NCCHTA

18th April 2007

Full proposal

Fourth version 4th May 2005

1 Title

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

(Short title: Dressings for diabetic foot ulcers)

2 How the proposal has changed since outline proposal

Not applicable

3 Planned Investigation

3.1 Background

Epidemiology and ulcer types

Ulceration of the foot of people with diabetes (diabetic foot ulcers) are 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[1-2].

Not only does diabetes make the foot more liable to ulceration, but it 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 UK[3] and approximately 15% of all ulcers in UK result in some form of amputation[4].

While the pathobiology of chronic wounds remains poorly understood, there is no logical framework to underpin many strategies of care[5]. The choice of dressings, in particular, is largely empirical and based more on professional experience and preference than on evidence of proven efficacy. One reason for the lack of evidence base relates to the lack of a widely accepted classification system for diabetic foot ulcers – which has made it difficult to recruit sufficiently large numbers of ulcers of similar type into multicentre studies of management technologies. This has to a large extent been offset by the recent evolution and validation of two broadly similar classification systems, which has given insight into the discriminating features of groups of similar ulcers[6,7].

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 systematic reviews [8-11]. O'Meara et al[12] could find no good evidence to substantiate the use of any of the preparations in widespread use. The effectiveness of some of the most recently introduced therapeutic agents (including growth factor preparations and bioengineered human skin products) has been demonstrated in industry-funded trials, but product costs are high and in the absence of robust evidence of cost-effectiveness, they have not been widely adopted in UK. The early promise of one growth factor preparation, becaplermin, has not been confirmed in clinical practice. Further trials are also needed to determine the place of bioengineered skin products (such as Apligraf, Graftskin and Dermagraft) but they would be extremely expensive in the absence of industry funding. Moreover, the planned marketing of Apligraf in Europe has recently (January 2002) been deferred. In the mean time, the fundamental question which needs to be answered is 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 this can be established, then the information gained will be invaluable as a comparator in the later evaluation of newer technologies. N-A and Inadine dressings are widely used in routine management in UK, as is the newer – and higher unit cost – hydrofibre product, Aquacel. In one small, short-term randomised trial Aquacel has been shown to be more effective in the management of deeper diabetic foot ulcers than saline moistened gauze [13]

Cost-effectiveness

In order to compare the effectiveness of traditional and more modern dressing materials, it is necessary to undertake a multicentre randomised controlled trial of sufficient power, such as that proposed. Assessment of cost is, however, complex because of its dependence on material unit cost, the frequency of dressing change and the time of professional staff [11,14]. In the case of older, less expensive dressings, the relative contribution made by professional time is potentially very much greater, especially if healing is delayed or if their use means that dressings are changed more frequently and this far outweighs the relatively low material costs [12]. On the other hand, it would be erroneous to assume that all dressing changes are actually performed by professional staff in routine clinical practice. Unpublished data from Nottingham City Hospital in 2001 revealed that 55% dressings are undertaken in the community by non-professional staff. Hence, this has to be taken into account in any study designed to evaluate comparative cost-effectiveness. Finally, an estimate is required of the costs arising from ulcers that do not heal – in order to undertake a Impact Analysis for the NHS and other care agencies.

Patient factors

Some assessment of the profound implications of diabetic foot ulcers on mood and quality of life has been produced in recent years[1,15] but even though the need for a robust disease-specific QoL assessment tool has been highlighted, none has yet been fully published and validated for diabetic foot ulcers. The (Rand) SF36 has been shown to discriminate well between those with and without ulcers[15], but not been between those whose ulcers are either active or healed[1]. This contrasts with the Euroqol EQ5D, which has been shown to discriminate between patients with active and former ulcers, despite its simple structure[14]. One factor likely to contribute significantly to the frustration and anxiety of having an ulcer is the 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 has demonstrated poor quality of life responses from patients with active ulceration [16,17], reflecting the qualitative work of Brod[18]. No previous study has attempted to examine this in the context of the overall psychosocial impact of the problem.

