



## PERSPECTIVE ARTICLE

# Fundamentals of randomized clinical trials in wound care: Reporting standards

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**ABSTRACT**

In wound care research, available high-level evidence according to the evidence pyramid is rare, and is threatened by a poor study design and reporting. Without comprehensive and transparent reporting, readers will not be able to assess the strengths and limitations of the research performed. Randomized clinical trials (RCTs) are universally acknowledged as the study design of choice for comparing treatment effects. To give high-level evidence the appreciation it deserves in wound care, we propose a step-by-step reporting standard for comprehensive and transparent reporting of RCTs in wound care. Critical reporting issues (e.g., wound care terminology, blinding, predefined outcome measures, and a priori sample size calculation) and wound-specific barriers (e.g., large diversity of etiologies and comorbidities of patients with wounds) that may prevent uniform implementation of reporting standards in wound care research are addressed in this article. The proposed reporting standards can be used as guidance for authors who write their RCT, as well as for peer reviewers of journals. Endorsement and application of these reporting standards may help achieve a higher standard of evidence and allow meta-analysis of reported wound care data. The ultimate goal is to help wound care professionals make better decisions for their patients in clinical practice.

In the present era of evidence-based medicine, the use of best available evidence has become an essential part of clinical decision making to ensure and improve quality of care. The requirements to meet this hunger for evidence are the following: first, a proper design and conduct of studies rendering convincing evidence, and second a clear and concise, but at the same time comprehensive and unbiased, description of the conducted research to show the validity of the study and the effect of the intervention investigated.

In wound care research, available high-level evidence according to the evidence pyramid<sup>1</sup> is rare, and is threatened by either a poor study design or inconclusive results.<sup>2-6</sup> Nevertheless, the number of scientific publications in wound care shows a 30-fold increase over the last five decades.<sup>7</sup> During this period, numerous guidelines and recommendations have been developed to improve the quality of design and conduct of wound care research.<sup>3,5,8</sup>

Unfortunately, upgrading the quality of a study design does not automatically improve the quality of reporting in wound

care publications.<sup>4,9-11</sup> First, positive study results tend to be published more often than indifferent or negative study results, known as publication bias. Second, adverse events may be neglected or reported selectively (also known as reporting bias, caused by the researchers). Third, the nomenclature of essential terms or presentation of the results may differ from other publications in similar areas.<sup>6,12-15</sup> These sources of bias emphasize the need for full and transparent reporting of wound care research, which will allow readers to assess the strengths and limitations of the research performed, and may also protect clinicians from integrating biased results in their clinical decision making.<sup>12</sup>

Besides improving the quality of a study design, the (updated) Consolidated Standards of Reporting Trials (CONSORT) statement has been published with the goal of improving the reporting standards of randomized clinical trials (RCT).<sup>16</sup> Many scientific journals have endorsed this statement or have incorporated it in their instructions for authors.<sup>17</sup> Even though these recommendations have had a

positive effect on the quality of reporting standards,<sup>18</sup> huge variation exists in terms of implementation.<sup>19,20</sup> Wound-specific barriers (e.g., variety of etiologies and multiple factors influencing wound healing) and the lack of specification in the CONSORT statement for wound care may prevent the uniform implementation of reporting standards in wound care research.<sup>21</sup>

Despite international recognition of RCTs as the putative “gold standard” for effectiveness,<sup>3,22,23</sup> this design is relatively seldom used for wound care treatments.<sup>2-4,24-26</sup> Specific barriers to perform RCTs in the realm of wound care<sup>27,28</sup> include the large diversity of etiologies and comorbidities, the plethora of treatment options, and invalid or unreliable assessment of outcome measures, which hamper adequate performance and reporting of RCTs. This often leads to the unsatisfying conclusion that “there is a need for large, high-quality RCTs in wound care.”<sup>29-31</sup>

To give high-level evidence the appreciation it deserves in wound care, we propose a step-by-step standard for comprehensive and transparent reporting of RCTs in wound care. These recommendations may result in uniformity of publication output, allow a meta-analysis of reported wound care data, and thus contribute to the potential for improving the quality of wound care delivery.

## REPORTING STANDARDS

### Title and abstract

The title should point out the major aim, result, or finding of your study.<sup>32</sup> The revised CONSORT statement requires identification of the study design in the title.<sup>16</sup> A carefully chosen title, keywords (if required), and a well-structured abstract helps in indexing your publication for easy retrieval as an RCT. At the end of the abstract, the trial registration number should be stated, as well as the database in which it is registered, for reasons given in the methods section. Common databases include <http://www.controlled-trials.com>, <http://www.icmje.org>, <http://www.clinicaltrials.gov>, and <http://www.trialregister.nl>.

