Received: 30 June 2020 | Revised: 8 September 2020 | Accepted: 21 September 2020

DOI: 10.1111/iwj.13506

ORIGINAL ARTICLE

IWJ WILEY

Quality of reporting of outcomes in trials of therapeutic interventions for pressure injuries in adults: a systematic methodological survey

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Abstract

Randomised controlled trials of therapeutic interventions for pressure injuries should include a clear description of outcomes to increase transparency and replicability and improve the construction of scientific evidence. The objective of this study was to assess the completeness of the descriptions of the outcomes of therapeutic interventions in adults with pressure injury (PI) and factors associated with completeness. This was a systematic methodological survey. The completeness of the outcome was assessed according to five criteria: domain (title), specific measure (technique/instrument used), specific metric, or format of the outcome data of each participant that was used for analysis, aggregation (method data from each group were summarised), and time that was used for analysis. Sixty-eight studies were included for analysis. A total of 265 outcomes were reported, and 46 trials (67.6%) had 73 primary outcomes, which were mainly intermediates/substitutes (78.8%). The main outcome evaluated was the ulcer area reduction (36.6%). Approximately 37.2% of the outcomes were incompletely reported, and the least described element was the data aggregation method (72.8%). Only 48.4% of the outcomes with the specified technique had the same reference or validation. Poor quality of reporting outcomes was associated with studies with an older year of publication and a small sample size, single-center studies, and those sponsored by industry. PI studies use many outcomes, mostly surrogates or intermediates, and some of them are incompletely described.

KEYWORDS

pressure ulcer, randomized clinical trial, treatment outcome, review

1 | INTRODUCTION

Pressure ulcer or pressure injury (PI) is damage located on the skin and/or underlying soft tissue, usually on the bone prominence, or may be related to medical equipment or other kinds of devices.[1] There is a great variation in either the incidence coefficients of PI found in critical patients (10.0%–62.5%)[2] or the evaluation periods of 1 or 15 months.[3,4] Globally, the PI incidence in the intensive care unit is between 3.2% and 39.0%.[5]

PIs cause considerable damage to patients, hampering the process of functional recovery, often causing pain and leading to severe infection development associated with prolonged hospitalizations, sepsis, and mortality.[6]

Although there is a relatively great volume of primary research on PI treatment (including PI prevention), the evidence quality results in a lack of direction for the practice. Furthermore, several published trials have been identified, more specifically in people with spinal cord injury, and there is a clear opportunity to develop more high-quality research in this field so that promising interventions can be evaluated in this group of patients.

Well-designed randomised controlled trials (RCTs) and studies that demonstrate the effectiveness and safety of a given treatment are the basis for clinical practice. In clinical trials, primarily, the development of a set of main outcomes is intended to help prevent inconsistencies that may exist in the selection of outcomes.[7,8] The lack of a well-defined and described outcome may result in omission or disregard of important study results together with the inconsistency of definitions of measurement techniques used to assess the outcome (information bias).[8] If the trials do not adopt clear efficacy outcomes that are properly reported, they risk selecting suboptimal outcomes, and it will be unlikely to contribute usable information.[9]

According to previous studies,[10,11] the outcomes in RCT must present five key elements. The five-element structure includes the following: (a) domain or title of the outcome, (b) specific technique or instrument used to make the measurements, (c) metric or specific format of the outcome data of each participant that was used for analysis, (d) method of aggregation or how the data of each group were summarised, and (e) time points used for analysis.

The main objective of this study was to analyse the completeness of the efficacy or effectiveness outcomes of therapeutic interventions in RCTs of PI in adults according to the five elements. The secondary objectives were to determine the frequencies of reported RCTs with primary and healing outcomes; describe the methods or measuring tools used to assess the outcome; and evaluate the quality of the result of the outcome as complete, incomplete, or unreported and the factors associated with outcome scores.

Key Messages

- Randomised controlled trials (RCT) of therapeutic interventions for pressure injuries (PI) should include a clear description of outcomes to increase transparency and replicability and improve the construction of scientific evidence.
- Although there is a relatively great volume of primary research on PI treatment the evidence quality results in a lack of direction for the practice.
- The lack of a well-defined and described outcome may result in omission or disregard of important study results together with the inconsistency of definitions of measurement techniques used to assess the outcome (information bias).
- The outcomes in RCT must present five key elements as follows: (1) domain or title of the outcome, (2) specific technique or instrument used to make the measurements, (3) metric or specific format of the outcome data of each participant that was used for analysis, (4) method of aggregation or how the data of each group were summarized, and (5) time points used for analysis.
- Our study showed that there is a heterogeneity of outcomes in RCTs of pressure injuries of therapeutic intervention in adults. The aforementioned reinforces the need for future designs of RCTs in this area with special attention to which outcomes will be analyzed, the complete details, and the form of evaluation so that there is an improvement in the quality of scientific evidence in the PI area.

