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Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes

WJ Jeffcoate, PE Price, CJ Phillips, FL Game, E Mudge, S Davies, CM Amery, ME Edmonds, OM Gibby, AB Johnson, GR Jones, E Masson, JE Patmore, D Price, G Rayman and KG Harding

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NIHR Health Technology Assessment programme

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/74/03. The contractual start date was in June 2003. The draft report began editorial review in October 2007 and was accepted for publication in January 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes

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Objectives: To determine the comparative effectiveness and cost-effectiveness of three dressing products, N-A®, Inadine® and Aquacel®, for patients with diabetic foot ulcers, as well as the feasibility and consequences of less frequent dressing changes by health-care professionals.
Design: A multicentre, prospective, observer-blinded, parallel group, randomised controlled trial, with three arms.
Setting: Established expert multidisciplinary clinics for the management of diabetic foot ulcers across the UK.
Participants: Patients over age 18 with type 1 or type 2 diabetes with a chronic (present for at least 6 weeks) full-thickness foot ulcer (on or below the malleoli) not penetrating to tendon, periosteum or bone, and with a cross-sectional area between 25 and 2500 mm^2.
Interventions: Participants were randomised 1:1:1 to treatment with one of N-A (a non-adherent, knitted, viscose filament gauze), Inadine (an iodine-impregnated dressing), both traditional dressings, or Aquacel, a newer product.
Main outcome measures: The primary outcome measure was the number of ulcers healed in each group at week 24. Secondary measures included time to healing, new ulcerations, major and minor amputations, and episodes of secondary infection.
Results: A total of 317 patients were randomised. After 88 withdrawals, 229 remained evaluable. A greater proportion of smaller (25–100 mm^2 ulcers healed within the specified time (48.3% versus 37.3%; $p = 0.048$). There was, however, no difference between the three dressings in terms of percentage healed by 24 weeks, or in the mean time to healing, whether analysed on the basis of intention to treat (Inadine 44.4%, N-A 38.7%, Aquacel 44.7%; not significant) or *per protocol* (Inadine 55.2%, N-A 59.4%, Aquacel 63.0%; not significant). There was no difference in the quality of healing, as reflected in the incidence of recurrence within 12 weeks. Likewise, there was no difference in the incidence of adverse events, although a greater proportion of those randomised to the non-adherent dressings were withdrawn from the study (34.9% versus 29.1% Aquacel and 19.4% Inadine; $p = 0.038$). The only statistically significant difference found in the health economic analysis was the cost associated with the provision of dressings (mean cost per patient: N-A £14.85, Inadine £17.48, Aquacel £43.60). The higher cost of Aquacel was not offset by the fewer dressings required. There was no difference in measures of either generic or condition-specific measures of quality of life. However, there was a significant difference in the change in pain associated with dressing changes

between the first and second visits, with least pain reported by those receiving non-adherent dressings ($p = 0.012$). There was no difference in the costs of professional time, and this may relate to the number of dressing changes undertaken by non-professionals. Fifty-one per cent of all participants had at least one dressing change undertaken by themselves or a non-professional carer, although this ranged from 22% to 82% between the different centres.

Conclusions: As there was no difference in effectiveness, there is no reason why the least costly of the three dressings could not be used more widely across the UK National Health Service, thus generating potentially substantial savings. The option of involving patients and non-professional carers in changing dressings needs to be assessed more formally and could be associated with further significant reductions in health-care costs.

Trial registration: Current Controlled Trials ISRCTN78366977.

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List of abbreviations

ABPI	ankle:brachial pressure index	OHA	oral hypoglycaemic agent
CI	confidence interval	PAD	peripheral arterial disease
CWIS	Cardiff Wound Impact Schedule	QALY	quality-adjusted life-year
df	degrees of freedom	QoL	quality of life
EQ–5D	Euroqol–5D	SAE	serious adverse event
GBP	pound sterling	SD	standard deviation
HRQoL	health-related quality of life	SF–36	short form 36 (Rand)
ICER	incremental cost-effectiveness ratio	SPSS	Statistical Package for Social Scientists
ITT	intention to treat	USD	US dollar

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

Executive summary

Aims

This study had five stated aims:

1. To test whether a modern dressing product is more clinically effective than traditional dressings in the treatment of diabetes-related foot ulcers.
2. To investigate changes in condition of foot ulcers associated with each dressing and recurrence during the study period.
3. To determine the relative cost-effectiveness of the three dressings.
4. To assess patients' health-related quality of life, physical and social functioning, and pain associated with each of the dressings.
5. To investigate the contribution made by patient and carer in terms of involvement with self-care.

Methods

This was a multicentre, observer-blinded, randomised controlled trial in which patients were randomised 1:1:1 to receive one of three dressing products: a simple non-adherent preparation [N-A® (Johnson & Johnson Medical, Berkshire, UK)], a widely used modern antiseptic preparation [Inadine® (Johnson & Johnson Medical, Berkshire, UK)] and a new hydrocolloid preparation of higher unit cost [Aquacel® (ConvaTec Ltd, Middlesex, UK)].

Results

A total of 317 patients were randomised. After 88 withdrawals, 229 remained evaluable. A greater proportion of smaller (25–100 mm^2 ulcers healed within the specified time (48.3% versus 37.3%; $p = 0.048$). There was, however, no difference between the three dressings in terms of percentage healed by 24 weeks, or in the mean time to healing, whether analysed on the basis of intention to treat (Inadine 44.4%, N-A 38.7%, Aquacel 44.7%; not significant) or per protocol (Inadine 55.2%, N-A 59.4%, Aquacel 63.0%; not significant). There was no difference in the quality of healing, as reflected in the incidence of recurrence within 12 weeks. Likewise, there was no difference in the incidence of adverse events, although a greater proportion of those randomised to the non-adherent dressings were withdrawn from the study (34.9% versus 29.1% Aquacel and 19.4% Inadine; $p = 0.038$). The only statistically significant difference found in the health economic analysis was the cost associated with the provision of dressings (mean cost per patient: N-A £14.85, Inadine £17.48, Aquacel £43.60). The higher cost of Aquacel was not offset by the fewer dressings required. There was no difference in measures of either generic or condition-specific measures of quality of life. However, there was a significant difference in the change in pain associated with dressing changes between the first and second visits, with least pain reported by those receiving non-adherent dressings ($p = 0.012$). There was no difference in the costs of professional time, and this may relate to the number of dressing changes undertaken by non-professionals. Fifty-one per cent of all participants had at least one dressing change undertaken by themselves or a non-professional carer, although this ranged from 22% to 82% between the different centres.

Discussion

The higher rate of withdrawal of patients randomised to receive non-adherent dressings was unexplained but may relate to the involvement in dressing changes of other professional staff – some of whom may have had their own preconceptions about the most suitable dressing for the wound in question. Such preconceptions could have triggered withdrawal of patient consent, or a protocol violation. Despite this we failed to observe any trend towards a difference in the effectiveness, safety or quality of life measures associated with the use of these three products, whether the results were analysed by intention to treat or *per protocol*. We also found no evidence that any particular dressing may be more effective in any one type of wound – for instance, an antiseptic product in ulcers which are covered with greater degrees of

surface slough. On the other hand we observed a significant difference in product costs, and this has implications for the choice of dressings in routine clinical practice. Many newer dressing products are also marketed on the basis that they need to be changed less often, with the associated implications for reduced costs of professional time. We observed, however, that almost 70% of all dressings were undertaken by non-professionals and there was no difference in professional time between the three groups.

Conclusions

As there was no difference in effectiveness, there is no reason why the least costly of the three dressings could not be used more widely across the UK National Health Service, thus generating potentially substantial savings.

Implications/ recommendations for practice

All dressing products should have their clinical effectiveness proven before they are widely adopted in clinical practice. Proof of effectiveness would usually require randomised trials using hard, clinically relevant, outcomes in well characterised populations. Any of the products used in this study could be adopted as the comparator for such trials. The wide difference observed between centres in the percentage of dressing changes undertaken on one or more occasions by non-professional staff may indicate that professionals may be involved more often than is necessary in some cases, and this may also have implications for routine care. The option to involve patients and non-professional carers needs to be assessed more formally and could be associated with significant reductions in health-care costs.

Recommendations for future research

1. The effectiveness of newer products currently in widespread use should be determined using a similar approach.
2. The specific effect of antiseptic products should be determined in terms of both healing and prevention of secondary infection of ulcers contaminated by lesser or greater degrees of slough.
3. The acceptability and cost-effectiveness of encouraging greater involvement of the patient and non-professional carers in routine management should be explored.
4. There is a clear need to establish a country-wide network of specialist units managing diabetic foot ulcers in order to facilitate the more ready conduct of such research.

Trial registration

This trial is registered as ISRCTN78366977.

Chapter 1
Background

Introduction

Ulceration of the foot of people with diabetes (diabetic foot ulcers) is common, and widely acknowledged to be a source of major distress and morbidity in a predominantly elderly population, as well as an enormous drain on health-care resources.[1–4] Not only does diabetes make the foot more liable to ulceration, but it also impairs the process of healing, and diabetic foot ulcers readily develop into chronic wounds. There are approximately 24,000 admissions for diabetic foot ulcers each year in the UK,[5] and approximately 15% of all ulcers in the UK result in some form of amputation.[6] Diabetic foot ulcers also have a significant negative impact on health-related quality of life (HRQoL).[1,4]

While the pathobiology of chronic wounds remains poorly understood, there is no logical framework to underpin many strategies of care.[7] The choice of dressings, in particular, is largely empirical and based more on professional experience and preference than on evidence of proven efficacy. The principal reason for this is the lack of available evidence, which is itself partly the result of the difficulty in conducting controlled trials in this field.

Evidence base for effectiveness of management strategies

The paucity of the evidence base for the treatment of diabetic foot ulcers has been highlighted in several recent reviews.[6–11] O'Meara *et al.*[12] could find no good evidence to substantiate the use of any of the preparations in widespread use, and this finding has been confirmed in a recent systematic review undertaken by the International Working Group on the Diabetic Foot of the International Diabetes Federation.[13] The effectiveness of some of the more recently introduced therapeutic agents (including growth factor preparations and bioengineered human skin products) has been suggested in some (but not all) industry-funded trials and remains to be confirmed. Even if effective, they are expensive in terms of both product costs and professional time, and in the absence of robust evidence of cost-effectiveness, they have not been widely adopted in the UK. The more recent introduction of a number of silver-impregnated dressings has been undertaken without evidence of effectiveness in this population. A recent trial of one such product suggested that the product tested was no more effective than conventional therapy.[14]

It is very necessary, therefore, to establish whether any difference can be demonstrated between the efficacy and cost-effectiveness of products which are currently in widespread use, including those which are well-established and of low material cost as well as those which are newer and more expensive. If any product is shown to have greater effectiveness and is relatively cost-effective, then this evidence should be used to underpin routine clinical practice in the UK. If no difference in effectiveness can be demonstrated, then clinical choice should be based primarily on issues of patient acceptability and on cost. Moreover, if no difference in effectiveness can be shown, the data will provide an invaluable benchmark in the later evaluation of newer technologies.

The aim of this study was, therefore, to compare the effectiveness and cost-effectiveness of three dressing products which are widely used in routine management in the UK: comparing two traditional preparations, a non-adherent, knitted, viscose filament gauze product [N-A® (Johnson & Johnson Medical, Berkshire, UK)] and an iodine-impregnated dressing [Inadine® (Johnson & Johnson Medical, Berkshire, UK)], with a newer product of higher unit cost [Aquacel® (ConvaTec Ltd, Middlesex, UK)]. N-A is thought to be metabolically inert, and is designed simply to be a non-adherent dressing which is easily changed, with minimal discomfor t and trauma to the regenerating wound bed. Inadine is a knitted viscose fabric impregnated with a polyethylene glycol base containing 10% povidone-iodine, equivalent to 1.0% available iodine. The potent antimicrobial, povidone-iodine, is released when in contact with wound fluid. Aquacel is marketed as a textile fibre which is bonded into the form of a fleece. The dressing is designed to 'absorb and interact with wound exudate to form a soft, hydrophilic, gas-permeable gel that traps bacteria

and conforms to the contours of the wound while providing a micro-environment that is believed to facilitate healing'.[15] In one small, short-term, randomised trial Aquacel has previously been shown to be more effective in the management of deeper diabetic foot ulcers than saline-moistened gauze,[16] but saline-moistened gauze is rarely used in clinical practice in Europe.

Issues surrounding the choice of outcome measures

The principal aim of dressing products is to promote healing, and hence the primary measure of effectiveness should be ulcer healing. Moreover, newly healed ulcers often break down within the first few weeks and so the chosen definition of healing should take this into account. Secondary measures of effectiveness comprise those that are ulcer-related, process-related and patient-related. Ulcer-related outcomes include time to healing, adverse events, incidence of recurrence and improvement in the appearance of the wound bed, incidence of secondary infection of the index ulcer and incidence of both minor and major amputation. Process-related outcomes include those relating to frequency of dressing changes.

Patient-related outcomes include mortality, pain, serious adverse events (SAEs) and quality of life (QoL). Some assessment of the profound implications of diabetic foot ulcers on mood and QoL has been produced in recent years,[17] but even though the need for a robust condition-specific QoL assessment tool has been highlighted, none has yet been fully published and validated for diabetic foot ulcers. The (Rand) short form 36 (SF–36)[18] has been shown to discriminate between those with and without ulcers, but not between those whose ulcers are either active or healed. The Euroqol–5D (EQ–5D)[19] has been shown to discriminate between patients with active and former ulcers, despite its simple structure. One factor likely to contribute significantly to the frustration and anxiety of having an ulcer is dependence on the frequent attention of health-care professionals. There are few condition-specific tools in this area, but work on the Cardiff Wound Impact Schedule (CWIS) has demonstrated poor QoL responses from patients with active ulceration,[20–22] reflecting the qualitative work of Brod.[23]

Cost-effectiveness

Assessment of cost is complex because of its dependence on material unit cost, the frequency of dressing changes and the time of professional staff.[11,17] In the case of traditional, less expensive dressings, the relative contribution made by professional time is potentially much greater, especially if healing is delayed. Similarly, the possible need for more frequent changes of traditional dressing products can outweigh the relatively low material costs because of the professional time involved.[11] On the other hand, it would be wrong to assume that all dressing changes are actually performed by professional staff in routine clinical practice. Unpublished data from Nottingham University Hospitals indicate that 55% of dressings are undertaken in the community by non-professional staff.

In assessing the cost-effectiveness of treatment strategies, and in particular dressings, cognizance has therefore to be taken not only of the unit cost of the dressings but also of the number and frequency of dressings used and the time of professionals and others involved in the process. Furthermore, the implications of non-healing have to be encompassed in the assessment of relative cost-effectiveness. It has been estimated that up to 15% of patients with diabetic foot ulcers require an amputation[6] – with direct costs ranging from USD 20,000–60,000[11] – which emphasises the need to maximise effective treatment.

The health economic evaluation in this study was planned primarily from the perspective of the UK NHS, but with some consideration given to travel costs incurred by patients. The full impact that the treatment and care of diabetic foot ulcers has on the family, friends and carers of the patients was not considered. The costs associated with dressings were assessed for the duration of active participation in the trial, and were not extended beyond healing or withdrawal.

Objectives

The overall objective of this study was therefore to determine the comparative effectiveness and cost-effectiveness of three dressing products in common clinical use for patients with diabetic foot ulcers in

the UK, as well as the feasibility and consequences of less frequent dependence on dressings by health-care professionals. This study had five specific objectives:

1. To test whether a modern dressing product is more clinically effective than traditional dressings in the treatment of diabetes-related foot ulcers. The dressings compared were: a simple non-adherent preparation (N-A), a widely used modern antiseptic preparation (Inadine), and a new hydrocolloid preparation of higher unit cost (Aquacel). All three dressings are widely used in clinical practice in the UK.
2. To investigate changes in the condition of each ulcer during the study period associated with each dressing, and the incidence of recurrence after healing.
3. To determine the relative cost-effectiveness of the three dressings by:
   i. identifying and assessing the cost components associated with the treatment of diabetic foot ulcers
   ii. assessing the relative effectiveness of the three dressings, based on findings from the randomised controlled trial
   iii. estimating the relative cost-effectiveness of the three dressings
   iv. determining the extent to which the cost-effectiveness is affected by changes in costs and effects.
4. To assess patients' HRQoL, physical and social functioning, and pain associated with each of the dressings.
5. To investigate the contribution made by patient and carer in terms of involvement with self-care.

Chapter 2

Study design and methods

Design

This was a multicentre, prospective, observer-blinded, parallel group, randomised controlled trial, with three arms. Patients with ulcers were randomised to treatment with N-A, Inadine or Aquacel.

The study was undertaken in accordance with the Declaration of Helsinki and followed the guidelines published by the Medical Research Council. The conduct of the study was supervised by a Trial Steering Committee with an independent chairman, and issues of recruitment, randomisation, retention and adverse events were scrutinised by an independent Data Monitoring and Ethics Committee.

Randomisation

Randomisation was stratified both by centre and by size, using a block size of nine. Randomisation was stratified across the whole population by ulcer area into three groups: 25–100 mm^2, 101–250 mm^2 and 251–2500 mm^2. Randomisation lists were created using SPSS (SPSS Inc., Version 14), using blinded dressing codes. The lists were held at Cardiff University and each recruiting centre telephoned a designated number during working hours; they were required to identify the centre and size of wound only. Records of the allocation details were kept at Cardiff University for data verification and checking at monitoring visits.

Setting

Patients were recruited from those attending, or newly referred to, established expert multidisciplinary clinics for the management of diabetic foot ulcers in Blackburn, Cardiff and Newport (University Hospital of Wales, Llandough and Royal Gwent Hospitals), Hull, Ipswich, Nottingham and Derby (City and University Hospitals, Nottingham and Derbyshire Royal Infirmary), London (Kings College Hospital), Leeds (Leeds General Infirmary and St James' Hospital), Swansea (Singleton and Morriston Hospitals) and Bristol (Southmead and Frenchay Hospitals) – each of which receive in excess of 100 new referrals each year. These centres reflect both NHS Trusts and University Teaching Hospitals across the UK.

Target population

Patients over age 18 with either type 1 or type 2 diabetes with a chronic (present for at least 6 weeks) full-thickness foot ulcer (on or below the malleoli) not penetrating to tendon, periosteum or bone, and with a cross-sectional area between 25 and 2500 mm^2 were invited to participate. If there was more than one ulcer on the foot, the largest ulcer that conformed to the inclusion criteria was selected as the index ulcer.

Inclusion criteria

- Type 1 or 2 diabetes.
- 18 years of age or more.
- A foot ulcer which had been present for at least 6 weeks and had a cross-sectional area of between 25 and 2500 mm^2.
- Able and willing to give informed consent.
- Reasonably accessible by car to the hospital base.
- Under routine review by the multidisciplinary clinic.

Exclusion criteria

- Those with a known allergy to any of the trial preparations (including iodine).
- Any ulcer on either foot extending to tendon, periosteum or bone.
- Infection of bone.
- Soft tissue infection requiring treatment with systemic antibiotics.
- An ulcer on a limb being considered for revascularisation.
- Those chosen for management with a non-removable cast without a dressing window.
- Gangrene on the affected foot.
- Eschar which was not removable by clinical debridement.