### Introduction

The introduction compactly defines the problem (i.e., the area of uncertainty) and its importance in general, and identifies what is known about the topic in the literature and what is yet unknown. This illustrates the importance of performing this particular wound care study.<sup>33,34</sup>

In the first part, summarize, refer, and elaborate on the scientific background related to your research question. A convincing identification of the key issues in current literature is required to set the scene for your trial.<sup>33,35</sup> In wound care, prevalence numbers of wounds or systematic (meta-)reviews regarding intervention are often limited. Nevertheless, strive to summarize the best available and up-to-date evidence, or refer to national databases to sketch the size of the wound-related problem, including the overall impact on health and social gain.

Furthermore, state the benefits of study completion. For this article, we state that the gain of reporting standards will be “uniformity of publication output and allowing meta-

analysis of reported wound care in the future.” You may want to use “what (will happen) if we have the results” scenarios to formulate these perspectives.

The last paragraph of the introduction section states the aim of the study, the rationale, the specific objectives, and the hypothesis or purpose. For example, “aging populations living with chronic wounds,” “variation in wound care,” or “innovative wound materials launched on the market without sufficient evidence for effectiveness” could motivate the initiative or perspective of the study. The aim of the study should preferably be formulated along the PICO acronym,<sup>36</sup> describing the Patient’s problem, the Intervention under study, the Comparator or standard intervention, and the Outcome parameter(s) of interest.

### Methods

In general, describe how you performed your RCT in such a way that any research-oriented reader could evaluate and repeat your work.

The method section is pivotal for the reader to appreciate the validity of a trial and to facilitate the choice for further reading. Assist your reader in interpreting the quality of the trial (“did you do the best you could?”) and the possible sources of risk of bias (“does the reader believe your results?”), as high-level research methods do not preclude important risks of bias.<sup>37</sup> Wound care research is sensitive to some particular forms of bias, which may have serious impact on the reliability and generalizability of the results. For example, an adequate and concealed randomization procedure, clear eligibility criteria, a priori sample size calculation and the powering of the study, intention-to-treat analysis, blinding of at least the outcome assessor, and duration and completeness of follow-up are regularly underreported or even overlooked, which may cause justified suspicion of bias.<sup>6</sup>

In wound care, terminology is known to vary among nations, disciplines, and caregivers.<sup>3</sup> Therefore, state or describe your definitions clearly, especially when confusing terminology exists, e.g., wound etiology, regarding debridement, measurement of wound healing, or categories of wound dressing materials.

To assist readers in judging your results and any potential sources of bias, report the following criteria, which are essential in wound care.

- Clearly define your inclusion and exclusion criteria, e.g., etiology of the wound, wound size, internal controls (e.g., whether two wounds are required or a single wound is split in half to test the intervention and control treatment), duration of the wound, previous treatment received (e.g., debridement and standard treatment), and prognostic factors that may impair wound healing (e.g., smoking, diabetes, obesity, weight loss, use of systemic corticosteroids, radiation therapy). This helps the reader judge the generalizability of your study results.
- Without a sample size calculation, the reader cannot assess whether observed differences are meaningful and representative of the truth in real life. When no preliminary data exist to determine your sample size, which is often the case with prevalence of (acute) wounds or complications, motivate why a certain anticipated wound occurrence, infection rate, or pain reduction is *clinically*

relevant. Small sample sizes in wound care often require the use of restriction (to achieve balance between groups in size or characteristics), as compared with the “simple randomization” in larger trials. The methods used to restrict the randomization, along with the method used for random selection, should be specified (such as blocking and block sizes). If stratified randomization is applied, report why variables are likely or known to influence the outcome in a substantial way (e.g., ulcer duration, wound size or center).

