Evidence-based and clinical views on acute wound healing and scar formation
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Chapter 4

Fundamentals of randomized clinical trials in wound care: design and conduct

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Abstract

The care for chronic and acute wounds is a substantial problem around the world. This has led to a plethora of products to accelerate healing. Unfortunately, the quality of studies evaluating the efficacy of such wound care products is frequently low. Randomized clinical trials are universally acknowledged as the study design of choice for comparing treatment effects, as they eliminate several sources of bias. We propose a framework for the design and conduct of future randomized clinical trials that will offer strong scientific evidence for the effectiveness of wound care interventions. While randomization is a necessary feature of a robust comparative study, it is not sufficient to ensure a study at low risk of bias. Randomized clinical trials should also ensure adequate allocation concealment and blinding of outcome assessors, apply intention-to-treat analysis, and use patient-oriented outcomes. This article proposes strategies for improving the evidence base for wound care decision-making.
Introduction

Evaluation of wound care procedures and products is a challenge for researchers and clinicians alike. Unfortunately, only few articles are based on randomized clinical trials (RCTs). This article provides a guide for designing and conducting high-quality research focusing on, and relevant to, clinical practice. Based on a clinical scenario we will lead you through various issues related to RCTs.

Clinical scenario

You, a vascular surgeon, performed a below-knee amputation in a 70-year-old man suffering from an acute Charcot foot with an extensive infection of the plantar fascia originating from a neuropathic foot ulcer. Although you administered prophylactic antibiotics, the patient develops an infection at the amputation stump. Hence, you remove most of the stitches to drain the wound.

The wound care nurse discusses with you whether or not to apply an iodine dressing or another antiseptic agent locally. As an evidence-based surgeon, you search the evidence that would support a choice. Three comparative trials come close to the problem you are facing with this patient, but these do not address amputation wounds and show contradicting evidence about which antiseptic is to be preferred.1-3

Optimum study design

While treating your patient according to local best practice, you realize there is a need for an RCT to answer this clinical quandary. The first dilemma that immediately arises is: Which study design is preferable and feasible at the same time? RCTs are acknowledged by some as the methodologically preferable design for investigating treatment effects because they eradicate important sources of bias, such as selection and confounding bias.4-6 Any positive treatment effect found in an RCT generally provides more confidence about the efficacy of an intervention than in non-comparative studies or registries because possible confounders are equally distributed over the study groups, while known prognostic factors can be dealt with by stratification. This is advantageous particularly in wound care, where there is a large variety in types of wound, different wound aetiologies, multiple comorbidities, and a wide range of treatment options (e.g., for local and systemic wound care). A pragmatic, real-life study design, e.g., through liberal patient inclusion from various settings and accepting relevant co-interventions or common comorbidities, would yield information about effectiveness rather than mere efficacy of wound treatments.
Some argue that there is no sound reason for wound care researchers to choose a design other than an RCT to evaluate wound care strategies. Yet, RCTs are inappropriate in situations such as in case of rare, life-threatening diseases, such as toxic epidermal necrolysis, and when randomization would be unethical. It can be considered immoral to conduct an RCT to determine if primary amputation is as effective as a surgical or radiological intervention to treat critical leg ischemia. In such circumstances, data from observational studies may be more appropriate and sufficient.

A general, internationally accepted guideline on how to report RCTs has been formulated in the recently updated Consolidated Standards of Reporting Trials (CONSORT) statement. This statement is also, albeit indirectly, useful for the preparation and conduct of RCTs. In this article, we will elaborate on issues particularly relevant for the internal validity of RCTs in wound care.

**Study preparation**

In the clinical scenario presented above, an RCT to investigate the effectiveness of interventions seems possible and preferable. The next step is to consider several criteria that are considered essential components of intervention research (see Table 1). Formulating the exact research question helps define the patients needed for the study, the intervention under study, the standard policy as comparator, and the most clinically relevant outcomes.

Patients for whom the intervention is intended determine the setting from which eligible patients are to be selected, e.g., home care, general hospital, trauma or emergency ward, specialized wound clinic, nursing home, or university centre. The same holds true for the patient characteristics. To ensure the appropriate spectrum of patients, consider whether vulnerable patients due to the presence of comorbidities (e.g., diabetes, kidney failure requiring dialysis) or certain types of medication (e.g., steroids) should be excluded. These factors may reduce the clinical success rate and/or increase the rate of complications; on the other hand, the question arises whether the clinical success under these different conditions is of particular interest because it reflects real life. In amputees, diabetics may be an important patient group to include, whereas the use of steroids is a likely exclusion criterion as it seriously hampers the normal immune response.

