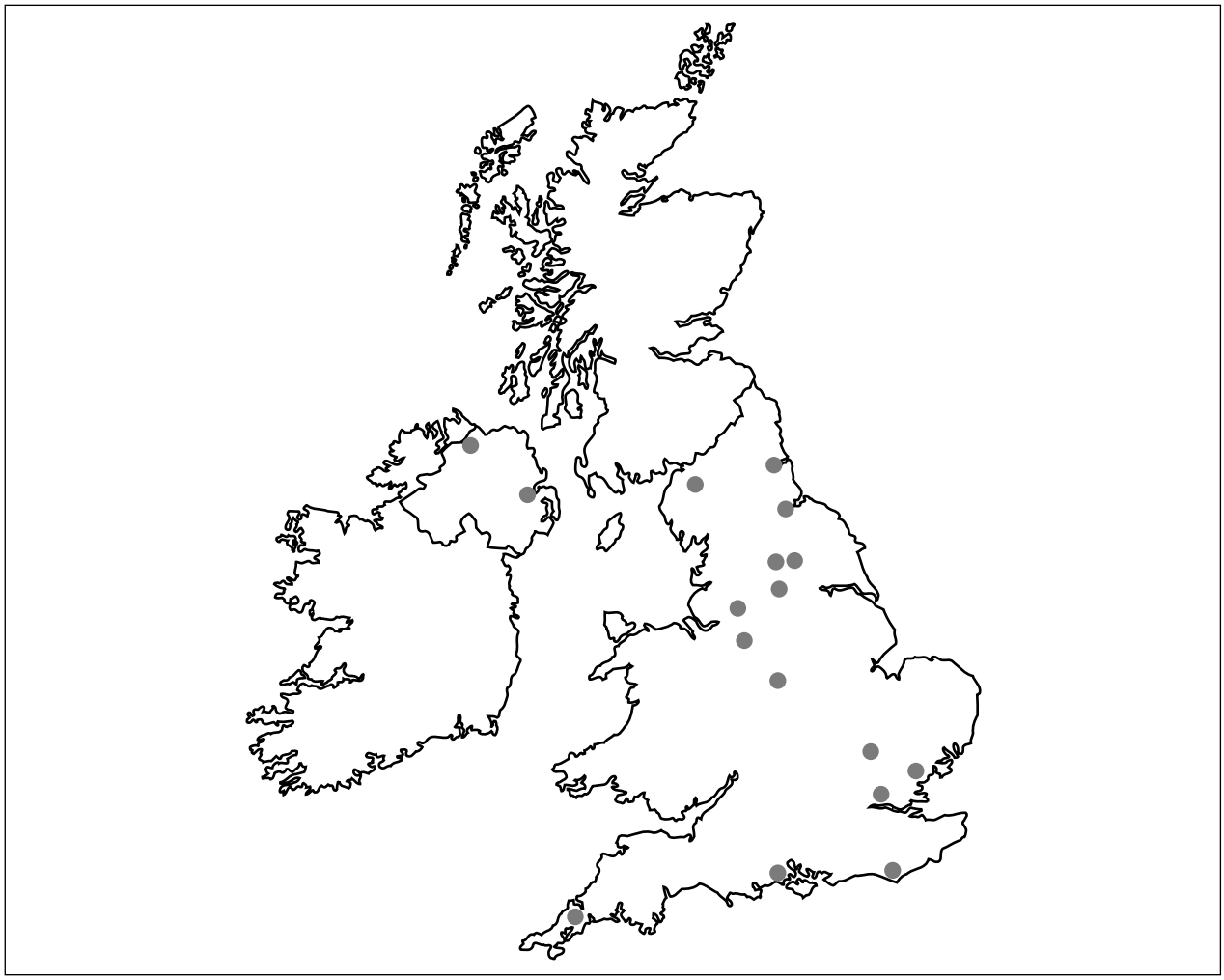

FIGURE 20 *Location of the 18 recruiting VenUS II trial sites (North Yorkshire and York PCT comprised two sites).*

Appendix 2

Patient information sheet

VenUS II
Larval Therapy Study

Site heading

Please read this document carefully.

We would like to invite you to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Feel free to discuss this with anyone else you wish to, for example, friend/nurse/doctor or relative. Ask us if there is anything that is not clear. We are happy to provide more information. Take as much time as you need to decide whether you want to take part.

Thank you for reading this.

What is the purpose of this study?

This is a study of larval therapy for the treatment of leg ulcers. Larval therapy involves the application of small, sterile maggots to a skin ulcer or wound. It is thought that larval therapy helps with healing but we need to find out if this really is the case.

Leg ulcers are common and can be very distressing for patients. Leg ulcers may contain dead skin cells and this dead tissue (called slough) is thought to delay healing. The removal of the dead tissue is undertaken in an attempt to speed up the healing process. Several different treatments can be used to clean a leg ulcer including different wound dressings and larval therapy. The use of hydrogel wound dressings is very common and simply involves applying a watery jelly to the ulcer. This treatment can work quite slowly, and it is thought that larval therapy may be a quicker way to clean up the ulcer and to help healing.

What is the treatment being studied?

We are looking at larval therapy (also called maggots). Larval therapy involves the use of larvae (sterile maggots). The larvae may be put onto the wound in a sealed bag or placed directly onto the wound and kept in place with a sealed dressing system. The main dressings containing the larvae are left in place for up to 5 days. The outer padding is changed as often as required. Most people only need one or two applications of larvae to clean up their ulcer (over 1 or 2 weeks), and can then have regular wound dressings until their ulcer heals.

Why have I been chosen?

Your nurse and/or doctor think that you might benefit from treatment to remove dead tissue from your leg ulcer. Across the UK about 300 people with leg ulcers will be asked to take part in this study.

Do I have to take part?

Participation in this study is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you do decide to take part you can still change your mind at any time. Your future care and treatment will not be influenced by your decision to take part or not. If you do agree to take part in this study and decide at a later time to withdraw then you are free to do so at any time without influencing your future care or treatment.

What will happen to me if I agree to take part?

We are interested in how quickly the ulcers heal, and also in your opinion about the treatment you receive. In order to compare the treatments we need to treat approximately 100 patients with the larval therapy in bags, 100 patients with loose larval therapy and another 100 with hydrogel wound dressings. If you agree to take part in this study you will be allocated to one of these three treatments. The decision regarding which treatment you will receive will be made after you agree to take part. The choice of treatment will be determined at random, that is we cannot predict which treatment you will receive. You will have an equal chance of receiving each treatment, in the same way that tossing a coin gives an equal chance of getting 'heads' or 'tails'. Two people out of every three in the trial will receive larval therapy.

What do I have to do?

You will continue seeing your community nurse or clinic staff for the leg ulcer dressings to be carried out. The ulcer will be traced and photographed at the start of the study and then regularly to see if the ulcer is reducing in size. The study will last for 12 months. You will be asked to complete several questionnaires, at entry into the study, and at 3, 6 and 12 months after that. We will send you questionnaires about your leg and how it affects you, even if your ulcer has completely healed. We do not anticipate that you will have to see the nurse or attend your clinic more frequently than would normally be required. For this reason we will not be able to pay any travel expenses incurred.

There are no restrictions on your activity when you are in the study. You will continue with any other medical treatment, such as taking regular medication.

Why do the study?

Larval therapy may be more effective than using hydrogel wound dressings. It is therefore important to carry out this study so that patients with leg ulcers can be provided with the most appropriate and effective care. We are also interested in how you feel while you have the leg ulcer treatment so that nurses, doctors and patients can make future decisions about which treatments are comfortable. Without this information patients may receive inefficient care, and precious NHS money may be wasted.

Are there any alternatives to the treatments being studied?

There are a number of treatments for removing dead tissue from leg ulcers. Wound dressings to keep the ulcer moist can be used. The body can remove dead tissue beneath moist dressings. Less commonly, the nurse or doctor can sometimes remove dead tissue using forceps.

Are there any side effects from the larval therapy?

There may be an increase in the amount of fluid coming from your wound. This is perfectly normal. The colour of the liquid will also change and will be slightly pink. There may also be a change in the smell of the wound – this is caused by the maggots and is perfectly normal. The smell is usually masked by the layers of bandages on top and will go as soon as the outer dressing is changed. It is sometimes possible to feel a different sensation in the wound after the maggots have been applied. If you wish to have the maggot therapy discontinued for any reason then you can have it removed.

Are there possible disadvantages to taking part?

We do not anticipate that being in this trial will harm you. Should this occur, however, normal NHS negligence procedures will apply.

In an emergency you should contact your community nurse or clinic nurse. The name of a contact nurse and telephone number where they can be reached is provided below.

What are the possible advantages of taking part?

We hope that your ulcer will improve with either treatment (larvae or gel). We cannot guarantee that your ulcer will improve by your being in the trial. The information we get from this study may help us to treat people with leg ulcers better.

What if new information becomes available?

Sometimes during a research project, new information becomes available. If this happens, your nurse/doctor will tell you about it. They will discuss with you whether you want to continue in the study. If you decide to withdraw from the study your care will continue without the trial treatments.

If you decide to continue, then you will be asked to sign an updated consent form.

If new information means that your nurse or doctor decides to take you out of the study, then she/he will discuss this with you. He/she will explain the reasons for this and arrange for your leg ulcer care to continue without the trial treatment.

What happens when the research study stops?

Larval therapy is only available in some clinics. Gel wound dressings are available to every nurse/doctor in the UK. After the research stops the gel treatment will continue to be available throughout the UK. Larval therapy may not be available in your area once the trial stops.

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

If you consent to take part in the research, the University of York (for purposes of analysing the results) may inspect any of your medical records. People from regulatory authorities may also look at them to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital/GP surgery.

Your GP will be notified of your participation in the trial.

What will happen to the results of the study?

The results of the study will be published in medical and nursing journals. This is likely to happen in 2008. You will be able to obtain a copy of the results from the University of York. You will not be identified in any publication arising from this study.

Who is organising and funding the research?

The study is being funded by part of the UK NHS (the Health Technology Assessment Programme). They have provided funds to pay for the larval therapy, for research nurses, and for the tests to monitor your wound (e.g. camera, wound tracing). The research nurses will work with your regular nurse/doctor to collect all the information needed. Your nurse or doctor is not receiving any money for including you in the trial.

The study is being organised by researchers from the University of York.

Who has reviewed the study?

