

An update on the progress of the VULCAN trial

Antimicrobial dressings are increasingly being used beneath compression therapy to treat venous leg ulcers. However, there is currently a lack of high-quality evidence to support their use in preference to substantially cheaper, low/non-adherent dressings. A cost-effectiveness study (the VULCAN trial) is currently underway which will compare the effectiveness of silver-donating dressings and low/non-adherent dressings for the management of venous leg ulcers. This article will discuss the purpose of the study and the problems faced by the research team in conducting a large randomised controlled trial.

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KEY WORDS

Antimicrobial
Silver
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Leg ulcer

Chronic wounds such as leg ulcers are often colonised by microorganisms (Halbert et al, 1992). A review by Collier (2004) discusses the different terms used when describing bacterial load present in a wound. The four most commonly used terms are defined as follows:

- ▶▶ Wound contamination – bacteria present in a wound without any host reaction (Ayton, 1985)
- ▶▶ Colonisation – bacteria are normally present in a wound through contamination and multiply but do not cause a host reaction (Ayton, 1985; Dow et al, 1999; Mustoe, 2004)
- ▶▶ Critical colonisation – a high level of bacterial load causing delayed healing with increased pain reported but

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still with no apparent host reaction (Falanga et al, 1994; Kingsley, 2001).

- ▶▶ Infection – the deposition and multiplication of bacteria in tissue with an associated host reaction (Ayton, 1985; Penhallow, 2005).

A complex process underlies whether or not a wound will become infected. It can depend on both the type of organism present, its virulence and numbers, and the condition of the host, including age, health status and comorbidities (Bowler, 2002; Kingsley, 2003; McGuckin et al, 2003). When wounds become critically colonised or infected, the presence of bacteria and other microorganisms can have an adverse effect on the patient and inhibit wound healing (Eriksson et al, 1984; Halbert et al, 1992).

Cutting and Harding (1994), more than 10 years ago, defined the criteria with which to evaluate the signs of wound infection. However, a recent series of articles has re-evaluated these clinical signs based on the type of wound (Gardner et al, 2001; Cutting and White, 2004). One of the reasons for this re-evaluation is that clinical signs of infection in venous ulcers can be masked by the presence of haemosiderin staining (Cutting and White, 2004). In addition, pain as a result of an acute infection cannot be easily distinguished from the pain that is a common characteristic of venous leg ulcers (Briggs and Nelson, 2003).

Cutting and White (2004) advocate that dull brick-red and blue/green discolouration, delayed healing, increased exudate, cellulitis and a change in the nature of a patient's pain should be used as an indication of infection in venous leg ulcers.

Treatment of infection and colonisation

There have been a large number of trials, including many randomised controlled trials (RCTs) examining the role of antimicrobial agents in the management of leg ulcers. High-grade evidence in the form of systematic reviews published by the NHS Health Technology Assessment Programme (NHS HTAP) (Bradley et al, 1999) and the Cochrane Collaboration (Palfreyman et al, 1998; Briggs and Nelson, 2003; Nelson and Bradley, 2003) have considered the data from these RCTs. The conclusion in the case of venous leg ulcers is that existing evidence is equivocal and generally of poor quality and there is no strong evidence to support any individual agent, including antibiotics, for either topical or systemic use.

However, dressing manufacturers have been marketing a growing number and range of antimicrobial dressings (Lansdown, 2005). These types of dressings have been recommended for use in both the prevention and treatment of infection in wounds (Alcaraz and Kelly, 2002; Ballard and McGregor, 2002; Dowsett, 2003, 2004; Lansdown et al, 2003; Vanscheidt et al, 2003).

Table 1

The hierarchy of evidence
(Mulhall, 1998; Harber and Miller, 2001)

Grade of evidence	Type of trial
1	Evidence from at least one systematic review of well-designed randomised controlled trials (RCTs) or RCT with a low risk of bias
2	Strong evidence from at least one appropriately designed 'large' RCT
3	Evidence from well-designed, non-randomised studies (before-after, cohort, case-controlled studies)
4	Evidence from well-designed, historical, non-randomised studies
5	Opinions of 'respected' authorities (including 'expert' committees)

The evidence cited by the manufacturers to support the use of these dressings can be misleading, as they are often low down in the hierarchy of evidence and so the results can be due to chance and prone to bias (Table 1). Examples of citations used as evidence of effectiveness by manufacturers include: studies presented at conferences that have not been published in peer-reviewed journals, review articles, case studies, and non-randomised cohort studies. In addition, the studies are frequently small, with few patients involved. The clinician should therefore remain sceptical of these studies and seek out higher quality evidence such as RCTs and systematic reviews.

