# Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers

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**Diabetic foot ulcers remain a major health care problem. They are common, result in considerable suffering, frequently recur, and are associated with high mortality, as well as considerable health care costs. While national and international guidance exists, the evidence base for much of routine clinical care is thin. It follows that many aspects of the structure and delivery of care are susceptible to the beliefs and opinion of individuals. It is probable that this contributes to the geographic variation in outcome that has been documented in a number of countries. This article considers these issues in depth and emphasizes the urgent need to improve the design and conduct of clinical trials in this field, as well as to undertake systematic comparison of the results of routine care in different health economies. There is strong suggestive evidence to indicate that appropriate changes in the relevant care pathways can result in a prompt improvement in clinical outcomes.**

Despite considerable advances made over the last 25 years, diabetic foot ulcers (DFUs) continue to present a very considerable health care burden—one that is widely unappreciated. DFUs are common, the median time to healing without surgery is of the order of 12 weeks, and they are associated with a high risk of limb loss through amputation (1–4). The 5-year survival following presentation with a new DFU is of the order of only 50–60% and hence worse than that of many common cancers (4,5). While there is evidence that mortality is improving with more widespread use of cardiovascular risk reduction (6), the most recent data—derived from a Veterans Health Adminstration population—reported that 1-, 2-, and 5-year survival was only 81, 69, and 29%, respectively, and the association between mortality and DFU was stronger than that of any macrovascular disease (7). Iversen et al. (8) have also shown that the occurrence of a DFU was an independent predictor of mortality even at 10 years.

The cost to health care services is also enormous. The estimated global cost of diabetes in 2015 was $1.3 trillion (9), and it has been reported that up to one-third of diabetes expenditure is on lower-limb–related problems in the U.S. (10). The latest data from the U.K. estimate that the total annual cost of management of DFUs exceeds £1 billion ($1.32 billion) and represents almost 1% of the total National Health Service budget (11). The equivalent figure from the U.S. has been estimated to be $9–13 billion (12).

## GEOGRAPHIC DIFFERENCES IN CLINICAL OUTCOME

There is also wide variation in clinical outcome within the same country (13–15), suggesting that some people are being managed considerably less well than others.

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Among the many possible reasons (16) is the lack of emphasis placed on DFUs in basic training and continuing education of doctors and nurses (15).

There is thus a clear need for acceptance of standard components of care (Table 1), as well as standard pathways for referral between general practice and specialty care and between different specialist groups. Such principles have been published by the International Working Group on the Diabetic Foot (17) and the National Institute for Health and Care Excellence (18); however, adherence by professionals is not generally monitored, and the lack of a firm evidence base to underpin many aspects of management means that treatment choice is still very much influenced by opinion, as was illustrated in one small but important study (19).

## CURRENT EVIDENCE BASE

### Primary Prevention: Reducing the Incidence of New DFUs

Data on community-wide ulcer incidence are very limited. Overall incidences of 5.8 and 6.0% have been reported in selected populations of people with diabetes in the U.S. (2,12,20) while incidences of 2.1 and 2.2% have been reported from less selected populations in Europe—either in all people with diabetes (21) or in those with type 2 disease alone (22). It is not known whether the incidence is changing, but it can be predicted that when expressed per total local population with diabetes, it is likely that there will be a short-term fall resulting from the impact of increased ascertainment of early diabetes through screening. But without major improvements in ulcer prevention, it can be predicted that this fall will be followed by a rise in the number of DFUs that will increase in step with the global epidemic of type 2 diabetes.

Although a number of risk factors associated with the development of ulceration are well recognized (23), there is no consensus on which dominate, and there are currently no reports of any studies that might justify the adoption of any specific strategy for population selection in primary prevention. Nevertheless, recent work has compared the performance of different scoring systems (24). Despite the probability and the belief that foot care education will reduce the occurrence of new ulcers, the evidence to justify the use of any educational intervention for primary prevention is weak: only a small number of randomized controlled trials (RCTs) have been published, and none that reported benefit were of high quality (25,26). As the overall incidence of new foot ulceration in unselected populations with diabetes is relatively low, the conduct of trials on primary prevention poses an enormous challenge because the numbers needed for study would be extremely high. Trials on ulcer recurrence are technically easier because the incidence in the 12 months following healing is of the order of 40% and the available evidence is rather better (10).