2 | METHODS

This was a systematic methodological survey. The search strategy in the databases (PubMed, Cochrane, CINAHL, Embase, LILACS, Scopus, and Web of Science) was directed to articles published from January 2006 to July 2020 with the terms “pressure ulcer,” “pressure injury,” “randomized controlled trials,” “treatment,” and “adults.” This period was chosen because it is part of the period during which there have been several articles published addressing the integrity of reports or adherence to various reporting guidelines.[12] This study protocol in

which there is a very detailed method description can be found.[13] Briefly, studies with the following criteria were included:

- RCTs of therapeutic interventions such as dressings, medications, and care guidelines (e.g., change of therapeutic regimens) for PI.
- Studies in English and Portuguese.
- Only stage 2 to 4 RCTs of PI. Stage 1 was not included because the interventions for this stage are more related to the prevention of progression to wound opening than to treatment for ulcer healing; therefore, the outcomes of these studies are different.

The exclusion criteria were as follows:

- RCTs that included chronic ulcers of different etiologies
- Studies whose main purpose was the economic assessment of the prevention and treatment of PI
- Studies not fully accessible
- Studies reporting prevention intervention
- RCTs focused on PI due to medical devices such as catheters, tubes, probes, appliances, and dressing adhesives.

The studies were selected in two steps: title screening and abstract and then full-text screening. We conducted the screening in duplicate.

The researchers solved any discrepancies by consensus or consulting a third author. If consensus could not be reached, a third author was contacted.

The extraction of data from each article was performed using a standard Microsoft Excel® worksheet. Two reviewers summarised the data, and any disagreement was resolved by consensus.

Bibliometric and general information, outcome characteristics, and result quality of the reported outcome were extracted from each RCT as follows:

- Bibliometric information: author, publishing year, journal, total number of patients that were recruited in the study, if the study was sponsored by industry, journal impact factor (website of the Journal Citation Reports: https: //jcr.incites.thomsonreuters.com), whether the journal required the use of CONSORT, whether the study was a single-center or multicenter study, and in which country or countries the study was conducted.
- Outcome characteristics

A. Presence of the primary and secondary outcomes
B. Completeness of outcome

To determine if the outcome was fully reported, the methods section of the RCT was searched. A score of 0 to 5 was given based on the number of elements reported. A "fully specified" outcome was considered if all five of the following elements were described:

1- Domain or outcome title: the domain or title of each outcome was noted and classified into two groups, namely, healing and nonhealing outcomes (surrogate or intermediate outcomes).

The domains of efficacy and effectiveness outcomes were classified according to the European Wound Management Association Patient Outcome Group Document [12] as follows:

i. Healing outcomes: wound closure and healing time
ii. Nonhealing outcomes (intermediates or substitutes)

- Reduction rate: decreased wound area
- Change in wound condition: debridement, increased granulation tissue, reduction of exudate, and odour
- Biomarkers: biochemical components of nonhealing wound exudate, physiological markers (wound surface pH, tissue oxygen measurement), and tissue markers (histological examination, dermal collagen, neovascularization)
- Bacteriology: reduction of bacterial load
- Infection signs: control of infection, prevention of local and systemic infection, and osteomyelitis
- Symptoms and signs: control or reduction of pain at the wound site, stabilisation of the wound, and without worsening
- Dressing performance: reduction in the number of dressing changes
- Quality of life

2- Specific technique or instrument used to obtain the measurement: the technique used was considered "specified" if the RCT authors stated which instruments, tools, scales, and scores and/or how the outcome was defined. They were considered as "unspecified" when they were not reported or relevant phenomena were not defined (e.g., if "wound healing" had not been defined).

3 - Specific metrics or data format of the outcomes of each participant that was used for analysis: a specific metric was considered "specified" if the RCT authors described how they analysed the data, including baseline change, point in time, or time to the event. If this information was not given, it was considered an "unspecified" metric. The metric type used was also noted.

4 - Method of aggregation or how the data of each group were summarised: we consider that the aggregation method was "specified" if the RCT authors described how the data were summarised, including average, median, percentage, or proportion or absolute number.

When the authors did not mention any method of aggregation, we classified it as "unspecified."

5- Time points used for analysis: we checked whether the authors specified the time points used for their analysis. When the authors declared the time of judgement of the result, they were considered as "specified."

- The quality of the reported outcome of each RCT was assessed in the results section and reported in one of the three levels, adapted by Cham (2004).[14] Thus, the reported result was considered "complete" when there was enough data to determine the size of the effect (odds ratio and relative risk) and measure of accuracy (confidence interval) or "incomplete" when only P-values or qualitative data were reported. When there was no data in the results, although the result was defined in the methods section, we categorised it as "unreported result."[15]

3 | ETHICAL CONSIDERATION

Ethics committee approval is not necessary for this study because we are dealing with published data.