One of the major groups of antimicrobial dressings donate silver to the wound. These dressings are based on the ability of silver to kill or limit the growth of a wide variety of antimicrobial organisms (Thomas and McCubbin, 2003). There are currently six silver-donating dressings on the Drug Tariff in the UK:

- ▶▶ Acticoat (Smith & Nephew Healthcare, Hull)
- ▶▶ Acticoat 7 (Smith & Nephew Healthcare, Hull)
- ▶▶ Urgotul SSD (Urigo, Parema Medical, Loughborough)
- ▶▶ Aquacel Ag (ConvaTec, Ickenham)
- ▶▶ Contreet Foam (Coloplast, Peterborough)
- ▶▶ Silvercel (Johnson & Johnson, Ascot).

However, there is the potential for this number to increase as more companies produce new silver products or a silver version of an existing dressing. These silver dressings are relatively expensive compared with standard dressings. For example, the cost of silver dressings ranges from £3 to £16 each compared with NA Ultra (Johnson & Johnson, Ascot) which costs 32p per dressing (The NHS Electronic Drug Tariff, 2006).

As is the case with other antimicrobial dressings, there are currently no high-quality RCTs evaluating silver antimicrobial dressings (Lansdown, 2004). The literature examining the area of silver-donating dressings has been criticised for perpetuating 'factual inaccuracies and misinterpretations' (Lansdown, 2004). Furthermore, there are no data on the likely development of bacterial resistance to silver (Lansdown et al, 2005). The lack of evidence, the high costs of dressings and the cost of leg ulcer management led the NHS to call for research to examine this area.

In response to this call members, of Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield University, and the Royal Devon and Exeter NHS Foundation Trust submitted proposals to examine the cost-effectiveness of dressings for venous leg ulcers. The bid was successful and the Venous Ulcer Cost-effectiveness of ANti-microbial dressings (VULCAN) study was commissioned. An outline of the study and the challenges encountered to date will be reviewed in the remainder of this article.

The VULCAN trial

The VULCAN trial is a cost-effectiveness study. These types of studies are used

in health economics to examine the costs (the relative expenditure usually expressed in terms of money but which can also include other costs such as side-effects) and the effectiveness (the outcomes) of an intervention. The VULCAN study is funded by the NHS through its Health Technology Assessment Programme (NHS HTAP). The NHS HTAP commissions research to answer questions that are of clinical relevance to the NHS.

Two centres are participating in the study, one in Sheffield and the other in Exeter. The trial team comprises clinicians and academics. It is led in Sheffield by Jonathan Michaels, Professor of Vascular Surgery, Academic Vascular Unit, University of Sheffield; and in Exeter by Bruce Campbell, Professor of Vascular Surgery, Royal Devon and Exeter Hospitals NHS Foundation Trust. The trial started in 2004 and is currently in the recruitment phase. Patients with venous leg ulcers are recruited at nurse-led community leg ulcer clinics in the trial areas. Some patients are also recruited via district/community nurses undertaking home visits. The study is due to be completed in the summer of 2007.

Aim and methods

The main aim of the VULCAN research trial is to assess the cost and effectiveness of silver-donating antimicrobial dressings for venous leg ulcers. A cost-effectiveness model will be developed and used to assess the efficacy of this group of antimicrobial dressings compared with standard low/non-adherent dressings, such as NA Ultra, used beneath compression bandages (and treatment hosiery where appropriate) for the management of venous leg ulcers.

Data to be included in the cost-effectiveness model will be obtained from a RCT and an observational group of patients. Figure 1 shows the recruitment algorithm for the VULCAN trial.