**Table 1—Aspects of management in the overall care of the foot in diabetes**

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| Primary prevention |
| Improving the healing of DFUs |
| Secondary prevention: reducing new ulceration after healing |
| Improved well-being: the patient agenda |
| Improving long-term survival |

### Failure of DFUs to Heal Promptly

#### *The Condition of the DFU at First Expert Assessment*

Ulcers that are graded as being more severe have a worse prognosis, and this is the basis of current grading schemes (1,27,28). Recent data have also shown a statistically significant association between ulcer severity and the time to first expert assessment, in both Norway and the U.K. (29,30). The longer the elapsed time to expert assessment, the more severe the ulcers and the worse the clinical outcomes.

#### *Effectiveness of Existing Treatments*

A number of systematic reviews of dressings (31) and other treatments designed to accelerate healing (32) have been conducted in recent years. The overall conclusion has been that with very few exceptions, the evidence available from published studies is of insufficient quality to recommend any particular treatment or dressing product in preference to any other. The main exception relates to the use of off-loading for plantar ulcers (33). The effectiveness of other treatments—such as the use of antibiotics for infection and the use of revascularization for peripheral artery disease (PAD)—is accepted even though the evidence to guide many of the precise circumstances of their use is not good (34,35).

#### *The Incidence of Major Amputation*

The incidence of major amputation is used as a surrogate measure of the failure of DFUs to heal. Its main value lies in the relative ease of data capture, but its value is limited because it is essentially a treatment and not a true measure of disease outcome. In no other major disease (including malignancies, cardiovascular disease, or cerebrovascular disease) is the number of treatments used as a measure of outcome. But despite this and other limitations of major amputation as an outcome measure (36), there is evidence that the overall incidence of major amputation is falling in some countries with nationwide databases (37,38). Perhaps the most convincing data come from the U.K., where the unadjusted incidence has fallen dramatically from about 3.0–3.5 per 1,000 people with diabetes per year in the mid-1990s to 1.0 or less per 1,000 per year in both England and Scotland (14,39). This apparent improvement in the U.K. has been documented using routinely collected data and seems to have been achieved without any major change in the use of particular treatments, although the change followed the publication of National Institute for Health and Care Excellence guidelines on the management of DFUs in 2004, updated in 2010 and 2016 (18). In addition, two regional centers in England have documented abrupt and major falls in the incidence of major amputation simply as a result of implementing change in the local structure of care, including the establishment of a single multidisciplinary service and encouraging early referral of all new DFUs for expert assessment (40,41). A similarly abrupt fall in the incidence of both major amputation and in-hospital mortality has been reported from Germany (42). The corollary of such improvements is the abrupt worsening that coincided with resources being withdrawn (40,43).

#### *The Link Between DFUs and Established Renal Failure*

A close temporal relationship has also been demonstrated between foot ulceration and the onset of dialysis for end-stage renal disease (44–46). While it may be assumed that the ulceration in such cases is the result of worsening renal function, it is equally—and possibly more—likely that it is the inflammation associated with the ulceration that triggers the final decline in renal function (47). It has also

been shown that mortality after undergoing major amputation was 290% higher in those on dialysis (48). Nephrologists should be more generally aware of these observations.

### New Ulceration After Healing

New ulceration after healing is high, with ~40% of people having a new ulcer (whether at the same site or another) within 12 months (10). This is a critical aspect of diabetic foot disease—emphasizing that when an ulcer heals, foot disease must be regarded not as cured, but in remission (10). In this respect, diabetic foot disease is directly analogous to malignancy. It follows that the person whose foot disease is in remission should receive the same structured follow-up as a person who is in remission following treatment for cancer.

Of all areas concerned with the management of DFUs, this long-term need for specialist surveillance is arguably the one that should command the greatest attention. As the study population with a recent history of DFU is that with the very highest short-term incidence of recurrent ulceration, the necessary RCTs can be relatively small and yet the long-term benefits—to both the individual and to health care services—are potentially very high.

#### *Specific Strategies to Reduce DFU Recurrence*

Apart from the provision of appropriate footwear for people with (in particular) plantar ulceration, targeted education is believed to be an essential part of secondary prevention. Despite this, there is currently no good evidence to demonstrate its effectiveness (49). In contrast, three studies have been reported by a single group to demonstrate the benefit of daily monitoring of foot skin temperature (50), although the approach has not yet been confirmed by any other groups.