Exclusion criteria will reduce the number of eligible patients. Keep in mind that narrow inclusion criteria, which should demonstrate more powerful treatment effects, lead to further difficulties in the recruitment of patients and the generalization of the results (external validity). Eligible patients should be fully informed about the treatment options...
and, if they decide to take part in the trial, they have to give written informed consent. Hence, it is advisable to perform an a priori sample size calculation (for more details, see section “Predefined plan for data analysis”) to achieve sufficient power to detect clinically relevant differences. Furthermore, this sample size provides a realistic estimate of the length of time needed to recruit patients.

To be able to include a sufficient number of patients within a reasonable time interval, one should consider increasing the number of recruiting centres. A multicentre trial is preferable, not only to accelerate recruitment but also to enhance the generalizability of the results. Admittedly, an (multicentre) RCT in wound care may be more time-consuming than a pharmaceutical study, at least in terms of the attending clinician’s time, and may subsequently interfere or disrupt daily practice routines. In addition, involving clinicians from different specialties in the trial will likely improve the implementation of the result.

### Table 1 Checklist of criteria to be defined and completed for an optimum design in wound care trials

<table>
<thead>
<tr>
<th>Setting</th>
<th>The trial setting (e.g. home care, general hospital, nursing home, or specialized (university) clinic) is defined</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Eligibility criteria for patients are described (inclusion and exclusion criteria)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Written informed consent will be obtained from every patient included</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interventions</td>
<td>The treatment to apply in each trial arm is standardized</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Co-interventions are allowed but prespecified (the same in both trial groups)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary and secondary outcomes are prespecified</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>It is described when and how outcomes are assessed</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sample size</td>
<td>Sample size is calculated (calculation based on expected clinical relevant difference in primary endpoint)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Randomization</td>
<td>The unit of randomization defined (e.g., the wound or the patient)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>The allocation sequence is randomly generated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>The treatment allocation is adequately concealed</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blinding</td>
<td>It is defined who is blinded after assignment to the intervention and how, including:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patients (recommend)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Caregivers (recommend)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Outcome assessors (strongly recommended)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>All randomized patients are to be analyzed in the group to which they were allocated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Funding</td>
<td>Funding through unrestricted grants only</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Duration of follow-up is defined</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ethics</td>
<td>Ethics review board approval</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Trial registration</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
of the trial by all invited specialties. Tissue viability nurses or specialized wound care nurses tend to be zealous in contributing to studies in their area of expertise and can therefore play an invaluable role. A drawback can be that multicentre RCTs are more expensive and pose logistic challenges, so financial support is a necessity to conduct a proper trial.

Generally, clinicians have had to rely ostensibly on financial support from commerce to extend the boundaries of our knowledge. In addition, the Food and Drug Administration (FDA) formulated some relevant patient outcomes for wound care (e.g., healing rate and pain relief) as the result of pharmaceutical interaction. Conversely, legislation in many countries does not consider wound care products as pharmaceutical agents, which may simplify the legal and safety requirements of such a trial. Ideally, first-choice funding should be obtained from independent (inter)national institutions. A second option is commercial funding from manufacturers to magnify valorisation of the knowledge obtained. Many of these manufacturers are relatively small and cannot afford lengthy and/or expensive studies, which calls for a joint effort by several stakeholders (e.g., wound care researchers, clinicians, manufacturers). To avoid any conflict of interest, analysis and reporting of the trial should remain the domain of the researchers. A legal agreement helps to ensure the grant is unrestricted. Unfortunately, there is a trend to publish only studies with positive results that favour the sponsoring industry. An “unrestricted grant” or a combination of sponsorships will assist in minimizing publication bias.

To demonstrate and document good clinical practice and patient safety, one should clearly describe the design of the RCT in sufficient detail in a research protocol. This protocol will need to undergo scrutiny by the local Ethics Review Board(s) before the study can start. In addition, one should register the research protocol in a publicly accessible database (http://www.isrctn.org or ClinicalTrials.gov) to announce the RCT is planned, ongoing, or completed. For many major medical journals this is a prerequisite for publication to reduce publication bias. Availability of a protocol can help to restrict post hoc changes to the methods during the inclusion period. Finally, a run-in period (e.g., pilot-inclusion of a few patients) can be useful to check the feasibility, logistics, and final success of the trial.