- Those with evidence of a sinus or deep track.
- Those in whom the hallux had been amputated on the affected side (preventing the measurement of toe pressure).
- Those with an ankle:brachial pressure index (ABPI) of less than 0.7 or toe systolic pressure less than 30 mmHg.
- Ulceration judged to be caused primarily by disease other than diabetes.
- Patients with any other serious disease likely to compromise the outcome of the trial.
- Patients with critical renal disease (creatinine greater than 300 µmol/l), and those receiving immunosuppressants, systemic corticosteroid therapy (other than by inhalation) or any other preparation which could, in the opinion of the supervising clinician, have interfered with wound healing.
- Those living at such a distance (generally further than 10 miles) from the clinic as would have made frequent assessment visits inappropriately expensive and/or impractical.
- Those who withheld consent.

Baseline assessment

Those who satisfied the inclusion and exclusion criteria and gave written informed consent to participate were assessed by a research nurse (the term research nurse is used to apply to any health-care professional involved in the conduct of the study, including research podiatrists) and their basic demographic and medical details noted.

The foot was examined and the following additional information recorded:

- toe pressure (systolic pressure in the hallux)
- ABPI
- peripheral sensation using a 10-g Semmes–Weinstein monofilament at four specified sites on the sole, as well as vibration perception threshold.

Following debridement in the clinic, details of the ulcer were recorded, including:

- history (cause, duration)
- pain at or close to the ulcer (10-cm visual analogue scale)
- cross-sectional area using a sterile marked acetate sheet
- the appearance of the surface of the wound: percentage granulation, percentage slough, percentage necrosis
- a digital image was made.

Questionnaires on pain, well-being and HRQoL

In the absence of a widely used condition-specific measure, participants were asked to complete the SF–36, CWIS and a 100-mm visual analogue scale for pain. The visual analogue scale was completed at each visit. SF–36 and CWIS were completed in private within 1 week of the baseline visit, and at visit 7 (12 weeks) and visit 13 (24 weeks) or any earlier healing confirmation visit. These assessment tools had all been used without problem in this sort of patient population in previous studies.

Clinical care

Patients remained under the supervision of the staff at their respective multidisciplinary clinic throughout the study. The frequency of clinic visits was determined by clinical need and was not affected by the trial. Ulcer management was in line with current guidelines for good practice, including appropriate and regular use of debridement and with a removable fibreglass or polyester boot being recommended for off-loading. In the absence of any significant deterioration or adverse event, clinic staff made no decision concerning dressings. Dressings were removed prior to examination by investigators who were not involved in the conduct of the trial and who were blind to the randomisation group.

Dressing changes

Once randomised, participants and, if appropriate, their usual carers were shown the dressing to be used and asked if they wished to change their own dressings (either entirely or just on some occasions), but with fortnightly monitoring by a trial nurse. Those who wished to do so received further training to ensure the dressings were applied correctly. Those who chose not to be responsible for this aspect of their care had their dressings changed by the district nurse or practice nurse, according to usual procedure, or by the trial nurse. Dressings were changed daily, on alternate days or three times a week according to need and/or availability of professional staff. Participants were advised to have a bath or shower as often as they wished – provided the ulcer could be redressed afterwards, and provided the ulcerated foot was not immersed in water for more than 5 minutes.

Supervision by research nurses

Every ulcer was monitored by a research nurse every 2 weeks – either in the patient's home or at the hospital if it coincided with a clinic visit. Frequency of dressing changes was recorded, as well as the number that were carried out by professional staff. The condition of the wound was recorded and any suggestion of significant adverse event or deterioration reported to the clinician in charge of care. The nurse was not blind to the randomisation and dressed the wound at the end of the visit. The participant and/or carer had the contact details of the trial nurse so that he or she could be contacted in an emergency.

Ulcers that healed were checked by the clinician supervising care who remained blind to the randomisation group. They were then followed bi-weekly for 4 weeks to ensure that they remained healed, and this was confirmed once again by the blinded observer. The time of the original closure was taken as the time to healing. Those that recurred within the 4 weeks were regarded as unhealed and continued in the study.

All participants with healed ulcers were re-assessed by the clinician in charge of their care 12 weeks after healing – to determine the incidence of recurrence or occurrence of new ulcers on either limb.

Participants with persistent ulcers were assessed by the clinician in charge at 24 weeks and withdrawn from the intervention phase of the study at that time. Participants were asked to complete SF–36 and the CWIS questionnaire in the same week. Thereafter, clinical management (including choice of dressings) was determined by conventional clinical criteria. They did, however, attend for a final assessment 36 weeks after recruitment to record clinical outcome, and questionnaires for postal return were distributed in the same week.

Withdrawal

Participants were withdrawn from the study at their request, in the event of a significant adverse event (including deterioration in the condition of the ulcer), other serious illness (such that it was either not appropriate or not possible for them to remain in the study) and protocol violation. Protocol violation was deemed to have occurred if two or more consecutive non-trial dressings had been applied (*Figure 1*).

End points

Primary end point

The primary end point was the number of index ulcers healed in each group within 24 weeks. Healing was defined as complete epithelialisation which was maintained with no drainage for 4 weeks and was confirmed by a blinded assessor.

Other end points

A variety of ulcer-related, process-related and patient-related observations were used to determine overall effectiveness and cost-effectiveness of the dressings employed. These comprised:

- ulcer-related end points
  - time to ulcer healing
  - reduction in ulcer area in those which did not heal
  - recurrence of ulceration within 3 months of healing
  - incidence of secondary infection of the index ulcer
  - incidence of both major and minor amputations
- patient-related end points
  - pain in the region of the ulcer
  - scores of HRQoL, physical and social functioning
  - adverse events, including deterioration of the index ulcer
  - incidence of SAEs, including surgery to the ulcerated limb and death
  - incidence of withdrawal
- process-related end points
  - frequency of dressings
  - frequency of visits by professional, or dressings by health professionals
  - frequency of dressing changes by non-professionals.

Economic evaluation

A bottom-up approach to costing was employed to construct a profile of costs associated with the treatment and care of diabetic foot ulcers. Only the costs that depended on and varied according to the dressings used were included in the cost profile; those that were fixed and unrelated to dressing choice (such as equipment) were excluded.

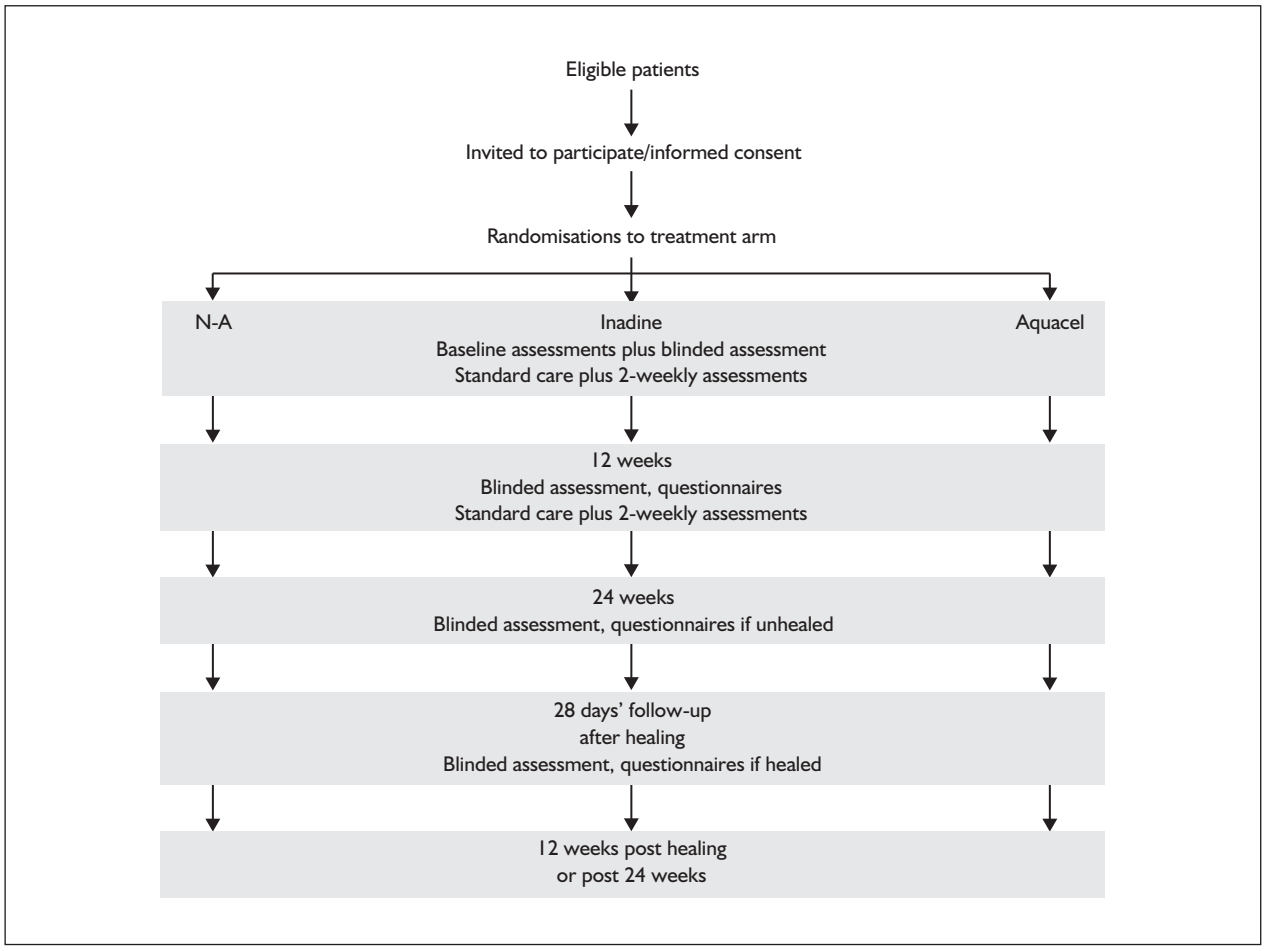

FIGURE 1 *Study design. If an ulcer appeared healed at any point up to and including 24 weeks, its status was checked after a further 2 and 4 weeks. It was only labelled as healed if it did not recur in that time. Healing was then verified by a blinded assessor and the patient was asked to complete the questionnaires. If the ulcer recurred within 4 weeks of apparent healing and at any point up to 24 weeks, the patient was re-entered into the study, using the allocated dressing. If the occurrence happened at or after 24 weeks, the ulcer was recorded as unhealed.*

Direct costs associated with dressings used

- Dressings.
  - The price of each of these was obtained from the *British National Formulary* current when dressings were purchased for use in the study.
- Staff involvement.
  - The number and duration of consultations with health-care professionals was obtained from patient diaries, which were based on patient recall and logged during each research-related visit to the hospital clinic.
  - The unit cost per minute and unit cost per consultation were obtained from published sources relating to the UK NHS. Cost of consultations per minute was obtained, wherever possible from the Personal Social Services Research Unit,[24] while cost per consultation/attendance was obtained from Department of Health data published in Reference Costs and NHS Tariffs.[23,24]
  - The cost profile for each dressing included total consultations, consultations for other diabetes-related problems and consultations for diabetic foot problems. Where any doubt existed it was assumed that the consultation was diabetic foot related.
- The costs associated with increased risk of amputation resulting from withdrawals (and non-healing) were based on the percentage of ulcers that lead to amputation[11] and the costs associated with amputations derived from Department of Health data published in Reference Costs and NHS Tariffs.[25,26]

Patient travel costs

Patients were also asked to log their mode of transport and how much cost they incurred in travelling to the consultation with the health-care professional. It was found, however, that only very limited responses to this item were provided by

trial participants and the quality of these data is poor – with those travelling by car not indicating that any costs were incurred. This component has not, therefore, been included in the analysis.

Outputs and outcomes

The measures of effectiveness were derived from the results of the randomised controlled trial of the three dressings. The particular measures of relevance for the health economic evaluation were:

- healed ulcers
  - numbers
  - time to healing
  - probability of healing and remaining free of recurrence
- ulcer-free days
- withdrawals – and increased risk of amputation
- HRQoL, physical and social functioning
  - SF–36
  - CWIS.

Sensitivity analysis

In order to assess the extent to which the findings can be regarded as being robust, a series of one-way sensitivity analyses were conducted. The key variables were adjusted so as to determine the extent to which differences in healing rates, consultation rates and the 'price' of dressings would impact on the baseline findings. The implications of non-healing in relation to risk of amputation were also considered as part of the sensitivity analysis.

Sample size

As healing was the primary objective, this was the basis for the calculation of sample size. Calculation of sample size was difficult because of the paucity of data on the healing rate of different types of ulcer, and although data are available for neuropathic ulcers on the plantar surface, they are inconsistent. Thus, Katz *et al.*[27] reported 61–89% healing of plantar neuropathic ulcers within 12 weeks, while an earlier meta-analysis of the control arm of published trials of similar (but not all identical) ulcers reported only 24% healing with accepted good clinical practice by 12 weeks, and 31% at 20 weeks.[28] Moreover, neuropathic ulcers with good vascular supply form a minority of ulcers cared for in the UK and, despite the lack of much published information, it is accepted that they heal more quickly than other types. The experience at the City Hospital, Nottingham, was that of all 449 individuals referred in the 4 years between January 2000 and December 2003, only 55% of index ulcers healed without amputation within 6 months of referral.[29] It is on these bases that we calculated that in order to demonstrate a 20% difference in healing between groups, with 80% power, and with alpha = 0.05, and allowing for 25% dropout, 300 recruits were required. This was based on equal distribution of the sample to the three arms of the study. The N-A group was treated as the reference arm of the study, with an anticipated healing rate of 30%. The size was powered to indicate a 20% increase in healing for those in the Inadine group (50% healed at 24 weeks), and a 25% increase for those receiving Aquacel (55% healed at 24 weeks).

Data management

All files were checked by hand, with outstanding data questions addressed with each individual site. All data were entered into SPSS version 14 by research staff at the Department of Wound Healing, School of Medicine, Cardiff University and random checks were completed on an entry basis. All variables were checked for valid entries, i.e. within the expected range for that variable. Fifty per cent of files were double checked for errors by a different research assistant: the error rate was less than 1% over all entries for all variables over 165 files.

Deviations from the planned protocol

EQ–5D was excluded to reduce patient burden in relation to questionnaires. It was anticipated that SF–36 scores could be converted into SF–6D scores in order to assess impact on HRQoL and utility scores for derivation of quality-adjusted life-years (QALYs), if considered appropriate.

Chapter 3
Results

Recruitment, retention and primary outcome

A total of 317 patients were recruited to the trial, with relatively equal allocation of different dressings to each of the nine centres (*Table 1*).

Allocation to the different dressings was also relatively equal when analysed by cross-sectional area at baseline (*Table 2*). As there was no statistical difference between the groups in terms of distribution by ulcer size at baseline, the two larger groups were combined for the purposes of analysis such that there were two final groups of roughly similar size (*Table 3*). There remained no difference between groups.

The index ulcers of 135 participants (42.6%) healed within the 24-week intervention phase (*Table 4*). Eighty-eight participants were withdrawn (27.8%), which is more than originally anticipated. Two hundred and twenty-nine participants completed the full study, however, and were evaluable (meeting the 80% power target) (*Table 4*). There were 19.4% withdrawals for Inadine, compared with 29.1% for Aquacel and 34.9% for N-A, and this difference was statistically significant different (*Table 5).* The flow of patients through the study is outlined in *Figure 2*.

Demographics of participants

The distribution of baseline demographics between the groups was very similar by intervention (*Table 6*). The proportion of male to female participants was higher than expected, with a 3.2:1 ratio in the study overall. It should be noted that one subject, being managed with N-A, underwent gender realignment during the course of the study and is not listed in the table as either male or female. The majority of the participants presented

TABLE 1 *Dressing allocation stratified by participating centre*

Centre	Inadine	Aquacel	N-A	Total
1	11	11	12	34
2	14	11	15	40
3	19	21	20	60
4	17	19	17	53
5	22	21	23	66
6	7	6	5	18
7	8	4	5	17
8	5	2	0	7
9	5	8	9	22
Total	108	103	106	317

TABLE 2 *Dressing allocation stratified by cross-sectional area*

Size	Inadine	Aquacel	N-A	Total
25–100 mm^2	48	53	50	151
101–250 mm^2	36	34	34	104
251–2500 mm^2	24	16	22	62
$\chi^2 = 1.900$, df = 4, $p = 0.754$.				

TABLE 3 *Dressing allocation, stratified by cross-sectional area and allocated to two groups for analysis*

	25–100 mm² (%)	101–2500 mm² (%)	Total
Inadine	48 (44.4)	60 (55.6)	108
Aquacel	53 (51.5)	50 (48.5)	103
N-A	50 (47.6)	56 (52.8)	106
Total	151 (47.6)	166 (52.4)	317
$\chi^2 = 1.053$, df = 2, $p = 0.591$.			

TABLE 4 *Healing outcome at week 24*

	Frequency	Percentage
Unhealed	94	29.7
Healed	135	42.6
Withdrawn	88	27.8
Total	317	100

TABLE 5 *Withdrawal from study by dressing group at week 24*

	Frequency	Percentage
Inadine	21	19.4
Aquacel	30	29.1
N-A	37	34.9
Total	88	100
$\chi^2 = 6.519$, df = 2, $p = 0.038$, Cramer's V = 0.143 ($p = 0.038$, low).		

with type 2 diabetes mellitus, in a ratio of 3.7:1, but with an equal distribution across dressing groups. Mean age was 60 years, and there were no statistical differences in age by group. The mean duration of known diabetes was 16 years, with no differences between groups. Approximately 8% were on diet alone, while one third were on oral hypoglycaemic agents (OHAs), 38% on insulin and 21% on a combination of OHAs and insulin. One third of participants had never smoked, while 17% were current smokers. Sixteen per cent had had a previous cerebrovascular complication, while 39% had cardiovascular complications, 57% had known retinopathy and 21% had nephropathy.

At least one additional significant medical problem was reported by 255 (80%) participants at baseline, which was either unrelated or partially related to diabetes, with the most frequently reported being hypertension ($n = 159$). Two additional significant medical problems were reported by 175 participants, while three were reported by 112 (*Table 7*).

The 10 most frequently reported additional medical problems at baseline were:

- hypertension 159 participants
- hyperlipidaemia 69 participants
- asthma 29 participants
- neuropathy 29 participants
- arthritis 28 participants
- angina 24 participants
- depression 13 participants
- anaemia 11 participants
- obesity 9 participants
- hypothyroidism 9 participants.