### Improving Well-being: The Patient Agenda

#### *Relationship Between DFUs, Depression, and Quality of Life*

The occurrence of a DFU has a marked impact on activity, and when combined with slow resolution, the condition is understandably linked with a reduction in quality of life (51). The data on the incidence of depression are, however, mixed. One group has reported that first ulcers are associated with depression and that this is independently associated with mortality at 5 years (52). Others, however, have reported that both quality of life and depressive symptoms are reversed by healing—either with or without amputation (53–55). Wukich et al. (56) have recently reported that people with diabetic foot disease fear major amputation more than they fear death. Interestingly, the same group has reported that 75% people who undergo major amputation experience a significant improvement in quality of life (57).

#### *Depression, Foot Self-Care, and Incident DFUs*

There is also evidence to suggest that depression is an important risk factor for first (but not subsequent) DFUs (58–60) even though this relationship is not mediated by reduced foot self-care (58,59). In contrast, patient cognitive and emotional appraisals of DFU risk are important predictors of foot self-care (61,62). Addressing neuropathy and DFU-specific cognitions and emotions may therefore be more meaningful and effective than initiating treatments specifically directed at clinical depression, especially as there is evidence to suggest that depression in those at high DFU risk is largely a function of the neuropathy/DFU-specific physical and emotional burden (63,64).

#### *Ulcer Healing, Adherence, and the Patient Agenda*

Early work on off-loading provided insight into the contribution of patient adherence to the effectiveness of off-loading in the treatment of plantar ulcers (65), and this has been extended by recent important publications in both ulcer prevention and treatment (33,66). As off-loading is the best validated of all current interventions, it is important that further work is undertaken to increase understanding of how the patient's agenda can be best incorporated into the process of considering, adopting, and assessing both off-loading devices and other interventions in routine clinical practice. While this may be partly the result of the constraints imposed by off-loading devices, as well as their appearance, there is also evidence that poor adherence may reflect unrecognized unsteadiness caused by neuropathy (67).

### Improving Long-term Survival

The reduced life expectancy associated with DFUs is well established, as is the parallel impact of major amputation on survival (4,5,7). It is possible that inflammation complicating ulceration is one reason for the strong observational evidence for an independent link between ulceration and increased vascular mortality. Apart from urging greater use of treatments to reduce cardiovascular risk (6), there are few data to suggest how awareness of such mechanisms might lead to strategies for clinical improvement.

## WHY IS THE EVIDENCE BASE SO POOR?

### Diabetic Foot Care Has Been Traditionally Neglected

Despite the high morbidity and mortality associated with diseases of the foot in diabetes and despite its cost to both health care providers and the patient and their families (68), it is a topic that has generally failed to attract the same level of interest by health care professionals as other diabetes complications. Not surprisingly, the field continues to attract relatively few clinicians who are interested in research.

### The Complexity of the Pathogenesis

DFUs are caused by multiple factors, including those that predispose to ulceration, those that trigger it, and those that prevent healing once ulceration occurs. Neuropathy and PAD are among the many factors that predispose to ulceration, and trauma is the principal trigger. But the failure of an established ulcer to heal can be the result of a number of further factors, and different ones among all of these may dominate at different times of the prolonged healing process. These are listed in Table 2, but our understanding of many of these processes is currently very limited.

#### *Impact of the Complex Pathogenesis on Trial Design*

This complexity of the mechanisms involved also undermines the attempt to establish the benefit of any intervention because interventions will generally be directed at a specific defect in the foot care process (whether prevention or treatment). And as this defect may be dominant only in certain people or intermittently in the same person at different times, it greatly increases the chance that the result of any trial to document benefit will be neutral (i.e., providing no evidence of either benefit or harm).

#### *The Complexity of the Care Process*

Not only are the mechanisms of ulcer onset and ulcer persistence potentially very complex, but the care and treatments are conducted by many different people,

**Table 2—Factors and pathways that may contribute to delayed healing**

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|---|
| Continuing trauma |
| Infection |
| Surface microorganisms not causing clinical infection |
| PAD |
| Neuropathies (potentially through multiple pathways) |
| Altered function of white blood cells, stem cells, and regenerating tissue, with abnormal cellular signaling |
| Abnormal wound biology, whether related to diabetes or its complications, to bacterial presence (with or without infection), or to effects resulting simply from the chronicity of the process |
| Patient-related factors, including impact of comorbidities and nonadherence to recommended management |

including professionals in secondary care (physicians, surgeons, podiatrists, other health care professionals) and in primary and community care as well as by nonprofessionals—the patient, family, and others. Time to first expert assessment is likely to be an important factor (29,30), with the severity at presentation being linked to outcome (1,27,29). It follows that while it may be relatively simple to document apparent benefit of an intervention in well-defined experimental circumstances, this may have limited relevance—or apply only to particular patient/ulcer groups—in routine practice.

#### *The Impact of the Complexity of the Problem on Industrial Investment*

Industrial investment is a key player in the advancement of health care knowledge, in postgraduate education, and in the promotion of better care processes, but all of these are hampered in the field of the diabetic foot. The need to link financial investment to product sales means that industry is relatively reluctant to invest in the conduct of the highly expensive clinical trials that are needed to improve the evidence base. Such investment is only likely to be made if a patentable intervention can be linked to a breakthrough approach that is beneficial to the broad spectrum of DFUs, and this is relatively unlikely until a mechanism can be found that is central to the delayed healing (in particular) of the majority of ulcers.

The very understandable need to maximize sales while limiting cost has also often led industry to base promotion on clinical studies of reduced scientific value: uncontrolled case series, and small trials of weak design. It is also more rewarding for industry to invest in research into the use of devices (including many topical applications and dressings) than into the use of medicines because the required evidence for the marketing of devices is largely limited to that of safety and it is not currently necessary for the manufacturer to demonstrate effectiveness through the conduct of a properly designed RCT.

## IMPROVING THE EVIDENCE BASE FOR CLINICAL PRACTICE

### RCTs

While some observational studies are of value (see below), the predominant need is for firm evidence of benefit, and that can only be provided by RCTs. Linked to systematic reviews and meta-analyses, RCTs are at the top of the hierarchy of study designs because they limit the likelihood that any result observed—whether positive or negative—may be affected by either chance or bias. In this respect, bias may be defined as an influence on an apparent difference (or lack of difference) resulting from factors other than the treatment being studied.

The difficulties posed vary to some extent in each of the main areas of foot ulcer care (see Table 1), but an attempt has been made to address them in a detailed summary written on behalf of the International Working Group on the Diabetic Foot and the European Wound Management Association (69). Twenty-one of the difficulties inherent in most trial circumstances have been proposed as criteria on which to score the quality of published studies (see Table 3). This approach goes a step further than existing criteria used to assess the quality of RCTs because it includes more details of trial conduct and trial reporting in addition to the accepted principles of good trial design. It should, however, be noted that these recommendations apply only to clinical studies and take no account of those (that are also much needed in this field) to investigate the basic physiology and pathology of wound onset and healing.

#### *Key Aspects of Study Design and Conduct*

Some of the items listed in Table 3 merit particular emphasis because they are frequent areas of weakness in the published literature. Such weaknesses increase the risk that any observed differences (or absence of differences) between intervention and control groups could have been biased by confounding factors and thereby weaken the conclusions that can be derived.

The focus of this section of the review is on trials of treatments for the management of existing DFUs. Similar principles apply to trials for primary and secondary prevention of ulcers, as well as reduction of mortality, but the details will differ in particular subgroups. Nevertheless, the following selected items relate to issues that are common to the majority.

#### Study Population

One of the most common weaknesses of published trials relates to the study population. Many studies either do not describe the population in sufficient detail or have included participants with relatively uncomplicated ulcers. Uncomplicated ulcers might be selected for study because they are more likely to heal in a shorter time and hence a primary outcome will be available in a greater proportion—and the total required for study will be lower. But this is not the group in which new treatments need to be tested. Uncomplicated neuropathic ulcers respond extremely well to the provision of effective off-loading (33,70,71), and what is currently needed is evidence of benefit in people with ulcers that fail to respond well to good standard care, i.e., in people with ulcers that have been shown to be "hard to heal." In this respect, it should be usual in trials to specify that the study ulcer has not decreased its cross-sectional area by more than a prespecified percentage (25–50%) during a run-in period of 2–4 weeks despite being managed according to accepted standards of good standard care.

#### Control/Comparator Group; the Components of "Good Standard Care"

A number of new treatments have previously been approved for use on the

**Table 3—Factors and pathways that may contribute to delayed healing**

21-point scoring system for reports of clinical studies of the prevention and management of disease of the foot in diabetes

| |
|---|
| Study design |
| 1. Are adequate definitions included for the terms "ulcer," "healing," and all other required aspects of the population and the outcomes? |
| 2. Was the choice of study population appropriate for the chosen intervention and the stated outcomes? |
| 3. Was the control population managed at the same time as those in the intervention group? |
| 4. Is the intervention sufficiently well described to enable another researcher to replicate the study? |
| 5. Are the components of other aspects of care described for the intervention and comparator groups? |
| 6. Were the participants randomized into intervention and comparator groups? |
| 7. Were the participants randomized by an independent person or agency? |
| 8. Was the number of participants studied in the trial based on an appropriate sample size calculation? |
| 9. Was the chosen primary outcome of direct clinical relevance? |
| 10. Was the person who assessed the primary outcome or outcomes blinded to group allocation? |
| 11. Was either the clinical researcher who cared for the wound at research visits or the participant blinded to group allocation? |
| Study conduct |
| 12. Did the study complete recruitment? |
| 13. Was it possible to document the primary outcome in 75% or more of those recruited? |
| 14. Were the results analyzed primarily by intention to treat? |
| 15. Were the appropriate statistical methods used throughout? |
| Outcomes |
| 16. Was the performance of the control group of the order that would be expected in routine clinical practice? |
| 17. Are the results from all participating centers comparable? Answer "Yes" if the study was done in only one center. |
| Study reporting |
| 18. Is the report free from errors of reporting, e.g., discrepancies between data reported in different parts of the same report? |
| 19. Are the important strengths and weaknesses of the study discussed in a balanced way? |
| 20. Are the conclusions supported by the findings? |
| 21. Is the report free from any suggestion that the analyses or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings? |

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basis of the demonstration of a statistically significant difference between the treatment and control groups when experienced clinicians will feel that the performance in the control group was considerably worse than it should have been. In such circumstances, the better outcome in the treatment group may be entirely the result of a "study effect," and the observed difference is misleading. Each RCT should therefore specify the components of good standard care that was provided to all participants in their study. These include appropriate and similar attention being paid to surveillance (expert assessment of each ulcer at the same intervals in the two groups), offloading, debridement, dressing choice, antibiotics for active infection, glycemic control, and nutrition. The majority of RCTs are necessarily large in order to assure sufficient statistical power to detect a clinically important effect, and this means that participants may be recruited from many different centers. But the greater the number (and hence the likely heterogeneity) of the participating centers, the less likely it is that all will provide the required elements of good standard care. It is for this reason that the 21-point checklist requires scrutiny of the uniformity of apparent effect in all centers.

### Choice of Outcome Measure

The primary outcome in the types of study being described should be clinically relevant. In studies of people with active ulcers, the ulcer-centered outcome of choice is healing by a fixed time or time to healing. An alternative measure is to document change in cross-sectional area (provided sufficiently precise and accurate methods are used to document it), and this may not always be easily accomplished because of the curved surfaces of the foot (and for this reason are best determined from an image of a wound tracing rather than of the wound itself). As change in early-phase cross-sectional area has been shown to correlate with later healing (72–74), the chosen primary outcome may be a relative short-term reduction in ulcer area. It is less precise as a measure but can potentially allow exploratory studies to be conducted more quickly.

But when expressed in person-centered terms—which is generally preferable—the outcome should ideally refer not just to the healing of the index ulcer but to the patient being ulcer free (because a person's quality of life is not much improved if one of their foot ulcers has healed while others persist). If such a person-centered outcome measure is adopted, it might be expressed in terms of "time to being ulcer free," "being ulcer free after a fixed interval" (e.g., 12 weeks), or "ulcer-free days" from the date of randomization to a fixed point (e.g., 20 or 24 weeks). The use of "ulcer-free days" as a primary outcome is also valuable in studies of attempts to reduce ulcer recurrence, just as "antibiotic-free days" may be used in studies designed to prevent or treat infection and "amputation-free survival" in people with limb-threatening PAD.

### Blinding of Outcome Assessment

It is essential that the primary outcome should be documented (or confirmed) by a clinical observer who is unaware of the group (intervention or control) to which the participant has been allocated. If the judgment is made by a researcher who is not blinded in this way, then it will be at risk for observer bias. Some trials claim that it is not possible to blind the observer, but this is rarely the case—with the only usual exception being in those in which the treatment involves some obvious change to the appearance of the foot.

Many trials are labeled as being "double-blind," but this term is technically imprecise. The main requirement is for a trial to be "observer-blind" whenever it is possible, but both the clinical researcher and the participant can also be blinded in some cases (e.g., in a placebo-controlled trial) and the study could be either double-blind or triple-blind. The term double-blind needs therefore to be defined (i.e., whether observer, researcher, or participant blind) whenever it is used.

## SYSTEMATIC REVIEWS AND META-ANALYSES

The purpose of this article is not to describe the conduct of systematic reviews and meta-analyses. It should, however, be noted from the comments made above on the assessment of the significance of the difference between a treatment and a control group that any systematic reviewer needs either specialist clinical experience or a very detailed knowledge of the literature in order to judge whether the performance in the control group is that which is expected. It follows that systematic reviews and meta-analyses in this field cannot be properly undertaken without such knowledge or experience.

## THE VALUE OF OBSERVATIONAL STUDIES AND SYSTEMATIC AUDIT

### Observational Studies

The emphasis of this review has been deliberately placed on RCTs because these will be the linchpin of the improved evidence base that is so very much needed to guide the management of DFUs. Other types of study may, however, have an important place, and these include well-designed observational studies. Observational studies have, for instance, been the basis of much of the work done to document the incidences of ulceration and of amputation, as well as other clinical outcomes and costs referred to above. Observational studies have also drawn attention to the very considerable variation in outcome that is present, even in industrialized countries.

#### *The Need for Case-Mix–Adjusted Data*

When observational comparisons are made between different communities or services, it is necessary that the results are case-mix adjusted. Whether the primary measure is one of incidence or of outcome, it is necessary to compare populations that are adjusted at least for age, sex, and race (as well as other factors that depend on the field of study).

### Audit

Audit involves repeated scrutiny of data either from one or multiple populations. Data on incidence (of major amputation, for example) require careful interpretation because of the possibility of conflicting influences, as described above. When expressed in terms of the population with diabetes, changes in the incidence of amputation that have occurred in the last 15–20 years will not just result from changes in the quality of care but will be influenced by changing diagnostic criteria for diabetes, screening programs (resulting in a greater proportion of identified cases being so far free from chronic complications of hyperglycemia), and the increase in prevalence of diabetes resulting from lifestyle change.

But audit can provide very powerful information on the changes that may occur in circumscribed populations in response, in particular, to the structures of care. In this way, some within-center studies have shown massive reductions in the incidence of major amputation resulting simply from the organization of care (40–42). Nationwide, the incidence of major amputation for diabetes has now fallen to 0.8 per 1,000 across England (75). Nevertheless, the persistence of considerable geographic variation, at least across England, suggests that the total should fall still more if all populations are managed to the same standard (76).

## FUTURE DIRECTIONS; NEW GUIDELINES

Much has been achieved in the last two decades with the incidence of major amputation being very much reduced, at least in some countries, but there is evidence that even more can be achieved. There is wide variation in the outcome of management, even in industrialized countries and those with nationalized health care systems—suggesting that many people do not receive optimal care. Two broad strategies are key to improving overall outcome. The first is a major investment in the conduct of the high-quality clinical trials that are necessary to improve the evidence base for routine clinical care. The second is to ensure that those responsible for the design and delivery of care for people with DFUs comply with such evidence-based guidance as is available.

### Evidence Base for Wound Care Treatments

There is currently little evidence to justify the adoption of very many of the products and procedures currently promoted for use in clinical practice. Guidelines are required to encourage clinicians to adopt only those treatments that have been shown to be effective in robust studies and principally in RCTs. The design and conduct of such RCTs needs improved governance because many are of low standard and do not always provide the evidence that is claimed. There should be new guidance on the conduct of RCTs in this field, and it should embrace items such as those covered in the 21-item checklist of study quality reproduced as Table 3. Clinicians need to be able to assess the relative validity of published work, including its strengths and limitations in trial design, conduct, and reporting.

Assessment of trial conduct requires appreciation of the relevance of reported findings to clinical practice, and this can often only be assessed by experts who work in the field. Such assessment requires careful scrutiny of the outcomes chosen and the quality of care in the comparator group: the report of a statistically significant difference between intervention and control arms is insufficient on its own. The current culture of trial planning by generic contract research organizations employed by industry that appoint chief and principal investigators in the expectation that they play no more than a token role is one that needs urgent review. Current evidence suggests it is one that does not provide the answers that are needed.

### The Structure of Care

However, in addition to improving the evidence base to justify the use of particular interventions, attention must also be paid to the structure of the care pathway. Available evidence suggests that very considerable improvements can accompany structural changes in the way professionals work and in the way that care is delivered. Available evidence suggests that such structural changes should focus on *1*) the creation of clear pathways to enable early assessment of DFUs by a specialist multidisciplinary service and *2*) the provision of structured surveillance and

care for those who have had a DFU and are in remission after healing.

If communities embrace these initiatives, it should be possible to trigger substantial improvement in outcomes relating to DFUs. Care of the foot needs to metamorphose from a subspecialty to a "superspecialty" of diabetes.

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