Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management

While there is a consensus that clinical practice should be evidence based, this can be difficult to achieve due to confusion about the value of the various approaches to wound management. To address this, the European Wound Management Association (EWMA) set up a Patient Outcome Group whose remit was to produce recommendations on clinical data collection in wound care. This document, produced by the group and disseminated by *JWC*, identifies criteria for producing rigorous outcomes in both randomised controlled trials and clinical studies, and describes how to ensure studies are consistent and reproducible

Section 1: Background

Non-healing wounds are a significant problem for health-care systems worldwide. In the industrialised world, almost 1–1.5% of the population will have a problem wound at any one time. Furthermore, wound management is expensive: for instance, in Europe the average cost per episode is €6,650 for leg ulcers and €10,000 for foot ulcers, which accounts for 2–4% of health-care budgets. This figure can be expected to rise with an increasingly elderly and diabetic population.

There is an urgent need to review wound strategies and treatments in order to reduce the burden of care in an efficient and cost-effective way. If patients at risk are identified sooner and aggressive interventions are taken before the wound deteriorates and complications occur, both patient morbidity and health-care costs can be significantly reduced. The question is: which interventions, technologies and dressing materials are the best from those available?

Ongoing controversy surrounds the value of various approaches to wound management and care. There is a need to consider alternative ways of achieving the highest level of evidence required by Cochrane for this patient group. The Cochrane Wound Group maintains that the standardised approach to randomised controlled trials (RCTs) can be used in this patient population: '…it is unclear why aiming for rigorous evaluations of wound care treatments should pose any greater difficulties than for other health-care treatments' (Bell-Syer et al, 2009).

However, there is fundamental confusion over the best way to evaluate the effectiveness of interventions in this complex patient population. This is illustrated by recent reviews of the value of various treatment strategies for non-healing wounds, which have highlighted methodological inconsistencies in primary research. This situation is confounded by differences in the advice given by regulatory and reimbursement bodies in various countries regarding both study design and the ways in which results are interpreted.

In response to this confusion, the European Wound Management Association (EWMA) has established a working group, the Patient Outcome Group, whose main objective is to implement revised pan-European evidence recommendations for clinical data collection in this patient group. The key stakeholders of the Patient Outcome Group are listed in Table 1.

Table 1. The EWMA Patient Outcome Group members

Clinicians/individuals
Finn Gottrup (chair)
Jan Apelqvist
Luc Gryson
Zena Moore
Patricia Price
Hugo Partsch
John Posnett
Industry representatives
Abbott (2010)
B. Braun
Coloplast (2008–2009)
ConvaTec
Covidien
KCI
Lohmann & Rauscher
Paul Hartmann AG
Mölnlycke Healthcare

For more information on the EWMA Patient Outcome Groups and its objectives, see http://www.ewma.org/english/patient-outcome-group

Evidence-based practice

Since the middle of the 20th century, there has been increased emphasis on the application of evidence-based practice in health care. While the term 'evidence' is often used informally in day-to-day conversations, 'evidence-based practice' specifically refers to clinical decision making that is based on the best available evidence, with practitioners reviewing information from powerful data, instead of relying on single observations or customs. Key components of this approach include the development of important clinical questions and critical assessment of the type and level of evidence available. Poor quality, contradictory or incomplete evidence make this much harder to achieve.

Nature and extent of the problem for wound management: the clinical perspective

Evidence-based practice is the integration of clinical expertise with the best available clinical evidence from systematic research.

Different types of evidence are available and their relative importance for changing clinical practice has been organised into a hierarchy. At the top of the hierarchy is the well-conducted meta-analysis of several well-conducted RCTs, which is considered by many to be the most robust type of evidence on which to base changes in clinical practice (Table 2).

The question for wound care practitioners is: which interventions, technologies and dressing materials are the best from the point of view of a single patient or group of patients, where the primary focus is healing and the absence of complications?

Through initiatives such as the CONSORT initiative on reporting RCTs (www.consort-statement.org), clinicians and clinical scientists have concentrated on improving the quality of evidence with a view to achieving better patient outcomes. Systematic reviews have indicated that there are substantial deficiencies in the quality of clinical research such that all stakeholders are concerned to increase the quality of work undertaken (www.cochrane.org, www.nice.org.uk).

Trials in wound management should, whenever possible, adhere to guidelines for conducting and reporting clinical studies. However, wound management has a paucity of high-quality evidence, as studies are often based on inadequate sample sizes, have short follow-up periods, non-random allocation to treatment groups, non-blinded assessment of outcomes, and poorly described control groups and concurrent interventions. This is the background to the current debate on the difficulties that wound management studies present to researchers and §clinicians.

The main problem is comparability of patients as many wound patients are old, fragile and have several other diseases. Furthermore, it is debatable whether the pharmaceutical approach to measuring efficacy is directly applicable to dressings and medical devices.

The extended definition by Sackett (1996) may be more relevant in the wound sector. This proposes that evidence-based medicine is not restricted to randomised trials and meta-analyses, but involves the exploration of all types of best external evidence. Prospective cohort studies may be particularly helpful, especially when cost and resource use are the major outcomes of interest.

Nature and extent of the problem for wound management: the policy maker and health-care system perspectives

Two issues arise from the point of view of the health-care system as a whole.

The first is whether or not a particular product or intervention is safe and effective when used as indicated — this is a question of regulatory approval. The Medical Devices Directive MDD 93/42/ECC

classifies wound care products according to the risk they pose to the patient, and different products require different conformity assessments and supporting data. This directive dictates the development of clinical data for regulatory approval but does not deal with reimbursement requirements.

The second issue is whether or not the product or intervention represents a cost-effective use of funds. This relates to reimbursement or payment. Regulatory approval does not guarantee that a technology will be funded, but it is a prerequisite for reimbursement. A comparative trial, therefore, is not necessary for regulatory purposes, but it is required for reimbursement — where a specified comparator must be used in each country (which can vary across European countries).

In European countries, requirements for regulatory approval are generally uniform. CE marking of a new wound management product requires evidence that the product is safe and performs as claimed in its indicated use, and that any potential hazards have been identified. The level of evidence required is determined by the type of product. Generally, evidence requirements will be more stringent for a completely novel product or one with a higher level of perceived risk. In the US, the principles are similar, although some details of the approval process are different.

Evidence requirements for regulatory approval depend on whether or not the product can be shown to be equivalent to an existing product (510K route), or substantially different (PMA route). The PMA route usually requires a RCT with healing endpoints.

One area of practice that differs by continent is the use of comparators: for example, some authorities will accept the use of placebo-based trials (e.g. using saline gauze as a comparator), while others prefer the comparator to be best available clinical practice.

The requirements for obtaining reimbursement differ between countries within Europe and between Europe and the US. In some systems with multiple payers, requirements might differ between payers. In general, reimbursement is a two-stage process.

Establishing eligibility for payment ('coverage') will usually require showing that a product or technology is safe and effective when compared with the current standards of care. Increasingly, coverage decisions demand the highest level of clinical evidence (RCT), even where this level of evidence is not required for regulatory approval.

If a product is eligible for payment, the second stage is to establish a payment amount. This type of decision usually cannot be made on the basis of clinical evidence alone, but also requires a cost-effectiveness or cost-utility analysis.

Unfortunately, there are very few good quality clinical (Table 3) or economic studies in wound care. Recent reviews have shown little or no compelling evidence of a significant difference in healing times or percentage reduction in wound size between patients treated with traditional and modern dressings, and this type of conclusion is not unusual. Some of the reasons for the lack of good quality clinical studies are discussed in later sections of this document.

This has resulted in challenges to the reimbursement of modern dressings in favour of supposedly better value traditional products. There are two points to bear in mind here: first, the absence of evidence from good quality randomised studies is not in itself evidence that there are no differences in patient outcomes between modern and traditional dressings; second, the question of reimbursement means that cost-effectiveness must be considered.

The current lack of evidence for modern products raises two important questions:

- Why has wound care research not achieved level 1a evidence in the Cochrane hierarchy?
- What are the relevant endpoints for comparing different treatment regimens?

Table 2. Levels of evidence*

Level	Description
1a	Systematic reviews (with homogeneity) of randomised controlled trials
1a-	Systematic review of randomised trials displaying worrisome heterogeneity
1b	Individual randomised controlled trials (with narrow confidence interval)
1b-	Individual randomised controlled trials (with a wide confidence interval)
1c	All or none randomised controlled trials
2a	Systematic reviews (with homogeneity) of cohort studies
2a-	Systematic reviews of cohort studies displaying worrisome heterogeneity
2b	Individual cohort study or low-quality randomised controlled trials (<80% follow-up)
2b-	Individual cohort study or low-quality randomised controlled trials (<80% follow-up/wide confidence interval)
2c	'Outcomes' research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3a-	Systematic review of case-control studies with worrisome heterogeneity
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

* www.essentialevidenceplus.com/product/ebm_loe.cfm?show=oxford (site accessed 14 November 2009)

Table 3. Endpoint categories split by wound types and evaluation of predefinitions

Statistics	Endpoints No. (%)	Type and no. of ulcers	Endpoint defined at study start	Endpoint not defined at study start
			No. (%)	No. (%)
Biomarkers	14 (4.5)	DFU 3 LU 6 PU 2 Mixed 3	11 (79)	3 (21)
Change in wound condition	28 (9.0)	DFU 3 LU 16 PU 5 Mixed 4	16 (57)	12 (43)
Circulation	6 (1.9)	DFU 0 LU 6 PU 0 Mixed 0	2 (33)	4 (67)
Costs and resources used	14 (4.5)	DFU 2 LU 9 PU 2 Mixed 1	8 (57)	6 (43)
Dressing performance	22 (7.0)	DFU 0 LU 12 PU 8 Mixed 2	9 (41)	13 (59)
Infection signs	14 (4.5)	DFU 8 LU 2 PU 2 Mixed 2	10 (71)	4 (29)
Quality of life	18 (5.8)	DFU 1 LU 14 PU 2 Mixed 1	11 (61)	7 (39)
Symptoms, signs	41 (13.2)	DFU 6 LU 25 PU 7 Mixed 3	17 (41.5)	24 (58.5)
Reduction rate	75 (24.1)	DFU 19 LU 32 PU 19 Mixed 5	40 (53)	35 (47)
Wound closure	53 (16.9)	DFU 18 LU 24 PU 9 Mixed 2	34 (64)	19 (36)
Healing time	28 (9.0)	DFU 7 LU 14 PU 6 Mixed 1	14 (50)	14 (50)
Total: endpoints	313 (100)			
Total: articles	176			

Nature and extent of the problem for wound management: an industry perspective

The issue from an industry perspective is that there are many different customers for clinical and economic evidence — including regulators, clinicians, reimbursement authorities and other payers — and each has slightly different requirements.

Initially, clinical care focused on a passive approach to symptom management, with its emphasis on the use of non-active topical treatments (medical devices). It is only very recently that the specialty has developed, allowing for more proactive biological or high-tech interventions (often considered medical drugs).

The problem for the medical device industry is that requirements, as well as the standard of care, are different in each country. In order to obtain certification and reimbursement, data must be prepared that support the safety, performance and therapeutic benefit of each wound dressing — from cotton gauze to foam with an ancillary antimicrobial component — by comparing it to the local standard care in many different 'wound' indications. Such data is based on clinical data gathered by literature search and/or by clinical investigation.

Nevertheless, for many generics or me-too products a faster assessment via the process of 'equivalence' is possible. Therefore, only where a product is significantly different from anything that has already been approved is a new comparative clinical study likely to be required.

Another problem is that RCTs are expensive and time-consuming. Very few wound care products have a sufficiently large potential market to justify this investment, and the pace of innovation in wound care limits the incentive to engage in long-term clinical research.

The cost of clinical research is compounded by differences between countries in the evidence requirements for reimbursement, including differences in standard care and other variations in clinical practice, which affects the choice of comparator as well as costs and patient outcomes. For most wound care products, it is not feasible to conduct a clinical study in each market.