4 | STATISTICS

For the primary outcome, the completeness of outcome reports was analysed in two ways. First, we computed the median (IQR) number of elements reported. Second, we computed the proportion (%) of studies with complete "fully specified" outcome reporting (i.e., all five elements reported). For the secondary outcomes, proportions (%) were computed for the numbers of studies that reported a primary outcome, at least one objective outcome, and the measurement method and the number of studies with complete, incomplete, or unreported outcomes.

All percentages will be reported within 95% confidence intervals.

To evaluate the possible factors associated with the outcome scores of each RCT, multiple correspondence analysis was performed, with the construction of the conceptual map[16]. The following variables were included in this model to evaluate the association with this score: publishing year, sample size, sponsored by industry, journal impact factor, if the journal required CONSORT use, multicenter study, continent where the study was performed, and systemic intervention. Variables with a factor loading >0.2 were included in the final model. The quantitative variables were divided into terciles.

The data were analysed using the statistical program *Statistical Package for the Social Sciences* (SPSS) 22.0 (SPSS, Inc., 2009, Chicago, Illinois).

5 | RESULTS

Through the search strategy, 1.190 articles were identified in different databases. There were 1.1056 articles excluded, most of them related to prevention intervention and studies with chronic ulcers of several etiologies. Sixty-eight studies were included for the final analysis, as shown in Figure 1 with a PRISMA flow diagram[17]. The supplementary file has all studies included with information about their interventions and outcomes.

Table 1 shows the characteristics of the included studies. It is noteworthy that more than half of the published RCTs were in journals requiring CONSORT (58.8%) and published after 2010 (70.6%). Most of the RCTs had less than 100 participants (83.8%). Only 30.9% were multicentric studies, and 33.8% had used topical therapy as an intervention.

We found 265 outcomes in the 68 RCTs included. From these, 71 were primary, 105 were secondary, and 89 were not defined.

Table 2 presents the information about the frequency and classification of the primary outcomes of RCTs. Forty-six RCTs reported primary outcomes (67.6%), with 46% presenting more than one primary outcome, totaling 73. These outcomes were mainly of the surrogate/substitute type (78.8%).

A total of 265 outcomes were reported, and 46 trials (67.6%) had 73 primary outcomes, which were mainly intermediates/substitutes (81.5%).

When evaluating the completeness of the 265 outcomes according to the score related to the five elements expected to report them, it was verified that more than half of the outcomes (63.0%) had a maximum score of 5. The minimum score was 2 (0.7%). Table 3 shows this result.

The frequency of reporting of each of the five elements of the 265 outcomes was also evaluated (Table 4). The time description is shown in every outcome (100.0%), and the aggregation method is the less described element (72.8%).

Regarding the outcome title, the categories for the grouping of the titles presented objective (healing and healing time) and surrogate/intermediate outcomes. There were 265 grouped outcome titles, as described in Table 5. The main outcome assessed in the included RCTs was the ulcer area reduction (36.6%).