3.2 Objectives

The overall objective is to determine the comparative effectiveness and cost-effectiveness of three dressings in common clinical use for patients with diabetic foot ulcers in the UK, and the feasibility and consequences of less frequent dependence on dressings by health care professionals.

This study has five specific objectives

1) The primary objective is to test whether modern dressings are more clinically effective than traditional dressings in the treatment of diabetes related foot ulcers. The dressings to be compared will be: a simple, traditional non-adherent preparation (N-A), a widely used modern antiseptic preparation (Inadine), and a new hydrofibre preparation of higher unit cost (Aquacel). All three dressings are widely used in clinical practice in the UK.

2) To investigate changes in ulcer size, condition and re-occurrence during the study period associated with each dressing
3) To determine the cost-effectiveness associated with each of the three dressings.
4) To assess patients' Health-Related Quality of Life (HRQoL), satisfaction 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, and to gain qualitative insights into the patient experience with each of the dressing interventions.

3.3 Design

This will be a multi-centre, prospective, single-blinded, parallel group, randomised controlled trial, with three arms. Ulcers will be randomised to treatment with non adherent (N-A) dressings, iodine impregnated dressing material (Inadine) or to carboxymethyl cellulose dressing (Aquacel). The study will be undertaken in accordance of the Declaration of Helsinki and will follow the guidelines published by the Medical Research Council.

3.4 Randomisation

Randomisation will be1:1:1 and within centre. Randomisation will also be stratified across the whole population by ulcer area, into three groups: 25-100mm^2, 101-250mm^2 and 251-2500mm^2. Adequacy of recruitment and randomisation will be monitored by the Data Monitoring and Ethics Group.

3.5 Setting

Patients will be recruited from those attending or newly referred to established expert multidisciplinary clinics for the management of diabetic foot ulcers in Blackburn, Hull, Ipswich, Newport, Nottingham (2 centres), Kings College Hospital, London and Leeds (LGI and St James') Hospitals 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.

3.6 Target population

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

3.6.1 Inclusion criteria

- Type 1 or 2 diabetes
- 18 years of age or more
- A foot ulcer which has been present for at least 6 weeks and with 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

3.6.2 Exclusion criteria

- Those with a known allergy to any of the trial preparations (including iodine)
- Any ulcer on either foot which extends to tendon, periosteum or bone
- Infection of bone
- Soft tissue infection which merits treatment with systemic antibiotics

- An ulcer on a limb which is being considered for revascularisation
- Those chosen for management with a non-removable cast without dressing window
- Gangrene on the affected foot
- Eschar which cannot be removed by clinical debridement
- Those with evidence of a sinus or deep track
- Those in whom the hallux has been amputated on the affected side (preventing the measurement of toe pressure)
- Those with an brachial:ankle pressure index of <0.7
- 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 >300 µmol/L), receiving immunosuppressants, systemic corticosteroid therapy (other than by inhalation) or any other preparation which may, in the opinion of the supervising clinician, interfere with wound healing
- Those who live at such a distance (generally >10 miles) from the clinic as would make frequent assessment visits inappropriately expensive and/or impractical
- Those who withhold consent

3.7 Interventions

3.7.1 Baseline assessment

Those who satisfy the inclusion and exclusion criteria and who give written informed consent to participate will be assessed by a research nurse and their basic demographic and medical details will be noted. These will include other causes of incapacity or immobility, the presence of other complications of diabetes, and visual acuity. The foot will be examined and the following additional information recorded:

- Toe pressure (systolic pressure in the hallux)
- Ankle brachial pressure
- Peripheral sensation using a 10g Semmes-Weinstein monofilament at three specified sites on the sole, and vibration perception threshold.