Scope of the initiative

To date, the obvious outcome measure in evaluating interventions in wound healing has been complete healing. However, this may not be the only appropriate outcome in wound healing studies. Other endpoints including clinical, intermediate and surrogate outcomes (such as infection rate, bacterial contamination, wound pain, resource utilisation and cost) also need to be considered.

Given the costs associated with adequately powered, multinational, multicentre studies with acceptable follow-up periods, it is important for the wound

management community to agree on a consistent approach to collecting evidence with appropriate outcomes that are measured in a consistent way.

This document aims to develop a consistent and reproducible approach to defining, evaluating and measuring appropriate and adequate outcomes in both RCTs and clinical studies in wound management. It addresses the difficulties in undertaking such studies from both clinical and industry perspectives.

It does not discuss animal and cellular models, acute wounds (e.g. surgical/trauma wounds), burns or surgical wounds. Acute wound healing follows a well-defined pattern resulting in complete wound healing, which makes it easier to objectively assess the wound's progression throughout the healing process. Furthermore, in most clinical trials and wound studies involving dressings, devices or drugs, 'healing' is considered to be the predetermined endpoint for both acute and chronic wounds.

Products that aim to achieve healing in acute wounds may not have the same effect on chronic, non-healing wounds due to the interaction of various confounding factors, including comorbidity, concurrent disease, exudate, an unhealthy wound bed, infection and ischaemia. As a consequence, this analysis focuses on chronic wounds, usually defined as those that fail to progress through an orderly and timely sequence of repair (in this document defined as 'non-healing'); time (number of days and weeks) is not a suitable parameter for identifying chronicity or non-healing.

The majority of non-healing ulcers occur in elderly individuals with underlying concurrent disease(s) and comorbidities. It is important to distinguish these from wounds in which healing is delayed due to other confounding factors, such as neglect, incompetence and misdiagnosis, or is compromised by inappropriate treatment strategies and care.

The majority of non-healing wounds are seen in the lower part of the body, especially in the lower extremities. Most non-healing (including complex and recalcitrant) wounds are predominantly leg ulcers, pressure ulcers or of neuropathic origin. As a consequence, this document focuses on leg ulcers (venous, arterial, and mixed), pressure ulcers and diabetic foot ulcers.

Table 4. Useful documents giving guidance for evidence collection

AQUA Institute, www.aqua-institut.de
DIN ISO EN 14155-1:'Clinical investigation of medical devices for human subjects – Part 1: General requirements'. Part 2: Clinical investigation plans' (edited by Beuth Verlag, http://www.beuth.de)
FDA: Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment Food and Drug Administration, June 2006 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071324.pdf
FDA Wound Healing Clinical Focus Group. Guidance for industry: chronic cutaneous ulcer and burn wounds — developing products for treatment. Wound Rep Reg 2001; 9: 258-268
ICH (International Conference of Harmonisation) e.g. Topic E 6: Guideline for Good Clinical Practice in the European Community, www.ich.org
IQWIG / D: General methods, www.iqwig.de/general-methods.428.en.html
IQWIG / D: Cost-benefit assessment
ISPOR guidance www.ispor.org/PEguidelines/index.asp
MEDDEV 2, 12–2 May 2004: Medical Devices: Guidance Document – Guidelines on post market clinical follow-up, http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_12-2_05-2004_en.pdf MEDDEV 2.7.1. Dec 2009: Guideline on Medical Devices – Clinical evaluation: Guide for manufacturers and notified bodies, http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf)
Nice/UK: Guideline manual 2009 www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp www.iqwig.de/cost-benefit-assessment.736.en.html
SIGN 50: A guideline developer's handbook (SIGN: Scottish Intercollegiate Guidelines Network) January 2008, especially the Annex B 'Key of evidence and grades of recommendations' and Annex C 'Methodology Checklist' www.sign.ac.uk/guidelines/fulltext/50/index.html
The Consort Statement: Revised recommendations for improving the quality of reports of parallel-group randomised trials, www.consort-statement.org/ Mohr, D., Schultz, K.F., Altman, D.G. (for the Consort Group). Lancet 2001; 357: 1191-1194
The Cochrane Collaboration, www.cochrane.org

Aim of document

This document provides recommendations on how to achieve rigorous outcomes in studies on wound management and describes an approach that will enable the design of RCTs and clinical studies to be both consistent and reproducible. The overall aim will be achieved by:

- Providing recommendations to medical device and/or pharmaceutical companies to use when planning clinical/economic studies in order to maximise the value of investments in research on (problem) wound management or treatment
- Providing a framework for clinicians when:

a. conducting and evaluating clinical studies

b. assessing clinical data, appropriate outcome measures and treatment strategies in order to improve clinical pathways in wound management

- Informing health technology assessment bodies and decision-makers about the key features of medical device research that should be taken into account when assessing the strength of evidence.

Table 5. Different types of clinical studies (Nice/UK: Guideline Manual 2009, Appendix M, abbreviations and glossary)

Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more likely to reliably confirm or refute a hypothesis than the individual trials
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups
Cohort study	A retrospective or prospective follow-up study. People to be followed up are grouped on the basis of whether or not they have been exposed to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the intervention of interest.
Prospective cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Prospective cohorts are assembled in the present and followed into the future
Cross-sectional study	The observation of a defined set of people at a single point in time or time period. This type of study contrasts with a longitudinal study, which follows a set of people over a period of time
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups (for example, cohort studies and case-control studies)
Case-control study	Comparative observational study in which the investigator selects people who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients
Case report	Report of one or two of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients

Section 2: Different types of evidence required by different authorities

Evidence that is produced on new or existing technologies can come in different forms. The type of evidence may differ depending on whether the information is required for a product to get approval for use, for reimbursement purposes or to be approved for routine clinical use.

Many key regulatory and government authorities have written guidance, recommendations and directives on how studies should be designed, to ensure that high-quality data are submitted when applications are made for approval or reimbursement. More information on the evidence-collection guidance provided by government authorities is available in the relevant documents and directives listed in Table 4.

Different types of evidence: the clinical research perspective

Over the past 20 years the concept of evidence-based practice has become increasingly influential within health care. Table 2 gives details of the hierarchy of evidence, which is increasingly being used to grade the quality of data available for clinical decision making. In wound management only a limited number of RCTs meet the requirements of the level 1a classification, particularly in studies published before 2003. Furthermore, there is also a paucity of observational data from cohort studies on which to base an analysis of improvements in outcomes (see Table 5 for a glossary of study designs).

Clinicians need to be aware of the strengths and limitations of different study designs if they are to effectively evaluate which health-care practices are worth considering for different patients in different health contexts.

Given that RCTs are listed at, or near, the top of the evidence hierarchy, it is important to consider which elements of this study design are considered to be quality indicators. Table 6 outlines the key elements of RCT reporting that are recommended by the CONSORT Group (www.consort-statement.org) and how they may apply to wound care studies.

Key issues regarding the use of RCTs in wound management include:

- It is essential that all individuals involved in data collection are trained to ensure that each person follows the same protocol. This is particularly important, given the variation in clinical approaches to diagnosing wounds, the variations in routine care at different centres (and in different countries) and the wide range of professions involved in the provision of wound care. The ongoing use of open studies means that issues relating to blinded assessment are particularly important to ensure that the data are robust

Table 6. Applying quality markers to wound management studies

Methodology checklists

	Reducing potential bias in intervention studies (enhancing internal validity to reduce uncertainty in estimates of expected costs and outcomes)	
Reporting trials	**Recommended action**	**How does this apply to wound care studies?**
Method: participants	Eligibility criteria for participants and the settings and locations where the data are collected	This should be possible in every study. The key issue is to select the appropriate patients with wounds in the appropriate condition for the research question under investigation, bearing in mind that wounds may deteriorate over time due to the nature of the underlying disease
Method: interventions	Precise details of the interventions intended for each group and how and when they were actually administered	There are no particular issues for wound care, although there is a range of different interventions that may be assessed (i.e. devices, technologies and drugs) either individually or in combination. Interventions may change during the healing process, so the condition of the wound OR the phase of healing must be documented
Method: objectives	Specific objectives and hypotheses	There should be no problems in reporting the objectives. However, at the design phase the objectives should be specific to the research question and the objective of the intervention (e.g. debridement of dead tissue)
Method: outcomes	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors)	These should be clearly predefined and reported, and related to the intervention (e.g. resolution of infection). The major controversy relates to the fact that outcomes are often not clearly defined, leading to poor reproducibility. Intact skin has been the most commonly used outcome to date, even where it is not directly related to the intervention of interest. The training of assessors is particularly important given the need for multicentre trials to recruit large samples
Method: sample size	How sample size was determined and, when applicable, explanation of any interim analysis and stopping rules	This is important, but many areas of investigation do not have sufficient preliminary data on which to base such calculations. Therefore, it is essential to obtain routine clinical data on the impact of standard care before starting a new study
Method: randomisation: 1. sequence generation 2. allocation concealment 3. implementation	1. Method used to generate the random allocation sequence, including details of any restrictions (e.g. blocking, stratification) 2. Method used to implement the random allocation sequence (e.g. numbered containers, central telephone), clarifying whether the sequence was concealed until the interventions were assigned 3. Who generated the allocation sequence, who enrolled the participants, and who assigned participants to their group	There are no specific issues for trials in wound care and essential details should be reported. Although there is still debate on the appropriate variables that should be used for stratification, most commonly they are ulcer size and duration. Given the need for an increased use of multicentre trials, the question of stratification by centre should be considered
Method: blinding (masking)	Regardless of whether or not they are study participants, those administering the interventions, and those assessing the outcomes should be blinded to group assignment. If done, how the success of blinding was evaluated	Many studies in wound care are open studies as the nature of the intervention often makes blinding complicated. This increases the importance of using a blinded assessment technique that is as objective as possible in order to maximise the chances of reproducible findings. The minimum requirement is an independent evaluation, when blinding or blinding assessment is less valid in practice
Method: statistical methods	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	There are no specific issues for wound care studies

Table 6. Applying quality markers to wound management studies (continued)

Methodology checklists

	Reducing potential bias in intervention studies (enhancing internal validity to reduce uncertainty in estimates of expected costs and outcomes)	
Reporting trials	**Recommended action**	**How does this apply to wound care studies?**
Results: participant flow	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the number of participants randomly assigned, receiving intended treatment, who complete the study protocol, and are analysed for the primary outcome	This is essential for wound studies due to the high attrition rate likely to be seen, particularly over long follow-up periods. This occurs as a result of the comorbidities associated with this patient group and the difficulties inherent in maintaining a strict protocol over many months
Results: recruitment	Dates defining the periods of recruitment and follow-up	This is not a specific problem for wound care studies, although there is a debate about the length of follow-up needed to establish healing (See section headed 'Study design considerations that relate to wound studies')
Results: baseline data	Baseline demographics and clinical characteristics of each group	This should not be a problem for wound care studies but is often not reported in enough detail: it is particularly important for studies with patients with an extensive range of comorbidities
Results: number analysed	Number of participants (denominator) in each group included in each analysis and whether the analysis was 'intention to treat'. State the results in absolute numbers when feasible (e.g.10 out of 20, not 50%)	There are no particular issues for wound care studies in reporting this information
Results: outcomes and estimation	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g. 95% confidence intervals)	There are no particular issues for wound care studies in reporting this information
Results: ancillary analysis	Address multiplicity by reporting any other analyses performed, including sub-analysis and adjusted analysis. Indicated those that are pre-specified and those that are exploratory	There are no particular issues for wound care studies in reporting this information. Information on improvement is usually reported. However, there is a need to include data on wound deterioration over time, particularly where this is a part of the natural course of the underlying disease or subsequent to the development of additional symptoms
Results: adverse events	All important adverse events or side effects in each intervention group	There are no particular issues for wound care studies in reporting this information
Discussion: interpretation	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes	This is particularly important as the patients are likely to present with a wide range of comorbidities, which can make interpretation difficult. Biases inherent in wound studies are discussed later in this document
Discussion: generalisability	Generalisability (external validity) of the trial findings	There are no particular issues for wound care studies in reporting this information. In the wound community there is a large disparity between the desire for high internal validity for approval or reimbursement studies compared with pragmatic studies that may provide more useful information for routine clinical interpretation
Discussion: overall evidence	General interpretation of the results in the context of current evidence	There are no particular issues for wound care studies in reporting this information

- The heterogeneity of the study population can pose particular problems as there is a tension between the requirement to maintain internal validity, by using restrictive patient inclusion criteria, and the need to be able to generalise the findings to the wide range of patients likely to use wound management services. To some extent, this can be managed through stratification of the sample by size and duration, but centre effects should be investigated if the sample size permits
- One particular problem in intervention studies in wound management is that wounds may not only heal or improve but may also deteriorate — often as a consequence of the underlying condition(s). This will have an impact on the attrition rates likely to occur over particularly long intervention and follow-up periods
- A purist approach to RCT design stipulates that a single intervention should be investigated until the primary outcome is achieved. In wound management this can be difficult as the presentation of the wound bed and associated symptoms may indicate that the intervention is no longer the appropriate method of treatment — even though the primary endpoint (e.g. healing) has not yet been achieved.