- In wound care, the unit of randomization might be patients’ wounds or clusters. Report and explain why either one is chosen as a subject of randomization. Inclusion of multiple wounds per patient may introduce problems such as interdependency and overestimation of the precision.
- Specify the method of sequence generation, such as a random-number table or a computerized random number generator, providing your reader sufficient information to assess the likelihood of bias in the group assignment.
- Report how the patient allocation is concealed, e.g., by central allocation or by sealed envelopes. This allows the reader to judge whether enrolment of patients can be influenced by foreknowledge of the treatment assignment.
- Report who generated the allocation sequence, who enrolled participants, and who assigned participants to trial groups. Even a perfect randomization schedule can lead to bias if implemented incorrectly.
- Many wound care products or interventions leave recognizable marks (e.g., negative pressure therapy or tissue adhesives), which makes blinding complicated. Report attempts to solve the blinding issues, e.g., covering the wound material with the same secondary dressings. If blinding is not possible, the importance of using a blinded assessment technique (as objective as possible) becomes vital and should be reported (e.g., wound healing was assessed by an independent caregiver who is blind to the treatment given).
- Define the wound treatment in terms of devices, materials, technology or drugs, brands, dressing change frequencies, dosages, and/or sizes of the materials used. If the interventions change during the healing process, also document the condition of the wound or the wound-healing phase at the time of change. Document possible influence of the caregiver providing the intervention (e.g., expertise, education level, or familiarity with the wound material or device). You may want to describe solutions to prevent expert-based bias by means of protocols (e.g., dressing instructions provided by the manufacturer, or documentation of the wounds with uniformly taken digital photographs). Furthermore, co-interventions should be reported (e.g., antiseptics used in case of local infection). Interventions like antibiotics, secondary dressings, or compression therapy can especially influence the outcome of wound healing or infection rate.
- Report how and when your outcome measures were assessed and why they are considered as patient-relevant. For example, (time to) complete healing seems to be more relevant to patients than a proportion of the wound area healed. This is especially true for acute wounds, whereas for complex wounds the reduction of pain or

slough, or the percentage of healing, can also be considered patient-relevant.

The relation of the outcome measure to the intervention needs to be explained, and why this is an objective measure (e.g., assessment was blinded by an independent caregiver or researcher with a validated outcome tool). Report these outcome measurements accurately, so that your study results are reproducible and their validity can be judged. Important outcomes in wound care research are wound healing, reoccurrence of wounds, number and proportion of complications/adverse events, quality of life, length of hospital stay, number of visits to the out-patient (wound) clinic, and costs.<sup>38</sup>

- State the duration of the follow-up period. This is especially important for the reader to interpret outcomes, such as wound healing, infection, scarring, or reoccurrence of the wound. Also, authors of systematic reviews can only perform meta-analysis when the follow-up periods are homogenous. To allow for this meta-analysis, report the mean and standard deviation. However, if your data are skewed, also present the median and interquartile range.

For larger trials, the study design and methodology may be published beforehand in the form of a study protocol, which will improve the standard of wound care research<sup>39</sup> by enabling:

- The publication of a comprehensive study protocol with relevant details, as in the final publication of the results of the study space is limited and it is often not possible to report all kinds of details;
- Researchers to obtain feedback on their study design through peer review;
- Readers to compare what was originally intended with what was actually done (thus preventing “data dredging” and post hoc revisions of study aims);
- Funders and researchers to see which studies are underway, and hence reduce duplication of research efforts; and
- Authors of systematic reviews to find trials (ongoing or unpublished), which may in turn reduce distortion of the evidence due to publication bias.

As an author you may refer to the published study protocol for further details on the protocol. Regardless of whether a protocol has been published, it is important to provide the fundamental elements of the CONSORT checklist in your manuscript to show that the conduct of the trial has been performed according to good clinical practice rules.<sup>3,16,40</sup>

Clinical trials should be registered in an international trial (meta-)register before they are started. State the registration number in your manuscript,<sup>41</sup> and preferably also in the abstract. Formal approval by the institutional review board or similar ethics board should be stated, or whether the study was deemed exempt from formal approval, for example, when subjects were studied anonymously without any intervention that might compromise their physical or psychological integrity. Furthermore, all ethical issues should be reported in order to demonstrate good clinical practice and ensure patient safety.

When discussing statistics, your reader should be able to judge the validity of the findings. Only use statistics as relevant to the data you have gathered, with respect to the under-

lying assumptions governing the use of the specific statistical test. Statistics should be used to scientifically corroborate your conclusion rather than to “chase” a statistically significant result. Avoid the use of statistics solely to impress your reader, as most readers will be deterred by elaborate or complicated statistical methods. Always report in advance planned (subgroup) analyses in your method section to avoid post hoc analyses that may have the appearance of data dredging. Explain why certain calculations were made to analyze your data. In case of stratified randomization, an adjusted time to event analysis needs to be reported to correct for the stratification. The data and/or statistical analyses are usually presented in the last subsection, as it leads the reader to the results section.<sup>33</sup>

## Results

In general, check for internal consistency of data and results within your manuscript, as minor differences in the data presented may be viewed unfavorably by the reviewers and editors.<sup>42</sup>

A flowchart or diagram of study participants through each stage is recommended.<sup>16</sup> This is vital for patients with difficult-to-heal wounds, who are more likely to be lost during follow-up, and thereby increase the risk of attrition bias. Report patient exclusion, protocol violations, losses to follow-up, crossover patients, and dropouts for each group, and the reasons for these occurrences (e.g., painful dressing changes, leakage, allergic reactions to materials, (serious) adverse events, poor compliance, logistical reasons, moved or deceased patients). As incomplete outcome data may result in bias, report the overall proportion of participants with missing outcome data, reasons for missing outcome data, and the difference in the proportion of participants with missing outcome data, and address the problem of these in your analysis.