The West Midlands Research Ethics Committee has reviewed the study. Your Local Research Ethics Committee has also been involved in reviewing the study.

What do I do now?

If you are interested in taking part please complete the enclosed questionnaire and sign the consent form, returning it to your study nurse in the envelope provided.

Where can I get more information about the study?

If you do not understand anything on this information sheet or would like further information please contact your local research nurse on the telephone number below.

Local nurse:	Telephone number: Address:
Research coordinator:	Telephone number: Address:

Thank you for taking the time to read this information sheet

Appendix 3
Data collection forms

Appendix 3.1

Date	Nurse Code
/ / (day/month/year)	-

VenUS II: Larval Therapy Trial - Pre-trial Screening Form (v5)

Centre

Patient DoB / / (day/month/year) Patient Sex: Male ☐ Female ☐

Consider patient eligibility using these criteria ANSWER ALL QUESTIONS	Yes
Patient has been in larval therapy trial previously	☐
Patient is a woman of child bearing potential, or pregnant or breastfeeding	☐
Patient is currently in a trial evaluating other therapies for leg ulcers	☐
Patient is allergic to hydrogel	☐
Patient is diabetic with HbA1c higher than 10%	☐
Patient is diabetic and not had HbA1c in last 3 months *(patient may be eligible if HbA1c becomes available)*	☐
ABPI is less than 0.6	☐
Patient has grossly oedematous legs, which in the opinion of the recruiting health care professional would not be suitable for treatment with larval therapy and/or hydrogel	☐
Leg ulcer equal to or less than 5cm2 and has shown signs of healing *(some measurable change in area in previous month)*	☐
Leg ulcer contains less than 25% slough and/or necrotic tissue	☐
Patient will not consider larval therapy *(please give patient a copy of the patient characteristics questionnaire)*	☐
Patient unwilling or unable to give informed consent	☐
Patient is under 18 years of age	☐
Patient is on one or more of the following anti-coagulants: warfarin, acenocoumarol and phenindione and could NOT be admitted to a healthcare facility for larval therapy	☐

If any box contains an 'X' this means the patient is **NOT ELIGIBLE** to enter the trial.
If this is the case please **RETURN THIS FORM** to your local research nurse

If the patient is **ELIGIBLE** to enter the trial, please give the patient the **patient information sheet**. Arrange to see them after at least 24 hours (you may wish to see them at your next scheduled appointment rather than arranging a special visit).

Please now give the patient information sheet to the patient

Nurses name Signature

5303402490

Appendix 3.2

Date ☐☐ / ☐☐ / ☐☐ *day/month/year*

Nurse Code ☐☐ - ☐☐☐☐☐☐

VenUS II: Larval Therapy Trial -
Reference Ulcer Healed Form (v3)

Complete this form when the REFERENCE ULCER HAS HEALED and ONE WEEK POST HEALED

Patient Trial Number ☐☐ - ☐☐☐☐

Reference Ulcer ID ☐☐ Date reference ulcer healed ☐☐ / ☐☐ / ☐☐
day/month/year

Please take a DIGITAL PHOTOGRAPH of the reference ulcer and confirm you have done so

Please confirm you have taken a digital photograph of the reference ulcer

Yes ☐ No ☐

Please make sure you have included the date, patient trial number and ulcer ID (e.g. R1, R2 etc.) on the colour target card. Send the compact flash card to your research nurse for storage.

Complete this section ONE WEEK POST HEALED

Nurse ID ☐☐ - ☐☐☐☐☐☐

Reference Ulcer ID ☐☐ Post Healed Date ☐☐ / ☐☐ / ☐☐
day/month/year

Please take a DIGITAL PHOTOGRAPH of the reference ulcer and confirm you have done so

Please confirm you have taken a digital photograph of the reference ulcer

Yes ☐ No ☐

Please make sure you have included the date, patient trial number and ulcer ID (e.g. R1, R2 etc.) on the colour target card. Send the compact flash card to your research nurse for storage.

Does the patient have any unhealed ulcers on either leg ?

Yes ☐ No ☐

If the answer is **NO** please complete the **TRIAL EXIT FORM**

If the answer is **YES** please continue to complete the dressing log until the patient is free from ulcers on both legs.

When patient is free from ulcers on both legs please complete a **TRIAL EXIT FORM.**

4091108092

Appendix 3.3

Date	Nurse Code
☐☐ / ☐☐ / ☐☐ day/month/year	☐☐ - ☐☐☐☐☐☐

VenUS II: Larval Therapy Trial -Patient Record Form (v3)

BEFORE completing this form please ensure that the patient has signed the consent form to take part in the trial

Date informed consent obtained ☐☐ / ☐☐ / ☐☐
day/month/year

If the patient is diabetic please provide HbA1c (glycated haemoglobin) below

HbA1c ☐☐ % Date of measurement ☐☐ / ☐☐ / ☐☐
day/month/year

Patient Data

Patient Initials

Surname

Postcode

Date of Birth ☐☐ / ☐☐ / ☐☐
day/month/year

Sex Male ☐ Female ☐

VenUS II
Larval Therapy Study

4622344690

1

Please follow the following checklist to confirm if the patient is eligible to enter the trial. Please answer every question by placing a cross in the appropriate box.

	Yes	No
Ulcer criterion The patient has grossly oedematous legs, which in the opinion of the recruiting health care professional would not be suitable for treatment with larval therapy and/or hydrogel	☐	☐
Debridement crierion The patient has an ulcer containing at least 25% slough and/or necrotic tissue	☐	☐
Hard to heal criterion Does the patient have an ulcer equal to or less than 5cm2 that has reduced in area over the past month.(YES-Trial exclusion)	☐	☐
Arterial supply criterion The ABPI equal to or greater than 0.6	☐	☐
Consent criterion The patient has provided written consent to enter the trial	☐	☐

For patients with diabetes only:

	Yes	No
Diabetes control criterion The patient has an HbA1c, measured in the last 3 months, equal to or less than 10%.	☐	☐

If any of the responses fall into the grey boxes then the patient is NOT ELIGIBLE for the trial

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2

Ulcer history and initial assessment

The **reference leg** will be the leg with the largest ulcer containing at least 25% slough and/or necrotic tissue and, if equal to or less than 5cm2, be non-healing.

Please indicate the leg being followed in the trial Left ☐ Right ☐

ABPI of the reference leg ☐.☐☐ Date taken ☐☐ / ☐☐ / ☐☐
e.g. 1.06 or 0.85) *day/month/year*

Total number of ulcer EPSIODES on reference leg since the first episode ☐☐

How long is it since the patient developed the FIRST leg ulcer ☐☐ years ☐☐ months

The **reference ulcer** is identified as the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be both non-healing and contain AT LEAST 25% slough and/or necrotic tissue.

Duration of the reference ulcer ☐☐ years ☐☐ months

Duration of the oldest ulcer on the reference leg ☐☐ years ☐☐ months

Mobility (place a cross in one box)

- Patient walks freely ☐
- Patient walks with difficulty ☐
- Patient is immobile ☐

Ankle mobility/ trial leg

- Has full range of ankle motion ☐
- Has reduced range of ankle motion ☐
- Ankle is fixed ☐

Patient Height ☐☐ feet ☐☐ inches **or** ☐☐☐.☐☐ cm

Patient Weight ☐☐ stone ☐☐ lbs **or** ☐☐☐.☐☐ kgs

Ankle circumfrence (reference leg) ☐☐.☐☐ cm

Current medication

Medication	Daily dosage	Reason
E.G. FRUSEMIDE	20MG	HEART FAILURE

Please ask the patient the following question.

In this trial, you will be treated with either loose maggots, bagged maggots, or a gel dressing. The local nurses and doctors have no influence over the treatment you will receive, choice will be determined randomly e.g. like tossing a coin, at the University of York. Before we find out which treatment you will receive we would like to know if you have a particular preference for any one of the trial treatments, expressing a preference will not affect the treatment you will receive. If you had a completely free choice, which treatment would you prefer; loose maggots, bagged maggots or a gel dressing or do you have no preference.
(PLACE A CROSS IN ONE BOX ONLY)

Loose maggots	Bagged maggots	Gel dressing	No preference
☐	☐	☐	☐

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4

Please draw and label clearly all ulcers on both legs and give each one an identification code. Label the largest ulcer R1 (if on the right leg) or L1 (if on the left leg). If there is more than one ulcer, order them in descending order of area, i.e. largest R1, next largest R2 etc..

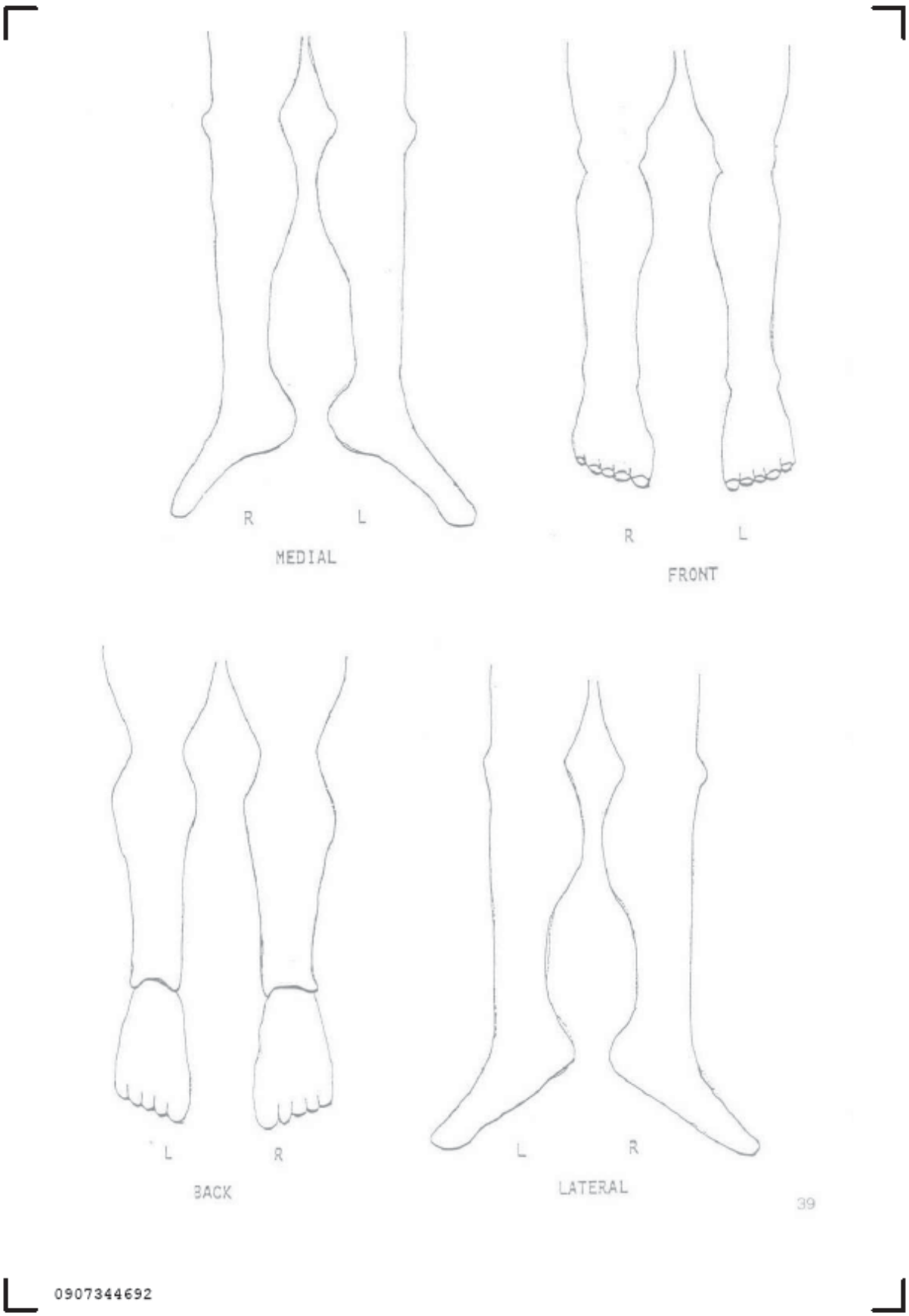
Please write the identification code of the **REFERENCE ULCER** in the box below and **CIRCLE** the reference ulcer on the diagram of legs below. The reference ulcer is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.