The most important element in establishing evidence in wound management is the choice and definition of outcome parameters. This will be described in detail in later in this document.

Different types of evidence: industry perspective

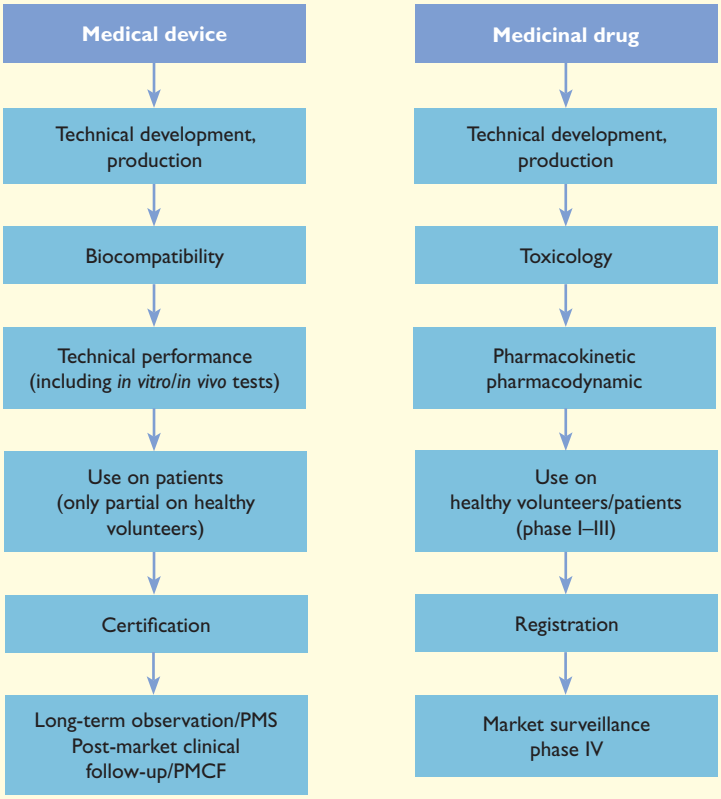
From an industry perspective, external evidence needs are set by the requirements of national regulatory and reimbursement authorities, and other payers. When developing a new product, there are also internal needs for evidence, which mirror the phases of the development process.

A typical pharmaceutical model for medicinal drugs is illustrated in the right column of Fig 1. This procedure is not comparable with the development process of medical devices, which is illustrated in the left column.

The biocompatibility tests used for medical devices are described in legally and obligatory harmonised norms (IS0 EN DIN 10993). The requirement for various toxicological studies depends on the intended use of the medical device (e.g. invasive/non-invasive, localised, duration of use).

The legally required clinical data are gathered using the 'literature route' and/or the 'clinical investigation route'. Phase I clinical studies on volunteers are not possible for medical devices such as implants. Wound dressings that are comparable to other products already on the market, such as generics and me-too products, must show equivalence of their technical, biological and clinical properties (see Table 7). For these types of product, the 'literature route' for obtaining clinical data may be sufficient.

Fig 1. Different development steps for medical devices and medicinal drugs in Europe



For a completely novel product making new claims that are not well-proven and known at the market level, clinical investigations are required. This also applies to medical devices that incorporate a new ancillary pharmaceutical compound, such as wound dressings combined with a new antimicrobial compound. These are classified as class III according to guideline MDD 93/42/EEC.

The different requirements for supporting evidence are also described in the recommendations and guidelines for post-marketing surveillance (PMS) and for post-market clinical follow-up (PMCF), in contrast to medicinal drugs. When seeking payment or reimbursement for a new product, the key issue will often be budgetary impact and/or cost-effectiveness, rather than healing.

As a general example of a development process, a possible test battery for wound management is described in Table 8.

When planning, conducting and evaluating clinical investigations, local or national laws concerning the conduct of clinical investigations take precedence over international guidelines. As different directives and guidelines may apply in different

Table 7. Data requirements for demonstration of equivalence in devices*

Technical
Similar conditions of use
Similar specifications and properties (e.g. tensile strength, viscosity, surface characteristics)
Must be of similar design
Similar deployment methods (if relevant)
Similar principles of operation
See also the harmonised norms for wound dressings and medical devices (further information is available on the EWMA website)
Biological
Use same materials in contact with the same human tissues or body fluids
Clinical
Used for the same clinical condition or purpose
Used at the same body site
Used in similar population (including age, anatomy, physiology)
Similar relevant critical performance in terms of the expected clinical effect for its specific intended use

* According to MEDDEV 2.7.1 and 2.12/2 (recommendations, not obligatory by law)

countries, it must be ensured that the relevant national instructions are taken into account. Given that directives and guidelines may change, it is important to ensure that the most recent version of these documents is identified and used. An overview of the international regulations for clinical investigation on medical devices is available on the EWMA website (www.ewma.org).

Statements

- A consistent approach to the definition of 'standard care' should be developed to assist with the utilisation of data on a pan-European basis
- The technical properties of wound dressings should be described using harmonised terminology. This will facilitate cross-country standards
- Data collected to establish the performance, safety and therapeutic benefit of wound dressings should be interchangeable across Europe, to reduce the need for replication by country
- Without baseline data from cohort studies, there are limited opportunities to conduct high-quality RCTs when urgently needed
- Investigators are recommended to adopt a framework for conducting clinical studies that is similar to the CONSORT agreement, which reflects the highest quality of design possible for the clinical question of interest
- The essential issue is to develop a consistent and reproducible approach to define, evaluate and measure appropriate and adequate outcomes in RCTs and other clinical studies such as cohort studies, comparison studies of treatment regimens using registry data and real-life studies
- The particular properties of a wound dressing, and its reasons for use, should guide the outcome measure of choice both for evaluation purposes and the development and certification/reimbursement process.

Section 3: Evaluation of outcome

Aetiology and basic standard of care in non-healing wounds

For the three major categories of non-healing cutaneous ulcers — leg ulcers (venous, arterial, mixed), pressure ulcers and diabetic foot ulcers — separate trials are generally considered appropriate as these ulcers have different aetiologies, standards of care and response(s) to therapy.

Non-healing ulcers may progress towards healing when the patient and/or care provider(s) adhere to standard treatment/care. 'Standard care' refers to generally accepted wound care procedures and the management of underlying disease, outside of the investigational product/device or drug that will be used in the clinical trial/evaluation.

A number of standard procedures for chronic cutaneous ulcers are widely accepted, and several professional groups have published care guidelines for ulcers (EWMA position documents, European Pressure Ulcer Advisory Panel/National Pressure Ulcer Advisory Panel [EPUAP/NPUAP] guidelines, Cochrane reviews, International Consensus on the Diabetic Foot [IWGDF]). It is essential that the standard care procedures/regimens used are consistent as this will minimise variability and enable assessment of the treatment effect.

Standard care procedures for non-healing cutaneous ulcers include:

- Offloading
- Optimising the general condition
- Nutritional support, including metabolic control (diabetes mellitus)
- Maintenance of the moist wound environment
- Removal of infected or necrotic tissue
- Wound cleansing
- Compression therapy for venous stasis ulcers
- Establishing adequate blood circulation or perfusion
- Bowel and bladder care for individuals with pressure ulcers at risk of contamination.

Table 8. Test battery for medical devices used in wound management, to prove the product's claims*

Technical category: *in vitro, in vivo, ex vivo*
Biocompatibility, product-specific effects: e.g. binding of inflammatory parameters; antimicrobial or anti-inflammatory actions, cytotoxicity, sensitisation, irritation etc.
Clinical stages in the pre-marketing category
Tolerability and patient safety in small groups of healthy volunteers or patients (case reports, case series, clinical feasibility, investigation). Purpose can include dosage range and identification of side effects; assessment of effect of product on various tissue parameters; case reports involving different types of chronic and acute wounds (if possible related to the specific product)
Comparison, clinical efficacy and tolerability on a small group of patients (clinical feasibility investigation)
The primary aim here is to compare the new treatment with existing standard treatment. These can be cohort investigations; randomised, adequately powered comparison investigations for clinical efficacy in a strictly defined population; monitoring side effects, cost-effectiveness, quality of life
Post-marketing surveillance (PMS) or post-marketing clinical follow-up (PMCF)
Pragmatic studies reflecting real-life usage to provide additional information on the benefits of the product and its optimal use (e.g. case series, cohort investigations, comparison investigations of real-life data with registries data, randomised comparison investigations)

* An example of the development process; not a regulatory/legal requirement

Currently, the majority of wound management studies recruit patients with one wound aetiology. However, the development of more targeted strategies specific to different phases of treatment (e.g. debridement) means that the condition of the wound (e.g. exudate rate, pain and necrosis) may be a better inclusion criterion.

For studies, the challenge has been to control the heterogeneity of individual patients, concurrent disease states and confounding factors, as well as variations in the type, site and condition of wounds and differences in health-care organisations. These problems cannot be solved by enrolling more subjects into a study.

Some of the healing-related challenges that occur when studying each aetiology are described below:

Leg ulcers (including venous leg ulcers)

Evidence from systematic reviews strongly suggests that sustained compression therapy is particularly effective in treating venous leg ulcers, making it difficult to observe any further improvement achieved as a result of dressing usage. Compression improves wound healing to such a degree that large sample sizes are required to show any improvement in healing rate.

All studies on venous leg ulcers must include compression as part of standard care. However, epidemiological data suggest that ulcers that are the result of varying degrees of arterial disease and other confounding factors are increasingly being presented. To date, only limited data are available on the natural outcome of arterial and mixed aetiology leg ulcers.

Pressure ulcers

Pressure ulcer studies are particularly challenging as they largely affect older populations with severe wounds, extensive comorbidities and long wound healing times. Factors such as pressure relief, bowel and bladder care and nutrition are essential. There is limited information available regarding the natural outcome of such wounds and specific factors related to outcomes in pressure ulcers, especially in a geriatric population.

Diabetic foot ulcers

The standard treatment of diabetic foot ulcers focuses on offloading and control of infection and ischaemia. The most important factors related to healing are the extent of comorbidity, the extent of tissue involvement at inclusion, infection and ischaemia. Most intervention studies concern pure neuropathic and not neuroischaemic foot ulcers. There is an increasing awareness that the majority of ulcers are of neuroischaemic origin and that infection is frequently present, but data on the natural progression of such wounds are limited.