The RCT will allocate participants to either the silver-donating dressing or low/non-adherent dressing arm. The choice of dressing within these groups will be left

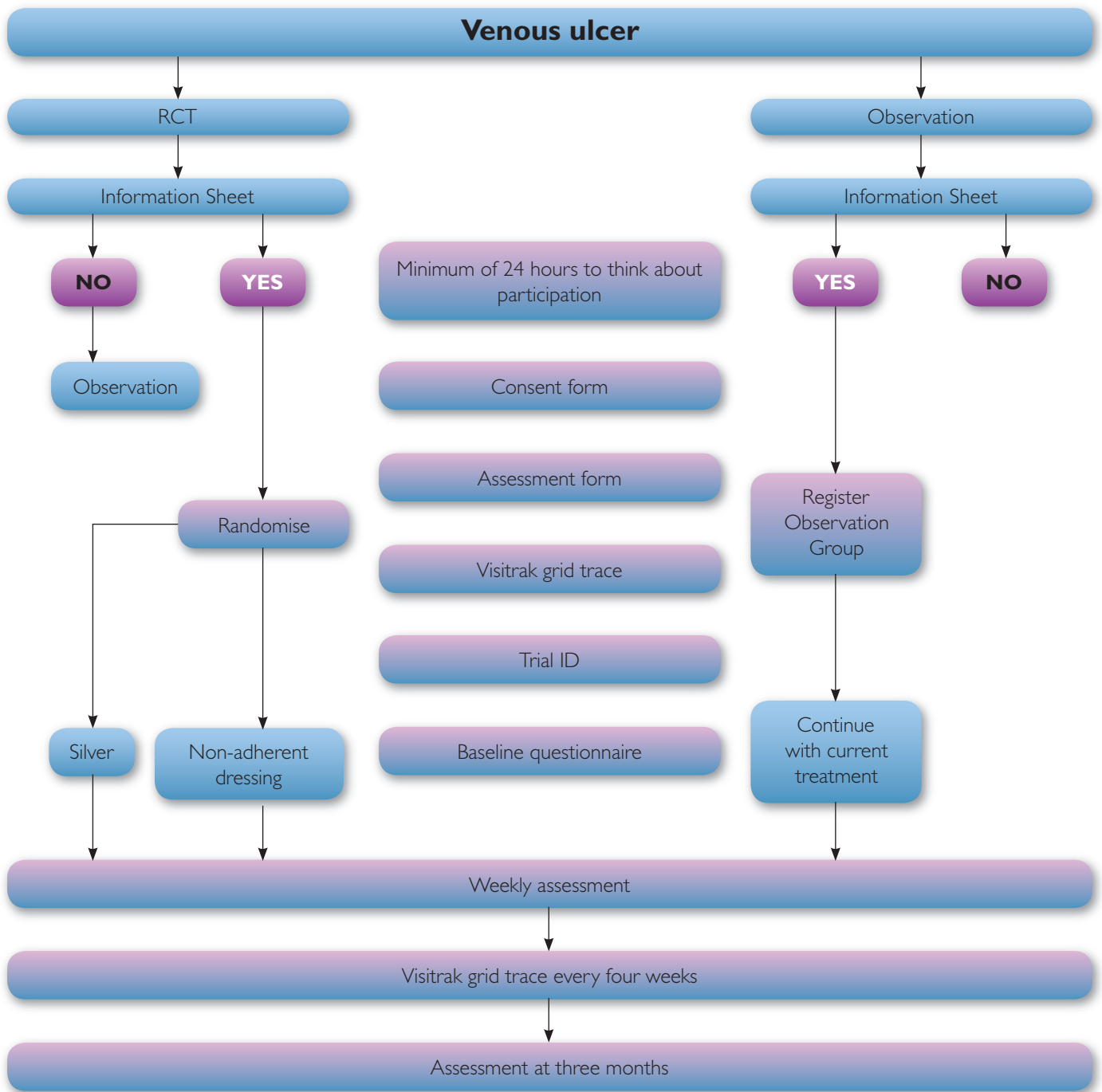


Figure 1. Recruitment algorithm for the VULCAN trial.

to the individual clinicians, as guided by the local leg ulcer management protocol devised by the community tissue viability service. They will use their clinical judgement based on the appearance of the wound and local practice. There will be the option of additional silver-donating dressings being included in the trial if they are released during the recruitment phase of the trial.

An observational group of patients will also be included in the study. This

group will consist of those patients who do not wish the dressing type to be decided at random and those who are unsuitable for the RCT as they are diet-controlled diabetics or currently using any type of antimicrobial dressing. The addition of an observational group to the trial means that data can be collected about those participants who have declined randomisation, for whatever reason. During the analysis of the data at the end of the trial, the

RCT and observation groups can be compared to detect any differences between the two sets of patients. If such differences were found they could indicate that the RCT had been prone to selection bias.