REFERENCE ULCER IDENTIFICATION CODE ☐☐

Please enter the other ulcer identification codes in the boxes below.

OTHER ULCER IDENTIFICATION CODES

☐☐	☐☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐☐



Using the grid provided please trace all ulcers on the reference leg

TRACING
Please confirm you have taken tracing(s) of ALL ulcers on the both legs

Yes ☐ No ☐

The tracings should be dated, labelled with the ulcer number (e.g. R1, R2) and the patient's trial number

THE FOLLOWING DATA IS TO BE COLLECTED FROM THE REFERENCE ULCER ONLY

The **reference ulcer** is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.

DIGITAL PHOTOGRAPHS-**Important:**Please ensure the colour target card is included in ALL photographs.
Please confirm that you have taken a close up digital photograph of the reference ulcer

Yes ☐ No ☐

Please confirm that you have taken a digital photograph of the reference leg, the leg containing the reference ulcer, from the knee to the toe.

Yes ☐ No ☐

Please ensure that the photographs include the following on the colour target card: date, patient trial number and reference ulcer ID.

The compactflash card should be returned to your local research nurse who will save the images onto a computer.

WOUND SWAB
Please confirm that you have completed the clinical checklist and taken a wound swab from the REFERENCE ULCER on the reference leg for microbiological culture and sensitivity.

Yes ☐ No ☐

Please ensure that you have included the following on the laboratory form: date, patient trial number and reference ulcer ID (e.g. R1, R2 etc).

REFERENCE ULCER IDENTIFICATION CODE ☐☐

CLINICAL CHECKLIST

Please assess the reference ulcer for infection using the following checklist. The **reference ulcer** is the largest ulcer on the reference leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.

Place a cross in the box relating to the most appropriate answer in the right hand column. Please answer all of the questions.

	Yes	No
In your clinical opinion, does the ulcer appear to be infected	☐	☐

Pain in the ulcer area: Ask the patient to select the most appropriate statement for their current level of ulcer pain from the following choices

(Please select one statement)

- I do not feel pain in or around the ulcer ☐
- I feel less pain now in or around the ulcer now than usual ☐
- I feel the same pain now in and around the ulcer as usual ☐
- I feel more pain in and around the ulcer than usual ☐

Delayed healing of the ulcer: Does the patient report a decrease in size, increase in size or no change in the ulcer size over the past 4 weeks ?

- The ulcer has increased in size ☐
- There has been no change in the ulcer size ☐
- The ulcer has decreased in size ☐

	Yes	No
Erythema: Is the skin immediately adjacent to the ulcer bright red, dark red or darker than normal ethnic skin tone ?	☐	☐
Heat: Using the skin on the back of your hand or wrist, compare the skin temperature adjacent to the ulcer with skin temperature 10cm away from the ulcer. Is the skin temperature near the ulcer warmer than further away ?	☐	☐
Purulent Exudate: Was there brown, creamy, yellow or green thick fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Serous Exudate: Was there thin, watery fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Discolouration of granulation tissue: Is the granulation tissue pale, dusky or dull in colour ?	☐	☐
Friable granulation tissue: Did the granualtion tissue bleed when the dressing was removed ?	☐	☐
Pocketing at base of wound: Are there smooth, non-granulating pockets of ulcer tissue surrounded by beefy red granulation tissue ?	☐	☐
Foul odour: Does the ulcer have a putrid or distinctly unpleasant smell ?	☐	☐
Wound breakdown: Are there small open areas in newly formed epithelial tissue which are not caused by re-injury or trauma ?	☐	☐

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If the patient **IS** ELIGIBLE for the trial please ask about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:
Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:
How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only

	Yes	No
Is the patient eligible for the trial	☐	☐
If 'Yes' place a cross in the box to confirm that the patient has completed the consent form	☐	
Then place a cross in the box to confirm that the patient has completed the baseline questionnaire	☐	

Now complete the randomisation section and call the randomisation service to randomise the patient.

Please attach the tracing(s) to the back of this form

Date	Nurse Code
/ / day/month/year	-

VenUS II: Larval Therapy Trial -Randomisation Form

Patients Full Name

Patients Address

Patients Postcode

Patient DoB / / day/month/year

Patient Sex: Male ☐ Female ☐

Trial Centre:

Altnagelvin	☐	Harrogate	☐
Bolton	☐	Hull	☐
Bradford	☐	Leeds Acute	☐
Burton on Trent	☐	Leeds Community	☐
Cumbria	☐	York	☐
Doncaster	☐	Other (specify)	☐

Size of ulcer: Equal to or less than 5cm2 ☐ More than 5cm2 ☐

Ulcer duration: Equal to or less than 6 months ☐ More than 6 months ☐

Type of ulcer:

Venous ulcer treated with high compression (ABPI 0.8 or above) ☐

Venous ulcer not treated with high compression (ABPI 0.8 or above - patient refuses or cannot tolerate high compression) ☐

Mixed venous arterial aetiology (ABPI greater than 0.6 but less than 0.8) ☐

Once these questions are complete call the randomisation service on 0800 0566682 and complete the allocation details

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Allocation Details

After randomisation complete the details below

Enter the patients trial number: ☐☐ - ☐☐☐☐

The patient has been assigned to:

Loose Larvae ☐

Bagged Larvae ☐

Hydrogel (Purilon) ☐

If the patient has been assigned to loose or bagged larvae enter the larvae order number below

☐☐ - ☐☐☐☐

If the patient has been assigned to loose or bagged larvae calculate the number of larvae or number of bags required for every ELIGIBLE ulcer.

Now the patient is aware of which treatment they are to receive are they still willing to take part ?

Yes ☐ No ☐

Nurses Name: _____

Nurses signature: _____

Please attach the tracing(s) to the back of this form and return it to your local research nurse

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Appendix 3.4

Patient Trial Number			-						
Larvae Order Number			-						

VenUS II: Larval Therapy Trial

PHASE 1

LOOSE LARVAE APPLICATION BOOKLET

Application Number
(Please place a cross in one box)

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

VenUS II
Larval Therapy Study

1555407928

Please report any patient event observed today and complete the relevant form. Please ensure you adhere to your employing Trust's adverse event procedure.

A list of possible adverse events is listed below. This is NOT an exhaustive list. If you suspect an event is serious please contact the trial co-ordinator. We would rather you err on the side of caution and report an adverse event.

Please complete an adverse event form for any of the following

Pressure damage

Skin breakdown

Leg ulcer infection

New ulcer

Limb compromise

Patient who experiences an adverse reaction to larvae (also complete a withdrawal from treatment form)

Patient who experiences an adverse reaction to hydrogel (also complete a withdrawal from treatment form)

Patient has died (also complete a trial exit form)

Patient admitted to hospital for more than 24 hours (also complete a withdrawal from treatment form)

IF A PATIENT HAS A CHANGE OF TREATMENT (DEVIATING FROM THE PROTOCOL_ FOLLOWING AN ADVERSE EVENT, PLEASE ALSO COMPLETE A WITHDRAWAL FROM TREATMENT FORM

Complete a withdrawal from treatment form if you report any of the following

Ulcer deterioration: no change in size, new slough and/or necrotic tissue.

Ulcer deterioration: Increase in size over two weeks

Change of treatment to reference ulcer- topical treatment/ primary dressing bandage or if patient requests to be withdrawn from trial treatment

Forward the adverse event for/ withdrawal form/ Trial exit form to your local reserach nurse

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LOOSE LARVAE THERAPY INTERVENTION

DAY OF APPLICATION

Date of application ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

_____

Before applying larvae to the reference ulcer* and any other ulcer eligible for treatment, please clean thoroughly. If you are applying larvae immediately after the previous application (the same day) you do not need to clean the ulcers.

Please confirm whether you have applied larvae to the reference ulcer

Yes ☐ No ☐

Reference ulcer identification code ☐☐

Number of larvae applied to reference ulcer ☐☐☐

Larvae batch number _____

If the reference ulcer is not treated please provide a reason below

_____

Please list ulcer identification codes of **any other** ulcer being treated with loose larvae and enter the relevant batch numbers

☐☐ Larvae batch number _____

☐☐ Larvae batch number _____

☐☐ Larvae batch number _____

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

* The reference ulcer is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.