Definition of endpoint

An endpoint is defined as the objective of an evaluation or study. This should always be clearly defined and stated in a manner that will allow the objectives to be investigated using objective and quantitative assessment of appropriate outcomes. The supporting evidence, which should be outlined in the background to and rationale of the study, should be linked logically to the study objectives. Study outcomes are more convincing when they apply to a single or small number of clearly defined objectives. The objectives should include:

- A precise statement of the degree of benefit expected from the intervention, and its duration
- Clear statements on the time frame of the study (especially in relation to how quickly the benefits might start)

Table 9. Literature search and analysis

Search
371 hits out of search in Medline and Embase
Search criteria
Limitations: • Search of all clinical and comparative studies on wounds • Humans only • Period: 2003–September 2009
Key words: chronic wound, pressure ulcer, venous leg ulcer, diabetic foot ulcer Regarding: intervention, wound management, dressings, treatment, devices, pharmalogical drugs/drugs
Analysis
176 articles were analysed and included in the statistics on the use of endpoints
Exclusion criteria
Not human
Reviews
Opinion papers
Acute wounds (burns etc)
Prevention
Case reports (if not dealing with specific endpoints)
Papers in foreign languages
Inclusion criteria
Venous, diabetic, pressure ulcers
Research
Comparative studies
Treatment
Only English papers (unless evaluated as highly relevant, in which case they were translated)

• A definition of the patients for whom the benefit is sought.

Objectives can be classified as either primary or secondary. Primary objectives provide the focus of the study. The collection and measurement of outcomes affecting the primary objective are critical and, if resources are scarce, this takes priority over any other, secondary, outcomes. An exception is the collection of safety information, which is always considered a high priority, regardless of whether or not safety is the focus of the study. It is crucial to minimise missing data relating to the primary objective.

Secondary objectives allow for the investigation of subsidiary questions that, while scientifically important, do not have the same priority of clinical interest in the patient group being studied. In most randomised trials, the efficacy of the intervention or its equivalence with standard care is the primary objective, whereas safety (e.g. toxicity, side effects) is usually a secondary objective. As with objectives, the outcomes of a trial require precise description and definition.

Standard measurement criteria are essential if results are to be accepted by the clinical community.

The chosen outcomes should be clinically relevant and, where possible, measured in an objective fashion. If objectivity is not possible, some control over a subjective assessment is desirable. Blinding assessors to the treatment allocation, for instance, is a powerful tool for reducing measurement bias. The frequency of outcome measurement should be clearly stated, as should strategies that will be undertaken if the pooled outcome rate is lower than anticipated (e.g. adjustment of study sample size). If composite outcomes are measured, precise statements on which aspects will be used to investigate the objectives must be made *a priori*.

Clinical versus surrogate endpoints

Intervention studies of cutaneous non-healing wounds rely heavily on observational data, and use outcomes with varying degrees of reproducibility that usually focus on the condition of the wound. In the past, the most commonly used *clinical* outcome (endpoint that directly relates to outcome) was visible reduction in wound size, particularly intact skin (full healing).

Over the past two decades, interest in the different phases of wound healing has grown markedly, with targeted treatment interventions being developed.

The development of tests and techniques to improve tissue sampling and analysis, imaging technology and scientific progress in cellular and molecular biology has enabled the development of more 'objective' wound outcome parameters (surrogate outcome parameters) that relate to both the wound condition and the treatment intervention being assessed (for example, exudation rate, pain, granulation rate, resolution of necrosis or infection).

Although there are now more data in the literature validating tests that use physiological changes and molecular biology to assess wound healing, these technologies are still not widely used in the clinical setting.

A surrogate endpoint is defined as a physical sign or a laboratory measurement that can be used as a substitute for a clinically meaningful endpoint, effectively directly measuring how a patient feels, functions or survives. The changes induced by a therapy that achieve a surrogate endpoint are

expected to reflect real-life changes in a clinically meaningful fashion. A valid surrogate endpoint is related to the outcome of interest, and is affected by the treatment to the same degree and in a manner that accurately reflects the effect of the treatment on the true outcome.

The challenge, especially with regard to non-healing wounds, is that these type of endpoints are difficult to achieve and maintain. If the only gold standard was total wound closure, no therapy would ever be considered efficacious. Conversely, if a non-specific endpoint is chosen, any positive findings may not translate into a clear clinical benefit at the bedside.

The ideal endpoint in, for example, debridement trials (e.g. topical enzymatic products) should be the achievement of a healthy and viable wound bed, consisting of good quality granulation tissue. This wound bed would then be suitable for novel treatments, such as tissue-engineered skin substitutes and growth factors, that require cell interaction or receptor-binding sites. In addition, this would also provide a suitable bed for skin grafting. An endpoint such as 'viable bed' or 'graft ready', as opposed to complete wound closure, might therefore be more appropriate for trials involving debriding agents.

Alternative endpoints are therefore needed, especially when a wound intervention is performed for reasons other than healing (for example, control of exudation, wound debridement, reduction of pain, rate of granulation, dressing performance). The primary outcome measure selected for any wound study should, therefore, be appropriate to the intended purpose of the intervention. For this reason, it is important that the study protocol clearly defines the primary intention of wound treatment/intervention and provides a rationale for the outcome measures selected to assess this.

The term 'intermediate' endpoint is also sometimes used in the literature; for instance, when describing a relative change in wound area. However, this document only uses the terms 'surrogate endpoint' and 'clinical endpoint.'

Statements

- It is essential that standard care procedures/regimens are consistent as this will minimise variability and allow the treatment effect to be assessed
- Large cohort studies of each wound type are needed to establish the outcomes achieved using standard care, as recommended by various international and national guidelines
- We recommend that guidance should be provided indicating how much the benefit observed when using a surrogate endpoint contributes to the main clinical outcome, and that a unified outcome approach to wound assessment be established and put into practice. This would allow standardised data assessment across the whole range of clinical research evaluating the efficacy of current and emerging technologies in wound healing
- While the ultimate goal of treatment is healing, many wound therapies focus on one specific issue or time phase within the healing process. In such cases, healing is not the appropriate primary endpoint.

Section 4: Outcome — endpoints in RCTs and comparative studies of non-healing wounds

Background and methodology for evaluating outcome measures

In 2002, an article search of wound studies from the period 1982–2002 was performed. In all, 28,301 published articles within the area of wound healing were found and a number of these were analysed. All articles containing 'wound healing' in the subject heading in Medline were selected. The total number of studies included in this analysis was 930. A number of outcome measures were reported in both clinical and experimental settings. More information about studies published before 2003 can be found in Matousek et al. (2007).

To achieve an updated status (2003–2009) on how outcome parameters are used, defined and evaluated, we performed a literature search on chronic/problem wounds/ulcers, with the objective of examining and registering their use of endpoints, the quality of their endpoint definitions and the robustness of their methodologies.

A general search revealed 50,248 articles, while a search of the wound types covered in this document (pressure ulcers, venous/leg ulcers and diabetic foot ulcers) for the same period resulted in 15,495 articles.

To limit the search to articles relevant to the above parameters, the search criteria were limited further (Table 9) and included comparative studies and RCTs published from 2003 to September 2009 only. The primary objective of the analysis was to identify outcome parameters used as primary and secondary endpoints and to examine how they were defined, evaluated and measured in various studies (Tables 3 and 10).

The limited computer search revealed 371 articles. Of these, 236 RCTs and comparative studies were identified for evaluation of the outcome parameters used in studies of venous/lower leg ulcers, diabetic foot ulcers and pressure ulcers. Following the evaluation of abstracts by three reviewers, 176 of these articles were selected for analysis.

Of these articles, 58 were on diabetic foot ulcers, 69 on leg ulcers, 37 on pressure ulcers and 12 on more than one type of ulcer (mixed).

All articles were reviewed with the primary objective of examining which outcomes were used as the primary or secondary endpoint(s) of the study, whether or not they were clearly defined in the arti-

cle, and the degree to which the measurement of outcome was reproducible, based on the descriptions in the article.

General results

Our analysis showed that 72 articles had a single endpoint, while 66 defined a primary endpoint and one or more secondary endpoints; 38 articles did not differentiate between primary and secondary endpoints. Many studies measured multiple endpoints — in total, this analysis generated a list of 313 different endpoints.

The endpoints were divided into the following categories (the percentages represent each category's proportion of the 313 registered endpoints):

- Reduction rate (24.1%)
- Wound closure (16.9%)
- Healing time (9%)
- Change in wound condition (9%)
- Biomarkers and bacteriology (4.5%)
- Circulation (1.9%)
- Infection signs (4.5%)
- Symptoms and signs (13.2%)
- Dressing performance (7.0%)
- Quality of life (5.8%)
- Costs and resources used (4.5%).

These categories were developed, in line with the objectives of this document, to give a comprehensive and exhaustive picture of the endpoints used. A full list categorised by wound type (diabetic foot ulcers, leg ulcers, pressure ulcers and mixed aetiology ulcers) is given in Table 3. As shown above, the most commonly used endpoints were reduction rate and wound closure.

A substantial number of endpoints (45%) were either not predefined or insufficiently defined (Table 3). Even for a clinical outcome like wound closure, in 19% of cases no clear definition was given, and for 'reduction rate' a clear definition was missing in 35% of cases.

As part of the analysis, the degree of robustness of the measurement techniques used in studies (defined as a level of information about the measurement technique, such that others could replicate the data collection in an identical way) and the degree of reproducibility (defined as the inclusion of a verifiable source of data, e.g. photos, to secure the possibility of validation from an external source by reproducing the study, or the involvement of an external validation source as part of the study design) were evaluated.

In 70% of cases, a standardised or clearly defined measurement technique was used to examine the endpoint (e.g. computerised planimetry or a standardised evaluation method). These were defined as meeting the criteria for an acceptable degree of robustness. However, 76% of these did not meet the criteria for reproducibility (Table 10).

In the following sections, we will discuss the findings of our analysis and suggest procedures for the successful measurement of some of the relevant endpoints used in these wound healing studies.

Wound healing-related outcomes (wound closure, reduction rate and healing time)

- **Wound closure** Intact skin has been used as an outcome measure in many clinical trials where 'healing' is a reasonable outcome directly related to the mode of action of the intervention under investigation. Definitions of 'healing' as a clinical outcome have been debated for some time. However, recent recommendations from the FDA support the view that complete closure of a chronic wound is the most clinically meaningful endpoint. This is defined as: skin re-epithelialisation without drainage or dressing requirements confirmed at two consecutive study visits two weeks apart.

In the present evaluation, 'wound closure' was most frequently defined as 'full epithelialisation and no drainage, without the need for additional dressing'. Alternative definitions were 'clean and healthy wound without discharge', 'intact skin for three months' and 'total wound closure'.

In almost all studies using wound closure as an endpoint, one or several control visits at the study site were carried out to confirm healing. In 15.4% of cases, the study intervention period was less than three months, while 38.5% of cases used exactly 12 weeks (three months) and 46.2% used more than 12 weeks (up to 71 weeks). A sufficient follow-up time for when a wound can be considered to have healed, compared with reopening/recurrence not related to the intervention, still needs to be clearly defined. Concerning robustness and reproducibility, 85% of the cases had an acceptable degree of robustness, but 67% of these were not considered reproducible (not confirmed by independent source or photo).

The potential disadvantage of using complete healing as a primary endpoint is that, in certain circumstances, it is not a feasible or appropriate outcome for the intervention under investigation (e.g. malignant ulcers).

- **Reduction rate** Currently, there is a debate over the usefulness of using reduction in wound area as a primary outcome as the 'clinical benefit of incremental wound size changes has not been established'. However, some studies have shown that reduction in wound area within a specified time frame can indicate the potential to achieve complete healing in the future. The debate focuses on defining the minimum area of reduction that can be considered clinically relevant. The length of the assessment period is also crucial.