Main methodological issues of design in RCT

Randomization and allocation concealment

Randomization evenly distributes both known and unknown prognostic factors between comparison groups. In addition, one may stratify patients by factors known to influence
treatment outcomes, for example, age, wound size, and comorbidity, to disperse these demographic and prognostic factors evenly between the treatment groups. This even distribution ensures that detected differences are attributable only to the intervention under investigation and not to confounding variables. To detect any between-group differences, the collection and reporting of relevant patient and wound characteristics is essential (e.g., age, comorbidities, co-interventions, wound characteristics).

A concealed allocation process helps to reduce the risk of selection bias when comparison groups are not created in a truly random fashion. Examples are allocation by the person’s date of birth, by the day of the week, by a person’s medical record number, or just allocating every alternate person. These quasi-random methods do not offer patients an equal chance to receive either treatment. Furthermore, caregivers may easily become aware of the treatment the next patient will receive, which can cause (un)intentional inclusion or exclusion of the patient. Therefore, it is best to assign a person unrelated to the study to perform the randomization, or to use a central randomization institute (particularly in case of a multicentre trial), or a Web-based randomization service. The crux is to conceal the randomization schedule to prevent manipulation of allocation to the different treatment arms. It is preferable to randomize as shortly before the intervention as possible. This prevents dropouts after randomization, for example, when a surgical treatment is inadvertently cancelled.

**Blinding patients and caregivers**

Blinding of patients and caregivers regarding the allocated treatment is recommended. This is the Achilles’ heel of most RCTs in wound care. Whenever possible, the test agents should be masked. This has been successfully performed when testing the effects of zinc oxide and ibuprofen. Blinding is obviously impossible when comparing, for example, negative pressure wound therapy (NPWT) with conventional wound dressing materials. This may introduce performance bias, i.e., patients and caregivers may act differently if they are aware of the treatment given (e.g., patients in the control group may be more likely to use additional care, and patients who know they are in the intervention group may experience placebo effects). Unequally applied co-interventions generally diminish the contrast between the treatment effects, for example, when the amount of antibiotics or analgesics given or the frequency of visits or follow-up intervals differs between the groups. Therefore, these should also be recorded. Some wounds may require a number of unavoidable procedural interventions to promote healing, e.g., regular episodes of debridement. This is acceptable when applied and recorded commensurately in both treatment groups.
Blinding outcome assessors

An independent outcome assessor who is unaware of the treatment given can conquer the challenge of blinding in wound care. It can be helpful to give patients instructions not to tell the independent outcome assessor to which intervention they were allocated. This is particularly relevant in studies in which it is difficult for patients not to discuss the intervention, for instance, when their wounds are treated with NPWT or debrided with maggots.

Blinding of the outcome assessors is important, particularly in wound care, because most of the outcomes (see the section “Study outcomes”) are subjective and open to overestimation in favour of the new intervention (e.g., wound healing). Only if the outcome parameters are objective, such as death, does this become less imperative. Some outcomes are difficult to measure objectively (e.g., patient comfort), while others (e.g., pain) can prove time-consuming and/or expensive.

Intention-to-treat principle

In wound care, some patients may switch from one intervention to the other due to side effects, apparent lack of effect, lack of treatment compliance, or simply a change in preferences. Despite these switches, one should analyse every patient in the group to which they were originally allocated, even if they did not receive the treatment as defined by the protocol or they withdrew from the study. The reason for this intention-to-treat principle is that it maintains treatment groups that are similar (apart from random variation). It therefore validates the use of randomization, and allows for handling of protocol deviations, further protecting the randomization process. If some patients would have been excluded who did not complete their treatment because it was too burdensome (e.g., the use of sheepskin as they developed skin irritation) or because they responded poorly, only the responders will contribute to the—obviously overestimated—treatment effect. Comparing the treatments the patients actually receive (also known as “per protocol” analysis), rather than to which they are allocated (e.g., after crossing over to the other treatment group), confounds the initially equal distribution of patients at randomization.