Figure 3 outlines a summary of the specific details of the reasons for patient withdrawal from each

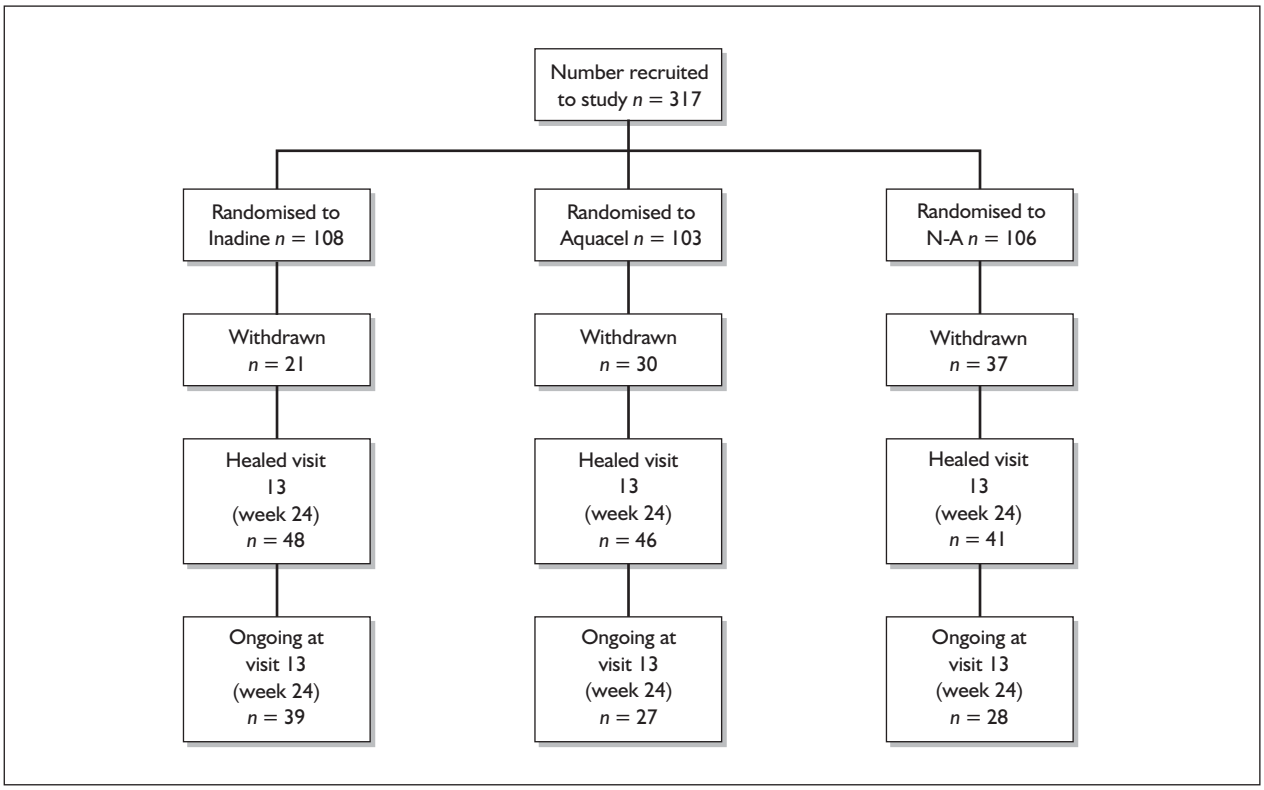

FIGURE 2 *Consort diagram for HTA dressing trial for diabetic foot ulceration.*

arm of the study. The most frequent reason for withdrawal in each group was 'adverse events', followed by 'protocol violation'. A more detailed account of the reasons for withdrawal, by dressing type, can be found in Appendix 4.

A more detailed section on patient withdrawals is presented in Withdrawals.

Total medications prescribed

The number and type of medications taken was recorded for each participant, and changes to medication were noted throughout the trial. *Table 8* outlines the details of the total number of medications taken by participants during the 24 weeks of the intervention phase. There are no differences in the median number of medications across the groups, with all groups taking a median of 8–8.5 different types of medication at some stage during the study. The median number of changes of medication was also similar for all groups. A detailed list of these medications and the conditions for which they were prescribed or taken can be found in Appendices 1 and 2.

Ulcer characteristics at baseline

The ulcer-specific details by intervention group are presented in *Tables 9* and *10*. Sixty-four per cent of participants had had a previous foot ulcer, and 19.9% had undergone a previous amputation, the majority of which were single toe or ray. There was equivalent presentation of ulcers on the right and left limbs, with the majority of ulcers being on either the toe or forefoot. Approximately half of the ulcers were small as per the definition in the protocol (25–100 mm^2), with an even distribution across dressing groups. The majority of participants had palpable dorsalis pedis and post-tibial pulses. Seventy-seven per cent of participants had loss of sensation under the first metatarsal head using the 10-g monofilament, while 70% had loss of sensation under the fifth metatarsal head, and 74% and 62% on the plantar aspect of the hallux and heel respectively.

The appearances of the wound bed are outlined in *Table 11*. There were no significant differences in the clinical condition of the ulcers by intervention. The majority of ulcers were not odorous, with 45%

TABLE 6 *Baseline demographics by intervention*

	Inadine (*n* = 108)	Aquacel (*n* = 103)	N-A (*n* = 106)	Total (*n* = 317)
Gender[a]				
Male	81	81	78[a]	240
Female	27	22	27[a]	76
Age				
Mean (SD) years	58.8 (13.2)	59.5 (11.5)	61.9 (12.8)	59.6 (12.6)
Min–max years	32–87	34–83	32–87	32–87
Type of diabetes				
Type 1	25	22	21	68
Type 2	83	81	85	249
Duration of diabetes				
Mean (SD) years	15.3 (9.8)	16.0 (11.4)	15.8(11.4)	15.7 (10.8)
Diabetes treatment				
Insulin	44	43	35	122
Insulin/OHAs	25	17	23	65
OHAs	33	35	36	104
Diet alone	6	8	12	26
Smoking status				
Yes	17	15	22	54
Past smoker	55	51	47	153
No	36	37	32	105
Missing	0	0	5	5
Cerebrovascular disease				
Yes	7	8	9	24
No	99	93	94	286
Missing	2	2	3	7
Cardiovascular disease				
Yes	40	37	46	123
No	67	63	58	188
Missing	1	3	2	6
Retinopathy				
Yes	62	62	58	182
No	46	40	47	133
Missing	0	1	1	2
Nephropathy				
Yes	19	22	26	67
No	88	80	78	246
Missing	1	1	2	4

a One patient in the N-A group underwent gender realignment during the trial and is not included in the data on gender.
OHAs, oral hypoglycaemic agents.

TABLE 7 *Number of significant additional medical problems*

Number of additional medical problems	1	2	3	4	5	6	7	8
Number of participant responses out of a total of 317	255	175	112	57	11	5	3	3

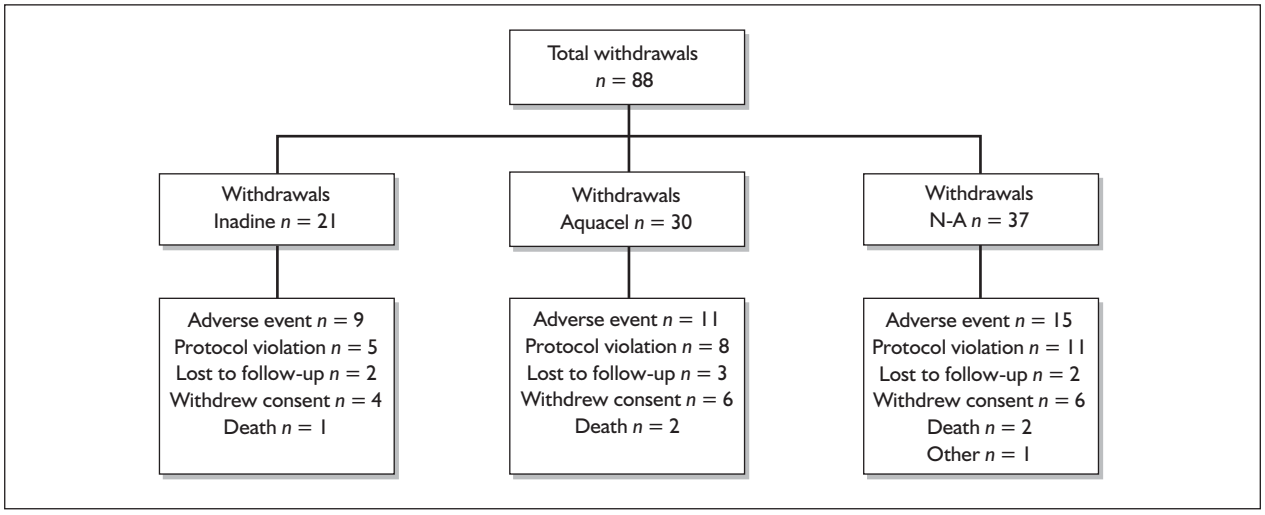

FIGURE 3 *Reasons for patient withdrawal.*

TABLE 8 *Total medications prescribed during the 24-week study, by dressing group allocation*

	Median	Minimum	Maximum	Median (minimum–maximum) medication changes
Inadine (*n* = 108)	8	0	44	1 (1–2)
Aquacel (*n* = 103)	8	1	31	1 (1–2)
N-A (*n* = 106)	8.5	0	25	1 (1–2)

TABLE 9 *Baseline ulcer characteristics by intervention – patient-specific data*

	Inadine (*n* = 108)	Aquacel (*n* = 103)	N-A (*n* = 106)	Total (*n* = 317)
First ulcer				
Yes	35	35	44	114
No	73	68	62	203
Previous ulcer at same site	21	27	13	61
Previous amputation				
Yes	21	27	15	63
No	87	76	91	254
Type of amputation				
Single toe/ray	15	18	9	42
Below ankle	2	0	0	2
Transtibial	2	5	3	10
Transfemoral	0	1	1	2
Not known	2	3	2	7

TABLE 10 *Baseline ulcer characteristics by intervention – limb- and ulcer-specific data*

	Inadine (*n* = 108)	Aquacel (*n* = 103)	N-A (*n* = 106)	Total (*n* = 317)
Peripheral arterial disease				
Dorsalis pedis felt	93	89	90	272
Posterior tibial felt	86	84	84	254
Loss of sensation (10-g monofilament)				
Under first metarsal head	87	85	82	244
Under fifth metarsal head	81	68	71	220
Plantar hallux	85	71	77	233
Plantar heel	74	57	66	197
Location of index ulcer				
Right foot	57	53	50	160
Left foot	51	50	56	157
Toe	45	38	37	120
Forefoot	38	44	44	126
Hindfoot	23	18	22	63
Malleolus	2	3	3	8

having 100% granulation tissue and no slough. The majority of ulcers had light or moderate exudate, with some associated callus, and approximately 30% reported maceration of the surrounding skin. Just over 20% of the participants reported pain in the region of the ulcer.

Methods of off-loading used at visit 1

The methods of off-loading used at visit 1 were variable. Only 132 (42%) of the 317 patients were provided with a removable fibreglass or polyester casting device, which was defined as the preferred method in the protocol. A further 97 (31%) had a proprietary removable device. There was no difference between dressing groups (*Table 12*). There was no apparent difference in the use of off-loading devices for those whose index ulcers were on the plantar aspect of the foot or were not (*Table 13*). For those patients ($n = 11$) who were identified as having a plantar ulcer and no off-loading at visit 1, five were reported as either awaiting bespoke footwear ($n = 3$) or considering a casted device ($n = 2$).

The use of off-loading devices by different centres is shown in *Table 14*. Two of the centres (centres 7 and 9) did not issue a casted device for any of their participants and one centre (centre 8) only issued one – indicating possible centre differences either in attitudes to off-loading or in the availability of resources.

Primary outcome – incidence of healing

The sample numbers recruited to this study were based on the following assumptions of estimated healing and non-healing at end point by intervention. These assumptions were that by visit 13 (24 weeks) 30% of ulcers managed with N-A would be healed, compared with 50% managed with Inadine and 55% managed with Aquacel. Intention to treat (ITT) analysis was carried out using the last value carried forward method, with strict adherence to the protocol such that only those who attended for a healing verification visit and reported as still healed at 28 days have been coded as 'healed' for the outcome classification.

Intention to treat at visit 7 (week 12)

The incidences of healing by 12 weeks for the three dressings were Inadine 29.6%, Aquacel 28.2% and N-A 25.5%. The differences between groups were not statistically significant (*Table 15*). At week 12 there was an overall withdrawal rate of almost 20%. The rate of withdrawal was least for Inadine (12%) and greatest for dressing N-A (26%), with a statistical difference between the groups ($\chi^2 = 6.54$, $df = 2$, $p = 0.016$).

When the incidence of healing was analysed by cross-sectional area at baseline, there was a trend in the healing rates such that more of the smaller

TABLE 11 *Clinical description of ulcers by intervention at baseline*

	Inadine	Aquacel	N-A	Total
Odour				
Yes	5	6	6	17
No	102	97	100	299
Missing	1	0	0	1
Granulation (%)				
0–50	15	26	20	61
51–99	34	38	41	113
100	59	39	45	143
Slough (%)				
0	59	39	45	143
1–50	36	43	44	123
> 50	13	21	17	51
Exudate				
None	5	6	5	16
Light	55	60	56	171
Moderate	43	32	39	114
Heavy	5	5	6	16
Healthy skin				
Yes	14	17	17	48
No	94	85	89	268
Missing	0	1	0	1
Skin callus				
Yes	72	79	80	231
No	36	23	26	85
Missing	0	1	0	1
Maceration				
Yes	49	29	31	109
No	59	73	75	207
Missing	0	1	0	1
Erythematous				
Yes	9	10	9	28
No	99	92	97	288
Missing	0	1	0	1
Oedematous				
Yes	4	2	5	11
No	104	100	101	305
Missing	0	1	0	1
Pain in area				
Yes	17	24	25	66
No	91	79	81	251

TABLE 12 *Method of off-loading by dressing allocation*

	Intervention			
	Inadine	**Aquacel**	**N-A**	**Total**
Casted device	46	38	48	132
Proprietary removable off-loading device	15	17	21	53
Bespoke shoes and/or insoles	25	21	19	65
Miscellaneous (e.g. crutches, padded shoes or modification to existing footwear)	9	15	10	34
None	8	6	5	19
Considering or awaiting an off-loading device	2	3	2	7
Total (missing data)	105 (3)	100 (3)	105 (1)	310 (7)

TABLE 13 *Method of off-loading by position of ulcer*

	Location of target ulcer		
	Plantar	**Non plantar**	**Total**
Casted device	90	42	132
Proprietary removable off-loading device	30	23	53
Bespoke shoes and/or insoles	50	15	65
Miscellaneous (e.g. crutches, padded shoes or modification to existing footwear)	15	19	34
None	11	8	19
Considering or awaiting an off-loading device	5	2	7
Total (missing data)	201 (4)	109 (3)	310 (7)

TABLE 14 *List of casted devices reported as method of off-loading at visit 1*

	Centre									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
Total participants per centre	34	40	60	53	66	18	17	7	22	317
Casted boot or shoe	18	4	19	20	38	5	0	1	0	105
TC insole and felt padding	0	0	0	0	0	1	0	0	0	4
Below knee, removable or with window	3	1	1	10	2	0	0	0	0	1
Total (% of centre participants)	21 (61.8)	9 (22.5)	23 (38.3)	30 (56.6)	42 (63.6)	6 (33.3)	0	1 (14.3)	0	132

TC, total contact.

TABLE 15 *Incidence of healing at 12 weeks analysed on the basis of intention to treat*

	Ongoing/withdrawn (%)	Healed (%)	Total (%)
Inadine	76 (70.4)	32 (29.6)	108 (100.0)
N-A	79 (74.5)	27 (25.5)	106 (100.0)
Total	155	59	214
$\chi^2 = 0.46$, df = 1, $p = 0.49$.			
Aquacel	74 (71.8)	29 (28.2)	103 (100.0)
N-A	79 (74.5)	27 (25.5)	106 (100.0)
Total	153	56	209
$\chi^2 = 0.19$, df = 1, $p = 0.66$.			
df, degrees of freedom.			

ulcers healed (33%) than the larger ulcers (24%), but this was not statistically significant (*Table 16*).

When the data were stratified by cross-sectional area at baseline and analysed by dressing group, there was a 13% difference between healing rates by dressing for small wounds (Inadine with the highest incidence of healing at approximately 40%), and a difference of 10% for larger wounds (Aquacel with the highest incidence of healing at 30%). However, neither of these differences was statistically significant (*Table 17*).

Intention to treat at visit 13 (week 24)

The ITT analysis at visit 13 was carried out on the same basis as for visit 7 (last entry carried forward, and only recorded as 'healed' if confirmed after 4 weeks).

The overall healing rates for the three dressings were: Inadine 44%, Aquacel 45% and N-A 39%. These differences were not statistically significant (*Table 18*). However, there was a trend in the data whereby N-A had the poorest healing and the highest withdrawal rate, and the withdrawal rates were statistically significant at week 24: Inadine 19%, Aquacel 29%, N-A 35% ($p = 0.038$, see *Table 5*).

When the incidence of healing was analysed by cross-sectional area at baseline, there was a statistically significant difference between groups with 48% of smaller ulcers (25–100 mm^2) healing by 24 weeks compared with 37% of larger ones (*Table 19*).

When the data were stratified by cross-sectional area at baseline and analysed by dressing group, there was an approximately 9% difference between healing rates by dressing for small wounds (Inadine with the highest healing rate), and one of almost 16% for larger wounds (Aquacel with the highest healing rate). However, neither of these differences was statistically significant (*Table 20*).

Per protocol analysis at visit 7 (week 12)

Table 21 contains the healing rates at week 12 on a *per protocol* basis, i.e. including only those participants who remained in the study until week 12 (and with withdrawals being excluded). The data suggest an overall healing rate of approximately 34% with no statistical difference between the groups [total ongoing = 169 (65.8%), total healed = 88 (34.2%)].

Per protocol analysis at visit 13 (week 24)

Per protocol analysis at week 24 suggested an overall healing rate approaching 60% with no statistical difference between the groups [total ongoing = 94 (41%), total healed 135 (59%)] (*Table 22*).

Influence of wound bed status on healing

A comparison was made between the outcomes in ulcers that were more or less sloughy at the time of entry into the study, in the anticipation that those that had a contaminated wound bed would be less likely to heal. It was also expected

TABLE 16 *Incidence of healing at 12 weeks analysed by cross-sectional area at baseline and on the basis of intention to treat*

Size	Ongoing/withdrawn (%)	Healed (%)	Total (%)
25–100 mm^2	102 (67.5)	49 (32.5)	151 (100.0)
> 100 mm^2	127 (76.5)	39 (23.5)	166 (100.0)
Total	229 (72.2)	88 (27.8)	317
$\chi^2 = 3.16$, df = 1, $p = 0.07$.			
df, degrees of freedom.			

TABLE 17 *Incidence of healing at 12 weeks in different treatment groups, stratified by cross-sectional area at baseline and analysed on the basis of intention to treat*

Size	Dressing	Ongoing/withdrawn (%)	Healed (%)
25–100 mm^2	Inadine	29 (60.4)	19 (39.6)
	N-A	34 (68.0)	16 (32.0)
$\chi^2 = 0.61$, df = 1, $p = 0.43$.			
25–100 mm^2	Aquacel	39 (73.6)	14 (26.4)
	N-A	34 (68.0)	16 (32.0)
$\chi^2 = 0.39$, df = 1, $p = 0.53$.			
> 100 mm^2	Inadine	47 (78.3)	13 (21.7)
	N-A	45 (80.4)	11 (19.6)
$\chi^2 = 0.07$, df = 1, $p = 0.78$.			
> 100 mm^2	Aquacel	35 (70)	15 (30.0)
	N-A	45 (80.4)	11 (19.6)
$\chi^2 = 1.53$, df = 1, $p = 0.22$.			
df, degrees of freedom.			