Following debridement in the clinic, details of the ulcer will be recorded, including

- History (cause, duration)
- Pain at or close to the ulcer (10 cm visual analog scale)
- Cross-sectional area using a sterile marked acetate sheet
- The appearance of the surface of the wound: % granulation, %slough, %necrosis, %epithelial migration
- A digital image will be recorded

Questionnaires on pain, satisfaction and HRQOL

In the absence of a widely used disease-specific measure, we will analyse the responses to four separate measures, all of which are completed in private and returned by post: (Rand) SF36, EuroQol EQ5D, CWIS and a 10cm visual analogue scale for pain. [A satisfaction questionnaire will be used at the end of the study]. These are all assessment tools that have been used without problem in this patient population in previous studies.

3.7.2 Clinical care

Patients will remain under the supervision of the staff at the multidisciplinary clinic throughout the study. The frequency of clinic visits would be determined by clinical

need and would not be affected by the trial in any way. Ulcer management would be in line with current guidelines for good practice, including appropriate and regular use of debridement and the choice of off-loading which is standard in the host clinic. Whilst this may result in different types of offloading being used, the aim is to reflect standard clinical practice. In the absence of any significant deterioration or adverse event, clinic staff would make no decision concerning dressings. Dressings would be removed prior to examination by clinic staff who were not involved in the conduct of the trial. Other clinic staff would remain blind to randomisation group.

3.7.3 Wound dressings

Once randomised, patients and, if appropriate, their usual carers would be 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 two-weekly monitoring by a trial nurse*. Those who wished to do so, would receive further training to ensure correct application. Those who chose not to be responsible for this aspect of their care would have their dressings performed by District Nurse or Practice Nurse, according to usual procedures. Dressings would be changed daily, on alternate days or three times a week according to need and/or nurse availability. Patients would be advised to have a bath or shower at whatever frequency they wished – provided the ulcer could be redressed afterwards, and provided the ulcerated foot was not immersed in water for more than 5 minutes.

*Reference is made throughout this document to the involvement of a trial nurse. While a nurse is most likely to be appointed, it could apply to any clinical health care professional with appropriate training and skills – for instance, to a podiatrist.

3.7.4 Supervision by research nurses

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

If wound closure occurs, the nurse would record the date, and arrange for the foot to be assessed by a blind assessor at the clinic after four weeks. The trial nurse would continue to visit every two weeks until after that assessment. Thereafter, the patient would simply be encouraged to contact the nurse if any new ulcer occurred, or if there was other cause for concern.

3.7.5 Blind assessment

Each patient would be assessed at three and six* months by the clinician who was supervising the patient's care and who would remain blind to the randomisation. The following information would be recorded: details of cross-sectional area of the ulcer and appearance of the wound surface (as above), and a digital image would be made. During the same week, the trial nurses would distribute questionnaires on HRQoL, satisfaction, mobility and pain score, together with stamped addressed envelopes for return to the central assessment centre.

Ulcers which heal would be examined four weeks after wound closure by the clinician supervising care and who was blind to the randomisation. They would remain under

two-weekly supervision by the trial nurse until this had been done, and records kept of dressings and other professional visits, if any. In those that remained healed at four weeks, the time of the original closure would be taken as the time to healing. Those that recurred within four weeks would be regarded as unhealed and would continue in the study.

All patients with healed ulcers would be 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. Questionnaires on HRQoL, satisfaction, mobility and pain score would be distributed within the same week for postal return to the assessing centre.

Patients with persistent ulcers would be assessed by the clinician in charge at 24 weeks and withdrawn from the intervention phase of the study at that time. Questionnaires for postal return would be distributed within the same week. Thereafter, clinical management (including choice of dressings) would be determined by conventional clinical criteria. They would, however, attend for a final assessment 36 weeks after recruitment to record clinical outcome and questionnaires for postal return would be distributed in the same week.

3.8 Withdrawal

Patients would be 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 would be deemed to have occurred if two or more consecutive non-trial dressings had been applied during any four week interval.