LOOSE LARVAE THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location place across in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Is today's visit related to leg ulcer treatment ? Yes ☐ No ☐

If Yes, please indicate reasons for visit (you may cross more than one box if appropriate)

Check visit for leg ulcer and no treatment needed	☐
Rebandage (dressing, change padding)	☐
Hydrate larvae	☐

NB: If larvae are removed please complete the removal of larvae page in this booklet

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a Withdrawal from Treatment Form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

LOOSE LARVAE THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location place across in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Is today's visit related to leg ulcer treatment ? Yes ☐ No ☐

If Yes, please indicate reasons for visit (you may cross more than one box if appropriate)

Check visit for leg ulcer and no treatment needed	☐
Rebandage (dressing, change padding)	☐
Hydrate larvae	☐

NB: If larvae are removed please complete the removal of larvae page in this booklet

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a Withdrawal from Treatment Form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

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LOOSE LARVAE THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location place across in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Is today's visit related to leg ulcer treatment ? Yes ☐ No ☐

If Yes, please indicate reasons for visit (you may cross more than one box if appropriate)

Check visit for leg ulcer and no treatment needed	☐
Rebandage (dressing, change padding)	☐
Hydrate larvae	☐

NB: If larvae are removed please complete the removal of larvae page in this booklet

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a Withdrawal from Treatment Form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

LOOSE LARVAE THERAPY - REMOVAL OF LARVAE VISIT

Date of visit ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location place across in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Please complete the following series of questions regarding reference ulcer

Reference ulcer code	Larvae removed	Completely debrided (no slough or necrotic tissue)	Further application needed
☐☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

DO NOT CLEAN THE ULCER WHEN LARVAE ARE REMOVED

1) If the reference ulcer is **NOT** completely debrided please calculate the number of larvae for the next application and arrange a date and time to apply the larvae.

2) If the reference ulcer is not completely debrided and **no further** applications are to be applied please state reason below.

3) If the reference ulcer is **completely debrided** please start Phase II of the treatment

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

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PLEASE COLLECT THE FOLLOWING OUTCOME DATA

CLINICAL CHECKLIST AND WOUND SWAB

Collect after **EVERY** removal of larvae until debridement **OR IF DEBRIDED WEEKLY** up to one month, then **MONTHLY**

DO NOT CLEAN THE REFERENCE ULCER BEFORE TAKING THE WOUND SWAB

Please confirm that you have completed and collected the following from the **REFERENCE ULCER** on the **reference leg**

Clinical checklist ☐ Swab ☐

Please ensure that you have included the following on the wound swab laboratory form: date, patient trial number and reference ulcer ID code (e.g. R1).

PLEASE PLACE THE WOUND SWAB IN THE FIRST CLASS POST TODAY

TAKE A DIGITAL PHOTOGRAPH WEEKLY

Please confirm that you have taken a digital photograph of the **REFERENCE ULCER** on the **reference leg** on this occasion.

Yes ☐ No ☐

Please ensure that you have included the following on the colour reference target: date, patient trial number and reference ulcer ID code (e.g. R1).

WHAT TO DO NEXT

If further loose larvae treatment is needed

Please continue to use the Dressing Log-between application form found at the end of this booklet each time the patient is seen until the next treatment with loose larvae.

On the day the next treatment of loose larvae are applied please start a new 'Loose larvae application booklet' and return this one to your local reserach nurse.

If NO further loose larvae treatment is to be given

Please start a 'Phase II Dressing Log' booklet today and return this 'Loose Larvae Application Booklet' to your local research nurse.

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CLINICAL CHECKLIST

REFERENCE ULCER IDENTIFICATION CODE ☐☐

Please assess the reference ulcer for infection using the following checklist. The **reference ulcer** is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.
Place a cross in the box relating to the most appropriate answer in the right hand column. Please answer all of the questions.

	Yes	No
In your clinical opinion, does the ulcer appear to be infected	☐	☐

Pain in the ulcer area: Ask the patient to select the most appropriate statement for their current level of ulcer pain from the following choices
(Please select one statement)

- I do not feel pain in or around the ulcer ☐
- I feel less pain now in or around the ulcer now than usual ☐
- I feel the same pain now in and around the ulcer as usual ☐
- I feel more pain in and around the ulcer than usual ☐

Delayed healing of the ulcer: Do the patient report a decrease in size, increase in size or no change in the ulcer size over the past 4 weeks ?

- The ulcer has increased in size ☐
- There has been no change in the ulcer size ☐
- The ulcer has decreased in size ☐

	Yes	No
Erythema: Is the skin immediately adjacent to the ulcer bright red, dark red or darker than normal ethnic skin tone ?	☐	☐
Heat: Using the skin on the back of your hand or wrist, compare the skin temperature adjacent to the ulcer with skin temperature 10cm away from the ulcer. Is the skin temperature near the ulcer warmer than further away ?	☐	☐
Purulent Exudate: Was there brown, creamy, yellow or green thick fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Serous Exudate: Was there thin, watery fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Discolouration of granulation tissue: Is the granulation tissue pale, dusky or dull in colour ?	☐	☐
Friable granulation tissue: Did the granualtion tissue bleed when the dressing was removed ?	☐	☐
Pocketing at base of wound: Are there smooth, non-granulating pockets of ulcer tissue surrounded by beefy red granulation tissue ?	☐	☐
Foul odour: Does the ulcer have a putrid or distinctly unpleasant smell ?	☐	☐
Wound breakdown: Are there small open areas in newly formed epithelial tissue which are not caused by re-injury or trauma ?	☐	☐

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DRESSING LOG - BETWEEN APPLICATIONS

Complete this form whenever you see the patient between loose larvae treatments

Date of visit ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

	Yes	No
Purilon hydrogel applied	☐	☐
Knitted viscose dressing applied	☐	☐

Trial bandages applied as per instructions (please cross one box)

4 layer high compression	☐
3 layer reduced compression	☐
Low compression	☐

Other trial bandages applied if recommended system is not suitable (please cross one box)

Short stretch	☐
2 layer high compression	☐
3 layer high compression	☐

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a withdrawal from treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PLEASE RETURN THIS BOOKLET TO YOUR LOCAL RESEARCH NURSE WHEN THE NEXT BOOKLET IS STARTED

Appendix 3.5

Patient Trial Number			-					
Larvae Order Number			-					

VenUS II: Larval Therapy Trial

PHASE 1

BAGGED LARVAE APPLICATION BOOKLET

Application Number
(Please place a cross in one box)

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

VenUS II
Larval Therapy Study

7851641990

Please report any patient event observed today and complete the relevant form. Please ensure you adhere to your employing Trust's adverse event procedure.

A list of possible adverse events is listed below. This is NOT an exhaustive list. If you suspect an event is serious please contact the trial co-ordinator. We would rather you err on the side of caution and report an adverse event.

Please complete an adverse event form for any of the following

Pressure damage

Skin breakdown

Leg ulcer infection

New ulcer

Limb compromise

Patient who experiences an adverse reaction to larvae (also complete a withdrawal from treatment form)

Patient who experiences an adverse reaction to hydrogel (also complete a withdrawal from treatment form)

Patient has died (also complete a trial exit form)

Patient admitted to hospital for more than 24 hours (also complete a withdrawal from treatment form)

IF A PATIENT HAS A CHANGE OF TREATMENT (DEVIATING FROM THE PROTOCOL_ FOLLOWING AN ADVERSE EVENT, PLEASE ALSO COMPLETE A WITHDRAWAL FROM TREATMENT FORM

Complete a withdrawal from treatment form if you report any of the following

Ulcer deterioration: no change in size, new slough and/or necrotic tissue.

Ulcer deterioration: Increase in size over two weeks

Change of treatment to reference ulcer- topical treatment/ primary dressing bandage or if patient requests to be withdrawn from trial treatment

Forward the adverse event for/ withdrawal form/ Trial exit form to your local reserach nurse

5601641991

BAGGED LARVAE THERAPY INTERVENTION

DAY OF APPLICATION

Date of application ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home ☐ GP Surgery ☐

Leg ulcer clinic ☐ Other (specify below) ☐

Nursing Home ☐

Before applying larvae to the reference ulcer* and any other ulcer eligible for treatment, please clean thoroughly. If you are applying larvae immediately after the previous application (the same day) you do not need to clean the ulcers.

Please confirm whether you have applied larvae to the reference ulcer

Yes ☐ No ☐

Reference ulcer identification code ☐☐

Number of bags applied to reference ulcer ☐

Number of larvae applied to reference ulcer ☐☐☐

Larvae batch number _____

If the reference ulcer is not treated please provide a reason below

_____

Please list ulcer identification codes of **any other** ulcer being treated with bagged larvae and enter the relevant batch numbers

☐☐ Larvae batch number _____

☐☐ Larvae batch number _____

☐☐ Larvae batch number _____

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

* The reference ulcer is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.

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BAGGED LARVAE THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Is today's visit related to leg ulcer treatment ? Yes ☐ No ☐

If Yes, please indicate reasons for visit (you may cross more than one box if appropriate)

- Check visit for leg ulcer and no treatment needed ☐
- Rebandage (dressing, change padding) ☐
- Hydrate larvae ☐
- Assessment of bagged larvae progress and left in situ ☐

NB: If larvae are removed please complete the removal of larvae page in this booklet

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a Withdrawal From Treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:
Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:
How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

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BAGGED LARVAE THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home ☐ GP Surgery ☐

Leg ulcer clinic ☐ Other (specify below) ☐

Nursing Home ☐

Is today's visit related to leg ulcer treatment ? Yes ☐ No ☐

If Yes, please indicate reasons for visit (you may cross more than one box if appropriate)

Check visit for leg ulcer and no treatment needed ☐

Rebandage (dressing, change padding) ☐

Hydrate larvae ☐

Assessment of bagged larvae progress and left in situ ☐

NB: If larvae are removed please complete the removal of larvae page in this booklet

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a Withdrawal From Treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

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BAGGED LARVAE THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Is today's visit related to leg ulcer treatment ? Yes ☐ No ☐

If Yes, please indicate reasons for visit (you may cross more than one box if appropriate)

- Check visit for leg ulcer and no treatment needed ☐
- Rebandage (dressing, change padding) ☐
- Hydrate larvae ☐
- Assessment of bagged larvae progress and left in situ ☐

NB: If larvae are removed please complete the removal of larvae page in this booklet

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a Withdrawal From Treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

BAGGED LARVAE THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home ☐ GP Surgery ☐

Leg ulcer clinic ☐ Other (specify below) ☐

Nursing Home ☐

Is today's visit related to leg ulcer treatment ? Yes ☐ No ☐

If Yes, please indicate reasons for visit (you may cross more than one box if appropriate)

Check visit for leg ulcer and no treatment needed ☐

Rebandage (dressing, change padding) ☐

Hydrate larvae ☐

Assessment of bagged larvae progress and left in situ ☐

NB: If larvae are removed please complete the removal of larvae page in this booklet

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a Withdrawal From Treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

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BAGGED LARVAE THERAPY - REMOVAL OF LARVAE VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location place across in one box only)

Home ☐ GP Surgery ☐

Leg ulcer clinic ☐ Other (specify below) ☐

Nursing Home ☐

Please complete the following series of questions regarding reference ulcer

Reference ulcer code	Larvae removed	Completely debrided (no slough or necrotic tissue)	Further application needed
☐☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

DO NOT CLEAN THE ULCER WHEN LARVAE ARE REMOVED

1) If the reference ulcer is **NOT** completely debrided please calculate the number of larvae for the next application and arrange a date and time to apply the larvae.