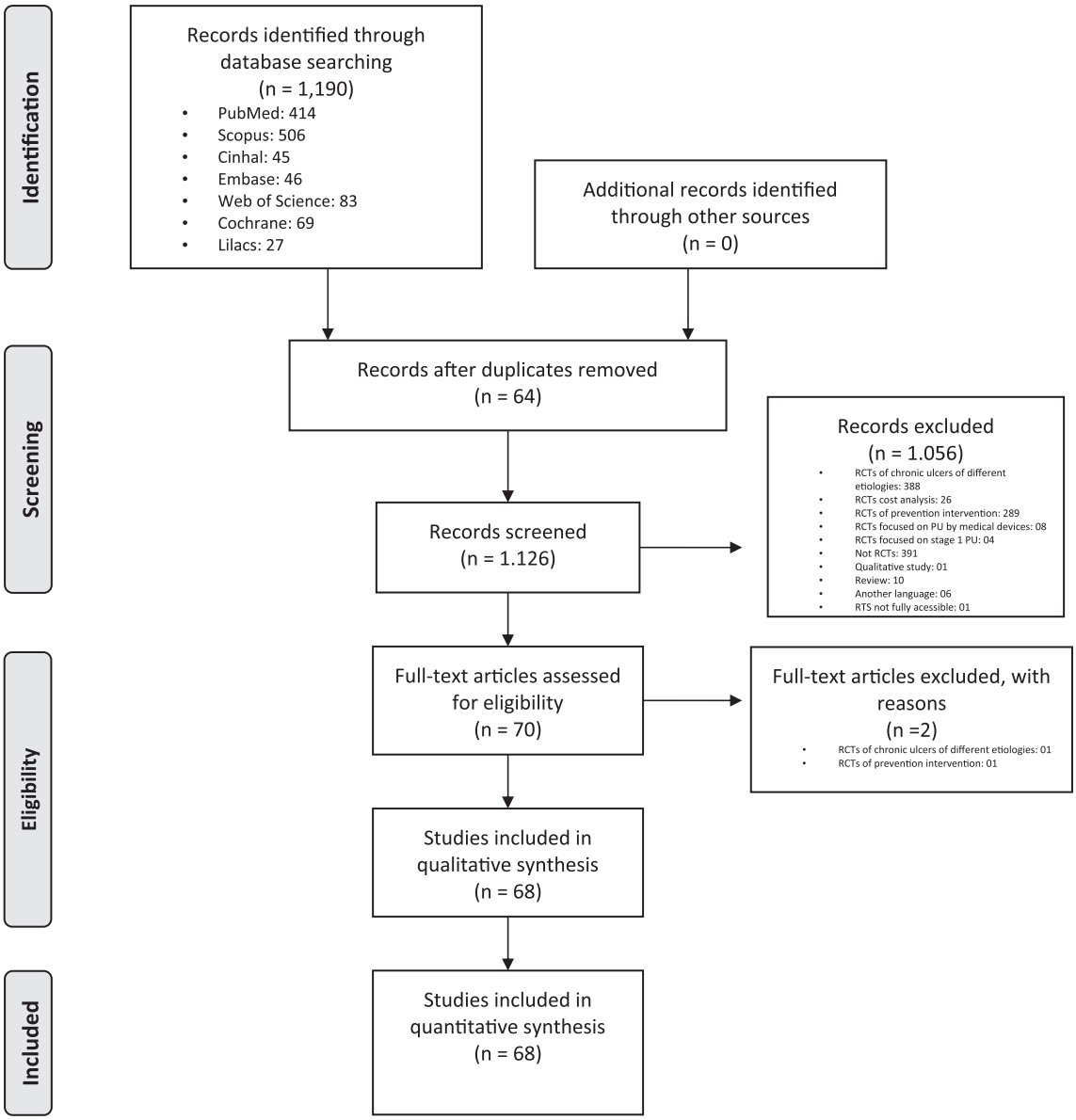

FIGURE 1 Prisma flow diagram showing the selection procedure of the studies

Regarding the technique for outcome measurement, only 48.4% of the outcomes with specific techniques had reference or validation.

Table 6 shows a grouping of techniques/instruments by domains for the three main outcomes (area reduction, change in wound conditions, and healing) because of the great heterogeneity of described techniques. The PUSH scale was applied to evaluate the outcome in 38.2.%. It is noteworthy that the technique was not described in 9.0% of the outcomes that evaluated the wound area reduction, 14.3% of the outcomes that assessed changes in wound conditions, and 32.3% of wound healing outcomes.

The outcome analysis time in the studies, described in days, was at minimum 7 and maximum 365 days, with the median of 56 days (p25 21.5 to p75 63). The assessment time of the three main outcomes was very heterogeneous, that is, the wound area reduction and changes in the wound conditions were at minimum 12 and maximum 365 days and healing/healing time was a minimum of 7 and maximum of 365 days.

The forms of presentation of the results of the 265 outcomes are shown in Table 7. Only 23.4% of the results were reported completely. Most of the results were compared using the *P*-value (76.6%). Seventeen outcomes (6.4%) were reported to be assessed using the method, but there was no analysis for their results.

Figure 2 represents the perceptual map with the association of the greatest scores of each study outcome with some general characteristics through the analysis of multiple correspondence. It is possible to observe that the

TABLE 1 Characteristics of included studies

Data	Frequency N = 68	Percentage (IC 95%)
Impact Factor (IF) of the Journal		
< 1.0	08	11.8 (6.1–21.5)
≥ 1.0 e < 3.0	50	73.5 (61.9–82.5)
≥ 3.0	07	10.3 (5.1–19.8)
Whithout IF	03	4.4 (1.5–12.2)
The jornal endorse the CONSORT	40	58.8 (47.0–69.7)
Year of publication		
Before 2010	20	29.4 (19.9–41.1)
After 2010	48	70.6 (58.9. – 80.1)
Continent where the studty made		
Asia	27	39.7 (28.9–51.6)
Europe	24	35.3 (25.0–47.2)
North America	11	16.2 (9.3–26.7)
Oceania	03	4.4 (1.5–12.2)
Europe-Asia	02	2.9 (0.8–10.1)
Not informed	01	1.5 (0.3–7.9)
Sample size		
< 100 participants	57	83.8 (73.3–90.7)
≥ 100 participants	11	16.2 (9.3–26.7)
Multicentric study	21	30.9 (21.2–42.6)
Funding Status		
Only other funding different of industry	26	38.2 (27.6–50.1)
Only Industry sponsored	11	16.2 (9.3–26.7)
Industry and others	03	4.4 (1.5–12.2)
No funding	04	5.9 (2.3–14.2)
No declared	24	35.3 (25.0–47.9)
Pharmacological intervention	24	35.3 (25.0–47.9)
Intervention category		
Topical	23	33.8 (23.7–45.7)
Physical therapy	17	25.0 (16.2–36.4)
Systemic Therapy	16	23.5 (15.0–34.8)
Negative pressure therapy	07	10.3 (5.1–19.8)
Others	05	7.3 (3.2–16.1)