3.9 Endpoints

3.9.1 Primary endpoint

The primary endpoint would be numbers healing in each group within 24 weeks. Healing will be assessed by the blind assessors as complete epithelialisation with no drainage on 2 consecutive visits.

3.9.2 Other endpoints

A variety of ulcer-related, process-related and patient-related observations will be used to determine overall effectiveness and cost-effectiveness of the dressings employed:

(i) Ulcer related

- Time to healing
- Adverse events, including deterioration
- Recurrence of ulceration within 3 months of healing

(ii) Process related

- Frequency of dressings
- Frequency of visits by professional, or dressings by health professionals

(iii) Patient related

- Scores of HRQoL and satisfaction.
- Scores of pain
- Incidence of serious adverse events, including surgery to the ulcerated limb and death

- Incidence of patient triggered withdrawal

[HRQoL questionnaires and pain assessments will be conducted at baseline, 12 weeks and 24 weeks. Satisfaction questionnaires will be conducted at 24 weeks.]

3.10 Economic evaluation

The costs of dressings is a function of:-

- Material costs
- Frequency of dressing change
- Frequency of professional attendance, at home or in GP surgery; type of staff involved
- Duration of the ulcer
- Costs to patients –attendance at clinic; GP surgery; carer time

Each of these factors will be determined in order to derive a measure of costs of patient management, and thus the relative cost-effectiveness of each dressing. In addition, the costs of patient management will be compared with the probable costs associated with non-healing and form the basis of an impact analysis on the NHS and other care agency budgets.

The cost per additional healed ulcer using different dressings will be the main indicator of cost-effectiveness but it is intended to undertake a cost-utility analysis as well, using the findings produced by relevant quality of life measures.

Sensitivity analysis will be undertaken and it is proposed to use the bootstrapping technique to identify the likely distribution of ratios in relation to the cost-effectiveness plane and estimate the probability that the cost-effectiveness ratio is within a certain threshold.

3.11 Sample size

As healing is the primary objective, this is the basis for the calculation of sample size. Calculation of sample size is difficult because of the paucity of data on the healing rate of different types of ulcer. Although data are available for neuropathic ulcers on the plantar surface, it is inconsistent. Thus, Armstrong et al[6] reported 61.4%-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 24.2% healing with accepted good clinical practice by 12 weeks, and 30.9% at 20 weeks [19]. Moreover, neuropathic ulcers with good vascular supply form a minority of ulcers cared for in 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, is that of 389 ulcers (in 179 patients) newly referred during 2000, 59.4% remained unhealed at 91 days, and 40.4% at 182 days (unpublished data). It is on this basis that we have 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% drop-out, 300 recruits are required. This is based on equal distribution of the sample to the three arms of the study. The N/A group will be treated as the reference arm of the study, with an anticipated healing rate of 30%. The size is powered to indicate a 20% increase in healing for those in the Iadine group (50% healed at 24 weeks), and 25% increase for those receiving Aquacel (55% healed at 24 weeks).

3.11.1 Feasibility of recruitment

Of the 389 new ulcers seen at the City Hospital, Nottingham in 2000, 257 (in 141 people) would have been suitable for this study. In 2001 there were 271 suitable new ulcers (in 136 people). By extrapolation from this experience, it is calculated

that any clinic serving a population of 300,000 can anticipate between 100 and 150 suitable new referrals each year. Hence it is likely that each of the participating centres would recruit the required 50 ulcers during an 18 month recruitment phase, especially as patients could be recruited from those already under long term follow-up. This equates to an average of 3 per month per centre, with allowances for Christmas, Easter and summer holiday periods.