TABLE 18 *Incidence of healing at 24 weeks analysed on the basis of intention to treat*

	Ongoing/withdrawn (%)	Healed (%)	Total (%)
Inadine	60 (55.6)	48 (44.4)	108 (100.0)
N-A	65 (61.3)	41 (38.7)	106 (100.0)
Total	125	89	214
$\chi^2 = 0.73$, df = 1, $p = 0.39$.			
Aquacel	57 (55.3)	46 (44.7)	103 (100.0)
N-A	65 (61.3)	41 (38.7)	106 (100.0)
Total	122	87	209
$\chi^2 = 0.77$, df = 1, $p = 0.38$.			
df, degrees of freedom.			

TABLE 19 *Incidence of healing at 24 weeks analysed by cross-sectional area at baseline analysed on the basis of intention to treat*

Size	Ongoing/withdrawn (%)	Healed (%)	Total (%)
25–100 mm^2	78 (51.7)	73 (48.3)	151 (100.0)
> 100 mm^2	104 (62.7)	62 (37.3)	166 (100.0)
Total	182 (57.4)	135 (42.6)	317
$\chi^2 = 3.91$, df = 1, $p = 0.048$.			
df, degrees of freedom.			

TABLE 20 *Incidence of healing at 24 weeks in different treatment groups, stratified by cross-sectional area at baseline and analysed on the basis of intention to treat*

Size	Dressing	Ongoing/withdrawn (%)	Healed (%)
25–100 mm^2	Inadine	22 (45.8)	26 (54.2)
	N-A	26 (52.0)	24 (48.0)
$\chi^2 = 0.37$, df = 1, $p = 0.54$.			
25–100 mm^2	Aquacel	30 (56.6)	23 (43.4)
	N-A	26 (52.0)	24 (48.0)
$\chi^2 = 0.22$, df = 1, $p = 0.64$.			
> 100 mm^2	Inadine	38 (63.6)	22 (35)
	N-A	39 (69.9)	17 (30.4)
$\chi^2 = 0.52$, df = 1, $p = 0.47$.			
> 100 mm^2	Aquacel	27 (54)	23 (46)
	N-A	39 (69.9)	17 (30.4)
$\chi^2 = 2.75$, df = 1, $p = 0.1$.			
df, degrees of freedom.			

TABLE 21 *Incidence of healing at 12 weeks analysed on a* per protocol *basis*

	Ongoing (%)	Healed (%)	Total (%)
Inadine	64 (66.7)	32 (33.3)	96 (100.0)
N-A	53 (66.3)	27 (33.7)	80 (100.0)
Total	117	59	176
$\chi^2 = 0.003$, df = 1, $p = 0.95$.			
Aquacel	52 (64.2)	29 (35.8)	81 (100.0)
N-A	53 (66.3)	27 (33.7)	80 (100.0)
Total	105	56	161
$\chi^2 = 0.07$, df = 1, $p = 0.78$.			
df, degrees of freedom.			

TABLE 22 *Incidence of healing at 24 weeks analysed on a* per protocol *basis*

	Ongoing (%)	**Healed (%)**	**Total (%)**
Inadine	39 (44.8)	48 (55.2)	87 (100.0)
N-A	28 (40.6)	41 (59.4)	69 (100.0)
Total	67	89	156
$\chi^2 = 0.28$, df = 1, $p = 0.59$.			
Aquacel	27 (37)	46 (63)	73 (100.0)
N-A	28 (40.6)	41 (59.4)	69 (100.0)
Total	55	87	142
$\chi^2 = 0.193$, df = 1, $p = 0.66$.			
df, degrees of freedom.			

that the simplest dressing, N-A, might be less effective as it would often not be selected for more contaminated wounds in routine practice. Outcomes were therefore compared in ulcers that were clean and free from slough (100% granulation tissue) at baseline or were not clean (defined as more than 50% wound surface covered by slough) (*Table 23*). The percentages of clean ulcers that healed, persisted unhealed or were withdrawn at 24 weeks were very similar for clean (44%, 27%, 29% respectively), covered with 1–50% slough (41%, 35%, 24% respectively) and with greater than 50% slough (43%, 25%, 31% respectively).

Outcomes for clean and contaminated ulcers were also compared between different dressing groups (*Tables 24* and *25*). There was a significant difference between groups in the outcome of

TABLE 23 *Outcome of clean and contaminated ulcers at 24 weeks*

	Ongoing (%)	**Healed (%)**	**Withdrawn (%)**	**Total (%)**
Clean 100% granulation	38 (26.6)	63 (44.1)	42 (29.4)	143 (100.0)
Wound bed with 1–50% slough	43 (35.0)	50 (40.7)	30 (24.4)	123 (100.0)
Wound bed with > 50% slough	13 (25.5)	22 (43.1)	16 (31.4)	51 (100.0)
Total	94 (29.7)	135 (42.6)	88 (27.8)	317
$\chi^2 = 2.98$, df = 4, $p = 0.56$.				
df, degrees of freedom.				

TABLE 24 *Healing outcome of clean ulcers (wound bed 100% granulation tissue at baseline) at 24 weeks by dressing*

	Ongoing (%)	**Healed (%)**	**Withdrawn (%)**	**Total (%)**
Inadine	21 (35.6)	27 (45.8)	11 (18.6)	59 (100.0)
Aquacel	7 (17.9)	18 (46.2)	14 (37.9)	39 (100.0)
N-A	10 (22.2)	18 (40.0)	17 (37.8)	45 (100.0)
Total	38 (26.6)	63 (44.1)	42 (29.4)	143
$\chi^2 = 7.4$, df = 4, $p = 0.115$.				
df, degrees of freedom.				

TABLE 25 *Healing outcome of contaminated ulcers (50% or more of wound bed covered by slough) at 24 weeks by dressing*

	Ongoing (%)	Healed (%)	Withdrawn (%)	Total (%)
Inadine	5 (38.5)	7 (53.8)	1 (7.7)	13 (100.0)
Aquacel	8 (38.1)	8 (38.1)	5 (23.8)	21 (100.0)
N-A	0 (0)	7 (41.2)	10 (58.8)	17 (100.0)
Total	13 (25.5)	22 (43.1)	16 (31.4)	51
$\chi^2 = 13.77$, df = 4, $p = 0.008$.				
df, degrees of freedom.				

contaminated ulcers (*Table 25*), and this was attributed to the variation in withdrawals which was identified in *Table 5*.

Effect of peripheral arterial disease in the affected limb on healing

In order to study the effect of underlying arterial disease in the affected limb, the population of ulcers was divided into those associated with both pulses palpable in the affected foot, and those in which one or both pulses were impalpable. Complete data were missing in eight (3%). No difference was observed between groups in outcome at 24 weeks (*Table 26*).

Secondary outcomes – ulcer-related outcomes

Time to healing

Time to healing for those ulcers healed at visit 7 (12 weeks)

Time to healing was analysed on an ITT basis with maximum number of days in the study ($n = 85$) substituted for all those with ongoing active ulceration at visit 7 and those withdrawn from the study. There were no significant differences between groups in time to healing using ITT (*Table 27*). There remained no statistically significant differences between the groups when the analysis was repeated on a *per protocol* basis (*Table 28*), nor when analysed including only those who healed by week 12 (*Table 29*).

TABLE 26 *Effect of peripheral arterial disease (missing pedal pulses) on outcome at 24 weeks*

	Ongoing (%)	Healed (%)	Withdrawn (%)	Total (%)
Both pulses palpable	71 (28.7)	107 (43.3)	69 (27.9)	247 (100.0)
One or both pulses missing	20 (32.3)	26 (41.9)	16 (25.8)	62 (100.0)
Total	94 (30.4)	130 (42.1)	85 (27.5)	309
$\chi^2 = 0.311$, df = 2, $p = 0.85$.				
df, degrees of freedom.				

TABLE 27 *Time to healing in days for those ulcers healed at 12 weeks analysed on the basis of intention to treat*

					95% CI for mean	
	Mean	SD	Minimum	Maximum	Lower bound	Upper bound
Inadine ($n = 108$)	74.1	20.6	14	84	70.2	78.1
Aquacel ($n = 103$)	72.4	20.6	14	84	68.4	76.5
N-A ($n = 106$)	75.1	18.1	14	84	71.6	78.6
One-way ANOVA, $F_{2,314} = 0.49$, $p = 0.61$.						
ANOVA, analysis of variance; CI, confidence interval; SD, standard deviation.						

TABLE 28 *Time to healing in days for those ulcers healed by 12 weeks analysed* per protocol

	Mean	SD	Minimum	Maximum	95% CI for mean	
					Lower bound	Upper bound
Inadine ($n = 96$)	72.9	21.6	14	84	68.5	77.3
Aquacel ($n = 81$)	69.3	22.3	14	84	64.4	74.3
N-A ($n = 80$)	72.3	20.1	14	84	67.8	76.8

One-way ANOVA, $F_{2,254} = 0.68$, $p = 0.5$.
ANOVA, analysis of variance; CI, confidence interval; SD, standard deviation.

Time to healing for those ulcers healed at visit 13 (24 weeks)

Time to healing was analysed on an ITT basis with maximum number of days in the study ($n = 169$) substituted for all those with ongoing active ulceration at visit 13 and those withdrawn from the study. There are no significant differences in time to healing using ITT (*Table 30*). The calculated mean time to healing for all 317 participants using these criteria was 129 days.

When the analysis was repeated on a *per protocol* basis, the descriptive statistics changed but there were still no statistically significant differences between the groups (*Table 31*); this pattern was repeated when the analysis was completed, including only those who achieved healing (*Table 32*).

Reduction in ulcer cross-sectional area in those which did not heal

These data were not analysed – see Data not presented (page 43) and Appendix 6.

New ulceration

Recurrence of ulceration at the same site within 3-month follow-up for those whose index ulcer healed during the intervention phase

Of the 135 patients who healed during the intervention phase, only 117 provided information on the clinical status of the ulcer during the 3-month follow-up review (*Table 33*). Twelve of those patients for whom data are available (10%) had a recurrence during the 3-month review, but the difference between groups was not statistically significant.

New ulceration at a different site on the same foot for those whose index ulcer healed during the intervention phase

One hundred and eighteen patients provided information on whether or not they had developed another ulcer on the target foot, but in a different location (*Table 34*). The occurrence rate is similar for all groups and is not statistically significantly different. If the data for recurrence at the same site (see *Table 33*) and occurrence at a new site are taken together (see *Table 34*), almost one third (30%) of participants had another new ulcer somewhere on the target foot during the 3-month follow-up.

Any active ulceration at the end of the 3-month follow-up phase in those whose index ulcer healed during the intervention phase

At the time of completing the 3-month follow-up, a total of 31 patients (26%) reported the presence of at least one active ulcer on either foot (*Table 35*). There was no difference between groups.

Incidence of any new ulceration in the 3-month follow-up phase (all participants)

Two hundred and thirty-three patients provided information about the incidence of another ulcer during the follow-up period; 42 patients reported another ulcer (18%), with no difference between the groups ($\chi^2 = 0.67$, df = 2, $p = 0.71$). The details, based on outcome at week 24 and dressing allocation are presented in *Table 36*.

Prevalence of active ulceration at the end of the 3-month follow-up phase (all participants)

Information on active ulceration at the 3-month visit was available from 232 participants. One

TABLE 29 *Time to healing in days for those ulcers healed by 12 weeks analysed for those who achieved healing*

					95% CI for mean	
	Mean	**SD**	**Minimum**	**Maximum**	**Lower bound**	**Upper bound**
Inadine ($n = 32$)	50.7	25.8	14	84	41.4	60.0
Aquacel ($n = 29$)	42.9	17.5	14	84	36.3	49.6
N-A ($n = 27$)	49.2	19.9	14	84	41.4	57.1

One-way ANOVA, $F_{2,85} = 1.08$, $p = 0.34$.
ANOVA, analysis of variance; CI, confidence interval; SD, standard deviation.

TABLE 30 *Time to healing in days for those healed at 24 weeks analysed on the basis of intention to treat*

					95% CI mean	
	Mean	**SD**	**Minimum**	**Maximum**	**Lower bound**	**Upper bound**
Inadine ($n = 108$)	127.8	54.2	14	168	117.5	138.2
Aquacel ($n = 103$)	125.8	55.9	14	168	114.9	136.7
N-A ($n = 106$)	130.7	52.4	14	168	120.6	140.8

One-way ANOVA, $F_{2,314} = 0.216$, $p = 0.80$.
ANOVA, analysis of variance; CI, confidence interval; SD, standard deviation.

TABLE 31 *Time to healing in days for those healed at 24 weeks analysed on a* per protocol *basis*

					95% CI for mean	
	Mean	**SD**	**Minimum**	**Maximum**	**Lower bound**	**Upper bound**
Inadine ($n = 87$)	118.1	56.3	14	168	106.1	130.1
Aquacel ($n = 73$)	108.5	58.2	14	168	94.9	122.1
N-A ($n = 69$)	110.7	55.6	14	168	97.4	124.1

One-way ANOVA, $F_{2,226} = 0.63$, $p = 0.53$.
ANOVA, analysis of variance; CI, confidence interval; SD, standard deviation.

TABLE 32 *Time to healing in days for those healed at 24 weeks analysed including only those who achieved healing*

					95% CI for mean	
	Mean	**SD**	**Minimum**	**Maximum**	**Lower bound**	**Upper bound**
Inadine ($n = 48$)	77.6	45.3	14	168	64.4	90.7
Aquacel ($n = 46$)	73.6	45.3	14	168	60.2	87.1
N-A ($n = 41$)	71.7	37.3	14	168	59.9	83.4

One-way ANOVA, $F_{2,132} = 0.218$, $p = 0.8$.
ANOVA, analysis of variance; CI, confidence interval; SD, standard deviation.

TABLE 33 *Ulcer status at 3-month follow-up (for those healed during trial)*

	Inadine	Aquacel	N-A	Total
Ulcer remained healed	32	35	37	104
Ulcer recurred at same site	7	3	3	13
Total	39	38	40	117
$\chi^2 = 2.77$, df = 2, $p = 0.3$.				
df, degrees of freedom.				

TABLE 34 *Presence of ulcer at another site on target foot at 3-month follow-up (for those healed during intervention phase)*

	Inadine	Aquacel	N-A	Total
No other ulcers	31	33	32	96
Ulcer at new site	8	6	8	22
Total	39	39	40	118
$\chi^2 = 0.441$, df = 2, $p = 0.8$.				
df, degrees of freedom.				

TABLE 35 *Active ulceration at the time of 3-month follow-up (for those healed during intervention phase)*

	Inadine	Aquacel	N-A	Total
No ulcers	29	30	29	88
Active ulceration	11	9	11	31
Total	40	39	40	119
$\chi^2 = 0.26$, df = 2, $p = 0.87$.				
df, degrees of freedom.				

TABLE 36 *Incidence of ulcer at another site during 3-month follow-up (all participants)*

	New ulcer	Inadine	Aquacel	N-A	Total
Ongoing at week 24	Yes	3	7	3	13
	No	32	16	16	64
Healed by week 24	Yes	8	6	6	22
	No	31	33	32	96
Withdrawn	Yes	2	1	4	7
	No	9	8	14	31
Total new ulcers (%)		13 (15.3)	14 (19.7)	13 (17.3)	

TABLE 37 *Presence of ulcer at the time of the 3-month follow-up (all participants)*

	New ulcer	Inadine	Aquacel	N-A	Total
Ongoing at week 24	Yes	23	15	16	54
	No	12	6	3	21
Healed by week 24	Yes	11	9	11	31
	No	29	30	29	88
Withdrawn	Yes	7	5	11	23
	No	4	4	7	15
$\chi^2 = 0.85$, df = 2, $p = 0.65$.					
df, degrees of freedom.					

hundred and eight patients (47% of 232) had an active ulcer at follow-up (*Table 37*).

However, if the data are considered in terms of healing status alone, then there was a statistically significant relationship such that those patients who healed during the intervention phase were less likely to have an active ulcer at the time of the follow-up (*Table 38*).

Episodes of secondary infection

As it is possible that the choice of wound dressing has an impact on the incidence of secondary infection, the number of cases of infection was analysed by dressing group. Thus, it might be expected that the incidence of secondary infection might be less in those managed with a topical antiseptic, such as Inadine. Secondary infection affected between 5.7% and 11.2% of all unhealed ulcers at each of the 12 visits after the start of the study (*Table 39*). Twenty-eight such episodes were registered as SAEs but there was no significant difference in incidence of SAEs between dressing groups (*Table 40*). A total of 207 instances of infection (of either foot) were reported as adverse events in the whole study population (*Table 41*), and a significant difference in the incidence of secondary infection was observed between the three dressing groups, with the lowest incidence observed in those managed with N-A. The greatest number of cases of infection (in both SAE and

TABLE 38 *Active ulceration at the time of 3-month follow-up by healing outcome*

	Ongoing	Healed	Withdrawn	Total
No ulcers	21	88	15	124
Active ulceration	54	31	23	108
Total	75	119	38	232
$\chi^2 = 42.6$, df = 2, $p < 0.001$.				
df, degrees of freedom.				

TABLE 39 *Number of cases of infection (% of all unhealed ulcers) at each of 12 follow-up visits after the start of the study*

	Visit											
	2	3	4	5	6	7	8	9	10	11	12	13
Number of episodes of infection	24	21	15	15	22	18	17	10	10	7	11	11
of all unhealed ulcers	7.8	7.4	5.7	6.4	10.1	9.8	10	6.4	7.4	5.7	9.8	11.2

TABLE 40 *Number of cases of infection reported as serious adverse events (SAEs) by dressing allocation*

	Inadine	Aquacel	N-A
Number of episodes of infection listed as SAEs	10	7	7
Number of episodes of infection listed as SAEs but unrelated to the index ulcer	2	2	0
Total	12	9	7
$\chi^2 = 1.68$, df = 2, $p = 0.43$.			
df, degrees of freedom.			

TABLE 41 *Number of cases of infection reported as adverse events by dressing allocation*

	Inadine	Aquacel	N-A
Number of adverse events related to infection in study foot[a]	71	54	48
Number of episodes of infection listed as adverse events but affecting the non-study foot	9	17	8
Total	80	71	56
df, degrees of freedom. a One-way test of proportion (χ^2) = 93.38, df = 2, $p < 0.001$.			

adverse event categories) was associated with the use of the antiseptic, Inadine. When, however, the different rate of withdrawal between the three groups was taken into account, and the incidence of secondary infection was expressed as a function of the total number of dressing changes, no difference was observed (Inadine 0.01, Aquacel 0.01, N-A 0.009). The lack of difference tends to negate any suggestion of a benefit from using antiseptic preparations.

Major and minor amputations

A total of seven amputations were reported during the study (*Table 42*). Two were below knee amputations and the remainder were minor (below the ankle). None of the amputees died during the course of the study. The distribution of amputations by centre is shown in *Table 43*.