Main clinical issues

Comparability of study treatments

The comparator treatment should be current best practice rather than placebo. Particularly in acute wound care, there may be little consensus about what constitutes
Design and conduct

standard policy, making the comparator choice difficult. Another consideration regarding the interventions in the trial groups is their uniform application. Factors such as dressing change frequency, leg elevation, adequate compression, pressure relief, moment of applying an antiseptic or drainage device, cleansing procedure, antibiotics, and treatment duration are important procedures to standardize. Those who will perform the intervention or apply the device, dressing, or topical agent will benefit from training and instructions on how to use the intervention before the start of the trial. It is also essential to define the indication for, and use of, additional treatments (“co-interventions”) such as wound bed preparation, debridement, pain management, additional medication, nutritional supplements, antiseptics or antibiotics, and surgical procedures to avoid differential application. If the latter occurs, the groups are not treated equally and the effect found cannot be attributed only to the intervention under investigation. This flaws the validity of the trial.

Study outcomes

One should choose primary and secondary outcomes carefully and beforehand, as well as how, through which (valid) methods, and after which time interval(s) these outcomes will be assessed.

Primary outcome(s)

This outcome should represent the main effect of the intervention and is used for the sample size calculation (see section Predefined Plan for Data Analysis). The clinical effect of any intervention should be based on outcomes that are meaningful to patients. One may choose a valid intermediate or surrogate outcome if complete wound healing is not the primary aim (e.g., suitability for secondary surgical closure in the case of vacuum assisted closure [VAC] treatment). Then, goals shift toward maintaining or enhancing functional status, optimizing wound condition, or relieving suffering, for example, pain relief in patients with chronic leg ulcers. One should not settle for such end points just to shorten the follow-up period. For example, a 50% reduction in bacterial count might seem an impressive result to the researcher, but the patient still suffers from having a colonized wound. The follow-up should be long enough to measure all predefined outcomes. By definition, chronic wounds are due to an underlying aetiology (e.g., venous hypertension in venous leg ulceration). Consequently, if the aetiology is not resolved, the risk of the lesion recurring over time has to be considered. This eventuality demands months or years of follow-up. Similarly, a study on quality of healing (e.g., hypertrophy, keloid) would also require an extended follow-up period. Moreover, many patients with chronic ulcers are subjected to polypharmacy, thus increasing the risk of drug-associated delays of wound healing. Unfortunately, sometimes less clinically relevant endpoints substitute primary outcomes when the latter were not as good as expected.
Secondary outcomes

In a study regarding preferences on ideal wound dressing characteristics, a short wound healing time, minimal pain during dressing changes, and short duration of hospital stay were valued most. Meticulous wound pain assessment, preferably using standardized Visual Analogue Scale, and proper documentation of pain and analgesics usage is essential to appreciate an important aspect of wound care. In addition, any complications or adverse effects should be recorded, such as toxic or allergic responses to dressing materials, blistering, infection, malodour, leakage, unexpected need for redressing, or wound recurrence. If there is a non-negligible risk of serious adverse effects, a data safety monitoring board is required to monitor these events. Adverse effects are usually underreported in publications, but are important to be aware of to weigh the benefits against the possible harms of an intervention. Examples of this are the underestimated adverse effects of silver sulfadiazine for burns and the overestimated ones of iodine as antiseptic agent.

It is of value to also consider assessing quality of life, functional status, and patient satisfaction because it provides valuable information on the patient-perceived burden of illness. Both generic questionnaires, e.g., the Medical Outcomes Study Short Form-36 or Nottingham Health Profile, and wound type specific questionnaires may be combined. In chronic wounds, these measurements should be repeated after larger intervals to determine the long-term effects of the interventions. For the purpose of comparability among studies, uniform time points for clinical follow-up are highly desirable. Furthermore, the cosmetic result after complete wound healing is an outcome often appreciated by patients.

In today’s economically constrained health services, the costs of treatment are an indispensable outcome parameter. Therefore, one should try to measure cost-effectiveness from a societal perspective, including all relevant medical costs and nonmedical costs. Analysis of medical costs should include the unit costs of all (dressing) materials used, costs of personnel involved in wound care, and inpatient treatment period required; costs of immediate and long-term complications; and costs of long-term outpatient monitoring and care. Additionally, the nonmedical costs may be calculated based on costs due to incapacity for work, transportation to the hospital, home adjustments, cleaning of soiled clothing, and so on.

The Cochrane Wounds Group also strongly advocates using only valid, objective outcomes. The proportion of wounds completely healed at a particular time, rates of healing, and incidence of new wounds or infection are considered suitable as primary outcomes. The FDA guidance formulated definitions of outcomes that can be used to
measure efficacy in wound care research. It helps to define outcomes for chronic and burn wounds, as well as for acute wounds.\textsuperscript{40}

Finally, it is mandatory to store the study database securely and ensure it is available for audit and access. Furthermore, these data may be also valuable for future meta-analysis.