2) If the reference ulcer is not completely debrided and **no further** applications are to be applied please state reason below.

3) If the reference ulcer is **completely debrided** please start Phase II of the treatment

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

4326641994

PLEASE COLLECT THE FOLLOWING OUTCOME DATA

CLINICAL CHECKLIST AND WOUND SWAB

Collect after **EVERY** removal of larvae until debridement **OR IF DEBRIDED, WEEKLY** up to one month, then **MONTHLY**

DO NOT CLEAN THE REFERENCE ULCER BEFORE TAKING THE WOUND SWAB

Please confirm that you have completed and collected the following from the **REFERENCE ULCER** on the **reference leg**

Clinical checklist ☐ Swab ☐

Please ensure that you have included the following on the wound swab laboratory form: date, patient trial number and reference ulcer ID code (e.g. R1).

PLEASE PLACE THE WOUND SWAB IN THE FIRST CLASS POST TODAY

TAKE A DIGITAL PHOTOGRAPH WEEKLY

Please confirm that you have taken a digital photograph of the **REFERENCE ULCER** on the **reference leg** on this occasion.

Yes ☐ No ☐

Please ensure that you have included the following on the colour reference target: date, patient trial number and reference ulcer ID code (e.g. R1).

WHAT TO DO NEXT

If further bagged larvae treatment is needed

Please continue to use the dressing log-between application form found at the end of this booklet each time the patient is seen until the next treatment with bagged larvae.

On the day the next treatment of bagged larvae are applied please start a new 'Bagged Larvae Application Booklet' and return this one to your local reserach nurse.

If NO further bagged larvae treatment is to be given

Please start a 'Phase II Dressing Log' booklet today and return this 'Bagged Larvae Application Booklet' to your local research nurse.

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CLINICAL CHECKLIST

REFERENCE ULCER IDENTIFICATION CODE ☐☐

Please assess the reference ulcer for infection using the following checklist. The **reference ulcer** is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.
Place a cross in the box relating to the most appropriate answer in the right hand column. Please answer all of the questions.

	Yes	No
In your clinical opinion, does the ulcer appear to be infected	☐	☐

Pain in the ulcer area: Ask the patient to select the most appropriate statement for their current level of ulcer pain from the following choices
(Please select one statement)

- I do not feel pain in or around the ulcer ☐
- I feel less pain now in or around the ulcer now than usual ☐
- I feel the same pain now in and around the ulcer as usual ☐
- I feel more pain in and around the ulcer than usual ☐

Delayed healing of the ulcer: Do the patient report a decrease in size, increase in size or no change in the ulcer size over the past 4 weeks ?

- The ulcer has increased in size ☐
- There has been no change in the ulcer size ☐
- The ulcer has decreased in size ☐

	Yes	No
Erythema: Is the skin immediately adjacent to the ulcer bright red, dark red or darker than normal ethnic skin tone ?	☐	☐
Heat: Using the skin on the back of your hand or wrist, compare the skin temperature adjacent to the ulcer with skin temperature 10cm away from the ulcer. Is the skin temperature near the ulcer warmer than further away ?	☐	☐
Purulent Exudate: Was there brown, creamy, yellow or green thick fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Serous Exudate: Was there thin, watery fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Discolouration of granulation tissue: Is the granulation tissue pale, dusky or dull in colour ?	☐	☐
Friable granulation tissue: Did the granualtion tissue bleed when the dressing was removed ?	☐	☐
Pocketing at base of wound: Are there smooth, non-granulating pockets of ulcer tissue surrounded by beefy red granulation tissue ?	☐	☐
Foul odour: Does the ulcer have a putrid or distinctly unpleasant smell ?	☐	☐
Wound breakdown: Are there small open areas in newly formed epithelial tissue which are not caused by re-injury or trauma ?	☐	☐

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DRESSING LOG - BETWEEN APPLICATIONS

Complete this form whenever you see the patient between bagged larvae treatments

Date of visit ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

	Yes	No
Purilon hydrogel applied	☐	☐
Knitted viscose dressing applied	☐	☐

Trial bandages applied as per instructions (please cross one box)

4 layer high compression	☐
3 layer reduced compression	☐
Low compression	☐

Other trial bandages applied if recommended system is not suitable (please cross one box)

Short stretch	☐
2 layer high compression	☐
3 layer high compression	☐

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a withdrawal from treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

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Appendix 3.6

Patient Trial Number | | | - | | | | |

VenUS II: Larval Therapy Trial

PHASE I

PURILON HYDROGEL APPLICATION BOOKLET
Application Number

VenUS II
Larval Therapy Study

1108421209

Please report any patient event observed today and complete the relevant form. Please ensure you adhere to your employing Trust's adverse event procedure.

A list of possible adverse events is listed below. This is NOT an exhaustive list. If you suspect an event is serious please contact the trial co-ordinator. We would rather you err on the side of caution and report an adverse event.

Please complete an adverse event form for any of the following

Pressure damage

Skin breakdown

Leg ulcer infection

New ulcer

Limb compromise

Patient who experiences an adverse reaction to larvae (also complete a withdrawal from treatment form)

Patient who experiences an adverse reaction to hydrogel (also complete a withdrawal from treatment form)

Patient has died (also complete a trial exit form)

Patient admitted to hospital for more than 24 hours (also complete a withdrawal from treatment form)

IF A PATIENT HAS A CHANGE OF TREATMENT (DEVIATING FROM THE PROTOCOL_ FOLLOWING AN ADVERSE EVENT, PLEASE ALSO COMPLETE A WITHDRAWAL FROM TREATMENT FORM

Complete a withdrawal from treatment form if you report any of the following

Ulcer deterioration: no change in size, new slough and/or necrotic tissue.

Ulcer deterioration: Increase in size over two weeks

Change of treatment to reference ulcer- topical treatment/ primary dressing bandage or if patient requests to be withdrawn from trial treatment

Forward the adverse event for/ withdrawal form/ Trial exit form to your local reserach nurse

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PURILON HYDROGEL - DAY OF APPLICATION

Date of application ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location place across in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Please confirm whether you have applied purilon hydrogel to the reference ulcer

Yes ☐ No ☐

Please confirm whether you have applied a knitted viscose dressing (KVD) to the reference ulcer

Yes ☐ No ☐

Trial bandages applied as per instructions (please cross one box)

4 layer high compression	☐
3 layer reduced compression	☐
Low compression	☐

Other trial bandages applied if recommended system is not suitable (please cross one box)

Short stretch	☐
2 layer high compression	☐
3 layer high compression	☐

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a withdrawal from treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

* The reference ulcer is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.

PURILON HYDROGEL THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Please indicate reasons for visit (you may cross more than one box if appropriate)

Leg ulcer treatment	☐
Patient requested a visit	☐
Unrelated to leg ulcer treatment	☐

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a withdrawal from treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

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PURILON HYDROGEL THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Please indicate reasons for visit (you may cross more than one box if appropriate)

Leg ulcer treatment	☐
Patient requested a visit	☐
Unrelated to leg ulcer treatment	☐

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a withdrawal from treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

PURILON HYDROGEL THERAPY - FOLLOW UP VISIT

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home ☐ GP Surgery ☐
Leg ulcer clinic ☐ Other (specify below) ☐
Nursing Home ☐

Please indicate reasons for visit (you may cross more than one box if appropriate)

Leg ulcer treatment ☐
Patient requested a visit ☐
Unrelated to leg ulcer treatment ☐

If you have **changed** the treatment applied to the reference ulcer or reference leg e.g. dressings or bandages other than those recommended for the trial, please provide details below. Please also complete a withdrawal from treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:
Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:
How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

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PURILON HYDROGEL THERAPY - REMOVAL OF HYDROGEL VISIT

Date of visit ☐☐ / ☐☐ / ☐☐

day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location place across in one box only)

Home	☐	GP Surgery	☐
Leg ulcer clinic	☐	Other (specify below)	☐
Nursing Home	☐		

Please complete the following series of questions regarding reference ulcer

Reference ulcer code	Completely debrided (no slough or necrotic tissue)	Further application needed
☐☐	Yes ☐ No ☐	Yes ☐ No ☐

If the reference ulcer is not completely debrided and **no further** applications are to be applied please state reason below.

If the reference ulcer is **completely debrided** please start Phase II of the treatment

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

PAIN ANALOGUE SCALE

Please ask the patient about any pain they may have experienced from the leg ulcer(s) on the reference leg in the past 24 hours. Read the instructions out to the patient about how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced ranging from no pain to the worst pain imaginable.

Question:

How intense has the pain been from your leg ulcer(s) in the past 24 hours ?

No Pain — Worst pain imaginable

Office Use Only ☐☐☐

8566421204

PLEASE COLLECT THE FOLLOWING OUTCOME DATA

CLINICAL CHECKLIST AND WOUND SWAB
Collect after **EVERY** removal of hydrogel until debridement **OR IF DEBRIDED WEEKLY** up to one month, then **MONTHLY**

DO NOT CLEAN THE REFERENCE ULCER BEFORE TAKING THE WOUND SWAB

Please confirm that you have completed and collected the following from the **REFERENCE ULCER** on the **reference leg**

Clinical checklist ☐ Swab ☐

Please ensure that you have included the following on the wound swab laboratory form: date, patient trial number and reference ulcer ID code (e.g. R1).

PLEASE PLACE THE WOUND SWAB IN THE FIRST CLASS POST TODAY

TAKE A DIGITAL PHOTOGRAPH WEEKLY

Please confirm that you have taken a digital photograph of the **REFERENCE ULCER** on the **reference leg** on this occasion.