Although the modelling will be based on data about silver-donating dressings it is envisaged that the model will also produce generalisable conclusions regarding the potential costs

and effectiveness of other antimicrobial dressings and interventions for venous leg ulceration.

A sample size of 300 patients has been calculated as being suitable to detect the difference between the two groups in the RCT.

Inclusion and exclusion criteria

All patients with active venous ulceration of the lower leg that has been present for a period greater than four weeks are eligible for inclusion in the RCT. Their ulcer must be at least 1cm in any direction. They must also have an ABPI (ankle brachial pressure index) of <0.8 and be able to tolerate compression in the form of either 4-layer bandaging, short-stretch bandaging or Class 4 treatment hosiery. They must also be able to understand any questionnaires provided regarding quality of life and be able to give informed consent. Patients who refuse to give informed consent, have an ABPI less than 0.8, have diabetes controlled by medication, are pregnant, have atypical ulcers, or have sensitivity to silver; will be excluded. Patients with an infected ulcer that is being treated with antibiotics will also be excluded.

Outcomes

The main outcome measure will be complete ulcer healing at 12 weeks. Other secondary outcome measures will include healing at six months and one year, and recurrence at six months and one year. In addition, quality-of-life data will be obtained from the patients by asking them to complete the EQ-5D (The EuroQol Group, 1990) and SF-36 (Ware and Sherbourne, 1992) health-related quality of life questionnaires. Full economic costings for the antimicrobial and standard dressing treatments will be undertaken from a health service perspective. Figure 2 shows the timeline of the data collected from the participants in the trial.

All patients are advised to wear class two compression hosiery post-healing based on the Royal College of Nursing (RCN) guidelines (1998). This is best practice but patients do not always follow this advice and may return with recurrent ulceration or new ulceration on another area/limb. This data will also be recorded if patients heal during the trial.

The data from the RCT, observational group and economic costing will be incorporated into a cost-effectiveness model.

Progress to date

The trial started in August 2004. The initial focus of the first six-month period of the trial was to establish the administrative framework, validate data-collection processes and comply with ethical and research governance requirements.

The first stage of the trial was the establishment and arranging of meetings for the trial steering,



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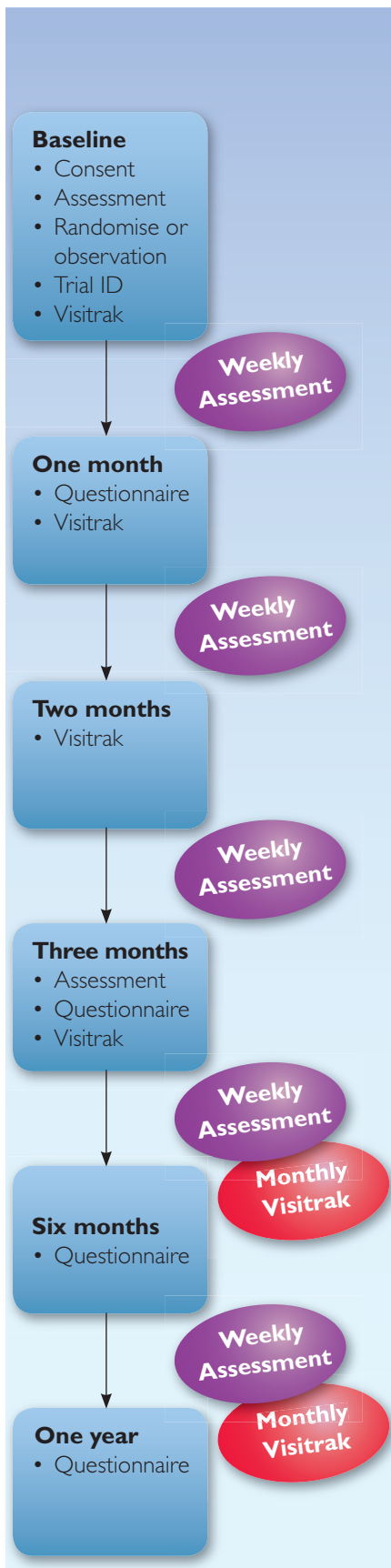


Figure 2. Timeline for participants in the VULCAN trial.

management, data-monitoring and ethics committees. The members of these committees were drawn from the researchers as well as academics and consumers independent of the research team.

The forms for data collection were created on the basis of both RCN (1998) and local guidelines regarding venous leg ulcers. The VULCAN researchers were keen to ensure that the data collected matched that which the clinicians would normally collect as part of their clinical assessment.

