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Randomised Controlled Trial & Economic Modelling to Evaluate the Place of Anti-Microbial Agents in the Management of Venous Leg Ulcers – The Venous Leg Ulcer Antimicrobial dressing trial (VULCAN).

Summary

Design. The project will use a combination of techniques including an RCT, an observational study, systematic literature reviews, economic modelling and utility evaluation.

Setting. Community and secondary care services in two health districts (Sheffield and Exeter) having different demographic patient profiles and existing organisational arrangements for the management of patients with leg ulcers.

Target Population. All patients presenting with leg ulcers to both primary and secondary care. For the RCT the target population would be restricted to those with proven venous ulcers and without specific contra-indications to the treatments.

Health Technologies. The economic modelling will take a holistic approach to the entire management of venous leg ulcers, and in addition to considering the specific cost effectiveness of silver donating dressings within the RCT. It will also consider the general issues of the potential cost effectiveness of other local and systemic anti-microbial agents and other aspects of the care and investigation of patients with venous ulcers.

Cost and Outcome Measures. The economic modelling will use cost data collected directly through both the RCT and the observational database, including all primary and secondary care costs, as well as costs falling upon patients and carers. The primary clinical end point for the RCT will be proportion healed at 12 weeks. Secondary outcome measures will include recurrence rate, quality of life (SF36, EQ and SG) and symptomatic measures, including pain, complications, and patient satisfaction, withdrawals and the need for systemic anti-biotic treatment will also be recorded. Societal

utility valuations for health states associated with leg ulceration will be obtained through a time trade-off (TTO) exercise.

Sample size. A database of patients with ulceration in Sheffield includes over 350 patients with current ulcers. With a similar database in Exeter and the recruitment of new cases, it is to be expected that about 800 cases will be available for observation. It is estimated that 20 - 25% of these will be suitable for randomisation within the RCT sufficient to detect a 20% improvement in healing rate at 3 months and a 0.075 change in EQ-5D health scores (5% significance, 80% power).

Lay Summary

This project will study whether antimicrobial dressings are cost-effective in the treatment of venous leg ulcers. The intention is to study whether the extra cost (in terms of money, time, side-effects etc) of antimicrobial dressings bring any additional benefits (particularly in terms of healing of the ulcer) compared to standard dressings.

The main outcome of the study will be the development of a computer model of the management of venous leg ulcers. This will involve a number of steps:

1) The first will be to establish the dressings currently being used by conducting a survey of district nurses, GP practices and leg ulcer clinics in the UK.

2) A randomised controlled trial (RCT) will be performed to compare the most commonly used anti-microbial dressing with a standard non-adherent dressing. Participants will be allocated randomly (i.e. by chance) to either an antimicrobial dressing or a standard dressing – both dressings will be applied beneath multi-layer compression bandages. Participants who do not want to take part in the RCT will be

asked to join an observational group. Patients will be recruited from leg ulcer clinics in Sheffield and Exeter.

The dressings will be applied until complete healing of the ulcer has occurred. The participants will also be asked to complete standard quality of life questionnaires (Euroqol/SF-36 and McGill Pain questionnaires).

3) A value (called a utility value) for the dressing treatments will be obtained from members of the general public using Time Trade-off (TTO). This is a well recognised method and involves participants scoring scenarios describing the experience of leg ulceration. The scenarios will be created from information obtained from the RCT and expert opinion

4) A computer model describing the care and outcomes (including healing, costs and complications) will be developed. The data from the RCT, observation group and TTO will be included in the computer model.

Planned Investigation

Aim

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

a) Assess the specific case of silver donating anti-microbial dressings currently used in the management of leg ulcers

b) Extend the model to provide generalised conclusions about the potential costs and effectiveness of other interventions in this condition.

Objectives

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

Existing Research

The Use of Anti-microbial Agents

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

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

Although in recent years there has been an increasing use of silver based dressings there are currently no high quality randomised controlled trials evaluating silver dressings(5). However, there is evidence for the ability of silver ion to kill or otherwise inhibit a broad range of bacteria, yeast, fungi and viruses(5;6). The silver based dressings currently available differ in their total silver donation and ability to release free silver ions into the wound(5).