Yes ☐ No ☐

Please ensure that you have included the following on the colour reference target: date, patient trial number and reference ulcer ID code (e.g. R1).

WHAT TO DO NEXT

If further purilon hydrogel treatment is needed
If a further treatment of purilon hydrogel is needed please start a new 'Purilon Hydrogel Application Booklet and RETURN this one to your local research nurse

If NO further purilon hydrogel treatment is to be given
Please start a 'Phase II Dressing Log' booklet today and return this 'Purilon Hydrogel Application Booklet' to your local research nurse.

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CLINICAL CHECKLIST

REFERENCE ULCER IDENTIFICATION CODE ☐☐

Please assess the reference ulcer for infection using the following checklist. The **reference ulcer** is the largest ulcer on the leg containing AT LEAST 25% slough and/or necrotic tissue. If the ulcer is SMALL (AREA equal to or less than 5cm2) it must be BOTH non-healing and contain AT LEAST 25% slough and/or necrotic tissue.
Place a cross in the box relating to the most appropriate answer in the right hand column. Please answer all of the questions.

	Yes	No
In your clinical opinion, does the ulcer appear to be infected	☐	☐

Pain in the ulcer area: Ask the patient to select the most appropriate statement for their current level of ulcer pain from the following choices
(Please select one statement)

- I do not feel pain in or around the ulcer ☐
- I feel less pain now in or around the ulcer now than usual ☐
- I feel the same pain now in and around the ulcer as usual ☐
- I feel more pain in and around the ulcer than usual ☐

Delayed healing of the ulcer: Do the patient report a decrease in size, increase in size or no change in the ulcer size over the past 4 weeks ?

- The ulcer has increased in size ☐
- There has been no change in the ulcer size ☐
- The ulcer has decreased in size ☐

	Yes	No
Erythema: Is the skin immediately adjacent to the ulcer bright red, dark red or darker than normal ethnic skin tone ?	☐	☐
Heat: Using the skin on the back of your hand or wrist, compare the skin temperature adjacent to the ulcer with skin temperature 10cm away from the ulcer. Is the skin temperature near the ulcer warmer than further away ?	☐	☐
Purulent Exudate: Was there brown, creamy, yellow or green thick fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Serous Exudate: Was there thin, watery fluid on the dressing removed from the ulcer at this dressing stage ?	☐	☐
Discolouration of granulation tissue: Is the granulation tissue pale, dusky or dull in colour ?	☐	☐
Friable granulation tissue: Did the granualtion tissue bleed when the dressing was removed ?	☐	☐
Pocketing at base of wound: Are there smooth, non-granulating pockets of ulcer tissue surrounded by beefy red granulation tissue ?	☐	☐
Foul odour: Does the ulcer have a putrid or distinctly unpleasant smell ?	☐	☐
Wound breakdown: Are there small open areas in newly formed epithelial tissue which are not caused by re-injury or trauma ?	☐	☐

Appendix 3.7

Patient Trial Number ☐☐ - ☐☐☐☐

VenUS II: Larval Therapy Trial

PHASE II

DRESSING LOG BOOKLET

Application Number

☐☐

Please complete a page in the Dressing Log Booklet at each visit to the patient and complete the following trial documentation at the appropriate times.

- When the reference ulcer has healed please complete a **Reference Ulcer Healed Form** (also complete a **Trial Exit Form** if the reference ulcer is the only ulcer on the leg).

- If there are unhealed ulcers on the leg continue to complete the Dressing Log Booklet until all ulcers on the reference leg have healed - when this occurs please complete a **Trial Exit Form**.

- If the reference ulcer OR reference leg is/are not healed in 12 months please complete a **Trial Exit Form** at this stage.

VenUS II
Larval Therapy Study

9918281424

Please report any patient event observed today and complete the relevant form. Please ensure you adhere to your employing Trust's adverse event procedure.

A list of possible adverse events is listed below. This is NOT an exhaustive list. If you suspect an event is serious please contact the trial co-ordinator. We would rather you err on the side of caution and report an adverse event.

Please complete an adverse event form for any of the following

Pressure damage

Skin breakdown

Leg ulcer infection

New ulcer

Limb compromise

Patient who experiences an adverse reaction to larvae (also complete a withdrawal from treatment form)

Patient who experiences an adverse reaction to hydrogel (also complete a withdrawal from treatment form)

Patient has died (also complete a trial exit form)

Patient admitted to hospital for more than 24 hours (also complete a withdrawal from treatment form)

IF A PATIENT HAS A CHANGE OF TREATMENT (DEVIATING FROM THE PROTOCOL_ FOLLOWING AN ADVERSE EVENT, PLEASE ALSO COMPLETE A WITHDRAWAL FROM TREATMENT FORM

Complete a withdrawal from treatment form if you report any of the following

Ulcer deterioration: no change in size, new slough and/or necrotic tissue.

Ulcer deterioration: Increase in size over two weeks

Change of treatment to reference ulcer- topical treatment/ primary dressing bandage or if patient requests to be withdrawn from trial treatment

Forward the adverse event for/ withdrawal form/ Trial exit form to your local reserach nurse

PHASE II DRESSING LOG
PLEASE COMPLETE THIS FORM EVERY TIME A PATIENT IS SEEN BY A NURSE

Date of visit ☐☐ / ☐☐ / ☐☐
day/month/year

Nurse Code ☐☐ - ☐☐☐☐☐☐

Location (place a cross in one box only)

Home ☐ GP Surgery ☐
Leg ulcer clinic ☐ Other (specify below) ☐
Nursing Home ☐

Reason for visit (please cross one box)

Leg ulcer treatment (rebandage, repad etc) ☐
Visit UNRELATED to leg ulcer treatment (pressure ulcer/diabetes care) ☐

Knitted viscose dressing (KVD) applied Yes ☐ No ☐

Please report any change to the primary dressings and state reasons why below (please put name of primary dressing/wound contact layer/topical agen applied apart from a KVD) AND complete a Withdrawal From Treatment form.

Compression bandages applied:

Trial bandages applied as per instructions (please cross one box)

4 layer high compression ☐
3 layer reduced compression ☐
Low compression ☐

Other trial bandages applied if recommended system is not suitable (please cross one box)

Short stretch ☐
2 layer high compression ☐
3 layer high compression ☐

Please report any change of compression therapy and state reason why below AND complete a Withdrawal From Treatment form.

Has there been a **patient event** since your last visit Yes ☐ No ☐

If **yes**, please complete the relevant form described at the beginning of this booklet

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Appendix 3.8

Date	Nurse Code
☐☐ / ☐☐ / ☐☐ *day/month/year*	☐☐ - ☐☐☐☐☐☐

VenUS II: Larval Therapy Trial -Inpatient Information

Please complete this form for any inpatient recruited to the trial

Patient Trial Number ☐☐ - ☐☐☐☐

Patient DoB ☐☐ / ☐☐ / ☐☐
day/month/year

Date of admission ☐☐ / ☐☐ / ☐☐
day/month/year

Reason for admission _____

Date of discharge ☐☐ / ☐☐ / ☐☐
day/month/year

Discharged to
(please select one option)

- Home ☐
- Nursing Home ☐
- Other Hospital ☐
- Other (please state) ☐ _____

Please place a copy of this form in the notes and a copy to your local research nurse

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Appendix 3.9

THE UNIVERSITY of York

VENUS II Larval Therapy Study

Three Month Questionnaire

ID Number			-						
Date			/			/			

VenUS II
Larval Therapy Study

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PLEASE READ ALL THE INSTRUCTIONS BEFORE COMPLETING THE QUESTIONNAIRE

Thank you for agreeing to take part in this study.

We would like to find out a little about your health and how your leg ulcer might affect your life. Please answer ALL the questions. Although some of the questions may not seem relevant to yourself they do give us valuable information about your leg ulcer.

If you find it difficult to answer a question, please do the best you can.

Please follow the instructions for each section carefully.

For each section, if you are asked to put a cross in the box, please use a cross rather than a tick, as if you were filling out a ballot paper.

For example in the following question, if your answer to the question is yes, you should place a cross firmly in the box next to yes.

Do you drive a car ? **Yes** ☒

No ☐

If you are asked to circle a number, please use a circle rather than underlining a number.

For example, in the following question if you are asked 'how happy are you today?' where '1' is 'very unhappy' and '5' is 'very happy', If you feel neither happy nor unhappy you may wish to answer 3. You do this by clearly circling the number 3.

1 **2** **(3)** **4** **5**

PLEASE USE A BLACK OR BLUE PEN.

Please do not use a pencil or any other coloured pen.

Please read all the instructions for each section.

This section asks about your health in general. By placing a cross in one box in each group below, please indicate which statement best describes your own health state today.

(Do not cross more than one box in each group)

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

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 ☐

Usual Activities (e.g. work, study, housework, family or leisure)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

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This section asks for your views about your health. This section will help us keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:
(please cross one box only)

Excellent	Very Good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. During a typical day does **your health** limit you in **moderate actvities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf ? If so, how much ?
(please cross one box only)

Yes, limited a lot	Yes, limited a little	No, not limited at all
☐	☐	☐

3. During a typical day does **your health** limit you in climbing **several** flights of stairs ? If so, how much ?
(please cross one box only)

Yes, limited a lot	Yes, limited a little	No, not limited at all
☐	☐	☐

4. During the past **4 weeks**, how much of the time have you accomplished less than you would like in regular daily activities **as a result of your physical health** ?
(please cross one box only)

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

5. During the past **4 weeks**, how much of the time have you been limited in performing any kind of work or other regular daily activities **as a result of your physical health** ?
(please cross one box only)

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

6. During the past **4 weeks**, how much of the time have you accomplished less than you would have liked in your work or any other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious) ?
(please cross one box only)

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

7. During the past **4 weeks**, how much of the time have you done work or other activities less carefully than usual **as a result of any emotional problems** (such as feeling depressed or anxious) ?
(please cross one box only)

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

8. During the past **4 weeks**, how much did **pain** interfere with your normal work (both outside the home and housework) ?
(please cross one box only)

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

9. This question is about how you feel and how things have been with you **during the last month**. Please give the one answer that comes closest to the way you have been feeling. How much during the **last month** have you felt calm and peaceful ?
(please cross one box only)

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

10. This question is about how you feel and how things have been with you **during the last month**. Please give the one answer that comes closest to the way you have been feeling. How much during the **last month** did you have a lot of energy ?
(please cross one box only)

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

11. This question is about how you feel and how things have been with you **during the last month**. Please give the one answer that comes closest to the way you have been feeling. How much during the **last month** have you felt downhearted and depressed ?
(please cross one box only)

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

12. 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, relatives etc.) ?
(please cross one box only)

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

Please enter today's date ☐☐ / ☐☐ / ☐☐

day/month/year

In order to accurately measure the cost of differnt leg ulcer treatments, we would like to know the number of times you have seen a health professional (e.g. doctor or nurse) **not** as part of this study.