Secondary outcomes – patient-related outcomes

Pain in the region of the ulcer

All patients in the study were asked to record the presence of pain in the region of the ulcer, as well as to assess its intensity, at each visit. The prevalence of pain per visit for the three dressing products is outlined in *Table 44*. Between 13% and 22% of patients reported pain in the region of the wound across all visits. There were no apparent differences in the number of participants reporting pain by dressing allocation at any of the visits.

The intensity of pain was graded at each visit on a 100-mm visual analogue scale. A change in pain experience was reported by 85 participants between baseline and visit 2 (2 weeks later), and these data are presented in *Table 45*. There was a statistically significant difference between groups in this change: Inadine and Aquacel were both associated with a mean increase in reported pain between baseline and visit 2, while for N-A there was a mean reduction – although the large standard deviations should be noted. Post hoc between-group analysis using Dunnett's T3 (assuming unequal variance) indicates that this result is accounted for by differences between Aquacel and N-A ($p = 0.016$).

Health-related quality of life

Patient self-reported HRQoL was assessed at three time points using a generic tool (SF–36) and a disease-specific one (CWIS).

TABLE 42 *List of amputations according to dressing allocation*

	Inadine	Aquacel	N-A
Minor amputations	1	3	1
Major amputations	0	1	1
Total	1	4	2

TABLE 43 *Amputations reported by centre*

	Centre								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Total patients	34	40	60	53	66	18	17	7	22
Minor	2	1	0	0	1	1	0	0	0
Major	1	0	0	0	1	0	0	0	0
Total	3	1	0	0	2	1	0	0	0

TABLE 44 *Presence of pain in the region of the wound by dressing allocation*

Visit	Inadine	Aquacel	N-A	Total (%)
1	17/108	24/103	25/106	66/317 (20.8)
2	17/103	21/95	12/94	50/292 (17.1)
3	16/89	10/75	10/82	36/246 (14.6)
4	11/85	9/57	12/73	32/215 (14.9)
5	13/81	7/54	10/61	30/196 (15.3)
6	9/74	9/54	11/60	29/188 (15.4)
7	8/65	10/53	11/51	29/169 (17.2)
8	10/57	7/45	11/44	28/146 (19.2)
9	7/51	7/45	11/44	28/126 (22.2)
10	7/49	3/35	8/31	18/115 (15.7)
11	5/46	6/31	3/29	14/106 (13.2)
12	5/42	5/27	7/29	17/98 (17.3)
13	5/41	4/27	6/28	15/96 (15.6)

TABLE 45 *Changes in pain intensity between visits 1 and 2*

	Mean	SD	Minimum	Maximum
Inadine ($n = 26$)	7.31	38.87	–76.00	100
Aquacel ($n = 31$)	10.39	35.70	–50.00	99
N-A ($n = 28$)	–17.14	37.14	–65.00	99

One-way ANOVA, $F_{2,82} = 4.69$, $p = 0.012$.
ANOVA, analysis of variance; SD, standard deviation.

Cardiff Wound Impact Schedule

Participants were asked whether they lived on their own and how often they saw their family and friends (*Table 46*). The majority of participants did not live on their own and saw their family or friends on a daily basis.

The data from CWIS were analysed using one-way analysis of variance to investigate whether the transformed scores were statistically different at baseline, 12 and 24 weeks (*Table 47*). For each of the three domains, scores were transformed onto a 0–100 scale, whereby higher scores indicate a more positive self-reported QoL (full psychometrics for the scale have been published previously[28]). Although the well-being scores were the lowest of the three domains, this was the same for all dressing groups. There were no statistical differences between the groups.

The CWIS data were also analysed by healing status at the two follow-up assessments. For each of the subsequent time points there were statistical differences between the groups such that those with healed ulcers reported higher levels of HRQoL with this condition-specific tool (*Tables 48* and *49*). These data show a statistically significant difference in physical functioning and well-being in those who were healed at both 12 and 24 weeks, and a difference also in social functioning at 24 weeks alone.

SF–36

The data from the SF–36 were also analysed by intervention at baseline and at the two follow-up visits. The scores for each of the domains were transformed onto a 0–100 scale, for which a higher score represents a more positive self-reported HRQoL – with the exception of the bodily pain domain, for which a higher score represents more self-reported pain. The psychometrics for the SF–36 are well established and have been published previously.[29]

The results are presented in *Tables 50–52*. No differences were observed between the groups across any of the domains at any of the time points. There are also no statistical differences between those who had a healed ulcer and those with ongoing ulceration/withdrawn at either 12 or 24 weeks (*Tables 53* and *54*). In line with standard practice for this questionnaire, those domains that contained less than 50% of responses for the item questions have not been included. There was a particularly large number of missing questionnaires at week 12.

The non-significance of differences in the SF–36 scores was also reflected in the SF–6D scores, and no further analysis was undertaken.

Adverse events and withdrawals

Adverse events

Adverse events were recorded at every visit, with each event being classified as either serious or not serious, and the relationship of the event to the dressing intervention defined. There were a total of 710 adverse events, of 321 different types (*Table 55*).

Serious adverse events

There were a total of 100 SAEs of 75 different types. *Table 56* indicates the number reported by dressing type. Details of the nature of the SAEs are given in Appendix 5. The nature of SAEs reported

TABLE 46 *Patient regular contact with others*

	Inadine	Aquacel	N-A
Live on own			
Yes	32	23	30
No	72	68	62
Missing	4	12	92
How often do you see family and friends?			
Daily	73	62	71
Weekly	20	26	21
Monthly	6	5	6
More than once a month	5	5	0
Missing	4	5	8

TABLE 47 *CWIS scores by dressing allocation by time point*

	Physical functioning Mean (SD), range	Social functioning Mean (SD), range	Well-being Mean (SD), range	
Baseline				
Inadine	64.6 (21.3) 6–100, $n = 107$	68.8 (22.4) 13–100, $n = 105$	49.2 (19.8) 7–100, $n = 107$	
Aquacel	66.6 (20.7) 10–98, $n = 98$	68.0 (25.9) 14–100, $n = 100$	47.3 (18.2) 14–96, $n = 100$	
N-A	66.7 (18.6) 0–98, $n = 100$	65.8 (24.9) 4–100, $n = 99$	45.8 (19.0) 7–89, $n = 99$	
One-way ANOVA	$F_{2,302} = 0.371$, $p = 0.069$	$F_{2,301} = 0.419$, $p = 0.66$	$F_{2,303} = 0.819$, $p = 0.44$	NS
12 weeks				
Inadine	69.2 (22.4) 4–100, $n = 84$	70.25 (23.9) 4–100, $n = 85$	52.9 (21.8) 4–100, $n = 82$	
Aquacel	71.6 (19.2) 26–100, $n = 77$	68.82 (26.1) 0–100, $n = 76$	53.5 (21.0) 11–100, $n = 79$	
N-A	69.9 (22.5) 3–100, $n = 70$	70.24 (27.1) 4–100, $n = 69$	51.9 (20.8) 7–100, $n = 70$	
One-way ANOVA	$F_{2,228} = 0.27$, $p = 0.76$	$F_{2,227} = 0.79$, $p = 0.92$	$F_{2,228} = 0.09$, $p = 0.91$	NS
24 weeks				
Inadine	67.1 (23.6) 7–100, $n = 104$	69.7 (24.1) 14–100, $n = 106$	51.0 (22.3) 4–100, $n = 102$	
Aquacel	71.4 (19.5) 22–100, $n = 97$	70.3 (25.4) 0–100, $n = 98$	53.1 (19.9) 11–100, $n = 100$	
N-A	68.9 (19.1) 7–100, $n = 99$	69.8 (23.5) 2–100, $n = 95$	50.2 (21.1) 4–100, $n = 98$	
One-way ANOVA	$F_{2,297} = 1.04$, $p = 0.35$	$F_{2,296} = 0.18$, $p = 0.98$	$F_{2,297} = 0.51$, $p = 0.6$	NS

ANOVA, analysis of variance; NS, not significant; SD, standard deviation.

by individuals who had more than one event are listed in Appendix 5. Only 11 of the 100 SAEs recorded were considered to be 'slightly or possibly' related to the dressing; these events were spread evenly across the intervention groups.

Withdrawals

There were a total of 88 withdrawals (21 for those using Inadine, 30 for Aquacel and 37 for N-A). The difference between groups was significant (see *Table 5*), and was most marked when more than 50% of the ulcer surface was covered by slough (see *Table 25*). The reasons for withdrawal are outlined in *Table 57*. There were more withdrawals related to adverse events and protocol violations for the N-A dressing than for the other dressing types, but when analysed by all five main reasons for withdrawal there were no statistically significant differences between the groups. Detailed descriptions of the reasons for withdrawal are listed in Appendix 4.

The demographics of the patients who were withdrawn from the study were very similar to those who healed during the intervention phase, and those who still had an active ulcer at the end of the study: the details are presented in Appendix 7.

Secondary outcomes – process-related outcomes

Frequency of dressing changes

Table 58 reveals that when patients/carers were involved in at least some of the dressing changes,

TABLE 48 *Descriptive statistics for the three domains of CWIS by healing status at 12 weeks*

Wound status by domain	*n*	Mean	SD	t-test	df	Significance (two-tailed)	95% CI Lower	95% CI Upper
Physical								
Healed	74	75.1	17.4	2.70	182	0.008	1.98	12.71
Not healed	156	67.8	22.7					
Social								
Healed	74	72.5	24.6	1.11	228	0.267	–3.08	11.09
Not healed	156	68.5	25.9					
Well-being								
Healed	75	58.8	22.3	3.05	227	0.003	3.17	14.73
Not healed	154	49.9	20.1					

CI, confidence interval; df, degrees of freedom; SD, standard deviation.

TABLE 49 *Descriptive statistics for the three domains of CWIS by healing status at 24 weeks*

Wound status by domain	*n*	Mean	SD	t-test	df	Significance (two-tailed)	95% CI Lower	95% CI Upper
Physical								
Healed	110	74.4	23.1	2.34	294	0.020	1.07	12.5
Not healed	186	67.6	24.7					
Social								
Healed	109	75.1	18.5	3.72	295	0.000	4.32	14.04
Not healed	188	65.8	21.6					
Well-being								
Healed	110	58.2	22.8	4.12	199	0.000	5.54	15.74
Not healed	186	47.5	19.2					

CI, confidence interval; df, degrees of freedom; SD, standard deviation.

there was no difference between dressing groups in either the mean or median number of changes made. This contrasts with the data in *Table 59* which reveal that there is a significant difference between groups (with Aquacel being changed least often) when dressing changes were undertaken only by professionals.

Health economic analysis

Costs

The mean number of dressings per patient is shown in *Table 60*. There was no statistical difference between the dressing types.

TABLE 50 *Baseline SF–36 domain scores*

	Inadine					Aquacel					N-A					
	n	Min	Max	Mean	SD	*n*	Min	Max	Mean	SD	*n*	Min	Max	Mean	SD	*p*-value
Physical function	106	0	100	42.6	28.3	100	0	100	39.1	28.8	101	0	100	43.7	28.9	NS
Role physical	103	0	100	40.6	32.60	99	0	100	43.8	32.7	101	0	100	41.0	31.4	NS
Bodily pain	107	0	100	56.1	29.0	101	0	100	61.3	30.4	101	0	100	60.0	29.7	NS
General health	107	0	100	42.1	21.7	100	0	97	44.4	22.5	100	0	100	42.7	22.1	NS
Vitality	106	0	100	45.9	21.5	101	0	100	45.4	24.3	101	0	93.7	46.4	18.9	NS
Social functioning	107	0	100	61.8	29.9	101	0	100	62.0	30.8	101	0	100	59.5	29.8	NS
Role emotional	105	0	100	62.5	33.2	98	0	100	59.5	35.4	101	0	100	60.5	32.9	NS
Mental health	106	5	100	69.3	20.6	101	0	100	67.8	21.5	101	0	100	68.9	20.4	NS
SF–6D scores	105			0.3976	0.1067	99			0.3807	0.1135	100			0.3977	0.1100	NS

Max, maximum; min, minimum; NS, not significant ; SD, standard deviation.

TABLE 51 *SF–36 domain scores at 12 weeks*

	Inadine					Aquacel					N-A					
	n	**Min**	**Max**	**Mean**	**SD**	***n***	**Min**	**Max**	**Mean**	**SD**	***n***	**Min**	**Max**	**Mean**	**SD**	***p*-value**
Physical function	84	0	100	40.4	30.3	78	0	100	40.8	30.4	71	0	100	39.2	28.4	NS
Role physical	82	0	100	39.9	32.5	77	0	100	43.7	34.8	71	0	100	40.1	30.6	NS
Bodily pain	86	0	100	58.3	27.9	78	0	100	64.2	29.3	71	0	100	55.5	32.1	NS
General health	84	0	97	41.2	22.9	77	0	100	43.7	23.9	71	0	100	45.1	23.3	NS
Vitality	85	6.3	100	47.6	21.7	78	0	100	53.3	23.2	70	0	100	49.4	24.9	NS
Social functioning	86	0	100	60.6	27.9	78	0	100	60.1	32.0	71	0	100	61.8	30.3	NS
Role emotional	84	0	100	54.8	33.6	77	0	100	59.9	36.2	71	0	100	58.6	33.8	NS
Mental health	85	15	100	66.1	21.8	78	0	100	67.9	23.5	70	0	100	66.8	22.9	NS
SF–6D scores	82			0.3734	0.1142	76			0.3776	0.1116	71			0.3949	0.1116	NS

Max, maximum; min, minimum; NS, not significant; SD, standard deviation.

TABLE 52 *SF–36 domain scores at 24 weeks*

	Inadine					Aquacel					N-A					
	n	**Min**	**Max**	**Mean**	**SD**	***n***	**Min**	**Max**	**Mean**	**SD**	***n***	**Min**	**Max**	**Mean**	**SD**	***p*-value**
Physical function	105	0	100	39.7	29.7	100	0	100	44.8	32.1	101	0	100	40.4	27.9	NS
Role physical	103	0	100	45.2	33.9	99	0	100	46.6	36.6	100	0	100	38.9	29.9	NS
Bodily pain	107	0	100	59.3	27.8	101	0	100	65.6	30.4	101	0	100	57.2	29.5	NS
General health	105	0	97	43.4	22.3	99	0	100	44.5	24.7	98	0	100	44.2	22.7	NS
Vitality	105	0	100	44.9	21.9	100	0	100	47.3	26.3	99	0	87.5	46.8	19.9	NS
Social functioning	106	0	100	62.7	30.2	101	0	100	59.6	32.2	101	0	100	58.3	29.5	NS
Role emotional	103	0	100	59.3	34.4	99	0	100	60.7	37.6	101	0	100	59.6	33.5	NS
Mental health	105	15	100	67.9	21.9	100	0	100	66.2	23.6	99	15	100	67.4	20.8	NS
SF–6D scores	103			0.3838	0.1085	98			0.3822	0.1153	100			0.3939	0.1093	NS

Max, maximum; min, minimum; NS, not significant; SD, standard deviation.

TABLE 53 *SF–36 domain scores at 12 weeks – comparison between those with ulcers that are either healed or ongoing/withdrawn*

	ITT	*n*	Mean	SD	*p*-value
Physical functioning	Healed	75	39.87	30.21	NS
	Ongoing and withdrawn	158	40.28	29.52	
Role physical	Healed	74	38.51	33.66	NS
	Ongoing and withdrawn	157	105.88	35.26	
Bodily pain	Healed	77	59.90	30.32	NS
	Ongoing and withdrawn	158	59.17	29.612	
General health	Healed	75	43.64	23.13	NS
	Ongoing and withdrawn	157	43.04	23.49	
Vitality	Healed	75	51.50	23.13	NS
	Ongoing and withdrawn	158	49.37	23.29	
Social functioning	Healed	77	58.93	31.34	NS
	Ongoing and withdrawn	158	61.71	29.31	
Role emotional	Healed	75	57.56	34.23	NS
	Ongoing and withdrawn	157	57.70	34.69	
Mental health	Healed	75	67.60	21.94	NS
	Ongoing and withdrawn	158	66.58	23.01	

ITT, intention to treat; NS, not significant; SD, standard deviation.

The unit cost of each of the dressings was Inadine £0.29, Aquacel £0.97 and N-A £0.32. The mean cost of dressings per patient per dressing type is shown in *Table 61*. There was a statistically significant difference between the costs of the three dressings, with the higher acquisition cost of Aquacel not offset by fewer dressings being used. In terms of the number of dressing changes, there were no statistically significant differences in the number of consultations with professionals for dressing changes between dressing type, with a mean of 17 consultations for Inadine, 14 for Aquacel and 14 for N-A. However, it should be noted that nearly 70% of dressing changes were undertaken by non-professionals, such as family members and friends.

The costs of staff time associated with changing dressings are shown in *Table 62*. These were based on the unit cost of professional time, as reported in published sources. No statistically significant differences emerged.

The total cost of dressings and professionals' time in changing them is shown in *Table 63*. There were no statistically significant differences between the dressings.

Participants were also asked to identify other consultations, relating to their condition – over and above those associated with dressing changes – with professionals during the trial. A large range of professionals were identified as being involved in the management of diabetic foot problems. The costs of these additional diabetic foot ulcer-related consultations per patient per dressing type are shown in *Table 64*. There were no statistically significant differences observed between the groups.

These data highlight the significant burden involved in managing patients with diabetic foot ulcers. However, given that the extent to which other consultations are related to the type of dressing used is highly subjective, for subsequent

TABLE 54 *SF–36 domain scores at 24 weeks – comparison between those with ulcers which are either healed or ongoing/withdrawn*

	ITT	*n*	Mean	SD	*p*-value
Physical functioning	Healed	131	43.01	31.25	NS
	Ongoing and withdrawn	175	40.53	28.99	
Role physical	Healed	130	44.42	35.34	NS
	Ongoing and withdrawn	172	42.99	32.42	
Bodily pain	Healed	132	62.61	28.78	NS
	Ongoing and withdrawn	177	59.23	29.75	
General health	Healed	130	45.95	23.99	NS
	Ongoing and withdrawn	172	42.55	22.48	
Vitality	Healed	128	47.41	22.97	NS
	Ongoing and withdrawn	176	45.49	22.69	
Social functioning	Healed	132	62.88	30.85	NS
	Ongoing and withdrawn	176	58.31	30.28	
Role emotional	Healed	129	62.02	34.75	NS
	Ongoing and withdrawn	174	58.24	35.40	
Mental health	Healed	128	68.75	22.04	NS
	Ongoing and withdrawn	176	66.10	22.05	

ITT, intention to treat; NS, not significant; SD, standard deviation.

analysis the cost of treatment will relate to the dressings cost and the cost of professionals' time involved in changing them, as per *Table 63*.

In summary, the only statistically significant difference in the groups in relation to costs was the costs incurred in the provision of the three dressings, with Aquacel being more expensive than the other dressings. While there were more dressing changes for Inadine and a greater cost of professional time than for the other two dressings, this was not statistically significant, and the overall cost of managing dressings for diabetic foot ulcers was the same for all dressing types.