outcomes with a score of less than 5 are associated with articles with a small sample size and an older year of publication, single-center studies, and those sponsored by industry. On the other hand, the outcomes with a score

TABLE 2 Frequency and classification of primary outcomes in included studies

Data	Frequency	Percentage (IC 95%)
RCT with primary outcomes (n = 68)	46	67.6 (55.8–77.5)
Number of primary outcomes per RCT (n = 46)		
One outcome	28	60.9 (46.5–73.6)
Two outcomes	12	26.1 (15.6–40.3)
Three outcomes	04	8.7 (3.4–20.3)
Four outcomes	01	2.2 (0.4–11.3)
Five outcomes	01	2.2 (0.4–11.3)
Classification of primary outcome (n = 71)		
Non-healing outcomes	56	78.8 (68.0–86.8)
Healing outcomes	15	21.1 (13.2–32.0)

TABLE 3 Score of the included studies

Completeness score of outcomes	Frequency (n = 265)	Percentage (IC 95%)
0	0	0.0 (0.0–1.4)
1	0	0.0 (0.0–1.4)
2	2	0.7 (0.2–2.7)
3	26	9.8 (6.8–14.0)
4	70	26.4 (21.5–32.0)
5	167	63.0 (57.1–68.6)

TABLE 4 Frequency of each of the five elements of completeness of outcome, in the included studies

Data	Frequency (n = 265)	Percentage (IC 95%)
Domain or title of the outcome	265	100.0 (98.6–100.0)
Specific technique / instrument used to make the measurement	225	84.9 (80.1–88.7)
Metric or specific format of data to be used for analysis	213	80.4 (75.2–84.7)
Aggregation method (how the data of each group will be summarised)	193	72.8 (67.2–77.8)
Description of the time for evaluation	265	100.0 (98.6–100.0)

TABLE 5 Classification of the titles of the outcomes of included studies

Outcome domain	Frequency (n = 265)	Percentage (IC 95%)
Reduction of wound area	97	36.6 (31.0–42.6)
Change in wound condition	56	21.1 (16.6–26.4)
Healing	35	13.2 (9.6–17.8)
Biomarkers	14	5.3 (3.1–8.7)
Performance of dressing	13	4.9 (2.9–8.2)
Quality of life	11	4.1 (2.3–7.3)
Healing time	9	3.4 (1.8–6.3)
Signals and symptoms	6	2.3 (1.0–4.8)
Signs of infection	5	1.9 (0.8–4.3)
Reduction of bacterial load	1	0.4 (0.1–2.1)
Others	18	6.8 (4.3–10.5)

TABLE 6 Grouping of techniques / instrument per domain to reduction of wound area, change in wound conditions and healing

Reduction of wound area (n = 97)	N^0 outcomes (%)
Described technique	89 (91.7)
Digital planimetry	35 (39.3)
Ruler (width x length)	15 (16.8)
Planimetry with acetate	14 (15.7)
Instrument / scale	11 (12.3)
Other techniques	9 (10.1)
Technique not described	8 (9.0)
Change in wound condition (n = 56)	
Described technique	48 (85.7)
Instrument / scale	32 (66.7)
Planimetry	6 (12.5)
Clinical evaluation	5 (10.4)
Biomarkers evaluation	1 (2.1)
Weight of dressing	2 (4.2)
Outros	2 (4.2)
Technique not described	8 (14.3)
Healing (n = 35)	
Described technique	24 (67.7)
Planimetry	13 (33.3)
Instrument / scale	7 (23.8)
Clinical evaluation	3 (14.3)
Questionnaire	1 (4.8)
Technique not described	11 (32.3)

TABLE 7 Classification of the quality of the results of the included studies

Results of reported outcomes	Frequency N = 265	Percentage (IC 95%)
Complete Odds ratio or relative risk and precision measurement (confidence interval)	62	23.4 (18.7–28.8)
Incomplete	203	76.6 (71.1–81.3)
Only value *p*	153	75.4 (69.0–80.8)
Only qualitative data	49	24.1 (18.8–30.5)
p value and qualitative data	01	0.5 (0.1–2.7)
Not reported	17	6.4 (4.1–10.0)

of 5 are associated with studies with more recent publications and not sponsored by industry, journals with high impact factors, and multicenter studies.