The reduction rate chosen should consider the margin of error for the method of measurement chosen, as well as the baseline size of the ulcer. particular

Table 10. Robustness and reproducibility*

Statistics	Endpoints		Robust		Robust, but not reproducible		Not robust	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Biomarkers and bacteriology	14	(4.5)	6	(42.9)	6	(100.0)	8	(57.1)
Change in wound condition	28	(9.0)	14	(50.0)	9	(64.3)	14	(50.0)
Circulation	6	(1.9)	4	(66.7)	4	(100.0)	2	(33.3)
Costs and resources used	14	(4.5)	8	(57.1)	8	(100.0)	6	(42.9)
Dressing performance	22	(7.0)	6	(27.3)	4	(66.7)	16	(72.7)
Infection signs	14	(4.5)	12	(85.7)	11	(91.7)	2	(14.3)
Quality of life	18	(5.8)	14	(77.8)	14	(100.0)	4	(22.2)
Symptoms, signs	41	(13.2)	27	(65.9)	28	(103.7)	14	(34.1)
Reduction rate	75	(24.1)	64	(85.3)	40	(62.5)	11	(14.7)
Wound closure	53	(16.9)	45	(84.9)	30	(66.7)	8	(15.1)
Healing time	28	(9.0)	20	(71.4)	13	(65.0)	8	(28.6)
Total no. of endpoints	**313**	**(100)**	**220**		**167**		**93**	
Total no. of articles included	**176**		70%		76%		30%	

*Robustness is defined as whether a predefined protocol was used for the study, allowing a second party to evaluate this and the parameters used
Reproducibility is defined as the inclusion of materials (e.g. photos) that will allow a second party to reproduce the parameters used in the study (external verification)

concern is that chronic wound healing processes have been shown to be non-linear. The assumption that wounds may heal in a linear fashion is predominantly based on studies of acute wounds.

The baseline wound size and wound dimensions may not be reliable indicators for predicting chronic wound closure as the factors that influence or delay healing are diverse and unpredictable; chronic wounds can become 'inert' or 'static' at any stage of the 'healing' process. Margolis et al. (1993) noted that healing rates fluctuated over the first few weeks of treatment and cautioned that while the initial rate of healing may be a predictor of complete healing (in some wounds), it cannot be extrapolated to calculate the actual time that complete healing will take. Likewise, in smaller wounds the percentage change in area over time exaggerates their healing rates, so a prediction of healing based on percentage change in area might be inaccurate.

A recent review of techniques for measuring area and volume has summarised the clinimetrics associated with a range of measurement techniques. Each chosen method was associated with varying degrees of error, but more sophisticated recent techniques resulted in the smallest amount of error with the highest degree of inter-operator agreement. In order to increase the quality of studies conducted in wound management, reproducible techniques that allow for independent verification need to be used.

Wound area reduction is frequently suggested as a substitute for wound healing/full epithelialisation, especially for ulcers with expected long healing times. A substantial number of RCTs and cohort studies have shown a strong correlation between wound area reduction at four weeks and outcome at 12 or 20 weeks. In studies where wound area reduction was used, a predefined reduction of >50% of the initial area has been considered relevant.

Although volume reduction is probably the optimal endpoint for cavity wounds, there are major methodological difficulties in assessing this parameter, such that few studies have taken this approach.

Wound surface area reduction was the most frequently reported outcome of healing progression in

our analysis, with 24% of cases using it as an endpoint (primary or secondary). Our analysis showed that this endpoint was usually measured as a relative change of wound area by tracing systems, either manual (21% of cases) or computerised (40% of cases). In the remaining cases, another measurement technique was used or the method was not described.

In 37% of cases, when wound area reduction was used as an endpoint (primary or secondary), 'clinically important reduction' was often not predefined, or not sufficiently described. Consequently, a 1% reduction in wound area would be considered as valuable as a 100% area reduction. The methodological issues regarding wound area measurements have previously been reviewed. When predefined in a study, the most frequently used definition of area reduction was a 50% reduction over a four-week period in venous ulcers and diabetic neuropathic ulcers on the plantar aspect of the foot.

• **Healing time** Use of wound healing time as an outcome measure has received increasing interest due to its importance from the clinical perspective and with regard to resource use and economic costs.

In the present evaluation, 9% of cases used time to healing as an outcome. In most of these cases, the time to healing was described as healing after a certain number of days or weeks, but it was not predefined how the exact time that healing occurred would be verified. The difficulty in using this approach is that the recorded healing time is dictated by the study protocol, and will be an approximation based on the assessment time slots dictated by the study design.

Alternatively, patients can self-refer once they are aware that their wound has healed. However, this depends on an agreed patient definition of healing and requires flexibility in the study design if staff are to be available to confirm the healing status.

For most studies reporting wound healing time, the major concern is that it is only reported for the minority of patients who have healed within a specific observation period, generally of 4–12 weeks. To date, the accepted time interval for resource studies is one year. Ideally, all patients should be followed until healing is achieved. However, this is often not feasible due to patient characteristics, comorbidity and the type of ulcer.

Change in wound condition

Due to the introduction of more targeted treatment strategies that focus on specific aspects of symptom management, rather than aiming for complete healing, it is important to ensure that the chosen outcomes reflect the modality under investigation. These endpoints may include:

Exudate level

This is usually measured using a subjective rating scale (from dry to heavy), although more sophisticated measures using water vapour transmission rate through the dressing can also be used

Necrosis/slough

An estimate of necrosis and slough in a wound, although crude, is an indicator of the status of the wound. This could be quantified in terms of scale or area measurement

Odour

Since traditional tests of sense of smell are subjective (such as the sniff test, gustatory smell test and trigeminus test), tests such as olfactory evoked potentials and cognitive negative variation have been developed, permitting evaluation of both odour perception and odour discrimination. Although a decrease in odour may suggest that a chronic wound is improving, all current objective assessments are complex, which precludes their use in everyday practice. Until simpler objective tests become available, variations in aroma cannot be used to assess the effectiveness of a product intended to minimise this feature in chronic wounds

Fibrous/fibrotic tissue

The quantification of fibrous tissue is difficult and there are no objective criteria for this at present. This could be quantified in terms of scale or by area measurement

Granulation tissue

The presence of healthy granulation tissue can be quantified in terms of percentage, and an increase in the amount of granulation tissue in the wound bed points towards healing. This could be quantified in terms of scale or area measurement. In trials where the primary endpoint is debridement, or when cavity ulcers are under investigation, assessment of granulation tissue has been used as an outcome measure.

The presence of healthy granulation tissue is considered a good marker of progress. Hence, if a non-healing wound has achieved 60–70% granulation over a six-month period, it is conceivable that we might consider this a valuable endpoint. However, further healing can be impeded due to various factors and the wound may remain static for prolonged periods. Nevertheless, the wound bed may be suitable for grafting or for the use of novel treatment modalities such as tissue-engineered skin substitutes or growth factors. It is still being debated whether or not this endpoint (i.e. 60–70% granulation) should be considered a valid surrogate endpoint in these types of wounds.

Change in the wound condition has been used as an endpoint, accounting for 9% of the total number of endpoints registered; examples include fibrin, necrosis, exudation and granulation rate. However, these endpoints were frequently not predefined

(42%) or did not meet the criteria for *robustness* (50%). This means that although scoring systems were used, in many cases they were not validated.

Some local treatment strategies are designed for use in a specific phase of healing, such as debridement. Therefore, even if a treatment strategy is applied and measured until full epithelialisation occurs, the results can be incorrect. In these situations, 'wound healing' or 'full epithelialisation' might not be a relevant endpoint. It is important, therefore, that these studies predefine their endpoints and ensure they can be validated by an independent source.

Biomarkers

A biomarker can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. The FDA draft 'Pharmaco-economics Guidance' further defines possible, probable and known valid biomarker categories, depending on available scientific information on the marker.

Biochemical markers

Biochemical markers in wound healing can include the biochemical components of non-healing wound exudate, which vary considerably from those found in acute wounds. Non-healing wound exudate contains a number of inhibitory and excitatory factors, including matrix metalloproteinases (MMPs), pro-inflammatory cytokines and growth factors, making them potential biochemical markers in chronic wounds. Further biochemical markers include neutrophil elastase and pro-MMP-9, which have been used as prognostic indicators of healing.

Physiological markers

These measure the physiological and tissue viability processes that underlie the basic mechanisms of healing. Examples of physiological markers include laser Doppler imaging of blood flow, wound surface pH, tissue oxygen measurement, durometry, extensiometry and wound ultrasonography.

Tissue markers

Histological examination of wounds has been used to examine factors, such as wound infection, dermal collagen, elastin content and epithelialisation.

Wound microflora has been assessed using classical bacteriological techniques, quantitative bacterial counts and immunohistochemistry. Although Robson et al. found that chronic wounds with a bacterial load greater than $1x10^5$ will heal normally, recent studies have shown that healing is impaired when there are more than $1x10^5$ organisms per gram of tissue. In addition to the number of organisms, the type, pathogenicity and the mix of organisms involved are all important determinants of whether or not infection occurs within a wound.

More recently, tissue biopsies of wounds have been subjected to cell culture and molecular biological examination. Fibroblast and keratinocyte cultures from chronic wounds have been used to delineate the underlying cellular pathology in non-healing wounds. Gene activation and/or inhibition in response to wound therapy is currently being performed utilising microarray analysis, to assess the possibility of using genetic markers in predicting healing outcomes.

Of the endpoints used, 6.4% (20) were categorised as biomarkers (biomarkers and bacteriology, circulation). Of these, the endpoint was not thoroughly predefined (including a description of change before and after the intervention) in three studies, while studies using circulation as an endpoint lacked sufficient definition.

Infection

Infection is the most frequently occurring complication of non-healing wounds. It can jeopardise the progression towards healing, result in longer treatment times and an increased use of resources. In the worst cases, it can result in a major amputation or a life-threatening condition.

Classification of infection

Different classification systems have been suggested for clinical infections, primarily relating to acute skin infection, acute surgical infection and chronic diabetic foot infections. Until recently, there was no widely accepted method for classifying the severity of an infection. However, two classifications have been designed to assess the severity of diabetic foot ulcer infection; they were developed by the International Working Group on the Diabetic Foot (IWGDF) and the Infectious Diseases Society of America (IDSA). These classification systems have been evaluated and were found to be useful tools for grading foot infections and predicting clinical outcomes.

Signs of infection

The traditional inflammatory signs are redness, swelling, hyperthermia, pain and limited function. In chronic wounds especially, the following additional parameters should also be considered:

- Increased exudate: a substantial increase in the amount of exudate, possibly with increased viscosity, change in colour and offensive odour
- Friable granulation tissue
- Slough
- Changed odour
- Changed pain
- Stagnation in the healing process
- Serological signs of systemic infection, e.g. leucocytosis and increased C-reactive protein (CRP).

At present, no universal definition has been established for the signs of critical colonisation or bacterial burden. Generally speaking, excessive proliferation of microorganisms will result in a critical microbial load, which may lead to infection or, as colonisation becomes critical, trigger an inflammatory process. This inflammation contributes to the non-healing status of a wound. Studies have shown that biofilms embedded in the wound bed cause the delayed healing of chronic wounds in the inflammatory state.

Resolution of infection in wound management

There is much controversy concerning how infection should be measured: should it be by examination of clinical signs, microbiology, or by the laboratory parameters indicating inflammation (single or in combination)?

Infection in wound management can be evaluated in different ways, focusing on the possibility of prevention, its resolution and/or the time to resolution.

It is beyond the scope of this document to discuss the mode of delivery of antibiotics; instead, we will focus on how outcomes are measured. Some composite measures have been suggested to overcome the variability that occurs when different clinicians are involved.

In our analysis, infection was used as an endpoint in only 4.5% (14) of the total number of endpoints recorded. In all cases, this was defined as a secondary/surrogate endpoint. It is not surprising that only a relatively small number of studies used this endpoint as most of the available data on infection relate to acute skin infections and use of systemic antibiotics.

In most cases (8 of 14), a case record form (CRF) was used to record data. While we have registered these as meeting the criteria for an acceptable level of robustness, these studies are not reproducible. In some cases, this was supported by a scoring system. As most forms were completed 'at the discretion of the physician', it is impossible to repeat these studies or for an independent observer to evaluate them. Only in one case using a CRF was an independent observer included in the study. Ten of the 14 endpoints registered in this category were predefined.