Outcomes

The healing rates and time to healing have already been reported in the previous two sections (Secondary outcomes – patient-related outcomes and Secondary outcomes – process-related outcomes), but with no statistically significant difference between the dressings, either in healing or in time to healing. The findings are summarised in *Tables 65* and *66*.

This translates into the number of ulcer-free days for each dressing, as shown in *Table 67*. No statistically significant differences emerged.

There were a small number of recurrences of ulceration at 3-month follow-up, as shown in *Table 33* – six cases for Inadine, three for Aquacel and three for N-A at the same location. It was not possible to quantify the number of days on which patients who suffered recurrences were ulcer free, but given that the number of ulcer free days reported in *Table 67* is based on those who were ulcer free at the 3-month follow-up, it is unlikely that there would be a significant difference in the overall number of ulcer-free days.

The probability of healing and remaining ulcer free at 3-month follow-up was 28% for Inadine, 33% for Aquacel and 35% for N-A. However, there was a difference between the withdrawal rates for

TABLE 55 *Episodes of reported non-serious adverse events by dressing allocation*

Number of adverse events	Dressing allocation			Total
	Inadine	Aquacel	N-A	
1	81	76	83	240
2	49	50	53	152
3	36	31	35	102
4	21	25	24	70
5	16	16	15	47
6	10	10	9	29
7	9	7	7	23
8	8	5	6	19
9	3	3	4	10
10	2	1	2	5
11	1	1	2	4
12	1	1	1	3
13	1	1	1	3
14	1	0	1	2
15	0	0	1	1
Total	239	227	244	710

$\chi^2 = 0.64$, df = 2, $p = 0.72$.

df, degrees of freedom.

TABLE 56 *Total number of serious adverse events (SAEs) reported by dressing allocation*

Number of SAEs	Dressing allocation			Total
	Inadine	Aquacel	N-A	
1	22	24	24	70
2	9	4	8	21
3	4	0	2	6
4	1	0	1	2
5	1	0	0	1
Total	37	28	35	100

Test of proportions, $\chi^2 = 1.34$, df = 2, $p = 0.512$.
df, degrees of freedom.

TABLE 57 *Reasons for withdrawal from the study by dressing allocation*

	Adverse event	Death	Protocol violation	Lost to follow-up	Patient withdrew consent	Other	Total
Inadine	9	1	5	2	4	0	21
Aquacel	11	2	8	3	6	0	30
N-A	15	2	11	2	6	1	37
Total	35	5	24	7	16	1	88

TABLE 58 *Number of dressing changes made of which at least one was undertaken by patients or carers, analysed by dressing type*

	Inadine (*n* = 61)	**Aquacel (*n* = 46)**	**N-A (*n* = 55)**
Mean	66.0	60.3	56.8
SD	49.3	61.59	50.6
Median	52	40	44
Minimum–maximum	4–174	5–316	1–208

H-value = 2.06, df = 2, *p* = 0.356.
df, degrees of freedom; SD, standard deviation.

TABLE 59 *Number of trial dressings used by professionals during intervention phase*

	Inadine (*n* = 107)	**Aquacel (*n* = 99)**	**N-A (*n* = 99)**
Mean	62.9	48.4	51.6
SD	50.0	50.8	45.2
Median	49	35	41
Minimum–maximum	1–206	0–316	1–208

H-value = 7.371, df = 2, *p* = 0.025.
df, degrees of freedom; SD, standard deviation.

TABLE 60 *Number of dressings per patient by dressing type*

	Mean	**95% CI**	**SD**	**Minimum**	**Maximum**
Inadine	60.0	50.7 to 69.3	48.6	0	206
Aquacel	45.0	36.1 to 53.8	45.2	0	169
N-A	46.4	37.8 to 55.0	44.7	0	208

TABLE 61 *Cost of dressings per patient by dressing type (GBP)*

	Mean	**95% CI**	**SD**	**Minimum**	**Maximum**
Inadine	17.48	14.71 to 20.09	14.09	0	59.74
Aquacel	43.60	35.04 to 52.16	43.81	0	163.93
N-A	14.85	12.10 to 17.61	14.30	0	66.56

TABLE 62 *Costs (GBP) of professional time in changing dressings per patient by dressing type*

	Mean	**95% CI**	**SD**	**Minimum**	**Maximum**
Inadine	166.17	112.35 to 219.98	282.12	0	1580
Aquacel	147.73	107.26 to188.19	207.05	0	1140
N-A	126.32	93.40 to 159.24	170.94	0	820

TABLE 63 *Total costs (GBP) associated with dressings management per patient by dressing type*

	Mean	95% CI	SD	Minimum	Maximum
Inadine	183.60	128.92 to 238.21	286.47	0	1626.11
Aquacel	191.33	148.41 to 234.25	219.63	0	1287.44
N-A	141.18	108.18 to 174.17	171.31	0	848.16

TABLE 64 *Costs (GBP) of professional time in managing diabetic foot-related problems per patient by dressing type*

	Mean	95% CI	SD	Minimum	Maximum
Inadine	556.90	422.32 to 691.48	705.51	0	4008.49
Aquacel	459.87	354.78 to 564.97	537.75	0	3086.57
N-A	448.86	348.68 to 549.03	520.17	0	2318.25

TABLE 65 *Probability of healing per patient by dressing*

	Intention to treat (%)		*Per protocol* (%)	
	Week 12	Week 24	Week 12	Week 24
Inadine	30	44	34	55
Aquacel	28	45	36	63
N-A	26	39	34	59

TABLE 66 *Time to healing (days) per patient by dressing*

	Intention to treat		*Per protocol*	
	Week 12 Mean (95% CI)	Week 24 Mean (95% CI)	Week 12 Mean (95% CI)	Week 24 Mean (95% CI)
Inadine	74 (70 to 78)	128 (118 to 138)	73 (69 to 77)	118 (106 to 130)
Aquacel	72 (68 to 77)	126 (115 to 137)	69 (64 to 74)	109 (95 to 122)
N-A	75 (72 to 79)	131 (121 to 141)	72 (68 to 77)	111 (97 to 124)

TABLE 67 *Number of ulcer-free days per patient by dressing*

	Mean	95% CI	SD	Minimum	Maximum
Inadine	40.2	29.8 to 50.5	54.2	0	168
Aquacel	42.1	31.2 to 53.1	55.9	0	168
N-A	37.3	27.1 to 47.4	52.45	0	168

the three dressings ($p = 0.038$) – see *Table 5* – with 19% for Inadine, 30% for Aquacel and 34% for N-A. Clearly, the issue relates to the implications associated with withdrawal and the risk of minor and major amputation. It has been suggested that 15% of ulcers will result in amputation.[6] There were seven amputations reported during the study, with two being recorded as major and the remainder as minor – out of a patient cohort of 317, which represents an incidence rate of 2%.

In summary, there were no statistically significant differences between the three groups in relation to the numbers healed, probability of healing, ulcer-free days and QoL. However, there was a difference between dressing types in the number of withdrawals, and it is conceivable that this may have implications regarding amputation risk and therefore potential additional costs per healed ulcer. Further work is required to estimate the relationship between withdrawals, non-healing and risk of amputation.

Cost-effectiveness

Given that there were no statistically significant differences in effects between the three groups, the nature of the economic evaluation resorts to that of cost-minimisation analysis, with Inadine having the lowest acquisition cost but, due to the number of dressings used, being more expensive than N-A – although there was no statistically significant difference between them, in relation to either number or cost of dressings.

However, due to the fact that the study was not set up to demonstrate equivalence, a series of cost-effectiveness ratios have been computed in order to determine which of the dressings represents best value for money.

Incremental cost-effectiveness ratios

The incremental cost-effectiveness ratio (ICER) provides an indication of the additional benefit generated relative to the additional costs incurred by using a more effective type of dressing. The costs incurred in securing a 1% likelihood increase in healing using the 'more effective' types of dressings are shown in *Table 68*.

The cost of securing a 1% likelihood increase in healing using Inadine rather than N-A is £8.48, while the cost of securing a 1% likelihood increase in healing using Aquacel as opposed to Inadine is £7.73. When comparing N-A with Aquacel, the difference in effect amounted to 6% while the difference in cost amounted to £50.15 and an ICER of £8.36. These findings indicate that the cost of generating a healed ulcer using N-A amounted to £362 while for each additional healed ulcer using Inadine or Aquacel, the cost would be £848 or £836 respectively.

The costs incurred in securing additional healing time using the 'more effective' types of dressings are shown in *Table 69*.

The cost of generating an ulcer-free day using N-A amounted to £3.79, while the cost of each additional ulcer-free day using Inadine or Aquacel would be £14.43 or £10.26 respectively. When comparing N-A with Aquacel, the difference in effect amounted to 4.89 ulcer-free days, while the difference in cost amounted to £50.15 and an ICER of £10.26.

Sensitivity analysis

The baseline cost per healed ulcer is shown in *Table 70*. The current prices of dressings are £0.30 for Inadine and £1.03 for Aquacel.[19] The effect of using these prices would be to reinforce the advantage of using N-A as shown in *Tables 70* and *71*.

Given the relative cost advantage that N-A has in terms of both cost per healed ulcer and cost per ulcer-free day, the extent to which this is affected by changes in the respective cost profiles is assessed by considering the distribution of costs and using the upper cost for N-A and the lower cost for Inadine/Aquacel. The results are shown in *Tables 72* and *73*. These results demonstrate that the findings are highly sensitive to changes in costs and that the acquisition cost of any particular dressing is inconsequential in relation to the overall costs associated with the management of dressings in patients with diabetic foot ulcers. It can be seen that Inadine dominates (is more effective and less expensive than) N-A, while Aquacel dominates both N-A and Inadine.

The additional risk of amputation, resulting from differences in non-healing rates, has not been included in the analysis as it is not clear what the implications of withdrawals – and non-healing – represent in terms of amputation risk, additional costs and over what period of time they occur.

TABLE 68 *Probability of healing, costs and ICER for each dressing type at 24 weeks*

	Probability of healing (%)	Difference in effect (%)	Cost (GBP)	Difference in cost	ICER
N-A	39		141.18		3.62
Inadine	44	5	183.60	42.38	8.48
Aquacel	45	1	191.33	7.73	7.73

ICER, incremental cost-effectiveness ratio.

TABLE 69 *Cost per ulcer-free day and ICERs for each dressing type*

	Number of ulcer-free days	Difference in effect	Cost (GBP)	Difference in cost	ICER
N-A	37.2		141.18		3.79
Inadine	40.2	2.94	183.60	42.42	14.43
Aquacel	42.1	1.95	191.33	7.73	3.96

ICER, incremental cost-effectiveness ratio.

TABLE 70 *Cost per healed ulcer per dressing at 24 weeks using 2007 prices*

	Probability of healing (%)	Difference in effect (%)	Cost (GBP)	Difference in cost	ICER
N-A	39		141.18		3.62
Inadine	44	5	184.17	42.99	8.60
Aquacel	45	1	194.03	9.86	9.86

TABLE 71 *Cost per ulcer-free day per dressing using 2007 prices*

	Number of ulcer-free days	Difference in effect	Cost (GBP)	Difference in cost	ICER
N-A	37.2		141.18		3.79
Inadine	40.2	2.94	184.17	42.99	14.62
Aquacel	42.1	1.95	194.03	9.86	5.06

TABLE 72 *Cost per healed ulcer per dressing at 24 weeks using upper cost for N-A and lower cost for Inadine/Aquacel*

	Probability of healing (%)	Difference in effect (%)	Cost (GBP)	Difference in cost	ICER
N-A	39		238.21		
Inadine	44	5	148.41	–89.80	Dominates
Aquacel	45	1	108.18	–40.23	Dominates

TABLE 73 *Cost per ulcer-free day per dressing at 24 weeks using upper cost for N-A and lower cost for Inadine/Aquacel*

	Number of ulcer free days	Difference in effect	Cost (GBP)	Difference in cost	ICER
N-A	29.8		238.21		
Aquacel	47.4	17.5	148.41	–89.80	Dominates
Inadine	53.1	5.7	108.18	–40.23	Dominates

Data not presented

Toe systolic pressures

Toe systolic pressures were included as one of two methods of excluding severe peripheral arterial disease (PAD) – the other being ABPI. In practice, routine measures of toe systolic pressure proved difficult to obtain and severe PAD was excluded on the basis of ABPI in nearly all cases. The number of missing data for toe systolic pressures was such that the mean results were not analysed.

Ulcer area

Change in the cross-sectional area of each ulcer was a planned secondary outcome measure for those that did not heal. Although the practice of taking an image was checked at monitoring, the quality of the images obtained was not, and many were of insufficient quality to allow analysis. Usable measures were obtained from only 87 of 167 ulcers still ongoing at visit 7 and from only 56 of 94 ongoing at visit 13. It was because of the number of missing data that no attempt was made to analyse those that were available (see Appendix 6).

Change in wound bed status

It has not yet been possible to analyse the relative changes in the description of the wound bed in the different dressing groups.

Chapter 4
Discussion

The principal finding of this study was that there was no difference between the three dressing products in the incidence of healing at either 24 weeks or 12 weeks. There was similarly no difference in the time to healing in those index ulcers which healed at either of these two times. These findings emphasise the need for clinicians to seek firm evidence of effectiveness of dressing products before adopting them, but the results also provide a benchmark against which other products can be compared in future, in similar well-characterised populations.

The definition of healing used was chosen to be one that was robust, by excluding ulcers which break down within the first 4 weeks of initial epithelialisation. The incidence of recurrence at the site of the index ulcer, and of occurrence of a new ulcer at a different site, within 3 months of healing was also examined – as the dressing may have contributed to the quality of the healing and integrity of the newly formed epidermis and dermis. No difference was observed, however, between groups, even though the overall incidence of recurrence was high, as in other published studies: 12 of the 115 (10%) participants on whom data were available suffered recurrent ulceration at the same site within 3 months of healing, while 22 of 118 (18.6%) participants who healed had an ulcer at another site. A total of 41 of the 233 (17.6%) of the total population for whom there were data developed a new ulcer in the 3-month follow-up phase, while the original ulcer was ongoing in 13. These findings highlight the extent of the suffering that may be caused by foot disease – suffering that may be underestimated if too much reliance is put on short-term ulcer-related measures, such as time to healing of an index ulcer or reduction in ulcer area, while neglecting long-term patient-centred measures.[28]

Randomisation was stratified by both study centre and cross-sectional area of the ulcers at baseline. Stratification by area was into three groups: 25–100 mm^2, 101–250 mm^2 and 251–500 mm^2, and the distribution between groups was relatively equal. For the purposes of analysis, however, the middle and largest categories of ulcer were combined and the results compared with those with a cross-sectional area of 25–100 mm^2. Stratification by area is important because it is known that the speed of healing is roughly linear in chronic ulcers and, hence, the percentage that heals in a fixed time is dependent on cross-sectional area at baseline. There was no difference in the numbers of ulcers of different area allocated to each of the three dressing groups. Peripheral arterial disease may also be associated with a delay in healing, although it was not demonstrated in the subgroup analysis of the data in this study and there was similarly no difference in the prevalence of PAD in the three groups. There was also no difference between the three groups in terms of any of the demographic and other social and clinical features recorded – even though none of these has been consistently shown to be associated with delayed healing in people with chronic foot ulceration of diabetes.

The population was, nevertheless, somewhat different from that previously reported in consecutive series of ulcers managed in the UK – including reports by ourselves – in that there was a rather higher proportion of males, who outnumbered females by a ratio of roughly 3:1 instead of the more usual 2:1. The population was also selected so that severe PAD was excluded, and *Table 10* indicates that for a UK population an unusually high proportion had at least one foot pulse palpable.

The apparently low prevalence of PAD in this population would have been expected to be associated with a higher incidence of healing by 24 weeks than that anticipated. In practice, the incidence of healing by 24 weeks was higher than predicted for N-A, the simplest of the three dressings, at 38.7%, but lower for Inadine (42.6% versus 50%) and for Aquacel (44% versus 55%).

The primary outcome measure (healing by 24 weeks) was analysed by both ITT and *per protocol*. In neither case was there any difference observed between the three treatment groups. There was similarly no difference between groups in the time (days) to healing in those who healed by 24 weeks. The lack of difference in the *per protocol* analyses is important as one of the findings of this study was that there was a significant difference

between groups in the numbers of participants being withdrawn from the study, with the highest number of withdrawals being observed in those who were randomised to N-A. Given that there was no difference in the incidences of adverse reactions to the three dressings, it is very possible that this higher rate of withdrawal reflected the preference of the person (professional or non-professional) who was undertaking the dressing changes. Such a preference may in some instances be based on the belief by this person that a simple dressing such as N-A was unsuitable for certain types of ulcers. The *per protocol* analysis indicates, however, that there was no difference between groups in those who continued on the dressing to which they had been randomised.

When making a choice of dressings, one of the factors that is commonly considered in clinical practice is the quality of the wound bed, with certain dressing types being selected for those that are, for instance, covered by surface slough. We found, however, no difference in eventual outcome of ulcers that were more or less sloughy. We also found no difference in the outcome of clean ulcers when different dressings were used. A difference between dressings was observed, however, in the outcomes of ulcers that were more than 50% covered with slough, but this was attributed to the greater number of participants who were randomised to N-A being withdrawn from both groups. Once again, the reason for this higher rate of withdrawal is not clear because no difference was observed between dressings in the incidence of adverse events (whether serious or not).

The choice of dressing might have been thought to have an influence on the incidence of secondary infection with, potentially, the incidence of secondary infection being lower in those managed with an antiseptic preparation, such as Inadine. It was therefore surprising to find that, although there was a significant difference in the incidence of secondary infection between the three groups, it was the antiseptic, Inadine, that was associated with the highest number of cases. It should be noted, however, that Inadine was associated with the least withdrawals and it is likely that this difference could be accounted for by the differences between the duration of use of each of the three products.

The majority of people with chronic ulceration of the foot in diabetes have distal symmetrical neuropathy, and it may be partly as a result of this that the prevalence of local pain and discomfort can be underestimated. We found, however, that such pain or discomfort was reported by over 20% of participants. In this respect, it should be noted that that those with significant ischaemia were excluded from the population selected for this study and it is likely that the prevalence of local pain may be even higher in a less selected population. The prevalence of local pain/discomfort remained unaltered in unhealed ulcers up to the end of the 24-week intervention phase. There was no difference in the prevalence of pain at baseline in participants randomised to each of the three dressing groups, although a difference between groups was noted when change in the severity of reported local pain between the first and second visits (the first 2 weeks of the intervention) was examined. Specifically, we found that while the mean pain score reduced in those managed with N-A, it increased in those randomised to Inadine or Aquacel. The difference between groups was significant and post hoc analysis suggested that it could be accounted for by the difference between N-A and Aquacel.

No differences were observed at baseline between groups in either generic (SF–36) or ulcer-specific (CWIS) measures of QoL. When those with healed ulcers were compared with those whose ulcers persisted unhealed, a significant difference was observed at 24 weeks in all three domains of CWIS: physical functioning, social functioning and well-being. A significant difference was observed also at 12 weeks for physical functioning and well-being, but not for social functioning. No differences were observed at either time using SF–36.