3.12 Analysis of data

Results would be analysed using SPSS version 10, with double entry and blinded to arm of the study. The success of randomisation will be assessed by comparing baseline characteristics. All available data will contribute to the analysis including information on subjects who drop out or withdraw from the study (intention to treat analysis). Data will be analysed by appropriate parametric or non-parametric methods, dependent on distribution – including Chi square, ANOVA, Kaplan-Meier and multifactorial analyses. A comparison of the baseline completers and non-completers will be included. Quality of life assessments will be made on the basis of changes over time, and comparisons made between the referent group and the other two arms of the study. When appropriate Bonferroni's correction will be used for multiple analyses. For the economic analysis, the total average costs will be linked to the main outcome (healing) for each group in the form of cost-effective analysis. A cost-utility analysis will be conducted on the SF-36 and EuroQOL data. This will allow for exploration of cost per quality adjusted life year (QALY) gained. The Data Monitoring Committee will be fully involved in the detailed formation of a statistical analysis plan, and the decision regarding an interim analysis.

3.13 Trial Management and Supervision

Application will be made to MREC to cover the six centres involved in the study; the LREC for each centre will then need to investigate potential local issues before final approval can be given. The study will be supervised by a Trial Steering Committee comprising professional (scientific, medical, nursing and podiatric) representatives from each of the participating centres, together with consumer representatives. The Steering Committee will agree final details of the protocol and will assume responsibility for overall supervision of the conduct of the trial, including the allocation of funds to participating centres, and will have an independent Chair. There will be an independent Data Monitoring and Ethics Committee of which the membership has no other involvement with the study. Research nurses will be recruited by participating institutions, while two part time graduate research assistants will be appointed (one in the north; one in the south) to co-ordinate the running of the trial. Other secretarial and administrative tasks will be co-ordinated by the Department of Diabetes and Endocrinology, City Hospital, Nottingham and the Wound Healing Research Unit at the University of Wales College of Medicine.

4 Project Milestones

Planned starting date Spring 2003

Months 1-5	Set up Steering and Monitoring Committees, recruitment and appointment of staff. Finalise protocol. Application for MREC. Develop documentation. Agree clinical techniques and training requirements. Coordinate with community nurses. LREC approval
Months 6-24	Active recruitment and intervention phase
Months 25-30	Complete intervention phase
Months 30-33	Complete three months' post-healing assessments Start analysis of data and write-up.

Months 33-36 Complete analysis and write-up results. Complete final report to funding body

Dissemination of findings is a key element of the research process. In addition to the final report and papers for peer reviewed journals, the information will be made available to the Cochrane Group, The Royal College of Physicians and the Royal College of Nursing, and placed on the web-sites of the participating centres. Presentations will be submitted to relevant conferences related to Diabetes and Diabetic Foot Issues, e.g., Malvern Conference. The economic model will be produced electronically and made available to health authorities, NHS Trusts, and PCGs/ LGHs to insert specific local data to assess the impact of adopting modern dressings as part of their care for patients with diabetic foot wounds.

5 Expertise

This study will be undertaken by a consortium of expert multidisciplinary clinics specifically designed for the management of diabetic foot ulcers. These clinics will work in close collaboration with academic units with an established track record in research into wound management, psychometrics and the economic evaluation of interventions in health care with particular reference to the diabetic foot.

5.1 Dr William Jeffcoate Lead Applicant
Dr Jeffcoate first established a multidisciplinary clinic for the management of diabetic foot ulcers at the City Hospital, Nottingham in 1982. Experience gained in the last 20 years is stored on a large database, and has been the subject of numerous publications. He is co-author (with Rosamund Macfarlane) of the textbook *The Diabetic Foot: an illustrated guide to management* (1995) and in the last 12 months has been invited to give lectures on the subject in several different countries. He converted his full-time clinical post to a part-time one in 1997, partly with the purpose of creating more time to undertake research. Since 1997 he has also been on the editorial board of The Lancet. His main recent interest in recent years has centred on the establishment of broad consensus on the classification of foot ulcers, with the express purpose of facilitating prospective trials into management of those with complex multifactorial aetiology – which form the majority. He has participated in several large multidisciplinary trials, involving diabetes and the foot as well as other aspects of endocrinology. He will take overall responsibility for the management of the project.