Other Treatments for Venous Ulceration

Venous ulceration is a common disease, and there are a large number of treatment modalities that have been used in its management. Many of these have been assessed through clinical trials, and there is a considerable body of secondary research, with a number of large systemic reviews looking at the results of these trials. The most convincing evidence is in favour of compression, with evidence that multi-layer compression bandaging and other techniques producing a high compression result in improved healing (7) (8). A systematic review of the use of Pentoxifylline suggested that this may have some added benefit (9), although the cost-effectiveness of this treatment is not proven, and patients on the treatment suffered some additional side effects. Other modalities, including the use of oral zinc (10), intermittent pneumatic compression (11), skin grafting (12), therapeutic ultrasound(13) , laser therapy (14), and electromagnetic therapy (15), have not provided clear evidence of benefit of any of these treatments. One recent randomised controlled trial of surgical treatment for superficial venous incompetence in suitable patients suggested a benefit from surgery in reducing ulcer recurrence rates (16).

Research into Outcomes

The majority of trials considering the treatment of venous leg ulcers have used time to complete ulcer healing or recurrence rate at one year as the main measures of outcome. Some attempts have been made to look at quality of life following leg ulceration. The SF36 (17) (18), Nottingham Health Profile (19) , and Freiburg Life Quality Assessment (20) have all been used in this respect (17).

In general the results have shown that most of the generic health related quality of life scales are not very responsive to the presence or absence of leg ulceration. In particular a recent randomised controlled trial, which showed significant differences in healing rates between two groups, failed to show any significant difference in the health status measured by the SF36 and Euroqol (EQ-5D)(21). There are no high quality published data relating to utilities in patients with leg ulceration that would be appropriate for the calculation of quality-adjusted life expectancy.

Cost-effectiveness

There have been a number of trials that have considered the cost-effectiveness of particular aspects of the management of venous ulcers. A recent trial from Sheffield considered the cost-effectiveness of community leg ulcer clinics(21). Other studies have considered cost-effectiveness of particular dressings (22), the use of pentoxifylline (9), and the effect of using care pathways and guidelines (23). These studies were carried out in several different countries and in different settings.

Implications of Existing Evidence

There are a number of aspects of the existing evidence that have been taken into account in planning the proposed trial. Firstly there are a very large

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

Existing research has identified multi-layer compression bandaging as current best practice for the healing of venous ulcers (8) (7).

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

Method

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

1. Collection of Data

Randomised Control Trial Data Collection

All eligible patients will be invited to participate in a randomised controlled trial comparing silver donating anti-microbial and non-adherent (N/A) dressings beneath compression bandages.

The choice of antimicrobial dressing to be included in the randomised trial was based on a number of factors. A survey was carried out of 175 acute NHS Trusts within the UK. The results showed that silver dressings were the primary antimicrobial dressing choice of clinicians 54% of the time. The other antimicrobial agents used were silver sulphadiazine (Flamazine, Smith and Nephew), povidine-iodine fabric dressing (e.g. Inadine, Johnson and Johnson) followed by cadexomer-iodine paste dressing (e.g. Iodoflex, Smith and Nephew).

However, concerns were expressed regarding the use of Iodine base dressings beneath compression bandages as the antimicrobial activity has been shown to be of limited duration when applied to wounds(24). In addition, current clinical practice by nurse specialists in both project centres precludes the use of Inadine beneath compression bandages.

Planned interventions

The initial approach will be from the clinician caring for the person with a venous leg ulcer. Once interest in taking part in the trial has been indicated to the clinician, a participant information sheet will given and time to reflect

allowed. Informed consent will then be obtained by a member of the research team for entry into both the randomised trial and observational arm.

The standard intervention will be the application of a low adherence knitted viscose dressing to the ulcer, with multi-layer compression bandaging. The comparative group will be the application of a “silver donating” dressing, with multi-layer compression bandaging. The clinician will be able to decide which silver dressing to apply to the wound from a list of identified silver donating dressings. The current list consists of Aquacel AG (Convatec), Acticoat and Acticoat 7 (Smith and Nephew), Contreet Silver (Coloplast) and Urgotul SSD (Urgo). There will be the option of additional silver donating dressings being included on the list if they are released during recruitment to the trial after their suitability has been considered by the trial management committee

The dressings and bandage will be revised weekly unless more frequent dressings are required on clinical grounds due to pain, discharge, or loosening of the bandage. Multi-layer compression bandaging will be continued until the ulcer is fully healed, with Grade II below-knee fitted compression hosiery applied following complete healing. If this is not tolerated then a Grade I stocking will be applied.

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

After the completion of the 12 week treatment period the decision regarding either the continuation of the allocated dressing or change to a new dressing will be by the clinician caring for the trial participant.