There were marked differences between centres in the number of participants (and/or carers) who undertook dressing changes on at least one occasion: between 22% and 82%, with an average of just over 50%. Almost 70% of all dressing changes were undertaken by non-professionals. This is relevant to the frequency of dressing changes recorded. The protocol stipulated that dressings should be changed no less frequently than three times each week, although older products, such as N-A and Inadine, are generally changed more often than newer products, thereby potentially involving an increased amount and cost of professional time. In this respect it is notable that we found that although the overall mean (and median) number of dressings used was lower for Aquacel than for the other two products (and the difference between groups was statistically significant), there was no such difference between groups in the frequency of dressing changes performed when participants/carers were involved

in dressing changes. This means that conclusions based on the cost-effectiveness of one or other product may be limited in practice by whether or not, or how often, dressing changes are dependent on the input of professionals.

Cost-effectiveness analysis

The only statistically significant difference between the three dressing types was in relation to their acquisition cost and the number of dressings used. The additional cost of Aquacel was not offset by a reduced frequency of dressing changes. There was no significant difference observed in the frequency of dressing changes between groups nor in the proportion of dressing changes undertaken by professionals, with nearly 70% of dressing changes undertaken by non-professionals. It might be the case that non-professionals changed Aquacel dressings more frequently than professionals would have done, but in the trial the overall mean material cost of using Aquacel per patient was significantly higher: approximately £44 compared with £15 for N-A. If these findings were generalisable across the UK, where the incidence of new ulcers is estimated at 40,000, it is possible to derive a potential increased annual cost that is attributable to using a product such as Aquacel in preference to one such as N-A, which would exceed £1 million in any 6-month period.

Further analysis of the effectiveness of the different dressing products was hampered by the difference in withdrawal rates between the groups, with N-A being withdrawn significantly more often. The reason for this increased rate of withdrawal is not clear because there was no difference in incidence of adverse events and SAEs between groups. It is possible, but unproven, that participants using N-A had their product withdrawn because either they, or their professional advisors, felt that this product was unsuitable for their chronic wound. Analysis of the reasons for withdrawal documented for each of the three dressings reveals that 17 of the withdrawals from the N-A group were attributable to protocol violation or withdrawal of consent, which was more than for both Aquacel (12) and Inadine (7). These two reasons could account for the difference in rate of withdrawal that was observed. There was no difference in the incidence of adverse events between the three groups, and in the incidence of infective episodes, in particular.

This difference in rate of withdrawal has implications for the health economic analyses that could be undertaken, because the analyses assume that the increased rate of withdrawal relates to the properties of the dressing rather than to – as may be the case – the beliefs of either participants or professionals concerning its properties. The implications of withdrawals (and non-healing) would add significantly to the overall costs associated with treating diabetic foot ulcers, if the withdrawals (and non-healing) contributed to an increased risk of amputation. There is, however, no evidence that this was the case. Further work is needed to determine the extent of the relationship between non-healing of ulcers and risk of amputation in order to fully assess the cost implications.

Two final caveats must be added to the assessment of these findings. The first is that the comparison of the secondary outcomes involved a very large number of statistical analyses, and caution must be attached to the significance of any differences found. The study was powered only for the primary end point, and other apparent differences must be regarded as being simply suggestive. The other caution relates to the part played by dressings in overall strategies regarding the management of chronic wounds. Despite the attention paid to choice of dressings in clinical practice, it is likely that the contribution that it makes to healing is relatively limited.

Chapter 5
Conclusions

We found no difference in the effectiveness of the three dressing products studied.

We confirmed the expectation that a greater proportion of smaller ulcers would heal within the specified time of 24 weeks: 48% versus 36%. We also found that in 115 participants for whom there were data, the ulcer recurred in 12 (10%) within 3 months, and during this time only 80% of participants remained entirely ulcer free.

In the health economic analysis, the only statistically significant difference was in the costs associated with the provision of dressings. There was no difference in the costs of professional time involved in dressing changes, while the fact that there was no difference in the effectiveness of the three dressings resulted in the economic evaluation taking the form of a cost-minimisation analysis. The additional costs incurred by the use of Aquacel do not appear to be justified given no difference in effectiveness between the dressing types.

We found no difference between dressings in terms of HRQoL, although differences were found between those with healed and with unhealed ulcers using the CWIS. We also found that there was a difference between dressing groups in pain recorded in the first 2 weeks of the intervention phase, with those managed with N-A having a greater reduction in pain than the other groups. There was, however, no difference between the three groups throughout the intervention phase in the prevalence of pain in all unhealed ulcers.

Overall we found that 51% of all participants had at least one dressing change undertaken by themselves or their carer, although this percentage ranged from 22% to 82% between centres. Almost 70% of all dressing changes were undertaken by non-professionals.

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Participating centres

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Cardiff
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Hull
Hull Royal Infirmary – Dr Ewan Masson, Dr Jane Patmore, Mr Alistair Hunt.
Ipswich
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Progress of the study

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First participants recruited – January 2004
New centres recruited – October 2004
Final participant recruited – June 2006
End of data collection – March 2007
Data entry and analysis – March–August 2007
Presentation of draft final report – September 2007
Receipt of reviewers' comments – September 2008
Presentation of revised final report – December 2008

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Appendix 1

Indications for taking other medications during the course of the study

Reason for taking medication	Number of reported episodes of medication prescription
Infection	560
Diabetes	529
Hypertension	495
Pain relief	204
Hyperlipidaemia	193
Antiplatelet	178
Depression	79
Asthma	55
Angina	46
Indigestion	42
Anaemia	27
Diuretic	26
Anticoagulant	23
Eyes	22
Gastric irritation	20
Nausea	19
Cramp	18
Hypothyroidism	17
Osteoporosis	15
Atrial fibrillation	14
Constipation	14
Gout	13
Erectile dysfunction	12
Prevent flu	11
Diarrhoea	7
Insomnia	7
Moniliasis	7
Obesity	7
Urinary tract infection	7
Arthritis	7
Arrhythmia	6
Psoriasis	6
Schizophrenia	5
Topical corticosteroid	5
General health	4
Hormone replacement therapy	4
Pernicious anaemia	4
Rehydration	4
Anxiety	3
Cardiovascular	3
Colitis	3
Methicillin-resistant *Staphylococcus aureus*	3
Mydriatic	3

Reason for taking medication	Number of reported episodes of medication prescription
Alcohol detoxification	2
Allergy	2
Barrier cream	2
Calcium	2
Hormone antagonist	2
Hypoglycaemia	2
Incontinence	2
Leg cramps	2
Malabsorption	2
Tinea pedis	2
Vitamin C	2
Irritable bowel	2
Anti-inflammatory	1
Cervical spondylosis	1
Cold	1
Conjunctivitis	1
Contraceptive pill	1
Chronic obstructive pulmonary disease	1
Cough	1
Dehydration	1
Ear infection	1
Epilepsy	1
Foot cream	1
Helicobacter eradication	1
Help stop smoking	1
Immunosuppression	1
Laxative	1
Migrane	1
Neurogenic bladder instability	1
Nutrition	1
Polycythaemia rubra vera	1
Postural hypotension	1
Prostate	1
Rheumatic fever prevention	1
Rhinitis	1
Sedative	1
Skin rash	1
Urinary retention	1
Vitamin D deficiency	1

Appendix 2

All other medications taken during the course of the study

Drug name	Number of episodes	Reason for taking medication
Acamprosate	1	Alcohol
Acarbose	2	Diabetes
Actrapid insulin	25	Diabetes
Adcal-D_3	1	Osteoporosis
Aledronic acid	6	Osteoporosis
Alfacalcidol	1	Vitamin D deficiency
Allopurinol	12	Gout
Alprostadil	3	Erectile dysfunction
Aminophylline	1	Asthma
Aminoquinoline	1	Rheumatoid arthritis
Amiodarone	5	Arrhythmia
Amitriptyline	14	Pain
Amitriptyline	19	Depression
Amlodipine	38	Hypertension
Amoxycillin	69	Infection
Amoxycillin (intravenous)	2	Infection
Amphoteracin lozenges	1	Moniliasis
Anastrazole	1	Hormone antagonist
Aquasept hair wash	1	Methicillin-resistant *Staphylococcus aureus*
Aqueous cream	1	Foot cream
Ascorbic acid	2	Vitamin C
Aspirin	153	Antiplatelet
Atenonol	32	Hypertension
Atorvastatin	67	Hyperlipidaemia
Atropine	2	Eyes
Atrovent	3	Asthma
Bactroban ointment	2	Methicillin-resistant *Staphylococcus aureus*
Balsalazide sodium	1	Colitis
Beclomethasone inhaler	12	Asthma
Beclomethasone nasal spray	1	Rhinitis
Bendroflumethiazide	37	Hypertension
Benorylate	1	Cervical spondylosis
Benzoxazocine	1	Pain
Betnovate cream	1	Topical corticosteroid
Bezafibrate modified release	1	Hyperlipidaemia
Bisoprolol	20	Hypertension/cardioprotection
Bovine hypurin isophane	1	Diabetes
Bovine hypurin neutral	1	Diabetes
Bronchial syrup	1	Cough
Bumetanide	9	Diuretic
Burinex K	1	Diuretic
Calcichew	4	Osteoporosis

Drug name	Number of episodes	Reason for taking medication
Calcium	2	Calcium
Candesartan	9	Hypertension
Captopril	2	Hypertension
Carbamazepine	6	Painful neuropathy
Carbamazepine	1	Epilepsy
Carvedilol	1	Hypertension
Cavilon cream	2	Barrier cream
Cefadroxil	2	Infection
Cefradine	1	Infection
Ceftazidime (intravenous)	4	Infection
Ceftriaxone (intravenous)	13	Infection
Celecoxib	2	Pain
Celevac	1	Laxative
Cerazette	1	Contraceptive pill
Chloramphenicol	3	Eye drops post-operatively
Chlordiazepoxide	1	Anxiety
Chlormethiazole	1	Alcohol detoxification
Chlorpromazine	3	Schizophrenia
Ciprofibrate	2	Hyperlipidaemia
Ciprofloxacin	70	Infection
Citalopram	5	Depression
Clarithromycin	2	Infection
Clindamycin	50	Infection
Clioquinol gel	1	Ear infection
Clomipramine	1	Depression
Clopidogrel	20	Antiplatelet
Clotrimazole cream	3	Moniliasis
Co-amilofruse	1	Diuretic
Co-amoxiclav	101	Infection
Cocodamol	19	Pain
Co-danthrusate	1	Constipation
Codeine	11	Pain
Co-dydramol	6	Pain
Colchicine	1	Gout
Colpermin	1	Colitis
Combivent nebuliser	1	Asthma
Coproxamol	5	Pain
Coracten	4	Hypertension
Cotenidone	1	Hypertension
Coumarin	1	Anticoagulant
Creon	2	Malabsorption

continued

Drug name	Number of episodes	Reason for taking medication
Cyclizine	7	Nausea
Cyclopentolate	2	Mydriatic
Dermovate cream	1	Topical corticosteroid
Desloratadine	1	Allergy
Detemir insulin	5	Diabetes
Dexamethasone	1	Anti-inflammatory
Dexamethasone eye drops	5	Eyes
Dextrose gel	1	Diabetes
Dextrose/saline (intravenous)	1	Rehydration
DF 118	1	Pain
Diamox eye drops	1	Glaucoma
Diclofenac	16	Pain
Digoxin	14	Atrial fibrillation
Dihydrocodeine	5	Pain
Diltiazem	15	Hypertension
Dioralyte	1	Dehydration
Diprobase cream	1	Skin rash
Dipyridamole	5	Antiplatelet
Domperidone	3	Nausea
Dorzolamide eye drops	1	Glaucoma
Dothiepin	3	Antidepressant
Dovobet cream	1	Psoriasis
Doxazosin	6	Hypertension
Doxycycline	29	Infection
Duloxetine	1	Incontinence
Dutasteride	1	Prostate
Enalapril	25	Hypertension
Enoxaparin	3	Anticoagulant
Epiderm cream	4	Psoriasis
Eprosartan	1	Hypertension
Erythromycin	11	Infection
Erythropoietin	3	Anaemia
Estraderm patches	1	Hormone replacement therapy
Etretinate	1	Psoriasis
Eumovate cream	2	Topical corticosteroid
Felodipine	15	Hypertension
Fenofibrate	5	Hyperlipidaemia
Ferrous sulphate	17	Anaemia
Finasteride	1	Hormone antagonist
Flu vaccine	11	Prevent flu
Flucloxacillin	63	Infection
Flucloxacillin (intravenous)	5	Infection
Fluconazole	1	Moniliasis
Fludrocortisone	1	Postural hypotension

Drug name	Number of episodes	Reason for taking medication
Fluoxetine	7	Depression
Fluvastatin	3	Hyperlipidaemia
Folic acid	3	Anaemia
Fortisips	1	Nutrition
Fosinopril	1	Hypertension
Frusemide	75	Hypertension
Fucibet cream	1	Topical corticosteroid with antibiotic
Fusidic acid	9	Infection
Fusidic acid eye ointment	1	Conjunctivitis
Fybogel	1	Constipation
Gabapentin	19	Painful neuropathy
Gaviscon	6	Indigestion
Gemfibrozil	1	Hyperlipidaemia
Gentamicin (intravenous)	8	Infection
Glargine insulin	45	Diabetes
Glibenclamide	5	Diabetes
Gliclazide	68	Diabetes
Glimepiride	3	Diabetes
Glucagon	1	Hypoglycaemia
Glyceryl trinitrate spray	4	Angina
Glyceryl trinitrate tablets	11	Angina
Heliclear	1	*Helicobacter* eradication
Heparin	3	Anticoagulant
Humalog insulin	20	Diabetes
Humulin S insulin	1	Diabetes
Hydralazine	1	Hypertension
Hydrochloroquinine	1	Arthritis
Hydroxyurea	1	Polycythaemia rubra vera
Hydroxyzine	1	Sedative
Hypostop gel	1	Hypoglycaemia
Hypurin neutral insulin	2	Diabetes
Ibuprofen	11	Pain
Imipenem	4	Infection
Imipramine	1	Depression
Indapamide	13	Hypertension
Indomethacin	1	Pain
Indoramin	1	Hypertension
Insulatard insulin	27	Diabetes
Ipatropium	2	Asthma
Irbesartan	9	Hypertension
Iron	4	Anaemia
Isophane insulin	3	Diabetes

continued

Drug name	Number of episodes	Reason for taking medication
Isosorbide mononitrate	15	Angina
Lacri-Lube	1	Eyes
Lactulose	4	Constipation
Lansoprazole	21	Indigestion
Latanoprost	2	Glaucoma
Lemsip	1	Cold
Lercanidipine	1	Hypertension
Levomepromazine	1	Anti-emetic
Liothyronine sodium	1	Hypothyroidism
Liquifilm	1	Eyes
Lisinopril	38	Hypertension
Lodoxamide eye drops	1	Allergy
Loperamide	6	Diarrhoea
Lormetazepam	2	Anxiety
Losartan	7	Hypertension
Magnapen	1	Infection
Magnesium tablets	2	Leg cramps
Mebeverine	1	Colitis
Meloxicam	2	Pain
Meptazinol	1	Pain
Metformin	147	Diabetes
Methotrexate	3	Arthritis
Methyldopa	1	Hypertension
Metoclopramide	3	Nausea
Metolazone	3	Cardiovascular
Metronidazole	37	Infection
Metronidazole (intravenous)	8	Infection
Minocyclin	1	Infection
Mirtazapine	2	Depression
Mixtard 30 insulin	67	Diabetes
Mixtard insulin	29	Diabetes
Moexapril	1	Hypertension
Morphine sulphate	5	Pain
Movicol	2	Constipation
Moxonidine	4	Hypertension
Multivitamin tablet	1	General health
Nateglinide	1	Diabetes
Nebivolol	1	Hypertension
Nefopam	1	Pain
Nicorandil	12	Angina
Nicorette patch	1	Help stop smoking
Nicotinic acid	1	Hyperlipidaemia
Nifedipine	12	Hypertension
Nifedipine	3	Angina

Drug name	Number of episodes	Reason for taking medication
Normacol	1	Constipation
Normal saline infusion	2	Rehydration
Nortriptyline	1	Depression
Nystatin	2	Moniliasis
Ofloxacin	7	Urinary tract infection
Olanzapine	1	Depression
Olmesartan	1	Hypertension
Omeprazole	20	Gastric irritation
Oramorph	6	Painful neuropathy
Orlistat	6	Obesity
Oxybutynin	1	Neurogenic bladder instability
Oxycontin	1	Pain
Oxygen	1	Chronic obstructive pulmonary disease
Oxytetracycline	2	Infection
Pamidronate (intravenous)	1	Osteoporosis
Pantoprazole	3	Indigestion
Paracetomol	43	Pain relief
Paroxetine	3	Depression
Penicillin	4	Infection
Penicillin (intravenous)	6	Infection
Peppermint oil	1	Irritable bowel
Perindopril	14	Hypertension
Phosphate enema	1	Constipation
Pilocarpine drops	1	Glaucoma
Pioglitazone	3	Diabetes
Pizotifen	1	Migrane
Pravastatin	20	Hyperlipidaemia
Prazosin	1	Hypertension
Prednisolone	2	Arthritis
Prednisolone	5	Asthma
Pregabalin	1	Painful neuropathy
Premique	1	Hormone replacement therapy
Prochlorperazine	4	Nausea
Propranolol	3	Hypertension
Quetiapine	2	Schizophrenia
Quinapril	1	Hypertension
Quinine sulphate	18	Cramp
Ramipril	86	Hypertension
Ranitidine	12	Indigestion
Rifampicin	2	Infection
Risedronic acid	3	Osteoporosis
Rosiglitazone	20	Diabetes

continued

Drug name	Number of episodes	Reason for taking medication
Rosuvastatin	5	Hyperlipidaemia
Salbutamol inhaler	22	Asthma
Senna	4	Constipation
Seretide	4	Asthma
Sertraline	3	Depression
Sibutramine	1	Obesity
Sildenafil	8	Erectile dysfunction
Simvastatin	87	Hyperlipidaemia
Sodium bicarbonate infusion	1	Rehydration
Sodium valproate	1	Painful neuropathy
Solpadol	5	Pain
Sotalol	1	Arrhythmia
Spirolactone	14	Diuretic
Sulfadiazine	1	Rheumatic fever prevention
Symbicort	1	Asthma
Tacrolimus	1	Immunosuppression
Tadalafil	1	Erectile dysfunction
Tamsulosin	1	Urinary retention
Teicoplanin	8	Infection
Temazepam	7	Depression/anxiety/insomnia
Terbinafine cream	2	Tinea pedis
Terbutaline inhaler	2	Asthma
Thiamine	3	General health
Thyroxine	16	Hypothyroidism
Tibolone	1	Hormone replacement therapy
Timolol drops	3	Glaucoma
Tolterodine	1	Incontinence
Tramadol	20	Pain
Trandolapril	5	Hypertension
Trazodone	1	Depression
Triamterene	1	Diuretic
Trimethoprim	20	Infection
Tropicamide	1	Mydriatic
Ultratard insulin	1	Diabetes
Uniphyllin	1	Asthma
Valsartan	13	Hypertension
Vancomycin	1	Infection
Venlafaxaine	5	Depression
Verapamil	1	Angina
Vitamin B12	4	Pernicious anaemia
Volterol	1	Pain
Warfarin	16	Anticoagulant
Zoperamide	1	Diarrhoea