Whole patient outcomes

Previously, the majority of studies focused on dressings and/or topical treatments. As more advanced therapies become available, which have the potential to intervene at the level of the patient's general health (e.g. ischaemia, infection), it is also essential to report factors such as comorbidities, limb salvage, amputation rate and mortality.

Symptoms and signs

The International Consensus on Harmonisation of Good Clinical Practice (ICHGCP) and the Food and Drug Administration (FDA) websites give details of the methods to use for reporting adverse and severe adverse events in studies (Table 4). There is no obvious reason why wound management studies should not use the same reporting practices that are used in other areas of health care.

Given the complex health states of participants in wound care studies, attrition/withdrawal rates are likely to be high. In some instances this will be due to the death of the patient. This is particularly relevant for wound studies involving patients at the end of life (such as pressure ulcer studies) or with rare wound aetiologies associated with extreme health states.

Pain

Pain, a complex sensation strongly modulated by cognitive influences, is a characteristic feature of many non-healing wounds. It may be constant or intermittent, and may be described by the patient as 'sharp', 'aching', 'stabbing', 'throbbing', shooting' etc. Constant pain may be due to ischaemia, neuropathy, tissue oedema, chronic tissue damage (lipodermatosclerosis), infection or scarring (atrophie blanche). Intermittent pain is often related to dressing removal or the recent application of new dressings. Studies suggest that pain intensity may increase at night and that there may be variations on a day-to-day basis or due to the weather and seasonal influence. Pain can affect the individual physically, psychologically and socially, and a reduction in pain can significantly improve the patient's overall health-related quality of life.

Accurate assessment of non-healing wound pain is important in identifying the cause and subsequently managing the wound. A detailed analysis of the various pain assessment tools is beyond the scope of this section.

Symptoms and signs were used as endpoints in 13% (41) of all the endpoints registered. Of these 41, 17 were categorised as 'pain'. Most of the endpoints in this category were from leg ulcer studies (25 of 41 endpoints, 60%). Many were not predefined (24 of cases, 59%) and 34% (14) did not meet the criteria for robustness.

Dressing performance

A key area of interest for clinicians working with patients who have non-healing wounds is the choice of primary and secondary dressing(s). Other than efficacy, the reasons for choosing one dressing over another will vary according to a wide range of factors relating to the needs of the patient, the wound characteristics, cost-effectiveness data and the resources available within the health-care setting. The importance attributed to each of these factors will vary depending on whether you are a purchaser or a provider of care.

For many patients, the most important characteristics of a dressing relate to its ability to manage their symptoms (for instance, by reducing odour or preventing leakage), particularly its potential to reduce pain at dressing change. In addition, a range of issues involving wound dressings have a significant impact on activities of daily living, particularly mobility. Bulky bandages, compression devices and different types of foot offloading can interfere with daily living to such an extent that concordance with treatment is jeopardised, while frequent dressing changes can result in a life dominated by clinical appointments.

From the clinician's perspective, a range of parameters must be considered when choosing a dressing. These might include how well the dressing can handle exudate, whether or not it will reduce the risk of infection and/or any pain associated with application or removal, and what the expected wear time will be. These factors are in addition to the usual cost and resource constraints. Each of these characteristics, singly or in combination, is considered alongside information gained from clinical trials that may be linked to a range of healing outcomes. Often the decision is negotiated between the clinician and patient.

To inform this decision-making process, clinicians need to be clear that studies have provided information on the safety of the dressing, its stability and storage requirements, as well as information, based on clear outcomes, on the dressing's ability to perform well in each of these key areas.

Clinicians might be interested in how a dressing performs in absolute terms (i.e. performance measured against industry standards) or in comparative terms (i.e. how well a dressing performs when compared with others that are already on the market).

If a dressing is assessed in terms of its absolute performance, then a range of laboratory tests, such as water vapour transmission rate, can provide this information. However, comparative performance assessment will require comparative studies, many of which will need to be clinical if factors such as wear time are to be fully evaluated.

In our analysis, we found that 7% (22) of the endpoints registered could be defined as 'dressing performance' endpoints (primary or secondary); 59% of these were not properly defined. In 38% (8) of the studies with this endpoint, clinical observation was the primary measurement technique; 72.7% (15) did not meet the requirements for robustness.

Quality of life

In recent years, health-related quality of life (HRQoL) has become a more routinely accepted outcome in health-care studies. As an outcome, HRQoL can be measured using three different approaches:

- Generic measures
- Condition-specific measures
- Utility measures.

In each case, it is important that assessments are made using tools with established psychometrics as this will ensure that they are valid, reliable, sensitive to change and can discriminate between health states.

Generic measures of HRQoL have been designed to look at the impact of a given disorder on everyday living, and compare a patient group with age- and sex-matched norms representing the healthy population. These tools allow for comparisons across a variety of disorders or diseases, enabling direct comparisons between patients with non-healing wounds and those with other health states (such as a hip replacement). Disadvantages include that they may be unresponsive to small but clinically significant changes in HRQoL that may be important determinants of outcome.

Condition-specific measures focus only on the HRQoL aspects pertinent to a particular condition. As a result, they are shorter, more relevant to the patient and more sensitive to subtle, yet important, changes in HRQoL relating to the health condition in question. Clinicians often prefer this approach as these scales provide a profile of outcomes that relate directly to their area of care and demonstrate their potential to make a difference. Disadvantages include that the items measured can be so specific to the condition of interest that the outcomes cannot be compared with other disease states. This may be particularly important for those involved in health economics.

HRQoL can also be measured using a utility approach, which reflects the strength of an individual's preference or value attached to a particular health outcome. The utility approach to HRQoL is based on economic and decision theory; utility scores range from 0 to 1, where 0 represents a preference for a health state equivalent to death and 1 a preference for a health state equivalent to perfect health. The advantage of this approach is that utilities can be used to calculate quality-adjusted life years (QALYs) and similar indices, which health economists use to inform policy makers on the comparative HRQoL outcomes by health state (see section 'whole patient outcomes'). For many clinicians, reducing HRQoL to a single index can be a disadvantage: it can be difficult for them assess how they can improve this index through high-quality routine care.

In our analysis, we found that QoL was used as an endpoint in 5.8% (18) of the total number of endpoints registered. This was usually done using questionnaires such as EuroQol and SF-36 or by other recognised scales and questionnaires. In 39% (7) of these studies, this endpoint was not satisfactorily predefined.

Table 11. Types of economic study design

Variables to be measured	Explicit comparison of alternatives?		
	No	Yes	
		Type of economic study	Measures of outcome
Cost	Cost description		
Outcomes	Outcome description		
Cost and outcomes	Cost and outcome description	Cost-effectiveness analysis	Natural units (e.g. probability of healing)
		Cost-utility analysis	Quality-adjusted life years
		Cost-benefit analysis	Money value of outcomes

Cost and resource utilisation

When seeking approval to introduce a new treatment strategy, it is mandatory to present evidence that includes health economic information due to the impact of non-healing wounds on the individual, society and care givers in a time of scarce resources. For this reason, there is an increasing need for more valid cost and resource utilisation studies. At present, there are few high-quality studies on wound management and there is confusion as to how they should be performed, especially with regard to endpoints and resource utilisation.

An economic approach to health-care decision-making

The distinctive feature of an economic approach to evaluating health-care interventions is that it involves explicit consideration of both the costs and the outcomes, or consequences, of an intervention. When resources are scarce, it is inappropriate to make choices on the basis of patient outcomes alone as maximising the benefits for one group of patients may mean reduced benefits for another. With a fixed budget, spending money on an expensive treatment that heals wounds faster may mean that fewer patients can be treated in total. Economic evaluation takes into account both the benefits and costs of an intervention, measuring the value of opportunities that are forgone.

Types of economic evaluation

There are different approaches to the way in which the costs and benefits of different programmes are combined and compared. (The term 'programme' is used here as shorthand for any proposed new intervention.) The most commonly used approaches are:

- Cost-effectiveness analysis
- Cost-utility analysis
- Cost-benefit analysis.

The difference is the way in which the benefits of the programme are measured. In cost-effectiveness analysis, programme benefits are measured in units (such as 'ulcer-free days' or 'probability of healing') that are common to the programmes being compared. In cost-utility analysis, programme benefits are measured in generic units, such as QALYs gained. A cost-benefit analysis measures benefits in monetary units. It is unique in that both costs and benefits are measured in the same units (Table 11).

The type of analysis that is appropriate will depend on the nature of the decision problem. Cost-effectiveness analysis is primarily of value when comparing programmes that affect the same patient group (patients with chronic wounds, for instance), whereas cost-utility analysis and cost-benefit analysis can be used to compare programmes in different areas of health care (such as chronic wound care versus hip replacement). A more complete discussion of the methods of economic evaluation in health care can be found in Drummond et al. (2005).

Cost or outcome descriptions are not, strictly speaking, economic studies but despite this, they can still provide valuable information. For instance, they might highlight the importance of a particular treatment area in terms of its resource use or current high rate of wound complications, and signal the potential for improvement.

Methods of economic evaluation

- *Choice of comparator*: an economic study involves an explicit comparison of the costs and consequences of at least two alternatives. The comparator will be either the most common or the best current practice. Economic analysis is pragmatic, designed to provide information that is relevant to real-world choices. Placebo comparators are of limited value in economic evaluation, unless 'doing nothing' is a valid treatment choice.

An economic evaluation is concerned less with the efficacy of an intervention ('can it work in a

defined patient population?') than with its effectiveness ('does it work in routine clinical practice?'). A good study will provide a clear description of the alternatives to be compared, and justify their relevance to the decision problem at hand.

- *Perspective of the analysis*: many of the design parameters of a study are dependent on the perspective of the analysis — that is, they depend on the perspective of the relevant decision maker. In wound care, decision makers include clinicians, hospitals or other health-care provider organisations, and third-party payers. The perspective of an analysis determines which costs and outcomes are relevant.

- *Estimating costs*: costing is a two-stage process. The first stage comprises measuring the quantities of resources used (see Table 12) and the second stage valuing these resources (see checklist in Table 13). Ideally, the prices used to value resources would reflect their opportunity cost — that is, their value in their best alternative use. In practice, opportunity costs are usually approximated by market prices.

  It is good practice to show resource use and costs separately. Where particular resources (such as theatre time or specialist nurses) are scarce locally, a decision may not be based solely on the difference in total costs between programmes, but also on the relative use of any resources that are in particularly short supply. Reporting resources separately also makes it possible to test whether or not differences between programme costs are sensitive to changes in unit prices.

- *Dealing with uncertainty*: not all of the costs and outcomes of competing programmes can be estimated with certainty. Uncertainty needs to be recognised and its potential impact explored through sensitivity analysis. It is good practice to highlight the variables that are most likely to affect the final conclusions of an analysis and to test the robustness of these conclusions to plausible changes in the values of these key variables. Where conclusions are sensitive to small changes in parameter values, there is a need for more detailed work to more accurately determine the value of these variables.

- *Measuring programme benefits*: in a cost-effectiveness analysis, the outcomes or benefits of different programmes are measured in common units that reflect the objectives of programmes. Examples of outcome measures in wound care might be the probability of healing or ulcer-free days (each specified within a particular time period) or infections prevented (for a programme designed to reduce the incidence of wound complications). Within a health-care provider organisation, aims might be more parochial, such as a reduction in wound-related surgical procedures or hospital readmissions.