Planned Inclusion/Exclusion Criteria

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

The following are specific exclusion criteria:

- Refusal to give of informed consent to participate in a randomised controlled trial
- Ankle brachial pressure index of less than 0.8 in the affected leg
- Diabetes Mellitus
- Pregnancy
- Atypical ulcers, including those where there is suspicion of malignancy, co-existing skin conditions or vasculitis
- Sensitivity to the anti-microbial treatment agent or specific contraindications to that agent. There have been reported incidences of sensitivity to silver containing antimicrobial agents such as silver nitrate and silver sulphadiazine. These included skin discolouration and irritation associated with the use of silver nitrate is well documented; absorption of silver, systemic distribution and excretion in urine has also been reported(5). However, the dressings being evaluated function by the sustained release of low concentrations of silver ions into the wound and the risks of adverse side-effects are thought to be unlikely(25) .

Proposed Outcome Measures

The primary outcome measure will be complete ulcer healing at 12 weeks. Other secondary outcome measures that will be included in the analysis are healing at six months and one year, recurrence at six months and one year, EQ-5D (26) and SF-36 (27) health related quality of life questionnaires, and the McGill pain questionnaire (28). In addition, information will be collected at

the time of each dressing change regarding clinical symptoms, ulcer size (maximum axial and circumferential ulcer diameter), adverse events and co-morbidity.

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

Recruitment and Randomisation

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

Observational data collection

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

In Sheffield the service is based around community leg ulcer clinics, which provide support and training for community nurses in the assessment, management, and bandaging techniques for patients with leg ulceration. Leg ulcer management is carried out in accordance with locally developed evidence-based guidelines that were recently revised as a collaborative

venture between community nursing experts in leg ulceration, the vascular surgical service at The Northern General Hospital, and the dermatology service at The Royal Hallamshire Hospital. All patients are assessed using a common protocol and data are entered onto an initial assessment form, which is recorded on a computer database and updated by communication with community nurses at regular intervals. The main support for leg ulcer services from secondary care is provided by leg ulcer clinics, which are nurse-led clinics running in parallel to the vascular surgical clinics. The database currently contains information on approximately 350 patients with active leg ulceration.

In Exeter there is a similar service, which is configured as a 'hub & spoke' arrangement through a central clinic at Franklyn House. There are 2.5 Whole Time Equivalent (WTE) nurses employed in this clinic who collaborate with nurses from the community to provide regular community clinics. There are reciprocal arrangements with nurses from the community attending the clinic at Franklyn House for support and training. Support from secondary care is provided by a dermatologist (Dr Bower - co-applicant), who attends the clinic at Franklyn House, with referrals being made to other services as necessary. The service in Exeter has also developed local evidence-based guidelines and assessment protocols, and data of all newly assessed patients are entered onto a computer database. In the past year 801 new patents have been identified and recorded on the database, of whom approximately 450 have active ulceration.

Cost Data Collection

Data will be collected regarding the major cost drivers for all patients entered into the randomised control trial and in the observational cohort. These data will include the frequency and type of dressings used; number of contacts with community nurses, general practitioner and hospital clinical staff; periods of

hospitalisation; and any interventions carried out relating to the leg ulceration and prescribed medications. Data regarding the use of hospital services (inpatient stay, outpatient visits and A&E attendance) will be obtained from the patient administration system at the NGH and Exeter DGH; frequency and type of dressing use and contacts by district nurses (from District nurse records and diaries); primary and other community care service use will be obtained from patients. All resources will be costed using national average unit costs. In addition to this, common procedures and interventions will be identified from the database and randomised controlled trial, and detailed specific costs for these will be calculated through observation and timing of a sample of the interventions.

Utility Data Collection

Societal utilities for the various health states identified in the model will be obtained through a separate evaluation exercise. For each of the defined health states a scenario will be developed describing the symptoms experienced by patients in that health state. This will be based upon the data collected in the randomised control trial and additional patient interviews, if required. The scenarios will be brief descriptions of less than a single page of text and will describe the current health state, including the symptoms, concerns, and the need for ongoing treatments. A general population sample will be selected and each of the scenarios evaluated using a standard time trade off method (29) in which the health state was compared to a state of full health to obtain a utility evaluation for that state. This process will be carried out through direct interview, with a trained interviewer, and previous experience suggests that 4 – 5 health states can be valued in this way in an interview lasting approximately ½ hour. A sample of 100 general population subjects will be identified through a local agency that has been used to identify such samples in the past.

Data Collection Procedures

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

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

2. Cost-effectiveness Modelling

The model will be developed by an iterative process in which a group of clinical experts in the field (the trial participants plus other invited experts), will develop a schematic model for the process of care and potential outcomes of treatment for patients with venous leg ulceration. The process will be

modelled from the time of clinical presentation, using a Markov process. The definition of clinical states for the model will be based upon expert opinion and information from existing databases. Discreet, clinically relevant states will be identified for which specific costs, transition probabilities, and outcomes will be ascertained.