6 | DISCUSSION

Our study showed that there is a heterogeneity of outcomes in RCTs of PIs of therapeutic intervention in adults, many of which are not completely reported. There were also several studies without primary outcome reports, and most of the outcomes were surrogates/intermediates and with inconsistency in the techniques used to measure them, regarding validation or related reference. The outcome results were, most of them, incomplete, making it difficult to analyse the intervention effect in the proposed outcomes.

Thus, evidence-based clinical decision-making for optimal PI patient care may be compromised by RCTs with several problems related to outcomes and their results, such as in the cases where there are no clearly defined primary outcomes, poorly described outcomes or outcomes described in an incomplete way, outcome measurement performed in variable time and through not validated or not described techniques or tools, and outcome results presented in an incomplete way and without assessment of the effect size. Therefore, assessing the quality of the outcome and its results may contribute to the reporting of future RCTs being more judicious in their description and assessment, thus decreasing inconsistencies and bias. An accurate presentation of outcomes and their results in an RCT is the cornerstone of data dissemination and its implementation in clinical practice.[18]

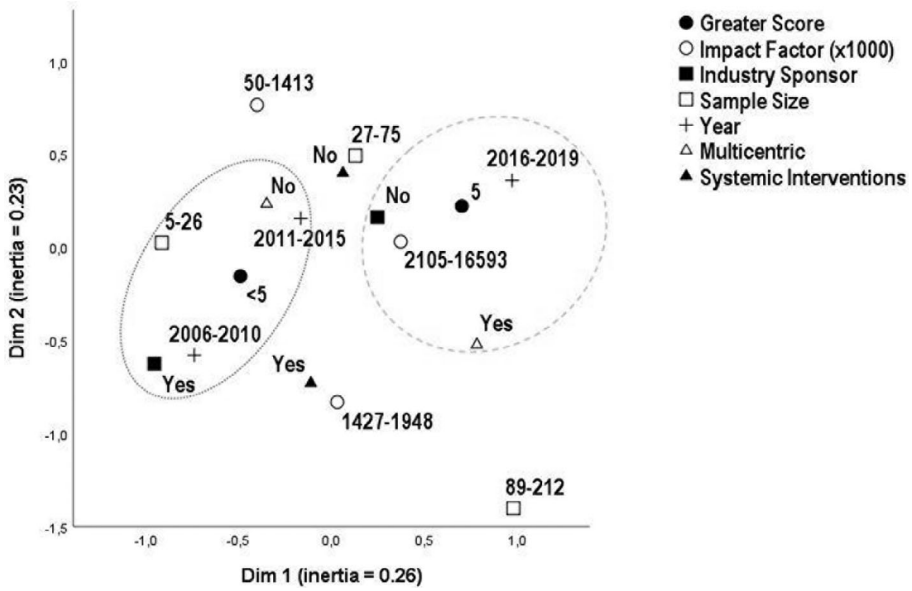

FIGURE 2 Perceptual map of multiple correspondence analysis between the highest outcome scores and study characteristics: the impact of the journal (x1000), sample size, whether the study was multicenter, systemic intervention, the year of publication, and whether it was sponsored by the industry

Effectiveness and efficacy outcomes in the RCTs are an event or measure that is performed in the study participants after a time that an intervention was instituted to assess whether an intervention reached the expected therapeutic effects in the studied population. The outcome choice must consider relevant perspectives for patients and society. The use of inappropriate, poorly defined, or unvalidated outcomes may lead to wasted resources or misleading information that over- or underestimates the potential benefits of an intervention.[19]

The outcome should be constantly clearly defined and declared in a way that allows the objectives to be investigated using objective and quantitative assessment. The study results are more convincing when they are applied to only a small number of objectives and outcomes. The study objectives must include an accurate statement of the expected degree of benefit of the intervention and its duration, clear statement about the study period (especially as to how quickly the benefits can start), and definition of the patients to whom the benefit is searched.[15]

In the present study, approximately 32% of the studies did not declare what was the primary outcome, and in those that declared, 39% presented more than one primary outcome, and 78.8% were surrogates/intermediates. Saldanha et al[10] found that the primary outcomes were better specified than the secondary outcomes. According to the CONSORT statement, the primary outcome must be prespecified in the study method, and it is considered of most importance to the relevant parts of interest, such as patients, policy makers, clinicians, and funders. It is also from the primary outcome that the study sample size is defined. Some RCTs may have more than one primary outcome. However, having several primary outcomes addresses the problems of interpretation associated with the multiplicity of analyses, and it is not recommended. The main outcomes should be explicitly indicated as in the RCT report. Other outcomes of interest were secondary (additional outcomes).[20]