5.2 Professor Patricia Price is Senior Research Fellow at the Wound healing Research Unit at University of Wales College of Medicine. She is a Chartered Health Psychologist and statistician, with a special interest in psychometrics and quantitative data analysis, working in the area of HRQoL and chronic wounds. She leads all the Health Services Research conducted in the area of Chronic Wounds at the Wound Healing Research Unit. She is trial manager for all randomised clinical trials conducted at the Wound Healing Research Unit and will work closely in the supervision of the trial, and will have overall responsibility for data analysis. She has published extensively in this area.

5.3 Dr Ceri Phillips is Reader in Health Economics at University of Wales, Swansea. He has undertaken a large number of economic evaluations of various interventions and therapies in health care, including one in diabetic foot ulcers. He is currently involved in projects totalling £1 million, funded by various research bodies and industry. He will be responsible for supervising the economic assessment of the interventions.

5.4 Dr. Michael Edmonds
Dr Mike Edmonds is Chairman of the Diabetic Foot Study Group of the European Association for the Study of Diabetes. He first established the multidisciplinary diabetic foot clinic at King's College Hospital in 1981 - a unit which has been able to demonstrate a 50% reduction in major amputations as a result of its work. He has published widely on the diabetic foot and is co-author (with Mrs Ali Foster) of a textbook *Managing the diabetic foot* (Blackwell, 2000). He has been Roger Pecoraro Lecturer at the American Diabetes Association.

5.5 Dr Owen Gibby
Dr Gibby is a Constultant Physician at the Gwent Healthcare NHS Trust. He has worked in the area of Diabetes for many years, and worked with Professor Keith Harding to establish the first multi-professional specialist foot clinic in South Wales. He has work extensively with a range of professions from specialist nurses to podiatrist to raise awareness of issues related to diabetic foot care. He has recently been heavily involved in the National Service Frameworks for Diabetes Care.

5.6 Dr Ewan Masson
Dr Ewan Masson is Physician and Senior Lecturer in the Department of Endocrinology at University of Hull. He established the multidisciplinary service for the management of diabetic foot ulcers soon after his arrival in 1993, and has continued to develop a major research interest in diabetic neuropathy and its relationship to foot ulceration.

5.7 Dr Geraint Jones
Dr Geraint Jones is lead Physician in Diabetes at Blackburn, Hyndburn & Ribble Valley NHS Trust where he has developed and implemented pathways for diabetic foot screening and ulcer management. This led to the launch of the joint RCN, Society of Podiatry and BDA (Diabetes UK) "Focus on Feet" campaign. The specialist multidisciplinary service has had a particular interest in the innovative use of off-loading devices and is widely recognised, both nationally and internationally, for its work. The unit has been involved in a number of multidisciplinary trials of foot management.

5.8 Dr Gerry Rayman
Dr Gerry Rayman has a specialist interest in vascular aspects of diabetes and the title of his MD thesis was "Microvascular haemodynamics in the diabetic foot". He also has a particular interest in the audit of effectiveness of structures of care on the management and costs of diabetic foot problems. The Ipswich Diabetic Foot Unit is well recognised both nationally and internationally and has been involved in a number of multicentre trials related to foot problems, including aspects of wound care and dressings. He is on the editorial board of the journal *Diabetic Foot* and is a regular reviewer of relevant articles for *Diabetic Medicine, Diabetes Care, Diabetologia and Practical Diabetes*. He is a member of the Diabetes UK Committee for Secondary (Specialist) Care and Chair of the Specialist Training Committee in Diabetes and Endocrinology in East Anglia, as well as RCP Regional Advisor in the specialty.

5.9 Professor Keith Harding is Director of the Wound Healing Research Unit and Professor of Rehabilitation Medicine at University of Wales College of Medicine. He has over 20 years experience in the area, and established a multi-disciplinary service in 1991. He has considerable experience in the management and supervision of multidisciplinary trials. With an international reputation, he has published extensively in the area based on his pioneering work in establishing a consultant-led service for

patients with chronic wounds. He has been the recipient of over £1 million of academic research funding, as well as £12 million of commercial sponsorship, for the purpose of research into issues relating to wound healing. He and Dr Price will take responsibility for data analysis.