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

3. Sensitivity Analysis

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

The model will be generalised in order to allow the evaluation of other possible changes in practice, including changes in antibiotic prescribing and

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

Ethical Arrangements

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

Proposed Sample Size

It is estimated that the existing databases in Sheffield and Exeter contain a total of approximately 800 patients with current active ulceration. Previous experience suggests that the majority of these patients would be prepared to be enrolled in the observational arm of the trial, and that approximately 40 – 50% would agree to randomisation. Allowing for the exclusion criteria, it is anticipated that a minimum of 300 patients (150 for each group) will be randomised in the trial of topical anti-microbial dressings. This will allow for a loss to follow-up or withdrawal rate of 25%. A cost-effectiveness study by Morrell et al (21) undertaken within the Trent region leg ulcer study gave a 3 month ulcer healing rates of 34% and 24% in the intervention and control

groups respectively. Basing the sample size calculation on these figures: a two group continuity corrected chi-squared test with a 0.050 two-sided significance level will have 80% power to detect the difference between a Group 1 proportion healed, of 24% at 3 months and a Group 2 proportion healed, of 44% (odds ratio of 2.488) when the sample size in each group is 97. A two group continuity corrected chi-square test with a 0.050 two-sided significance level will have 80% power to detect the difference between a Group 1 proportion, of 34% and a Group 2 proportion, of 54% (odds ratio of 2.279) when the sample size in each group is 106.

It is likely that it would be possible to recruit considerably larger numbers of patients and this would allow the potential to carry out a three-way randomisation with similar power if the initial work suggested that this was appropriate. A three-arm trial the simplest strategy is to adopt, in terms of analysis, will be the approach which regards a three-treatment comparison as little different from carrying out a series of three independent trials, and to use conventional significance tests without adjustment as argued by Saville(30). As a consequence, the sample size will be estimated as if three independent comparisons are to be made and as a consequence the trial would need to recruit approximately 450 patients (i.e. 150 into each arm).

The sample size for the Time Trade-Off study will be based on the tables produced by Furlong et al(31) which indicate that a sample size of between 100 and 110 participants would have an 80% power and 5% significance to detect a mean difference of $\pm$ 0.06 in utility values for the health state scenario descriptions.

Consumer Involvement

A consumer panel of patients who have a healed ulcer, and who are attending outpatients for follow-up, will be recruited to provide guidance on the conduct of the trial. Recruitment will be via an invitation letter and an informal interview. Examples of areas the consumer panel will be asked to comment

on include patient information sheets, questionnaires, recruitment issues and dissemination. The panel will consist approximately five members and will meet initially every two months but meet more frequently if the panel feels it would be appropriate. One of the members of the panel will be invited to be on the Trial Steering Committee.

Independent Supervision of Trials

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

Dissemination

The results of the study will be disseminated across the participating primary and secondary care Trusts. A final report will be produced for the NHS HTA programme and this will be published. In addition, aspects of the research will be published in peer-reviewed journals and presented at national and international conferences. A summary of the findings of the project will be circulated to GP's in the study areas.

Project Timetable and Milestones

0 – 6 Months	Validation and standardisation of existing databases. Identification of all patients with active ulceration and provision of information regarding the trial, with requests to participate.
6 – 18 Months	Retrospective review of past history of participants, including identification of duration of ulceration, prior treatments, and antibiotic prescribing (topical and systemic).
	Recruitment of eligible patients to the randomised controlled trial of topical anti-microbial agents.
18 – 30 Months	Follow up period for patients in randomised controlled trial of topical anti-microbial agents.
6 – 30 Months	Continuing data collection for all patients in the RCT and observational arms of the trial.
12 – 24 Months	Development of cost-effectiveness model.
18 – 24 Months	Development of scenarios describing health states
24 – 30 Months	Societal utility valuation through Time Trade-Off (TTO) interviews.
24 – 30 Months	Collation and Analysis of collected results to provide data for economic model.
30 – 36 Months	Finalisation of economic model analysis, sensitivity analysis and report preparation.

Expertise

The project team is based upon an existing collaboration between Sheffield and Exeter, which has been responsible for a large randomised controlled trial of varicose vein treatment, which has been funded by the HTA and has successfully recruited 1,000 patients to a similar project with both randomised

and observational arms associated with cost-effectiveness analysis. In addition both Sheffield and Exeter have well established community programmes for the management of leg ulcers, and the leaders of these programmes in both centres are joining the trial team as participants. The research team includes nurses, medical staff and academics; and also collaboration between primary and secondary care; and consumers.

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