In the wound area, the obvious outcome in evaluating the efficacy or effectiveness of wound interventions is complete healing. In our study, approximately 32% of the healing outcomes were not described as they were evaluated, and therefore, significant deviations in the results were observed. There are rational definitions for wound healing outcomes, and these should be used in RCTs. The Food and Drug Administration (FDA) defines complete wound closure or healing as "cutaneous re-epithelialization without drainage or need for dressing, confirmed in two consecutive visits of the study with two weeks of interval, and the time must be specified when analyzed."[21]

Only 21.1% of the primary outcomes in RCTs in this study were healing outcome or healing time. However, these may not be the only adequate outcomes in studies of chronic wound healing. Other outcomes, including intermediates and surrogates such as infection rate, bacterial contamination, wound pain, resource utilisation, and cost, also need to be considered. A purist approach to RCT design stipulates that a single intervention should be investigated until the primary outcome is achieved. In the treatment of wounds, this can be difficult because the presentation of the wound bed and associated symptoms may indicate that the intervention is no longer the appropriate method of treatment although the primary outcome (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.[15]

Intermediate outcomes usually occur during treatment and are intended to predict a true and significant clinical outcome. This point could be anywhere along the healing process, whether at the initial, intermediate, or late stages, depending on the criteria (e.g.,>75% of the granulation tissue) used. As they occur earlier than the wound healing outcome or healing time, they can be used to make clinical trials more efficient (e.g., less follow-up time and smaller sample size). Unlike a single clinical outcome, there may be several intermediate outcomes, which provide opportunities for conducting trials and developing therapies to achieve a certain aspect (stage) of the healing process. In addition to allowing a clinician to evaluate the patient's response to therapy during treatment, valid intermediate outcomes help to accelerate the development of new effective therapies and minimise patient exposure to ineffective ones (at the developmental stages).[22] Thus, the intermediate outcome represents a clinical state that is progressing toward the expected outcome; a surrogate outcome, instead, is a substitute for a clinically significant outcome (which is a real benefit to the patient). Although the FDA guidelines have consistently established that only a healed wound is a real benefit to a patient,[21] due to the complexities of chronic wound healing, surrogate and intermediate outcomes can be considered as prognostic indicators of improvement in such wounds.

It is acceptable that complete closure of the wound may often not be an adequate outcome in chronic wounds. Alternatively, surrogate or intermediate outcomes must be used considering the wound characteristics, such as duration, status, and progress, and patient's need. The importance of managing exudate, controlling infection, relieving pain, and minimising odour in a nonhealing wound should be established and accepted as legitimate outcome measures. However, it is extremely important that these outcomes are well described and evaluated, when possible, by validated techniques and instruments. It should be recognised that the goals related to care among elderly patients with chronic wounds are not static. Prioritisation of goals will gradually change as the patient's wound becomes recalcitrant and healing becomes less realistic.

Wound area reduction was the most frequent outcome in RCTs in the present study (36.6%). Currently, there is debate about the utility of wound area reduction as a primary outcome since the "clinical benefit of incremental changes in wound size has not been established." However, some studies have shown that reducing the wound area within a specified period may indicate the potential for complete healing in the future. The discussion focuses on the definition of the minimum area of reduction that can be considered clinically relevant. The length of the assessment period is also crucial.[15] The rate of reduction chosen should consider the margin of error for the chosen method of measurement as well as the baseline ulcer size. A concern is that chronic wound healing processes have been proven to be nonlinear. The assumption that wounds can heal in a linear way is predominantly based on studies of acute wounds. Baseline wound size and wound size may not be reliable indicators for predicting chronic wound closure because the factors that influence or delay healing are diverse and unpredictable. Although volume reduction is probably the ideal outcome for cavity wounds, there are great methodological difficulties in the evaluation of this parameter, in such a way that few studies have adopted this approach.[15]

The use of wound healing time as an outcome measure has received increasing interest due to its importance from a clinical point of view and regard to the use of resources and economic costs. In our study, only 3.4% of the outcomes were for this domain. The difficulty in using this approach is that the healing time recorded is dictated by the study protocol and will be an approximation based on the evaluation times dictated by the study design. For most studies reporting wound healing time, the major concern is that it is reported only in a minority of patients who healed within a specific observation period, usually 4 to 12 weeks. To date, the accepted time frame for studies of this type is 1 year. Ideally, all patients should be followed until healing is achieved. However, this is often not feasible due to patient characteristics, comorbidity, type of ulcer, and budget available for study. For healing/healing time, we found 365 days as the maximum evaluation time and 7 days as the minimum time. Studies of PIs are particularly challenging as they affect, in large part, the elderly populations with severe wounds, extensive comorbidities, and long healing time. Factors such as pressure relief, faecal and urinary incontinence care, and nutrition are essential. There is little information available on the natural outcome of such wounds and specific factors related to outcomes in PI, especially in a geriatric setting.[15]

It is possible to observe that the outcomes with a score of less than 5 are associated with articles with a small sample size and an older year of publication, single-center studies, and those sponsored by industry. On the other hand, the outcomes with a score of 5 are associated with more recent publications, studies not sponsored by industry, journals with high impact factors, and multicenter studies.