1. In the last 3 **months** have you seen a doctor at your **doctor's surgery** OR seen a **doctor at home** for any reason relating to your health ?

Yes ☐

No ☐

If **Yes**, how many times...

have you seen a doctor at the surgery ? ☐☐

have you been visited at home by a doctor ? ☐☐

Were any of these visits because of your leg ulcer ?

Yes ☐

No ☐

If **Yes**, how many times ? ☐☐

2. In the last 3 **months** have you seen a nurse at your **doctor's surgery** OR seen a **nurse at home** for any reason relating to your health ?

Yes ☐

No ☐

If **Yes**, how many times...

have you seen a nurse at the surgery ? ☐☐

have you been visited at home by a nurse ? ☐☐

Were any of these visits because of your leg ulcer ?

Yes ☐

No ☐

If **Yes**, how many times ? ☐☐

3. In the last 3 **months** have you **been to hospital** for any reason relating to your health ?

Yes ☐
No ☐

If **Yes**, how many times... ☐☐

Were any of these visits because of your leg ulcer ?

Yes ☐
No ☐

If **Yes**, how many times... ☐☐

4. In the last 3 **months** which of the following have helped you around the house, to do the shopping etc. ?
(place a cross in the box for all of those who have helped and then enter the number of hours per week they have helped you, if you have not needed any help put a cross in the 'I have not needed any help' box)

I have not needed any help ☐

Home help ☐ approximately how many hours per week ☐☐

Relative ☐ approximately how many hours per week ☐☐

Friend/ neighbour ☐ approximately how many hours per week ☐☐

Other (please state relationship in box below) ☐ approximately how many hours per week ☐☐

☐

5. Since you joined the study, **about three months ago**, have you had larvae (maggots) applied to your ulcer, either loose or in a bag ?
(please cross one box only)

Yes ☐

No ☐

Appendix 4
Larvae calculators

Appendix 4.1

TABLE 54 *LarvE® Calculator*

LarvE® Calculator

Instructions for use:

1. Measure the dimensions of the wound in centimetres.
2. Pick the nearest size from the measurements on the left of the chart.
3. Move sideways to the appropriate percentage of wound coverage.
4. State the number of pots required from within the cell.

Maximum wound size (cm)	Percentage of wound covered with slough/necrotic tissue				
	20%	40%	60%	80%	100%
up to 2 × 2	1	1	1	1	1
5 × 5	1	1	1	1	2
5 × 10	1	1	1	2	2
10 × 10	1	1	2	2	2
10 × 15	1	2	2	2	3
15 × 15	2	2	2	3	3
15 × 20	2	2	3	3	3
20 × 20	2	3	3	3	4
20 × 25	3	3	3	4	4
25 × 25	3	3	4	4	5
25 × 30	3	4	4	5	5
30 × 30	4	4	5	5	5

Note that the calculator only measures the surface area of the wound. If the wound has significant depth, more larvae may be required.

Appendix 4.2

TABLE 55 *Larval calculators for loose and bagged larvae*

Approximate wound size (cm)	Percentage of wound area covered with necrotic tissue				
	20%	40%	60%	80%	100%
2 × 2					
5 × 5					
5 × 10					
10 × 10					
10 × 15					
15 × 15					
15 × 20					
20 × 20					
20 × 25					
25 × 25					
30 × 30					

Approximate number of free-range sterile larvae required

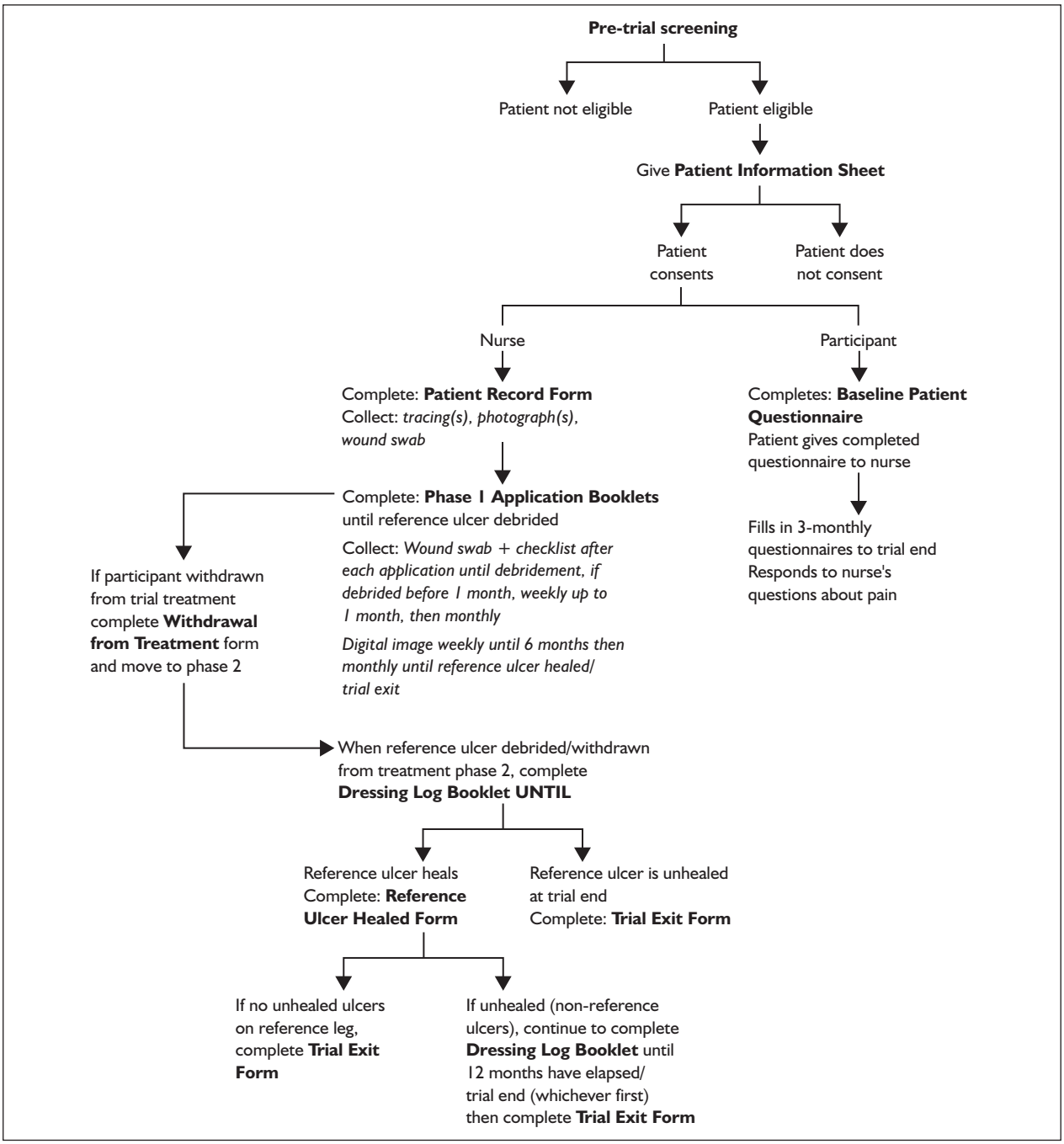
	50		100		200		300		400	500

Biobags are available in the following sizes:

BioBag Mini	50 larvae	2.5 × 4 cm
BioBag Small	100 larvae	4 × 5 cm
BioBag Medium	200 larvae	5 × 6 cm
BioBag Large	300 larvae	6 × 12 cm

Appendix 5

Flow chart of VenUS II



Appendix 6
Digital image protocol

Every digital photograph must include the colour reference target card, which includes a centimetre measuring scale and colour targets. The patient's trial number and date must ALWAYS be clearly written on the colour target card. Please make sure that the colour target card is included in the photograph otherwise the photograph cannot be used as data collected.

Please take **two** photographs at baseline and at healing.

1. reference leg toe to knee (colour target card placed near to toe end of leg)
2. reference Ulcer Only – ** See 'Taking the Weekly Photographs' overleaf.

Please always try to take a photograph of the reference leg ulcer from directly above the wound, if it is photographed at an angle it may be difficult to assess the wound accurately.

In the case of circumferential wounds additional adjacent photographs may be required.

Every reasonable effort must be made to take all consecutive photographs from the same viewpoint and distance using the same camera and same zoom facility.

Please ensure that the ulcer and surrounding area are cleaned thoroughly before taking the photograph. This is to reduce the possibility of blinded assessors being able to predict the treatment received by the patient (e.g. zinc paste around the wound might indicate the patient had received loose larval treatment).

All consecutive views of the reference ulcer area to be photographed using the trial camera.

All cameras have been calibrated so they are standardised to the same specification – **please do not change any of these settings at any time.**

All digital photographs to be kept confidential and secure for the duration of the trial. Patient confidentiality will be maintained throughout trial by the use of unique trial numbers.

No film, recording media or data to be manipulated or changed in any way with the intention of affecting the results of the trial.

Copies of all photographs taken during the trial will be:

- saved on a Compact flash card
- stored on the Local Research Nurse's computer
- sent on the Compact flash card to the Trials Unit, University of York.

The photographs will then be transferred from the Compact flash card onto a trial database at the Trials Unit in York and then be deleted from the Compact flash card and the card returned to the Local Research Nurse to be used again.

All cameras have been calibrated to the same specification as follows:

- automatic mode – the camera responds to the shooting conditions at the time and controls the majority of camera settings
- white balance is automatically set and used to preserve the natural colours under types of lighting
- the flash is set to automatic
- image quality/size – set to 3M (normal – 2048 × 1536)

All cameras are supplied with a guide and it might be helpful to read this before you start to use the camera.

Taking photographs – framing the picture

Hold the camera steadily in both hands about 18 inches to 2 feet (45–60 cm) away from the patient.