Table 12. Important items of resource utilisation in wound studies

Initial patient and wound assessment
Clinician time
Facility cost (e.g. outpatient clinic visit)
Diagnostic tests (e.g. X-ray)
Laboratory tests (e.g. microbiology)
Dressings, drugs and other disposables
Patient and carer travel time*
Patient out-of-pocket payments*
Patient/carer lost work time*
Wound treatments
Clinician time for dressing changes
Facility cost (clinic or outpatient setting)
Clinician travel time (to patient's home)
Dressings, drugs and other disposables
Antibiotics
Diagnostic and laboratory tests
Special equipment (e.g. orthotic insoles)
Patient and carer travel time*
Patient out-of-pocket payments*
Patient/carer lost work time*
Inpatient costs
Inpatient bed-days
Dressings, drugs and other disposables
Antibiotics
Diagnostic and laboratory tests
Surgical procedures (theatre time, clinician time, disposables)
Rehabilitation costs
Outpatient follow-up visits
Special equipment (e.g. orthotic insoles)
Patient out-of-pocket payments*
Patient/carer lost work time*

* Depending on the perspective of the analysis (patient/carer costs; social costs)

Table 13. A checklist for economic study design

Does the study involve explicit comparison of the costs and outcomes of at least two alternative interventions?
Are the comparators relevant to the decision-problem that is to be addressed (e.g. are they representative of normal clinical practice)?
Is the perspective of the analysis clear, and is the perspective relevant to the decision-problem?
Are all of the details of study design consistent with the chosen perspective, such as which costs and outcomes to include?
Are costs and outcomes measured over a sufficiently long period of time such that all important programme effects are captured?
Is resource use measured separately from the cost of resources? Are all relevant resources included in the analysis?
Are resources valued appropriately, e.g. do prices adequately reflect the opportunity costs of resources?
Are programme outcomes defined and measured appropriately, e.g. are outcomes clinically meaningful and relevant to the alternatives to be compared? Are all relevant outcomes included in the analysis?
Is the type of economic study (cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis) appropriate to the decision problem?
Are alternatives compared in terms of incremental costs per unit of outcome gained?
Are the effects of uncertainty adequately addressed in the analysis and in the interpretation of results?
Is the interpretation of results consistent with the analysis, e.g. have all relevant findings been discussed?

Different programmes can then be described in terms of the cost per unit of outcome: cost per ulcer-free day, or cost per infection avoided. The relative cost-effectiveness of alternative programmes is assessed by the incremental cost per unit of outcome gained (incremental cost-effectiveness ratio). Where one programme offers similar or better outcomes at a lower cost, or costs the same or less and heals more patients, it is unambiguously more cost-effective than the alternative. Where one option heals more patients but at a higher cost, cost-effectiveness is a subjective judgement, determined by comparing the magnitude of this additional cost with the benefits that could be achieved using this same resource on a different programme.

In cost-utility analysis, programme outcomes are measured in terms of the cost per QALY gained. QALYs combine a measure of life-expectancy with the value or preference that individuals place on different health outcomes, such as wound healing. Measuring health-state preferences is a two-stage process. In the first stage, respondents (patients) are given a set of descriptive attributes and asked to rate their current health on each. Standard instruments used to obtain health-state ratings include EQ-5D and SF-6D. EQ-5D has five attributes (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) and three possible levels (no problem, some problems and major problems). A relative preference score ranging from 0.00 (dead) to 1.00 (perfect health) is then assigned to each respondent, using their particular health-state combination. Preference scores for each possible health-state combination have been derived from a random sample of the general population.

QALY gains are calculated by combining additional years of life expectancy (if any) with the gain in utility associated with an improvement in health. In the most straightforward case, if healing a wound increases the health state utility from, say, 0.75 to 0.9, the QALY gain is 0.15 per year over the remaining years of life (or until the wound recurs), so healing a wound in a patient with an expected life expectancy of 10 years generates 1.5 QALYs. The relative cost-effectiveness of two programmes (A and B) is measured in the incremental cost per QALY gained.

Cost-utility analysis makes it possible to compare programmes that affect different patient groups — such as wound care and cancer services — whose outcomes cannot be compared using the same units. This type of comparison is important for payers whose choices include the allocation of budgets between different patient groups, and cost-utility analysis is often a requirement for submissions to national health technology assessment bodies, such as the National Institute for Health and Clinical Excellence (NICE) in the UK.

Cost-utility studies in wound care are rare, possibly because the generic instruments currently used to generate utility scores are not sufficiently sensitive to capture the impact of wound healing on quality of life. Where improving quality of life (QoL) is an important aim of an intervention, it is probably more appropriate to use a wound-specific QoL instrument within the framework of a cost-effectiveness analysis.

In a cost-benefit analysis, programme benefits are valued in monetary terms. For example, if a programme reduces the probability of infection, its benefit is measured not in terms of the number of infections avoided, but by the monetary value of an infection avoided. The uniqueness of this approach

is that it allows programme costs and benefits to be compared directly, using the same units. It also provides an objective way of estimating whether or not the benefits exceed the costs. The drawback is that placing a monetary value on outcomes such as faster healing or improvements in patient quality of life is difficult, and in some cases contentious. For these reasons, cost-benefit analysis is not often used in health-care decision making.

Through our analysis, we found that cost and resource utilisation was used as an endpoint in 4.5% (14) of the total number of endpoints registered. It appeared in various forms including: economic costs related to healing, institutional costs, cost per week, resources used, number of dressing changes, cost savings and costs per patient per year.

Most of these cases were primarily descriptive and six of 14 cases did not include a thorough description of the primary endpoint. Other concerns regarded items included, the perspective of the study and a lack of distinction between resources, costs and charges. In 42.6% of these cases, the study did not meet the criterion for robustness.

Statements on endpoints

- Wound closure, defined as total epithelialisation without discharge, is the most important endpoint relating to ulcer healing. It must be confirmed by an independent source (photography) and there must be sufficient follow-up to confirm healing
- Wound area reduction is a valid endpoint with regard to wound healing but it must be confirmed by tracing and include a predefined relevant cut-off to ensure that 'reduction rate error' (described in section: 'reduction rate') does not occur
- There is enough evidence to support the use of a 50% reduction in wound surface area over time as a useful outcome, provided that the initial wound size and the measurement technique are taken into consideration. The time interval used in such assessment will vary depending on the wound type. Any reduction of less than 50% cannot be supported by the current literature; in these instances, more objective measures of size reduction must be used
- Time to heal is an important outcome. However, the study protocol must consider the substantial methodological difficulties entailed, particularly confirmation of the exact date of healing for each patient during the specified observation period. To date, the accepted time interval for resource studies is one year
- There is an urgent need for a validated scoring system with regard to wound condition
- When using changes in the wound condition as an outcome parameter, they must be predefined and measured in such a way that they can be validated independently, wherever possible (for instance, by photograph)
- When using biological markers as a primary outcome, they should be clearly predefined, and a clinically relevant unit of change should be specified; reliable and valid quantitative assessment methods should be used
- When using wound infection as a primary outcome marker, it should be clearly predefined. At present, this could be either a binary measure of presence/absence or a composite score focusing on clinical signs and symptoms
- Regardless of the assessment tool used, when using pain as an outcome measure it is important to predefine the amount of wound pain reduction that is clinically important
- When surrogate parameters such as symptoms and signs, or composite endpoints such as scales, are used as primary endpoints, it is essential that both their basic definition and what is considered to be a clinically relevant difference are predefined. When used as an primary endpoint, it is favourable for it to be verified by an independent evaluator
- When assessing dressing performance in an objective manner, with a focus on a specific aspect of symptom management, a comparative study may not be needed; the relevant data could be better assessed using a cohort study with a standardised, reproducible and validated protocol that includes resource utilisation (when appropriate)
- HRQoL assessments must be based on tools with established psychometrics
- The type of assessment must fit with the purpose of the data collection: if HRQoL data are to be used for health technology assessment reviews, then generic and/or utility methods must be included
- When cost is used as an outcome parameter in wound management, it is essential to measure all the quantities of resources used and then add the value of those resources, according to a predefined protocol. It is recommended that resource use and cost are shown separately
- Wherever resources have alternative uses, decisions on the adoption of new technologies or new procedures cannot be made on the basis of clinical outcomes alone. Rational choice requires evidence of the costs and benefits of alternatives
- In order to maximise the value of investments in clinical research, studies should be designed to address the relative cost-effectiveness of alternatives from the outset, as well as their safety and effectiveness.

Section 5: Performance bias and interpretation of findings

When evaluating interventions in wound management it is a substantial challenge to avoid performance bias. Designing studies with the aim of obtaining sufficient information regarding outcomes is particularly hazardous.

Table 14. Potential sources of bias

Sources of bias	Accepted practice	Application to wound management
Selection bias		
All eligible patients should have the same chance of receiving the intervention. Both groups are similar at baseline	Random allocation. Concealed allocation	There are no particular issues for wound management studies, and all efforts should be made to randomly allocate patients to groups
Performance bias		
All patients should receive exactly the same treatment with the exception of the study intervention	Participants are blinded to treatment allocation. Clinicians (who administer an intervention) are blinded to treatment allocation	The details of standard treatments should be made explicit. It may be difficult to achieve, but the highest level of blinding should be used within an RCT. Double-blind studies are often difficult but blinded (or independent) assessment of outcome/endpoint should be mandatory (especially if the study is not blinded). Blinded analysis of data should be feasible
Attrition bias		
There should be no differences between groups in the number of patients lost or in the characteristics of patients who are lost and those who remain	All groups are followed up for the same time. Drop-out rates are not high in either group. Both groups should be similar in terms of patients remaining in the analysis (and similar to baseline)	Studies often have high drop out rates due to the nature of the participants, and these details must be reported. Using a run-in period to address the change in wound status can help to increase homogeneity of groups and reduce drop-out rates. Studies should plan their recruitment to allow for potential drop-outs due to the long intervention periods
Detection bias		
Outcomes should be objectively measurable (and repeatable) or investigators blinded to treatment allocation	Outcomes are precisely defined. Valid and reliable methods exist to measure outcomes. Length of follow-up is adequate to identify outcomes. Investigators (who assess outcomes) are blinded to the initial treatment allocation. Investigators are blinded to other important confounding or prognostic factors	All outcomes/endpoints should be precisely defined, with adequate follow-up periods that allow for recurrence rates to be noted. Outcome assessors should be blinded to intervention, whenever possible. The risk for healthy selection bias has to be considered in terms of generalisability of the findings
Publication bias		
All data should be available through publication	All research results should undergo an independent peer- review evaluation and be made available to the public	There is concern that a substantial number of studies on wound interventions are not published or are not available in indexed journals
Study conduct and data analysis		
	Ideally, independent study conduct and independent data analysis and reporting	There is no reason why this should not apply to wound management studies

This chapter describes some of the considerations that should be made when designing studies on interventions for the treatment of wounds.

Performance biases that could influence outcome/evaluation of studies

Table 14 outlines some of the potential biases that can be introduced into a study design, unless great care is taken at the planning stage. In many cases, the issues are similar, regardless of the intervention, and are not specific to wound management studies. However, the key points relating to the wound community are discussed below.

There is always a potential to introduce bias into studies; the RCT design aims to reduce bias as much as possible. Table 14 highlights particular difficulties that may apply to wound management studies.

The design of studies is always debated as different audiences have different requirements. For example, regulatory authorities require the purest form of a RCT, which has a restricted population, in order to reduce the heterogeneity of the population and ensure that the study has sufficient internal validity to demonstrate efficacy. However, this restrictive approach to study design will not allow for the generalisation of the findings to patients who routinely present at clinics. For clinical practitioners, an effectiveness study, with its emphasis on whether or not the treatment works pragmatically in routine practice, may be more appropriate.

There are certain situations where the outcomes of a RCT may be extremely predictable — for example, when using healing as an outcome for certain dressing trials. This contradicts a basic premise for conducting a RCT: that the researchers should be in a state of equipoise (i.e. uncertain about which intervention works best). In such circumstances, a comparative cohort study may be more appropriate as here the aim is to investigate the resources used to achieve similar outcomes.