We found that outcomes with lower scores were associated with articles with an earlier year of publication and a small sample size, single-center studies, and those sponsored by industry. Some published papers with these

characteristics probably did not adhere to the guidelines, such as the CONSORT, which were designed to improve the quality and clarity of the studies. According to a systematic review to evaluate adherence to study reporting guidelines[23], articles with an older year of publication and journals with a smaller sample size are two factors associated with the poor quality of their reports. Regarding studies sponsored by industry, our result is the opposite of that found in this review since they found that studies with an industrial sponsor were associated with better reporting quality. Therefore, the influence of industry-sponsored studies on the quality of outcomes is still uncertain, requiring further studies to evaluate this relationship.

Our findings show that most RCTs did not present their results adequately, leading to errors in interpreting the impact of the intervention on the study population. Most of the reports of the outcomes were incomplete, presenting only the *P*-value (76.4%), denoting that there is a gap in the presentation of these results, preventing a full understanding of the effect of the intervention. According to the CONSORT Statement 2010,[20] for each primary and secondary outcome, the results for each group should be presented, and the effect size and its accuracy are calculated with a 95% confidence interval. For binary outcomes, the presentation of both the absolute effect size (risk difference) and relative effect (relative risk or odds ratio) is recommended because neither the absolute measure nor the relative measure alone provides a complete picture of the effect and implications.[24]

The present study has limitations. First, we analysed only RCTs published in English and Portuguese. Second, all the problems related to the outcomes were not evaluated but those related to their specification in the method and quality of their results. And finally, we did not evaluate safety outcomes. The strength of our study is that it is the first systematic methodological survey to assess how the outcomes of the efficacy or effectiveness of therapeutic interventions are described in RCTs on PI. Our results showed that the descriptions of the outcomes and their results in RCTs in PI are suboptimal and require improvements in future studies.

The PI RCTs used many outcomes, mostly surrogates or intermediates, and some of them were incompletely described, provided no definition of the primary outcome, and were assessed using unvalidated techniques or instruments. Our findings reinforce the need for future designs of RCTs in this area to pay special attention to which outcomes will be analysed, their complete details, and the form of their evaluation so that there is an improvement in the quality of scientific evidence in the PI area.

Therefore, we recommend that PI RCTs should preferably have only one primary outcome and this should be a "healing time" in a maximum assessment of 1 year and a minimum of 12 weeks. To prevent the establishment of a primary wound healing outcome, it has the aforementioned period of evaluation and an intermediate outcome of change in wound condition (e.g., increased granulation tissue and increased epithelialization) with evaluations using validated instruments. Surrogate outcomes may not predict healing, and wound area reduction does not necessarily lead to a linear progression to closure; therefore, these are not recommended and do not act as realistic outcomes for RCTs in PIs.

In addition to these recommendations, it is of paramount importance that all primary and secondary outcomes of the study be fully described, that is, according to the five elements already mentioned (domain, specific technique or instrument used to make the measurement, specific format of the data of the outcomes of each participant that will be used for analysis, aggregation method or how the data of each group will be summarised, and time points that will be used for analysis).

Thus, larger investments in this area should be stimulated, and research should be directed toward the use of the primary healing outcomes and for the evaluation of the results of PI treatment interventions to clarify the direction of clinical practice.

ACKNOWLEDGEMENTS

we would like to thank Editage (www.editage.com) for English language editing. This research did not receive any specific grants from any funding agency in the public, commercial, or nonprofit sectors.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Jéssica Steffany Miranda and Luciana P F Abbade were involved in the search strategy, design, testing of the data extraction form, and writing of the initial draft. Lehana Thabane was responsible for the conception, design of the review, and critical review of the final draft. Arthur Pollo Deonizio and Jéssica Steffany Miranda were involved in the data extraction form. Joelcio Francisco Abbade and HAM verified the analytical methods. Lawrence Mbuagbaw and Lehana Thabane contributed to improvements in the manuscript and critically revised the final draft. All authors contributed to and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Miranda JS, Deonizio AP, Abbade JF, et al. Quality of reporting of outcomes in trials of therapeutic interventions for pressure injuries in adults: a systematic methodological survey. *Int Wound J*. 2021;18:147–157. https://doi.org/10.1111/iwj.13506