Before any patients could be recruited, ethical and research governance approval was needed for the two areas involved in the study. This meant that ethical approval was required from the local research ethics committees (LRECs) in both Sheffield and Exeter. This process was started early in 2004 and all the necessary approvals from the LRECs were obtained by July 2004. However, the new research governance arrangements meant that approvals were needed at both sites from the primary and secondary care trusts where the research was being undertaken. There were a number of delays in receiving these approvals and it was not until February 2005 that research governance approval for the project was finalised.

It therefore took almost a year for the necessary research governance and ethical approval hurdles to be completed. Much of the delay was caused by the project seeking these approvals during a time of change and flux in the research governance and ethical committee arrangements. Processes and procedures were still being established, particularly in the primary care trusts.

Recruitment to the trial began in March 2005 and it was anticipated that a period of a year would be sufficient to recruit the target of 300 participants. However, a number of issues have impacted on recruitment. Two of the main delays with

recruitment are related to personnel issues and mandatory approvals. Staffing difficulties as a result of maternity leave and the appointment of personnel at both sites had a significant effect on recruitment (these issues have now been resolved). Delays in gaining ethical and research governance approvals meant that there was a delay of three months before recruitment could commence.

Recruitment has progressed since March 2005 but at a lower rate than it was anticipated when the trial was first conceived. It may therefore be necessary to extend the recruitment period to ensure that the target of 300 patients can be met.

Once the recruitment period has been completed the next focus of the trial will be concerned with collecting data on the costs for both the silver-donating and low-adherent dressings. The costings will be based on the perspective of the NHS and will use a bottom-up approach (where costs are calculated from scratch rather than using tariff costs charged by trusts) to ensure that all the relevant costs are included. The costs will be incorporated with the data from the research trials into the cost-effectiveness model.

Discussion

In addition to staffing and governance issues there have been a number of additional challenges related to undertaking research in this area.

Meeting the criteria

Despite large numbers of patients being identified as potentially suitable for the trial on the basis of a referral for Doppler assessment, the majority are for diagnostic purposes rather than because the patient has a current wound that may need compression bandaging or hosiery. In addition, where patients, on the basis of referral letters, appeared to meet entry criteria for the trial, in the time between the assessment and being seen by the research nurses the ulcer became too small for inclusion in the trial or the ulcer had healed.

Perception of trial research nurses

Members of the VULCAN research team have experience of working as clinicians in the community and efforts were made to minimise the impact of the trial on the workload of community nurses. Such measures included the collection of data being based on routine data already collected and the recruitment of patients being undertaken by research nurses. However, some nurses have been very suspicious, not only of the trial but also of the research nurses, and feel there is an ulterior motive for their involvement.

The research nurses were also seen as wound experts and were asked to comment on which antimicrobial dressing to use, which conflicts with their role as researchers. However, overall, the clinical nurses are becoming more confident of the research nurses' role as well as their own role within the trial and are thus more open to handing out trial information and identifying potential participants.

Ownership

Some clinical nurses have reported a tendency for colleagues working in GP practices to continue to treat patients with non-healing lower leg wounds for much longer than recommended by local and national guidelines before referring them for assessment by tissue viability specialists. This could be because of a lack of knowledge or awareness of local and national guidelines. In order to overcome this problem the trial is helping the community tissue viability service in the trial area to publicise the local referral guidelines. In addition, practice nurses are being targeted as a source of potential recruitment.

Patients unwilling to enter the trial

Several patients who met the inclusion criteria were reluctant to enter the trial. These patients frequently stated that the reason for this was their age. The majority of patients with leg ulcers are elderly as the incidence increases with age (Callam et al, 1985) and having a leg

ulcer is perceived as stressful enough, without the added burden of being in a trial. In these instances there is little that the research nurse can do to influence the patient's decision apart from offering support and education about leg ulcers and how the trial hopes to benefit future patients.

Clinicians treating venous leg ulcer patients need to have the skills to critically review the evidence and determine what it means for their patients and clinical practice. These are skills promoted through the evidence-based nursing agenda, but sadly nurses have been slow to acquire them.

Demographics

The logistics of covering a large population and a wide area can be daunting. The Exeter branch of the trial employs two part-time nurses (one FTE) with experience of leg ulcer management in both an acute and community setting. These nurses have to visit 27 leg ulcer clinics spread over 685 square miles. Many of the clinics run on the same day making it impossible to be present at each clinic, every week. The nurses rely on referrals from the district and community nurses who run the leg ulcer clinics. They also utilise a large central database of leg ulcer assessments sent to the community tissue viability service and have had ongoing support and input from the tissue viability nurse specialists.

In Sheffield, there are only three dedicated leg ulcer clinics and the majority of leg ulcer patients are cared for by community nurses in the patient's home or by practice nurses based in GP surgeries. The two part-time (one FTE) research nurses in Sheffield are covering individual community nurses and GP practices rather than groups of patients based in clinics. The amount of time available to the research nurses to recruit patients at both trial centres can be significantly reduced by the amount of travelling and liaison with large

numbers of community nurses, GP practices and leg ulcer clinics.

The marketing of dressings

Clinicians in the wound care area can be bombarded with information regarding new and improved dressings. They are the targets of marketing representatives from industry who want to promote their dressings. There have been concerns expressed regarding the lack of data about how nurses deal with such pressure and the potential conflict of interest caused by industry promotions and decisions regarding best care (Brody, 2002; Moynihan, 2003; Crigger, 2005).

The multi-million pound marketing campaigns promoting antimicrobial dressings run the risk of blinding clinicians to the current lack of high-quality evidence available to support the cost-effectiveness of these dressings.

Evidence for antimicrobial dressings

The evidence for the use of antimicrobial dressings for venous leg ulcers is currently equivocal (Palfreyman et al, 1998; Bradley et al, 1999; Bouza et al, 2005). The VULCAN trial aims to produce evidence of both the costs and effectiveness of antimicrobial dressings for venous leg ulcers. The trial has no agenda and aims to evaluate whether these products should be used.

Much of the literature currently being cited in the marketing brochures for the various antimicrobial dressings can be cited low down in the hierarchy of evidence (*Table 1*) and may not necessarily have been subjected to the same level of rigorous peer-review associated with journal publications. Clinicians treating venous leg ulcer patients need to have the skills to critically review the evidence and determine what the evidence they are being presented with means for their patients and clinical practice. These are skills that are being promoted through the evidence-based nursing agenda and sadly nurses have been slow to acquire them compared with other groups (Palfreyman et al, 2003; Tod et al, 2004).

Demands on clinicians

The current climate within the NHS caused by recent projected deficits in both primary care and hospital trusts, and the restructuring of the primary care trusts (Cole, 2006) has impacted on the VULCAN research trial. Clinicians caring for patients with venous leg ulcers, in common with others in the NHS, have increased workloads and pressures. This can mean that identifying patients to participate in research trials and helping with research in general are seen as low priorities. This can have a negative effect on trials being conducted within primary care and needs to be taken into account when undertaking trials within the community setting.

Conclusion

The lack of good evidence for the use of antimicrobial dressings for the management of venous leg ulcers means that the clinician has to make judgements regarding which dressing to use on the basis of local and national guidelines. The current shortage of

evidence means that there is likely to be a wide variation in local practice and decisions on dressing type may be being made on the basis of cost; comfort; ease of use; and clinician and patient preference. Currently,

It is difficult to justify the use of a particular silver dressing or other dressing type in preference to any other, based on what is currently known. Indeed, it has been said that the type of dressing used beneath compression may not affect the final healing at all....

it is therefore difficult to justify the use of a particular silver dressing or other dressing type in preference to any other, based on what is currently known. Indeed, it has been said that the type of dressing used beneath compression may not affect the final healing at all, as it is the application of

compression that is ultimately responsible for the healing of the ulcer (Bouza et al, 2005).

There is a clear need for high-quality evidence for the use of antimicrobial dressings for venous leg ulcers. The VULCAN trial will provide grade I (Table 1) evidence for the cost-effectiveness of the new silver-donating dressings that are increasingly being used on venous leg ulcers. This will allow clinicians caring for patients with venous leg ulcers to make an informed choice regarding the best dressing to use to give the patient's ulcer the best chance of healing. **WUK**

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Key Points

- ▶ There is a need for high-quality evidence for the use of antimicrobial dressings for the treatment of venous leg ulcers.
- ▶ The VULCAN trial will provide grade I evidence for the cost-effectiveness of the new silver-donating dressings that are increasingly being used in leg ulcer treatment.
- ▶ This will allow clinicians to make informed choices regarding the best dressing to use to promote healing.

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