State whether you performed an intention-to-treat analysis, and whether or not patients received or completed the wound care treatment they were allocated to. This helps the reader judge whether those not adhering to the protocol may have inferior outcomes.

Furthermore, precisely report the eventual duration of the follow-up period. For example, report the range of follow-up duration, mean follow-up period with standard deviations, and if your data are skewed also report median values with interquartile ranges. Avoid empty terms like “until sutures were removed” or “until complete wound healing” without providing the actual figures.

Given the diversity of wounds, provide the reader with a detailed and full description of your population and setting at baseline, including the eligibility criteria mentioned in your method section. Important demographic characters in particularly complex wound care research are age, sex, ethnics, type of wound (in relation to etiology), duration of existence of the wound, size and depth of wound, and concurrent illnesses. Medications and relevant prognostic characteristics may influence wound healing or adverse events. These demographic and prognostic factors are usually summarized for each trial arm in the first table. Here, *p*-values should be avoided because any baseline differences between the randomization groups, if the randomization is applied correctly, are due to chance. The *p*-value represents this possibility of

differences being due to chance, and are therefore by definition a *p*-value of 1.0.

Provide absolute numbers when feasible, in addition to percentages (i.e., 30/60 [50%]) and averages (e.g., mean or median) with their variability (standard deviation or interquartile range). Means and standard deviations are preferred in order to perform future meta-analysis. However, they are sensitive to outliers, and in case of skewed data a median with accompanying interquartile range should also be reported. If patient imbalances occur, report the post hoc subgroup analysis for each outcome separately.

Always report predefined outcomes, benefits, and harms as mentioned in the method section to prevent selective reporting. When presenting the results, illustrate the size of the treatment effect (effect size) and the estimate of this treatment effect (point estimate or precision). Effect size should be presented in terms of relative risks (RR), risk difference (RD) (also known as absolute risk reduction [ARR]/increase [ARI]), number needed to treat (NNT) or number needed to harm (NNH) with their precision expressed as 95% confidence intervals (CI). This modern presentation of study results helps your readers understand the clinical relevance behind the statistical significance.

When reporting time-dependent parameters (e.g., time to wound healing), remember that these events should be analyzed by means of survival methods (time to event) and log-rank tests rather than by presenting averages (e.g., average time to wound healing). Mean healing time is solely justified if all patients stayed in and healed during the study period. To report on wound-related harms, such as pain, infection, and scar formation, use the time of measurement, the scale of the tool used for assessing adverse events (e.g., validated pain assessment scale [numeric rating scale or visual analog scale], or scar assessment scale [e.g., Patient Observer Scar Assessment Scale or Vancouver Scar Scale]), relevant co-interventions (e.g., antibiotics when assessing infection), and prevalence or background risk of the adverse event (e.g., wound infection usually is such a rare event that the numbers are too low for a meaningful comparison).

Finally, it is important to disclose any financial subvention, whether this is an unrestricted grant or sponsored. This may reflect the degree of involvement of the sponsor in the interpretation and presentation of the trial results.

## Discussion

The main purpose of this section is to answer your research question and help readers understand its consequences in terms of its implication for practice, policy, education, or future research.

Do not repeat all your results; instead, start the discussion with your factual results, its interpretation, and what these mean for clinical practice and clinical decision making. The section provides an opportunity to give theoretical explanations, to compare your results to other, similar research, to extrapolate to other wound types, to discuss any weaknesses in your methods or results, and to provide suggestions for future research.

Wound care research often has to deal with limitations, such as open studies (no blinding), small sample sizes (power), subjective outcome measures (e.g., leakage of wounds), presence of comorbidities (e.g., diabetes influencing the outcomes of wound infection or wound healing), short

**Table 1.** Summary of important reporting criteria

Manuscript section	Issue to be described	Clarification	Done <input checked="" type="checkbox"/>
Introduction	PICO	The aim of the study should preferably describe the <b>P</b> atient's problem, the <b>I</b> ntervention under study, the <b>C</b> omparator or standard intervention, and the <b>O</b> utcome parameter(s) of interest.	<input type="checkbox"/>
	Wound care terminology	State or describe your definitions clearly, especially when confusing terminology exists, e.g., regarding debridement, type of wound, measurement of wound healing, or categories of wound dressing materials.	<input type="checkbox"/>
Methods	Clear eligibility criteria	Define your inclusion and exclusion criteria to help the reader judge the generalizability of the study results.	<input type="checkbox"/>
	Definition of outcomes	State a clear definition of the patient-relevant outcomes, which are to be measured in a valid and reliable manner. Good examples are complete wound healing and pain scores using validated assessment tools.	<input type="checkbox"/>
	Adequate and concealed randomization procedure	Specify the method of sequence generation to provide the reader with sufficient information to assess the likelihood of bias in the group assignment process. Report how patient allocation was concealed, e.g., by means of central allocation or sealed envelopes. This helps the reader judge whether patient enrollment was influenced by foreknowledge of treatment assignment.	<input type="checkbox"/>
	Blinding or objective outcome assessment	Blinding is usually difficult in wound care trials. Report any blinding issues and attempts to solve them, e.g., using a blinded outcome assessor.	<input type="checkbox"/>
	A priori sample size calculation	Without a sample size calculation, the reader cannot assess whether observed differences are meaningful. Therefore, motivate why your study sample is large enough to detect a clinically relevant difference.	<input type="checkbox"/>
Results	Intention-to-treat analysis	State whether or not the patients received or completed the wound care treatment they were allocated to. This helps the reader judge whether those not adhering to the protocol may have worse outcomes.	<input type="checkbox"/>
	Follow-up duration	Define the exact duration of the follow-up period. Avoid empty terms like "until sutures were removed" or "until complete wound healing."	<input type="checkbox"/>
	Demographic characteristics of the participants	Provide a detailed description of your population at baseline, including wound characteristics and eligibility criteria, to illustrate which spectrum of patients is investigated.	<input type="checkbox"/>
	Outcomes	Report on all predefined outcomes, benefits, and harms, as stated in the methods section to prevent selective reporting. Describe the effect size, expressed as relative risk (RR), risk difference (RD), number needed to treat (NNT), or number needed to harm (NNH), with its precision expressed as 95% confidence intervals. Time-dependent parameters (e.g., time to wound healing) should be analyzed by means of survival methods (time to event) rather than by means of averages (e.g., mean time to wound healing).	<input type="checkbox"/>
Discussion	Limitations	Discuss study design issues like no blinding, small sample size, subjective outcome measures, or specific patient groups investigated (e.g., diabetics), short follow-up period, and industry sponsorship.	<input type="checkbox"/>

follow-up periods, and industry sponsorship. For example, report the possible influence of lack of blinding on the outcome measurement.

All too often, a positive message of effectiveness is conveyed, whereas the benefits and relevance to patients of the intervention should be weighed against its possible harms, adverse effects, and costs. Also, while pragmatic wound care studies may provide more useful information for routine clinical interpretation (external validity or applicability), they also introduce the possibility of bias (e.g., local differences in treatment of patients, assessment, or treatment given are influenced by different wound care providers with different levels of knowledge or experience regarding the wound material).

Depending on journal style, you may conclude with perceived study results and their possible implications for practice at the end of your discussion or in a new subheading "Conclusions." When writing your conclusions make sure they are coherent to your study results and your discussion.

## FINAL CONSIDERATIONS

In general, the first preparatory step of the writing process is to contemplate the scope and requirements of a suitable journal to entrust your manuscript to. The multidisciplinary character of wound care should influence your decision about your intended readership (e.g., doctors, nurses, educators, or managers of wound clinics) before choosing an appropriate journal.

Broad endorsement of reporting standards is needed to improve the quality of evidence-based wound care. Explanation and elaboration of uniform reporting standards specific to wound care will help clinical readers, reviewers, and journal editors to interpret and critically appraise the wound care literature. Furthermore, they help overcome the ambiguity between quality of reporting and the quality of the underlying research (i.e., flaws in study design vs. poor reporting).

Regardless of the ongoing debate regarding whether RCTs in wound care are uniquely difficult, wound care continues to be a substantial problem, and the need for adequate design, conduct, and reporting of scientific research remains standing.<sup>25,27,43,44</sup> Any (potential) flaws in the design and conduct of RCTs in wound care should at least be appropriately addressed and reported in detail in order to reduce confusion regarding the inference of the research.

Table 1 summarizes some critical reporting issues based on the step-by-step reporting standard for RCTs in wound care as described here. This can be used as guidance for authors who write their RCT, as well as for reviewers of journals. Endorsement and application of these reporting standards may help achieve a high standard of evidence, with the ultimate goal of helping wound care professionals make better decisions for their patients in clinical practice.

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