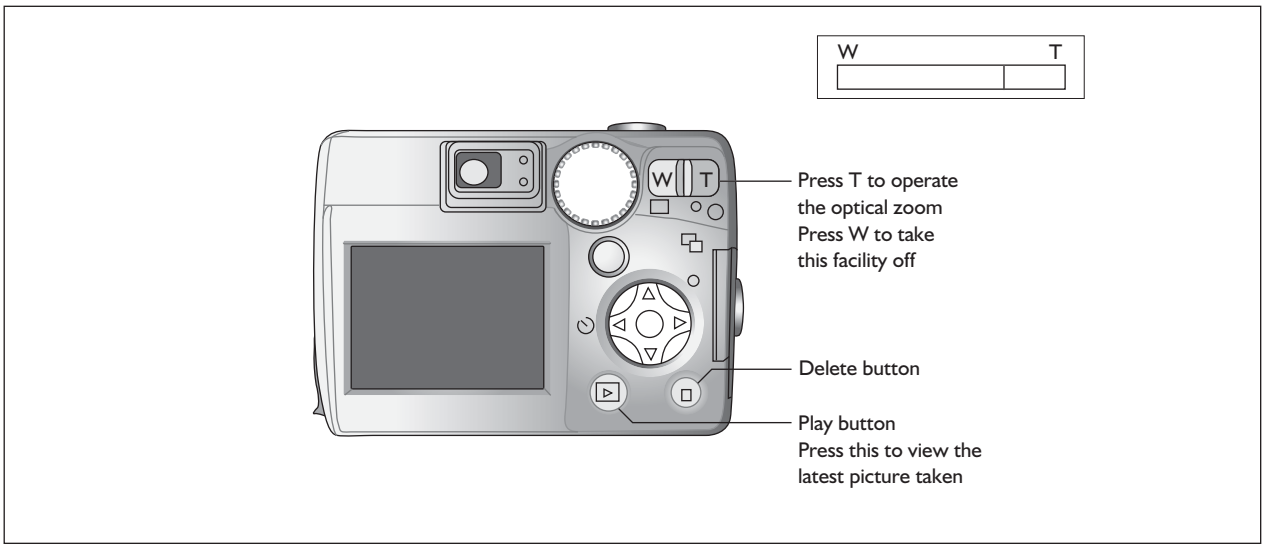


FIGURE 21 *Nikon Coolpix 4600.*

Zoom in using the optical zoom facility on the camera (*PRESS T*) ensuring that the whole of the wound area and the colour reference target card are included in the picture (see page 18 in your camera guide book).

When you press the 'T' button a white oblong box will appear in the top of the viewfinder and a bar will move towards the line (two-thirds along the box) until it stops. Stop pressing the 'T' button at this stage and take your photograph. Press the 'W' button to zoom out.

Appendix 7
Wound swab protocol

Specimen collection

Explain to the participant that you are about to take a wound swab from their leg ulcer.

Please DO NOT clean the wound before taking the swab to ensure the maximum numbers of bacteria are present.

Take the swab from an area of the wound containing viable tissue if possible (e.g. granulating tissue).

Avoid taking the sample from areas of the wound covered with slough or necrotic tissue.

Collection method

SWAB: rotate the swab, moving across the area in a zigzag fashion, applying light pressure with the aim of saturating the swab.

If the wound is very dry you may moisten the swab with sterile water or sterile saline to aid in the collection of the specimen.

When you have collected the specimen

- place the swab in the swab container
- write the patient's trial number and date of birth on the sticky label provided and seal the container with this label
- write the same information on the pathology specimen form
- THE INFORMATION ON THE SWAB LABEL AND THE FORM MUST MATCH OTHERWISE THE SPECIMEN WILL NOT BE VALID
- place the sealed swab inside the plastic bag provided, fold the form and place it in the outer pocket of the polythene bag then place in the prepaid, addressed, padded envelope.

Appendix 8

Qualitative interviews: participant and nurse information sheets

Site heading

Patient information sheet

Patients' beliefs and experiences of larval therapy in the treatment of leg ulcers

You are being invited to take part in a research study. Before you decide it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your relatives and the nurse if you wish. Ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Your involvement is entirely voluntary.

The information gathered from this study will provide information about how people with leg ulcers view larval therapy (sterile medical maggots) and will not influence the treatment of your leg ulcer in any way. If you do decide to take part you will be asked to sign a consent form, and will be given a copy of this to take away. You will be able to leave the study at any time, without giving a reason. This will not affect any aspect of your care. If you decide not to take part this will not affect any aspect of your care.

Background to the study

Larval therapy is another name for the use of maggots in wound care. A large clinical study is being undertaken to find out if leg ulcers heal more quickly by using maggots. The maggots used are small, sterile maggots. The maggots are placed on the ulcer and covered by a bandage. As part of this study, we are interested in knowing your views about the use of maggots in the treatment of wounds.

What would the study involve?

A nurse researcher will ask patients with a leg ulcer to agree to be interviewed on one occasion. This can be done in a place of your choosing: in the setting you usually receive care for your leg ulcer, in your home or at the leg ulcer clinic. The interview would be tape recorded and then typed out in full. During the interview you will be asked about treatments you have received for your leg ulcer and how you feel about the use of maggots.

All information that is collected about you during the course of this study will be strictly confidential. Your name and personal details will be removed so that you cannot be recognised.

What will happen to the results of this study?

This study will lead to a better understanding of how acceptable the use of larval therapy is to people with leg ulcers. This information will be used in the large study of larval therapy to help us identify the reasons people agree to this form of therapy or why they might not want this form of therapy.

Administrative information

This study has been commissioned by the Department of Health Research and Development Health Technology Assessment Programme. The funding has enabled a researcher to be employed to interview patients who is not involved in your care in any way and is not employed by the hospital or community.

This study has been reviewed and approved by a multicentre research ethics committee.

Thank you for considering this study. If you have any questions about the study at any time, please contact:

Dorothy McCaughan
Department of Health Sciences
University of York, YO10 5DD
Tel: 01904 000000

Site heading

Nurse information sheet

Nurses' beliefs and experiences of larval therapy in the treatment of leg ulcers

You are being invited to take part in a research study. Before you decide it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information carefully. Please contact the researcher if there is anything that is not clear or if you would like more information. Your involvement is entirely voluntary. If you do decide to take part you will be asked to sign a consent form. You will be able to leave the study at any time, without giving a reason.

Background to the study

A large clinical study is being undertaken to find out if leg ulcers heal more quickly by using larval therapy (sterile medical maggots). As part of this study, we are interested in knowing your views about the use of maggots in the treatment of wounds.

What would the study involve?

A researcher is interested in talking to nurses who are involved in caring for people with leg ulcers to find out your views about the use of maggots in clinical care. You will be asked to participate in one interview which can be done in a setting convenient to you. The interview would be tape recorded and then typed out in full.

All information that is collected about you during the course of this study will be strictly confidential. Your name and personal details will be removed so that you cannot be recognised.

What will happen to the results of this study?

This study will lead to a better understanding of how acceptable the use of larval therapy is to nurses involved in caring with people who have leg ulcers.

Administrative information

This study has been commissioned by the Department of Health Research and Development Health Technology Assessment Programme. The funding has enabled a researcher to be employed to interview nurses who is not employed by the hospital or community.

This study has been reviewed and approved by a multicentre research ethics committee.

Thank you for considering this study. If you have any questions about the study at any time, please contact:

Dorothy McCaughan
Department of Health Sciences
University of York, YO10 5DD
Tel: 01904 000000

Appendix 9

Qualitative interviews: patient and nurse interview schedules

Patient interview schedule

This schedule includes generic questions for all participants. The participant will be asked specific questions dependent on their experience of larval therapy.

Introduction to the study
Explain about confidentiality and tape recording

1. Background
   a. age
   b. ethnic origin
   c. household composition
2. How long have you had a leg ulcer?
3. What impact has the leg ulcer had on you?
4. What treatments have you had on your leg ulcer?

The following questions will be posed to those participants who HAVE NOT had experience of maggots.

5. What do you think about 'natural treatments' for leg ulcers (such as maggots)?
6. How do you feel about maggots being used in the treatment of your leg ulcer?
7. Why do you think you feel this way?
8. Have you had any previous experience of maggots (e.g. fishing)?
9. Have you talked to any members of your family about your leg ulcer/treatment of your leg ulcer?
10. How do you think they would view the use of maggots in the treatment of leg ulcers?

The following questions will be posed to those participants who HAVE had experience of maggots.

5. How did you feel when larval therapy was suggested for the treatment of your leg ulcer?
6. Have you had any previous experience of maggots (e.g. fishing)?
7. What is the maggot treatment like (e.g. do you have any pain)?
8. How do you think the maggots are helping your wound?
9. Have you talked to members of your family about the treatment of your ulcer?
10. How do you think they view the use of maggots in the treatment of leg ulcers?

Is there anything else you would like to tell me about your leg ulcer and its treatment?

Reiterate about confidentiality

Thank you

Nurse interview schedule

This schedule includes generic questions for all participants. The participant will be asked specific questions dependent on their experience of larval therapy.

Introduction to the study

Explain about confidentiality and tape recording

1. Background
   a. age
   b. ethnic origin
   c. employment details – position/grade and where based
2. How long have you been involved in caring for patients with leg ulcers?
3. What treatments have you used on leg ulcers?
4. Have you been involved in using larval therapy before?

The following questions will be posed to those participants who have NOT HAD experience of maggots.

5. How do you feel about maggots being used in the treatment of leg ulcers?
6. Why do you think you feel this way?
7. If a patient were prescribed larval therapy for the treatment of their leg ulcer, would this concern you?
8. Have you had any previous experience of maggots (e.g. fishing)?
9. Have you talked to colleagues about the use of maggots in the treatment of leg ulcers? If so, what were their views?

The following questions will be posed to those participants who HAVE had experience of maggots.

5. Tell me about your experiences of using larval therapy. Were these loose or bagged?
6. Did anything concern you about using maggots?
7. Did you encounter any problems in the ordering or supply of the maggots?
8. What did the patients say about the use of maggots on their wounds?
9. Have you had any previous experience of maggots (e.g. fishing)?
10. Have you talked to colleagues about the use of maggots in the treatment of leg ulcers? If so, what were their views?

Is there anything else you would like to tell me about the use of larval therapy?

Reiterate about confidentiality and anonymity

Thank you

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We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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