Drug name	Number of episodes	Reason for taking medication
Zopiclone	7	Insomnia
Other antibiotics	5	Infection
Other antibiotics (intravenous)	2	Infection
Other antidepressant	1	Depression
Other anti-emetic (intravenous)	1	Anti-emetic
Other corticosteroids	1	Asthma
Other eye drops	2	Glaucoma
Other hormone replaacement therapy preparation	1	Menopausal symptoms
Other insulins	52	Diabetes
Other proton pump inhibitor	1	Stabilise bowel movement
Other statin	1	Hyperlipidaemia

Appendix 3

Methods of off-loading by dressing allocation

	Intervention			
Off-loading method	**Inadine**	**Aquacel**	**N-A**	**Total**
Scotchcast boot	31	26	40	97
Total contact insole	5	1	2	8
Bilateral insoles	0	1	0	1
Focus rigidity slipper cast	2	1	1	4
Clinical felt padding	2	3	1	6
Orthotic/bespoke footwear	18	12	11	41
None used	4	2	2	8
Rest	0	0	1	1
Rocker bottom shoes	0	0	1	1
Aircast walker/boot	5	1	3	9
Considering a Scotchcast boot	0	1	1	2
Awaiting bespoke shoes	2	2	0	4
Shoes modified (e.g. hole cut in shoe)	0	1	1	2
Footwear/shoe with clinical padding	3	7	4	14
Total contact insole and surgical footwear	1	0	0	1
Contact cast	1	0	0	1
Bespoke shoes plus clinical padding	1	0	0	1
Temporary shoe	1	1	1	3
Half shoe	2	3	3	8
Total contact cast	1	0	0	1
Bespoke shoes with insoles	0	5	2	7
Bespoke footwear with calliper	0	0	1	1
Patient's own boots/shoes	4	3	2	9
Aircast and bespoke footwear	1	1	0	2
Darko shoe	1	1	1	3
Semi-compressed felt	0	2	2	4
Bandaging	2	1	1	4
Removable total contact insole and felt padding, below knee soft cast	0	1	0	1
Removable total contact cast	2	0	0	2
Blackburn boot	2	3	2	7
Total contact cast with window	2	1	2	5
Bivalve total contact cast	0	3	1	4
Prafo boot	0	1	1	2
Below knee calliper	0	1	0	1
Royce boot	0	3	4	7
Royce boot plus bespoke insole	0	0	1	1
None at present, Royce boot ordered	0	0	1	1
Ventoprin boots	1	1	1	3
Below knee removable cast	0	2	1	3
Ring pad	0	0	1	1
Roho heel pad, wheelchair	1	0	0	1
Crutches	1	0	0	1

	Intervention			
Off-loading method	**Inadine**	**Aquacel**	**N-A**	**Total**
Bespoke shoes and Scotchcast boot	0	2	0	2
Scotchcast boot and crutches	1	0	0	1
Orthoses	1	0	2	3
Orthoses, leg brace, bespoke footwear	0	1	0	1
De Royal healing shoe	1	1	2	4
Specialised footwear	0	0	1	1
Scotchcast boot but surgical boot for driving	0	1	0	1
Sandal with insole	1	0	0	1
Insoles	3	2	1	6
Medi shoe	0	1	0	1
Slippers	0	1	0	1
Padded shoe	1	0	1	2
Total (missing)	105 (3)	100 (3)	105 (1)	310 (7)

Appendix 4

Reasons for withdrawal by dressing allocation

Numbers refer to individual patient code.

D1 Inadine

104 adverse event – SAE – probable infection of bone at ulcer site
217 patient withdrew consent – going away for 2 months
219 adverse event – SAE – study ulcer breakdown
233 adverse event – SAE – osteomyelitis and cellulitis
313 protocol violation
315 adverse event – non-compliant with scotch-cast boot: ulcer worse
333 lost to follow-up
358 adverse event – study ulcer infected and macerated
407 adverse event – SAE – fever, vomiting and infection; patient admitted to hospital
430 patient withdrew consent – adverse event also recorded; ulcer infected
436 patient withdrew consent
501 lost to follow-up
510 protocol violation
528 patient withdrew consent
544 death – recorded as adverse event – SAE – shortness of breath, admitted to hospital with abdominal pain and diarrhoea, died
601 adverse event – SAE – abscess probed from ulcer, admitted to hospital
603 protocol violation
701 protocol violation – SAE – ulcer deteriorating with osteomyelitis, admitted to hospital for intavenous antibiotics
717 recruited in error/protocol violation
806 adverse event – patient collapsed at home
901 patient gone to USA for 8 weeks

D2 Aquacel

103 adverse event – SAE – amputation of first toe (site of study ulcer)
106 lost to follow-up – 4 weeks between visits
115 SAE – infection on study ulcer foot
134 creatinine
203 adverse event – swelling and increase in temperature – Charcot
221 adverse event – study ulcer infected
228 patient withdrew consent
238 protocol violation
301 adverse event – dryness of trial dressing caused pain; study ulcer infected
323 adverse event – on compliance – SAE – infection of study ulcer
327 adverse event – patient went into full contact cast – study ulcer infected and wound deteriorated
334 adverse event – wound deteriorated, total contact cast required
343 protocol violation
347 lost to follow-up – SAE – study ulcer infected
402 adverse event – SAE – chest infection, patient admitted to hospital
410 adverse event – SAE – fractured pelvis, admitted to hospital
431 protocol violation
443 lost to follow-up – adverse event – wound infection
445 protocol violation
447 protocol violation
502 patient withdrew consent
516 death
532 death
534 renal transplant patient, recruited in error – adverse event study ulcer infected
550 protocol violation – adverse event – study ulcer infected
551 adverse event- non-study ulcer sloughy and painful
607 patient withdrew consent
704 patient withdrew consent
805 protocol violation
916 lost to follow-up

D3 N-A

109 patient withdrew consent
116 adverse event – infection/sinus
120 protocol violation
205 adverse event – SAE – admitted to hospital with cellulitis
207 adverse event – increasing maceration
208 non compliance
209 protocol violation – adverse event – increasing maceration
218 adverse event – study ulcer infected; tracking in study ulcer

222 adverse event – study ulcer infected
223 death
224 adverse event – study ulcer infected
229 patient withdrew consent
237 adverse event – study ulcer deeper and infected
311 patient withdrew consent
341 protocol violation
353 lost to follow-up
401 patient withdrew consent
411 protocol violation
422 protocol violation – fractured hip
437 death
450 protocol violation
505 lost to follow-up
512 protocol violation
522 adverse event – ulcer erythematous, possible reaction to dressing
529 adverse event – *Pseudomonas* infection around wound site
530 patient withdrew consent
546 protocol violation – SAE – admitted to hospital for infected study ulcer – below knee amputation
563 protocol violation
615 patient withdrew consent
616 adverse event – SAE – renal failure caused by sepsis in study ulcer, patient admitted to hospital
617 adverse event – SAE – cellulitis – admitted to hospital
706 adverse event – ulcer worse
903 adverse event – ulcer infection, admitted to hospital, trial dressing no longer suitable, not absorbent – SAE – admitted for abscess on right hip
906 protocol violation – patient went into full contact cast
914 adverse event – wound infection and deterioration, total contact cast required
918 trial dressing no longer appropriate – excessive discharge
922 adverse event – wound infection

Appendix 5

Serious adverse events

Serious adverse events in participants who reported only one event

	Dressing allocation		
Description of SAE	**Inadine**	**Aquacel**	**N-A**
Abdominal pain		1	
Abscess probed	1		
Admitted for angiogram	1		1
Admitted for angioplasty			1
Admitted for bypass and ulcer debridement			1
Admitted for debridement of non-study ulcer	1		
Admitted for sliding scale insulin			1
Admitted to hospital	1	1	2
Admitted with abscess in hip			1
Admitted with chest infection		1	
Admitted with chest pain			1
Admitted with headaches and high blood pressure	1		
Admitted with high potassium levels			1
Admitted with infection in non-study ulcer	1		
Admitted with infection in study foot			1
Admitted with liver problems			1
Admitted with renal failure			1
Cellulitis			4
Chest and hip pain		1	
Collapsed due to poor diabetic control	1		
Died		1	
Eye operation	1	2	2
Eye vitrectomy	1		
Fever, vomiting and infection	1		
Foot infection	1	1	
Fractured pelvis/hip		1	1
Gastric bypass			1
Haemoptysis	1		
Heart attack			1
Foot inflamed		1	
Hypoglycaemia	1	1	
Infection	1		
Infection in new ulcer		1	
Infection in study ulcer	1	4	
Infection of toe joint		1	
Leg and back pain		1	
Myocardial infarction			1
Necrosis		1	
New non-study ulcer	2		
Osteomyelitis	1		
Osteomyelitis and cellulitis	1		

	Dressing allocation		
Description of SAE	**Inadine**	**Aquacel**	**N-A**
Physical assault		1	
Planned admission for surgery			1
Hyperglycaemia	1		
Rigors		1	
Superficial femoral artery occlusion – urgent angiography		1	
Shortness of breath	1		
Slurred speech and unable to talk		1	
Study ulcer broken down	1		
Surgery for hammer toe		1	
Unable to move leg			1
Total	22	24	24

Serious adverse events in participants who reported two events

	Dressing allocation		
Description of SAE	**Inadine**	**Aquacel**	**N-A**
Admission for eye vitrectomy	1		1
Admission with infection in study ulcer	1		
Admitted with headaches and high blood pressure	1		
Admitted with vomiting and abdominal pain	1		
Alcohol detoxification	1		
Amputation			1
Amputation of toe		1	
Cellulitis			1
Collapsed		1	
Died		1	1
Femoro-popliteal bypass			1
Foot infection in non-study foot	1		
Infection in study ulcer and admission for revascularisation	1		
Infection of study ulcer		1	
Planned admission for rehabilitation			1
Possible infection of bone at ulcer site	1		
Pulmonary emboli, abdominal pain	1		
Septicaemia			1
Shortness of breath			1
Total	9	4	8

Serious adverse events in participants who reported three events

	Dressing allocation		
Description of SAE	**Inadine**	**Aquacel**	**N-A**
Abdominal swelling			
Admission for observation; history of vomiting			1
Admitted for angioplasty	1		
Leg infection	1		
Ruptured aortic aneurysm	1		1
Shortness of breath	1		
Total	4	0	2

Serious adverse events in participants who reported four events

	Dressing allocation		
Description of SAE	**Inadine**	**Aquacel**	**N-A**
Hospital admission with painful foot			1
Vomiting and diarrhoea	1		
Total	1	0	1

Serious adverse events in participants who reported five events

	Dressing allocation		
Description of SAE	**Inadine**	**Aquacel**	**N-A**
Patient died	1		
Total	1	0	0

Appendix 6

Changes in cross-sectional area of the ulcers between baseline and visits 7 (12 weeks) and 13 (24 weeks)

Those with baseline, visit 7 and visit 13 results

Patient code	Dressing allocation (A = Inadine, B = Aquacel, C = N-A)	Baseline (post or pre debridement ulcer size)	Visit 7 (post or pre debridement ulcer size)	Visit 13 (post or pre debridement ulcer size)	Increase or decrease in ulcer size
423	A	4.12	0.44 (pre)	0.05	Decrease
518	A	0.17	0.00	0.08	Decrease
212	A	0.19	0.10	0.10	Decrease
213	A	0.08	0.21	0.12	Increase
523	A	1.44	0.68	0.26	Decrease
515	A	2.14	1.74 (pre)	0.29	Decrease
710	A	1.72	0.11	0.3	Decrease
708	A	2.3	0.13	0.33	Decrease
540	A	1.24	1.36	0.44	Decrease
562	A	1.31	1.75	0.56	Decrease
509	A	1.80	0.51 (pre)	0.66	Decrease
117	A	16.18	1.48	0.68	Decrease
330	A	4.44	1.50	0.72	Decrease
564	A	1.98	1.94	0.81	Decrease
911	A	0.37	0.82	0.94	Increase
804	A	3.32	0.96	0.95	Decrease
429	A	1.61	1.72	1.06	Decrease
420	A	6.16	4.08	1.20	Decrease
225	A	0.52	0.68	1.24	Increase
517	A	2.98	1.73 (pre)	1.82	Decrease
713	A	5.1	4.65	3.38	Decrease
513	A	1.96	2.40	6.28	Increase
610	A	3.60	3.52	7.95	Increase
909	B	0.04	0.03 (pre)	0.21	Increase
538	B	0.29	0.25	2.43	Increase
507	B	0.25	0.43	0.25	Same
418	B	2.03	1.37	1.48	Decrease
803	B	0.42	1.86	0.58	Increase
406	B	1.61	3.40	2.31	Increase
113	B	0.91	3.81	4.09	Increase
303	B	4.39	3.86	3.10 (pre)	Decrease
405	B	5.46	5.45	6.72	Increase
511	B	2.93 (pre)	5.78	1.28	Decrease
408	C	2.95	0.14	0.04	Decrease
902	C	0.02	0.06 (pre)	0.05 (pre)	Increase
539	C	1.00	1.95	0.05	Decrease
554	C	0.43	0.47	0.08	Decrease
707	C	2.38	0.35	0.16	Decrease
428	C	0.55	0.05	0.34	Decrease
716	C	0.51	0.31	0.51	Same

Patient code	Dressing allocation (A = Inadine, B = Aquacel, C = N-A)	Baseline (post or pre debridement ulcer size)	Visit 7 (post or pre debridement ulcer size)	Visit 13 (post or pre debridement ulcer size)	Increase or decrease in ulcer size
537	C	1.80	1.14	0.60	Decrease
211	C	1.93	0.27	0.75	Decrease
349	C	3.98	2.50	0.87	Decrease
543	C	0.53	1.69	1.05	Increase
566	C	6.68	0.20	1.07	Decrease
230	C	1.39	0.61	1.25	Decrease
521	C	1.02	1.95	1.52	Increase
417	C	2.00	2.05	1.86	Decrease
419	C	5.27	8.61 (pre)	16.50	Increase

A: baseline range = 0.08–16.18; visit 7 range = 0.00–4.65; visit 13 range = 0.05–7.95.
B: baseline range = 0.04–5.46; visit 7 range = 0.03–5.78; visit 13 range = 0.21–6.72.
C: baseline range = 0.43–6.68; visit 7 range = 0.05–8.61; visit 13 range = 0.04–16.50.

Those with baseline and visit 13 results only

Patient code	Dressing allocation (A = Inadine, B = Aquacel, C = N-A)	Baseline (post or pre debridement ulcer size)	Visit 7 (post or pre debridement ulcer size)	Visit 13 (post or pre debridement ulcer size)	Increase or decrease in ulcer size
232	A	0.47	No scale	0.07	Decrease
326	A	1.34	Not done	0.08	Decrease
565	A	4.06 (pre)	Not done	0.82	Decrease
312	B	0.53	–	0.87	Increase
348	B	2.44	Healed?	1.24 (pre)	Decrease
317	C	1.81	–	0.05	Decrease
318	C	0.64	–	1.62	Increase

A: baseline range = 0.47–4.06; visit 13 range = 0.07–0.82.
B: baseline range = 0.53–2.44; visit 13 range = 0.87–1.24.
C: baseline range = 0.64–1.81; visit 13 range = 0.05–1.62.

Those with baseline and visit 7 results only

Patient code	Dressing allocation (A = Inadine, B = Aquacel, C = N-A)	Baseline (post or pre debridement ulcer size)	Visit 7 (post or pre debridement ulcer size)	Visit 13 (post or pre debridement ulcer size)	Increase or decrease in ulcer size
912	A	0.19	0.11		Decrease
111	A	0.22	0.17		Decrease
324	A	0.38	0.99		Increase
346	A	0.56	0.00		Decrease
220	A	0.70	0.78		Increase
425	A	0.71	1.88		Increase
215	A	1.17	1.02		Decrease
231	A	2.01	0.31		Decrease
801	A	3.29	3.35		Increase
612	A	6.93	4.41		Decrease
310	B	0.25	0.19		Decrease
438	B	0.32	0.26		Decrease
216	B	0.38	0.12		Decrease
210	B	0.45	0.89		Increase
606	B	0.48	0.39 (pre)		Decrease
413	B	0.49	0.40		Decrease
227	B	0.82	0.12		Decrease
206	B	1.03	0.35		Decrease
226	B	1.19	0.18		Decrease
905	B	1.29	0.63		Decrease
557	B	2.44	0.89 (pre)		Decrease
434	B	2.48	4.20		Increase
558	B	10.54	6.30 (pre)	No scale	Decrease
421	C	2.23	0.15 (pre)		Decrease
404	C	0.59	0.21		Decrease
614	C	0.27	0.28		Increase
328	C	2.99	0.38		Decrease
536	C	0.85	2.71		Increase
424	C	4.06	4.17		Increase

A: baseline range = 0.19–6.93; visit 7 range = 0.00–4.41.
B: baseline range = 0.25–10.54; visit 7 range = 0.12–6.30.
C: baseline range = 0.27–4.06; visit 7 range = 0.15–4.17.

Those with either baseline missing or no later measures

Patient code	Dressing allocation (A = Inadine, B = Aquacel, C = N–A)	Baseline (post or pre debridement ulcer size)	Visit 7 (post or pre debridement ulcer size)	Visit 13 (post or pre debridement ulcer size)	Increase or decrease in ulcer size
321	A	–	–	–	–
325	A	0.42			–
618	A	0.39			–
306	B	Not done			–
415	B	6.80			–
412	C	1.87	Not done		–
441	C	1.19			–
611	C	0.46			–
432	C	Missed	0.52	0.96	Increase

Appendix 7

Baseline demographics by outcome status

	Withdrawn (*n* = 88)	Active ulcer at end of study (*n* = 94)	Healed (*n* = 135)	Total (*n* = 317)
Gender				
Male	70	69	101[a]	240
Female	18	25	33[a]	76
Age				
Mean (SD) years	60.3 (13.2)	58.7 (12.6)	60.8 (12.1)	59.6 (12.6)
Minimum–maximum	32–85	33–88	32–88	32–87
Type of diabetes				
Type 1	23	18	27	68
Type 2	65	76	108	249
Duration of diabetes				
Mean (SD) years	16.4 (10.7)	15.6 (10.1)	15.3 (11.5)	15.7 (10.8)
Diabetes treatment				
Insulin	36	36	50	122
Insulin/OHAs	18	22	25	65
OHAs	27	28	49	104
Diet alone	7	6	11	26
Smoking status				
Yes	16	14	24	54
Past smoker	49	39	65	153
No	23	39	43	105
Missing	0	2	3	5
Cerebrovascular disease				
Yes	7	7	10	24
No	79	85	122	286
Missing	2	2	3	7
Cardiovascular disease				
Yes	38	31	54	123
No	47	61	80	188
Missing	3	2	1	6
Retinopathy				
Yes	47	58	77	182
No	39	36	58	133
Missing	2	0	0	2
Nephropathy				
Yes	14	17	36	67
No	73	75	98	246
Missing	1	2	1	4

OHAs, oral hypoglycaemic agents.
a One patient in the healed group underwent gender realignment during the trial and is not included in the data on gender.

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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