6 Justification of costs

Application is being made for the following expenditure to enable the completion of this study:

(i) Two 0.5 fte research nurses (Grade F point 2, or equivalent health care professional) per centre. The study requires nursing staff to be appointed to undertake observations at baseline, undertake two-weekly (non-blind) monitoring visits, maintain patient contact, and complete (non-blind) trial documentation. The appointment of two 0.5 fte staff will ensure continuity for sickness and holidays. Travel to patients' homes is an essential part of their role. With the recruitment rate set at 3 per month one nurse will be appointed per centre at month 5 of the study, with the second to start at month 11 once the recruited numbers require more than one part-time member of staff. As the patients will be in the study for 6 months (24 weeks) with a one month follow-up the second nurse will not be required for the last 6 months of the active data collection period as the numbers actively in the study start to fall. This means that one nurse per centre will be appointed for 30 months and the other nurse for 18 months. In addition costs have been allocated for the blind assessors to assist in the assessment of the wounds at the specified time points.

(ii) Two 0.5 fte study co-ordinators
It is anticipated that these will be graduates in health related science. There will be one for the north part of the country, and one for the south, although they will work closely together. Their responsibility will be coordination of the implementation of the study between centres, combined with collection and collation of record forms. They will also monitor data accuracy and protocol violations. Travel between centres is an essential part of their role.

(iii) Qualitative analysis
In order to complete the qualitative interview at one of the centres approximately 20 patients will be selected by stratified methods to ensure representation from each of the arms of the trial. In depth interviews will be conducted and recorded, with the permission of the subjects. It is anticipated at each interview would last a maximum of 1 hour. However numbers cannot be definite at this point, as interviews will continue until thematic exhaustion has been completed. The tapes will be transcribed and data analysed for themes using a phenomenological approach. The estimated time for transcriptions and analysis are based on previous research conducted at the Wound Healing Research Unit.

(iv) Data handling and statistical analysis
Costings have been included for the input of data into specialist statistical packages using data input staff. A research assistant working alongside a qualified health services researcher and statistician will be involved in the analysis of data. The Health Services Researcher will be involved throughout the study and is a co-applicant. If, on the advice of the Data Monitoring and Ethics Group, an interim analysis should be completed, then the statistician will be fully involved.

(v) Economic analysis
A research assistant working alongside a qualified health economist will be involved in the analysis of the cost data. The research assistant will set up the health economic database/coding frame, conduct the economic

analysis, and write up the economic evaluation of the study. A qualified Health Economist is one of the co-applicants and will be involved throughout the study.

(vi) Equipment

Not all centres use the clinical equipment required by this protocol (toe arterial pressure measurement, 10g monofilaments, vibration perception threshold, digital imaging) on a routine basis. In order to ensure consistency of images for record of wound progress, each of the centres will need a dedicated digital camera. This method has been used successfully in previous studies. The photographs will be recorded digitally and then stored on CD-ROM. These steps will reduce the cost of film processing and the inherent delays in viewing the image and provide for efficient storage of collected data.

The two project organisers will need lap-top computers; much of their work will involved travelling to the centres in their regions, and will need ready access to project related information.

(vii) Standardisation

It will be necessary for involved clinical staff to meet in order to achieve harmonisation on the conduct of the trial, including clinical definitions, observations and organisational aspects.

(viii) Supervision

It will be necessary to remunerate the travel costs of independent members of the Trial Steering Committee and Data Monitoring and Ethics Committees.

(ix) MREC

The anticipated costs of securing MREC approval have been included.

(xi) The Principal Investigator works 5 sessions at present for Nottingham City Hospital. In order for him to complete this project he will need to be available for two additional sessions per week throughout the duration of the project.