A further level of bias may be introduced if interventions are not used appropriately, in line with the manufacturer's instructions or as appropriate to the wound condition. Enforcing a purist approach can be particularly troublesome; the RCT design requires that the same intervention be used throughout the study period, which directly contradicts the clinical need to adapt treatment to the condition of the wound. There is a real tension between maintaining a purist approach and being pragmatic about the ways in which treatments are used in routine practice.

Study design considerations that apply to wound studies

The scope of this document is not to give a detailed description of how to conduct an RCT but instead to describe some of the special considerations that apply when conducting research studies in wound management. Some common methodological errors in wound-dressing studies are described in Table 15 and a suggested checklist for clinical trials in wound management is given in Table 16.

Table 15. Common methodological errors in wound-dressing trials

Lack of validation of subjective assessments
Lack of description of objective or subjective measures
Lack of comparable baselines for patient groups
Lack of blinding for the evaluation of primary outcomes
Incorrect randomisation methods
Poor definition of primary and secondary objectives
Number of patients not based on *a priori* sample size calculation
Randomisation method poorly/not described
Assessment of outcomes is not completely objective
Time to wound healing not used as primary outcome
Intention-to-treat analysis not used
No use of single reference wounds
Heterogeneous study population
Number of and reason for dropouts not stated
No specification of adjuvant treatments (such as pressure-relieving surfaces or offloading devices for neuropathic ulcers)
Small sample size combined with multiple outcome measures
Reporting of multiple outcomes over multiple time points (increases chance of type I error)
Poor overall study reporting

Characteristics of the target study group

Depending on the audience receiving the evidence and the decisions they have to make, study populations may be different. We need to recognise that there are conflicts between the data requirements of authorities making decisions about reimbursement, and those for clinicians who need to know if a treatment works in routine practice. From the clinician's perspective, it is desirable to recruit a broad range of patients to studies with the minimum possible exclusion criteria as this will enhance generalisability of the results.

Table 16. Checklist for objectives and outcomes in clinical trials

Are the intervention and control (e.g. usual care) described in detail?
Has the target patient population been specified?
Has the degree of benefit from the intervention on a particular outcome, and the time frame, been specified?
Has the primary outcome, including how and when it is to be measured, been specified?
Have any secondary outcomes been pre-specified in similar detail?
Are the outcomes clinically relevant, objective (wherever feasible) and unambiguous?
Can the outcomes be measured for all patients and, where possible, assessed by researchers who are blinded to the allocated treatment?
Is the frequency and duration of outcome measurement explicity stated?
Has the study been specially planned from a statistical viewpoint when multiple outcomes are measured?
If the outcome is a surrogate, will it adequately reflect a main outcome? And is there an indication of how much a benefit relating to the surrogate outcome will translate into a benefit for the main outcome?

(Reference: Appendix B, Quality of Literature, ECRI Institute Study Quality Assessment Instrument, Negative Pressure Wound Therapy Devices, www.ecri.org)

As a consequence, stratification is needed. Size, site and duration of ulcer are the most frequently used criteria for stratification.

Definition of non-healing wounds

In most previous studies, the term 'chronic wound' has been used to describe a wound that has not healed for at least 4–6 weeks from its first observation at a trial screening visit.

We suggest that the definition 'chronic' be replaced with the definition 'non-healing' as this better reflects the clinical problems experienced by such patients. Using the term 'chronic' focuses too much on wound duration, rather than the presenting condition. Ulcers included in studies using this terminology must be separated from those that will spontaneously improve once appropriate treatment is started. Consequently, a run-in period should always be considered.

It has been suggested that the response rate after the run-in should be used as a nominator for the intervention. For example, a decrease in ulcer area of >30% during the first two weeks could be used.

Wound types

Studies that include a single type of wound are the most straightforward to interpret and should be strongly considered (i.e. all enrolled patients would have the same wound type — venous ulcers, diabetic ulcers, pressure ulcers).

For studies enrolling patients with multiple types of wound, that have wound healing failure and the technology studied in common, it is important to show both aggregate results across all wounds and separate results for each type of wound.

Setting of care

The setting of care (such as hospital, home care) for the study should be described. The rationale for including a variety of settings in the study should be given.

Exclusion criteria

The exclusion criteria should be minimised to the greatest extent possible, and an explanation provided for each criterion whose rationale is not self-evident. Patients with non-healing wounds often have several comorbidities and the exclusion of such patients would limit the generalisability of the study results.

Study protocol

The study protocol should provide a detailed description of the elements of standard care provided to the patients enrolled into the study. Any significant divergence from these standard care practices in these patients must be explained.

Multicentre versus single-centre trials

Multicentre trials are usually recommended because they better address the problem of patient heterogeneity and provide access to a sufficiently large number of patients. Reasonable efforts should be made to enrol sufficient numbers at each site, in order to evaluate potential differences in outcomes across sites. This is particularly important when there are significant differences in expertise across sites, if a high degree of protocol standardisation is not feasible, or the same mix of patient characteristics at all centres is not feasible.

An inadequate study sample size is a major factor preventing valid and reliable trial results. Patient recruitment for wound intervention trials is notoriously challenging, but if patient numbers are not high enough, then a type 1 error (incorrectly concluding that a difference exists) or a type 2 error (incorrectly concluding that no difference exists) may occur. Furthermore, the number of patients in a trial should be based on an *a priori* sample-size calculation (i.e. the number of patients needed to find a difference between dressings should be calculated).

Study and follow-up period duration

If the primary endpoint is wound closure, a 12-week study period is recommended. However, when selecting an appropriate study duration, the type(s) of ulcer and the relevant natural outcome(s) must be considered.

Table 17. Statements from the Patient Outcome Group used in this document

Different types of evidence required by different authorities
A consistent approach to the definition of 'standard care' should be developed to assist with the utilisation of data on a pan-European basis
The technical properties of wound dressings should be described using harmonised terminology. This will facilitate cross-country standards
Data collected to establish the performance, safety and therapeutic benefit of wound dressings should be interchangeable across Europe, to reduce the need for replication by country
Without baseline data from cohort studies, there are limited opportunities to conduct high-quality RCTs when urgently needed
Investigators are recommended to adopt a framework for conducting clinical studies that is similar to the CONSORT agreement, which reflects the highest quality of design possible for the clinical question of interest
The essential issue is to develop a consistent and reproducible approach to define, evaluate and measure appropriate and adequate outcomes in RCTs and other clinical studies, such as cohort studies, comparison studies of treatment regimens using registry data, and real-life studies
The particular properties of a wound dressing, and its reasons for use, should guide the outcome measure of choice both for evaluation purposes and the development and certification/reimbursement processes
Evaluation of outcome
It is essential that standard-care procedures/regimens are consistent as this will minimise variability and allow the treatment effect to be assessed
Large cohort studies of each wound type are needed to establish the outcomes achieved using standard care, as recommended by various international and national guidelines
We recommend that guidance should be provided indicating how much the benefit observed when using a surrogate endpoint contributes to the main clinical outcome, and that a unified outcome approach to wound assessment be established and put into practice. This would allow standardised data assessment across the whole range of clinical research evaluating the efficacy of current and emerging technologies in wound healing
While the ultimate goal of treatment is healing, many wound therapies focus on a specific issue or time phase within the healing process. In such cases, healing is not the appropriate primary endpoint

Outcome: endpoints in RCTs and comparative studies on non-healing wounds
Wound closure, defined as total epithelialisation without discharge, is the most important endpoint relating to ulcer healing. It must be confirmed by an independent source (photography) and there must be sufficient follow-up to confirm healing
Wound area reduction is a valid endpoint with regard to wound healing but it must be confirmed by tracing and include a predefined relevant cut-off to ensure that 'reduction rate error' (described in section: 'reduction rate') does not occur
There is enough evidence to support the use of a 50% reduction in wound surface area over time as a useful outcome, provided that the initial wound size and the measurement technique are taken into consideration. The time interval used in such assessment will vary depending on the wound type. Any reduction of less than 50% cannot be supported by the current literature; in these instances, more objective measures of size reduction must be used
Time to heal is an important outcome. However, the study protocol must consider the substantial methodological difficulties entailed, particularly confirmation of the exact date of healing for each patient during the specified observation period. To date, the accepted time interval for resource studies is one year
There is an urgent need for a validated scoring system with regard to wound condition
When using changes in the wound condition as an outcome parameter, they must be predefined and measured in such a way that they can be validated independently, wherever possible (for instance, by photograph)
When using biological markers as a primary outcome, they should be clearly predefined, and a clinically relevant unit of change should be specified; reliable and valid quantitative assessment methods should be used
When using wound infection as a primary outcome marker, it should be clearly predefined. At present, this could be either a binary measure of presence/absence or a composite score focusing on clinical signs and symptoms
Regardless of the assessment tool used, when using pain as an outcome measure it is important to predefine the amount of wound pain reduction that is clinically important
When surrogate parameters such as symptoms and signs, or composite endpoints such as scales, are used as primary endpoints, it is essential that both their basic definition and what is considered to be a clinically relevant difference are predefined. When used as an primary endpoint, it is favourable for it to be verified by an independent evaluator

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Supporting references for this document are published below. A bibliography, comprising the articles evaluated by the Patient Outcome Group, can be found at www.ewma.org/english/patient-outcome-group

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Table 17. Statements from the group used in this document (continued)

When assessing dressing performance in an objective manner, with a focus on a specific aspect of symptom management, a comparative study may not be needed; the relevant data could be better assessed using a cohort study with a standardised, reproducible and validated protocol that includes resource utilisation (when appropriate)	Wherever resources have alternative uses, decisions on the adoption of new technologies or new procedures cannot be made on the basis of clinical outcomes alone. Rational choice requires evidence of the costs and benefits of alternatives
HRQoL assessments must be based on tools with established psychometrics	In order to maximise the value of investments in clinical research, studies should be designed to address the relative cost-effectiveness of alternatives from the outset, as well as their safety and effectiveness.
The type of assessment must fit with the purpose of the data collection: if HRQoL data are to be used for health technology assessment reviews, then generic and/or utility methods must be included	**Performance bias and interpretation of findings**
When cost is used as an outcome parameter in wound management, it is essential to measure all the quantities of resources used and then add the value of those resources, according to a predefined protocol. It is recommended that resource use and cost are shown separately	The choice of study duration must consider the type and size of the wound and its natural outcome. This information is also important for the stratification of data
	The term 'chronic' should be replaced with 'non-healing' as this better reflects the clinical problems experienced by such patients

There is controversy regarding the appropriate length of follow-up for ascertaining that an ulcer has actually healed after wound closure has been achieved. Recommendations range from two weeks up to 12 months. In our analysis, we found that the most frequently used follow-up period was three months. This is supported by other sources. For example, the FDA also suggests that patients remain under review for three months post-healing in order to distinguish wound healing from 'transient wound coverage'. In relation to wound closure, using a time interval that is relevant to the underlying disease process should also be considered.

It is important that researchers are able to differentiate between ulcer recurrence and the development of a new ulcer on the same site.

For a cost-effectiveness analysis in venous leg ulcers, a follow-up period of 12 months is recommended.

Statements

- The choice of study duration must consider the type and size of the wound and its natural outcome. This is also important for the stratification of data
- The term 'chronic' should be replaced with 'non-healing' as this better reflects the clinical problems experienced by such patients.

Section 6: Summary and recommendations

This document, the first joint document based on position documents, systematic reviews and an analysis of comparative studies within wound management, describes the challenges relating to the evaluation of outcomes in intervention studies on non-healing diabetic foot ulcers, lower leg ulcers and pressure ulcers.

The aim of this document is to provide recommendations on the accepted level of rigour for studies in wound management and to develop a consistent and reproducible approach to defining, evaluating and measuring appropriate and adequate outcomes in both RCTs and clinical studies.

The document provides statements on how to improve evaluations of new treatment strategies regarding outcome, in order to meet the requirements for evidence-based information in wound management. It also describes particular considerations that must be recognised when evaluating treatment strategies in non-healing wounds.

All of the group statements included throughout this document are repeated in Table 17 for ease of reference. ■

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