**Predefined plan for data analysis**

A comprehensive study protocol includes a predefined plan for statistical data analysis, which underpins the formulated hypothesis and helps to answer the research question. A meaningful comparison between treatment groups is possible only if an RCT is adequately powered to detect a predefined, clinically relevant difference in the primary outcome, should such a difference exist. For this purpose, one can make a calculation of the required number of patients to be included before the start of the trial. A power \((1 - b)\) of at least 0.80 is considered acceptable, which indicates that there is a 20% risk that a true difference in treatment effect remains undetected, should such a difference exist. In addition, a significance level \((a)\) of usually 0.05 is considered appropriate, meaning that it is accepted that there remains a 5% risk that a difference found is not a true treatment effect, but merely based on chance. We strongly recommend consulting a biostatistician or clinical epidemiologist for the study design and statistical analysis before designing the protocol.

When analysing the data, remember to use the intention-to-treat principle for the reasons explained above. Subgroup analysis may also be considered to examine the treatment effect in a specific group of patients or wounds in the trial, in which the treatment is expected to be more effective. It is important to define such analysis before starting the RCT to avoid the suspicion of “data dredging.” Moreover, such a comparison with less than the initial, complete set of patients is always underpowered and any differences found may be coincidental.

**Discussion**

The scale of the worldwide wound care problem seems to match the high volume of publications, with at least 150,000 hits in Medline related to wound care. These PubMed-indexed studies include opinion-based reports, epidemiological studies, and studies of diagnosis, prognosis, and therapy. A strikingly small proportion of the publications on therapeutic interventions are comparative or randomized studies, and even fewer are (Cochrane) systematic reviews. Most of these Cochrane reviews end by concluding that
the volume and quality of the existing research is low, the consistency of study design is lacking regarding study outcomes, few replication studies exist, meta-analysis is mainly impossible due to heterogeneity of the studies, and most studies are at high risk of bias.\textsuperscript{7}

To enhance the depth and validity of newly generated evidence needed to support clinical decision-making in wound care, we propose this comprehensive framework for wound care researchers to undertake properly designed and executed RCTs. Timely contemplation of methodological rigor is pivotal to achieve the desired scientific knowledge. Many barriers and issues of RCTs can be overcome by proper design and conduct. Understanding the rationale for this comprehensive framework is also important for policymakers to help with decision-making with regard to the plethora of wound care products and the limited financial resources.

A more consistent approach as to the design and conduct of RCTs will facilitate meta-analysis of original studies. Many researchers and clinicians plead for more consistency in the choice of comparators and outcomes to be measured and reported in future research.\textsuperscript{37,41,42} We hope the recommendations given here will help contribute to uniform, high-level research in this realm. Thus, the framework should ultimately help caregivers in decision-making for their patients with wounds. We do realize that this framework does not address the reporting of a trial, which is another essential aspect besides appropriately designing and conducting a trial.\textsuperscript{43}

The obstacles we face when initiating and performing RCTs in wound care are also shared by other clinical areas such as surgery.\textsuperscript{44,45} Indeed, Farrokhyar et al. identified several factors that influence the internal validity of surgical trials. Nevertheless, many of these challenges can be overcome, and in most cases, these issues do not restrict the conduct of an RCT\textsuperscript{45}. This seems to be in contrast with the European Wound Management Association position document\textsuperscript{37}, which also supports the use of cohort studies in wound care. According to Bell-Syer et al., the use of observational studies for evaluating treatment effects is only recommended in very specific circumstances, such as studying rates of diseases or harmful effects.\textsuperscript{7}

Another reason for the seemingly reluctant attitude toward rigorous trials may be the fact that commercially available wound care products, such as dressings and topical agents, do not (yet) need to undergo the scrutiny that pharmaceuticals do before being marketed because they are not subjected to the same rigor by FDA or good clinical practice regulations. Therefore, this does not force manufacturers to perform extensive research on their products. Nevertheless, evidence-based practice has become necessary in an area where clinicians increasingly have to justify their decisions toward patients, insurance companies, and government, and liability issues have become too common.
Given the worldwide magnitude of the wounds problem, health care professionals as well as manufacturers of wound care products should take every effort to improve the quality of care for patients with wounds. The recommended standards presented here for optimum trial design in wound care research are an earnest attempt toward achieving this goal while recognizing that their implementation is not without its own particular challenges.
References