(x) Travelling for both the project organisers (between centres in their region) and for the nurse staff to the patients homes have been included in the costings. In exceptional cases a patient (for example illness of trial nurse) a patient may be required to make an additional journey to the clinic and these costs will also be covered under this item. Total journeys are calculated on a maximum of 300 patients requiring 12 unblinded assessments over the 24 weeks of their involvement; travel has been estimated at a maximum of £10 per trip. Although we would attempt to restrict recruitment to a 10 mile radius of each centre, previous studies in the centres have shown this to restrict recruitment, and that covering travel is a vital component of study success.

7 References

1. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. *Am J Surg* 1998; 176 Suppl 2A: 5S-10S.
2. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diab Care* 1999; **22**: 382-87
3. Currie CJ, Morgan CL, Peters JR. The epidemiology and cost of inpatient care for peripheral vascular disease, infection, neuropathy, and ulceration in diabetes. *Diab Care* 1998; **21**: 42-48.
4. Oyibo SO, Jude EB, Tarawneh I, et al. The effects of size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med* 2001; **18**: 133-38
5. Harding KG, Morris HL, Patel GK. Healing chronic wounds. *Brit Med J* 2002; **324**: 26-63.
6. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: the contribution of depth, infection, and vascular disease to the risk of amputation. *Diab Care* 1998; **21**: 855-59
7. MacfarlaneRM, Jeffcoate WJ. Classification of diabetic foot ulcers: the S(AD) SAD System. *Diabetic Foot* 1999; **2**: 123-31.
8. De P, Scarpello JHB. What is the evidence for effective treatment of diabetic wound ulceration ? *Pract Diab Int* 1999; **16**: 179-84.
9. Mason J, O'Keeffe C, Hutchinson A, et al. A systematic review of foot ulcer in patients with type 2 diabetes mellitus. II: treatment. *Diabet Med* 1999; **16**: 889-909.
10. Bradley M, Cullum N, Nelson EA, et al. Systematic reviews of wound care Management: (2) Dressings and topical agents used in the healing of chronic wounds. *Health Technol Assess* 1999; **3**: No 17 pt 2.
11. Harding K, Cutting K, Price P. The cost-effectiveness of wound management protocols of care. *Brit J Nurs* 2000; **9**: Suppl 19.
12. O'Meara S, Cullum N, Majid M, et al. Systematic reviews of wound care management: (3) antibiotic agents for chronic wounds; (4) diabetic foot ulceration. *Health Technol Assess* 2000; **4B**: No 21.
13. Piaggesi A, Baccetti F, Rizzo L, et al. Carboxy-methyl-cellulose dressings in the management of deep ulcerations of the diabetic foot. *Diabet Med* 2001; **18**: 320-24.
14. Ragnarsson-Tenvall G, Apelqvist J. Health-related quality of life in patients with diabetes mellitus and foot ulcers. *J Diabet Comp* 2000; **14**: 235-41.
15. Meijer JW, Trip J, Jaegers et al. Quality of life in patients with diabetic foot ulcers. *Disabil Rehabil* 2001; **23**: 336-40.
16. Price P E and Harding K G (2000) The SF-36 and Cardiff Wound Impact Schedule in the measurement of health-related quality of life (HRQoL) in patients with chronic leg ulceration. 10th Annual Meeting of European Tissue Repair Society, 24 – 27 May, Brussels, Belgium
17. Price P E and Harding K G (2000) Acute and chronic wounds: differences in self-reported health-related quality of life. *Journal Wound Care*, **9**(2): 93 – 95
18. Brod M. Quality of life issues in patients with diabetes and lower extremity ulcers: patients and their care givers. *Quality of Life Research* 1998; **7** (4): 365-372.
19. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic foot ulcers receiving standard treatment. A meta-analysis. *Diabet Med* 1999; **22**:692-95.

STUDY DESIGN: