Outcomes for Pressure Ulcer Trials (OUTPUTs) project: review and classification of outcomes reported in pressure ulcer prevention research

Running head: OUTPUTs project: review on outcomes in pressure ulcer prevention research

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What's already known about this topic?

- Systematic reviews on pressure ulcer prevention described difficulties to summarise study results due to heterogeneity and inconsistency of reported outcomes.
- As the creation of systematic reviews or meta-analyses is thereby impeded, the quality of evidence-based knowledge is unnecessarily limited.
- To improve the quality and the comparability between trial results, the concept of core outcome sets has been introduced.

What does this study add?

- Outcomes as well as concepts that represent potential outcomes for future pressure ulcer prevention trials were identified.
- All extracted outcomes and concepts were inductively compiled to 68 outcome domains and additionally sorted into a pre-existing outcome classification system.
- “Pressure ulcer occurrence – whole body”, “costs”, ”pressure ulcer occurrence - defined body sites” and “acceptability of intervention and comfort” were most frequently reported.
Abstract

Background
In order to overcome inconsistencies in the reporting of outcomes in clinical trials, core outcome sets (COS) have been developed in many clinical areas and the awareness of this concept is growing steadily. The Outcomes for Pressure Ulcer Trials (OUTPUTs) project aims to improve the quality of evidence on pressure ulcer prevention trials by developing a COS.

Objectives
As an initial step in the COS process we aimed to identify and classify outcomes as well as concepts that represent potential outcomes for future trials that have been reported in pressure ulcer prevention research.

Methods
A review was conducted in twelve major databases covering the literature indexed until 2016. Outcomes and relevant concepts reported in primary studies and/or reviews on pressure ulcer prevention in adult patients were extracted as presented in the articles, and afterwards inductively grouped into outcome domains. The domains were then categorized according to the outcome domain taxonomy recently proposed by the Core Outcome Measures in Effectiveness Trials Group.

Results
332 studies were included and 68 outcome domains were identified, covering multiple aspects of pressure ulcer prevention. Pressure ulcer occurrence was reported in 71% of all included studies representing the most frequent outcome, followed by costs (22% of all studies), and acceptability of intervention and comfort (18% of all studies).
Conclusion

A plethora of different outcomes is applied in pressure ulcer prevention research and substantial variations in definitions and reporting of similar outcomes were observed. A COS for pressure ulcer prevention trials is needed to overcome the non-comparability of outcomes.

Study registration

The OUTPUTs project is registered in the COMET database (http://www.comet-initiative.org/studies/details/283) and is part of the Cochrane Skin-Core Outcome Set Initiative (http://cs-cousin.org/outputs/).

Key words: Outcome, Core Outcome Set, Core Domain Set, Domain longlist, Review
Introduction

A pressure ulcer is defined as “localized damage to the skin and/or underlying tissue, as a result of pressure or pressure in combination with shear”. Patients whose ability to move or to position themselves is impaired are especially vulnerable to the development of pressure ulcers due to prolonged tissue exposure to pressure. Pressure ulcer prevention comprises different strategies (see Figure 1).

Figure 1 Conceptual scheme of pressure ulcer prevention

Interventions aim to reduce the magnitude and duration of mechanical load such as pressure or shear forces, or intend to enhance tissue tolerance, e.g. by applying skin care products.\(^1,2\)

Important efforts to establish and improve pressure ulcer prevention have been made in the past. Overall, the availability and quality of evidence to make recommendations for pressure ulcer prevention is weak.\(^3\) Thus, further research is necessary.\(^4-6\)

There are many clinical trials testing pressure ulcer prevention strategies. Unfortunately, there is also huge heterogeneity and inconsistency of outcomes used in pressure ulcer prevention trials. Outcomes are dependent variables measured during interventional studies and enabling researchers to make statements about the effects, effectiveness and/or safety of interventions.\(^7\)

The selection of patient-relevant and valid outcomes in clinical trials is crucial for the quality of study results.\(^8,9\) In order to generate meaningful evidence, it is also important that study results of the same clinical area are comparable, as otherwise they cannot be summarized and pooled in systematic reviews or meta-analyses.\(^10\) The incomparability of outcomes restricts evidence-based knowledge and aggravates decision making for clinicians in practice. To improve this situation, the concept of ‘core outcome sets’ (COS) has been introduced and is promoted in many clinical areas now. It represents an agreed standardised set of outcomes that should be reported as a minimum in all clinical trials of a specific area.\(^11,12\) Developing a COS is a multi-step consensus process and defines what to measure (Core Outcome Domain Set) and the measurement methods to quantify the determined core outcomes (Core Outcome Measurement Set). To date, no COS for pressure ulcer prevention trials exists. Thus, the ‘Outcomes for Pressure Ulcer Trials project’ (OUTPUTs project) has set the objective to develop a COS for this field following latest methodological standards and recommendations.\(^13-15\) The aim is to develop a COS for the
evaluation of the clinical efficacy, effectiveness and safety of pressure ulcer prevention strategies. According to the “Harmonizing Outcome Measures for Eczema (HOME) roadmap” a suggested starting point for developing a COS is a list of all outcome domains (‘long list’). Within this review outcomes and outcome domains are regarded as synonyms because both are intended to measure the “what” of outcomes. However, differences exist of how broad or abstract the outcome domains are defined. The aim of this research was to compile a list of outcome domains for clinical trials as comprehensive as possible. We sought to identify and classify outcomes as well as concepts that represent potential outcomes for future trials that have been used and/or described in previous pressure ulcer prevention research literature.

Material and methods

A protocol describing the steps of the OUTPUTs project to develop a COS has been published. As one first step of this project, a scoping review was conducted to identify as many potential outcomes for pressure ulcer prevention trials as possible, including patient reported outcomes (PROs), which are defined as outcomes that are directly reported by patients. Compared to a systematic review, a scoping review has less depth, but is favourable to get an overview of a broad topic and can cover a broader conceptual range. Unlike a systematic review this review did not aim to assess the ‘weight’ of evidence or appraise the methodological quality of studies, but aimed to provide a comprehensive overview of outcome domains.

Search strategy

Systematic searches were conducted between February and August 2016 in following electronic databases: Cochrane Wounds Group/Cochrane Skin Group Cochrane Wounds Group Specialised Register, Cochrane Central Register of Controlled Trials, Ovid MEDLINE, Ovid EMBASE, EBSCO CINAHL, PsychINFO, British Nursing Index, Allied and Complimentary Medicine Database, Web of Knowledge, Clinical trials.gov and the WHO International Clinical Trials Registry Platform Search Portal. Database-specific search strategies were used covering the concept of “pressure ulcer” (see example in Appendix 1). The search strategies comprised controlled terms and free-text words retrieved from existing systematic reviews on pressure ulcer prevention efficacy. Electronic searches for evidence on PROs regarding pressure ulcer prevention based for most
An update of the searches was not planned because it can be assumed that outcome saturation is reached using our comprehensive search strategy.

Eligibility Criteria

The COMET Handbook recommends that the scope of a review “should be carefully considered in the context of the COS to ensure that outcomes are included from all relevant studies without unnecessary data collection”.\textsuperscript{11} It emphasizes, as well as the Cochrane Skin-Core Outcome Set Initiative, that not only clinical trials, but also other study types like qualitative work should be considered.\textsuperscript{11,15} Therefore, even though our future COS should be applicable only for clinical trials on pressure ulcer prevention also other study types were eligible for inclusion as they could contribute additional outcomes. In this review, controlled trials and systematic reviews investigating the efficacy, effectiveness and/or safety of pressure ulcer prevention interventions, full health economic evaluations and any kind of primary studies and systematic reviews exploring PROs related to pressure ulcers or pressure ulcer prevention, were eligible. If a publication, e.g. a position paper, appeared to the reviewer as relevant for the identification of pressure ulcer prevention outcomes, this criteria took precedence over the exclusion criteria regarding the study design and it was included as well. Due to the objective of this review the eligibility assessment process was therefore carried out in an inclusive rather than exclusive way. For feasibility reasons, papers had to be published in English language. No restrictions were set in terms of health care settings or publication date, except for the primary studies on PROs, which were only taken into account when they were published after 2008, as a systematic review by Gorecki et al. (2009) on PROs related to pressure ulcer and other chronic wounds already existed.\textsuperscript{31} Studies with a target population aged <18 years and which included healthy volunteers only, were excluded. A detailed list of the in- and exclusion criteria is shown in Appendix 2.

Study selection

All identified publications were imported to the Covidence platform,\textsuperscript{32} which was used for the study selection procedures. After removal of duplicates, the references were assessed for eligibility based on title and abstract screening, followed by a full-text screening. The evaluation
was performed independently by pairs of two reviewers of the project team. Discrepancies were discussed within the project team in order to do a final decision.

Data charting and synthesis

Data on key study characteristics (author, year, country, study type, type of intervention, healthcare setting and target population) and outcomes as well as concepts that present potential outcomes for clinical trials were extracted into standardized data files by means of IBM SPSS 23. The data extraction was performed by two reviewers independently and cross-checked by a third reviewer. Cases of disagreement were solved within the data extractors through discussion. The concepts of outcomes were extracted as presented in the studies. Based on an inductive approach, the identified potential outcomes of the literature were compiled to overarching outcome domains by two project members in cooperation and reviewed by the whole project team. Identified outcome domains were then assigned to broader outcome domains and core areas according to the taxonomy of Dodd et al. (2018).33 This newly developed taxonomy of Dodd et al. comprises 38 overall domains, allocated to the five core areas “Death”, “Physiological/clinical”, “Life impact”, “Resource use” and “Adverse Events”. Health Related Quality of Life (HRQL) measurement tools, which comprised several questions and therefore covered multiple outcome domains were classified within each of the separate domains, as recommended by COMET and Dodd et alia.33,34 Outcomes were only allocated to “global quality of life”, when patients were generally asked to assess their quality of life. Specifically reported Adverse events were classified within the suitable outcome domain and marked as adverse event.33,34

Results

Study selection

Searches identified 4498 references. After removal of duplicates and title/abstract screening, 668 full-text publications were evaluated for eligibility. Finally, 357 publications were included for data extraction (Figure 2).

Figure 2 Flowchart of the screening and eligibility assessment process

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Included publications

The included publications were composed of 51 reviews and 281 primary studies. Twenty five publications were identified as additional articles of a study already included. Most of the included studies were RCTs or CTs (n = 190). The other primary studies were identified as qualitative studies (n = 24), full health economic evaluations (n = 21) or were allocated to the category “other” (n = 46). The category “other” comprised among others pre- and post-implementation studies, a series of single case studies, a quasi-experimental study with interrupted time-series design and case-control studies. These studies were included as the reviewers assessed these publications as beneficial in the identification of pressure ulcer prevention outcomes, which took precedence over the study design.

Identified outcomes

Based on all identified outcomes of the included studies, 68 outcome domains were inductively created (Table 1). A detailed description of the extracted terms per outcome is shown in the Appendix (Appendix 3). Most of the identified outcomes belonged to the outcome domain “skin and subcutaneous tissue outcomes” according to Dodd et alia.\textsuperscript{33} To this broad outcome domain of Dodd et al., we have allocated 21 outcome domains such as “tissue oxygenation”, “skin temperature” or “pressure ulcer occurrence”. Pressure ulcer occurrence referring to the whole body (nr. 18) was reported in 168 studies (95 clinical trials, 36 other primary studies and 37 reviews) and pressure ulcer occurrence referring to distinct body sites (nr. 19) in 64 studies (51 clinical trials, 7 other primary studies, 6 reviews). Therefore, pressure ulcer occurrence was the most frequently captured outcome overall. There was a great variety in terminology and reporting of pressure ulcer (see Appendix 3, nr.18). In order to report the frequency of pressure ulcer occurrence the included references stated among others the incidence or the prevalence of pressure ulcers, hospital-acquired pressure ulcer prevalence, the raw numbers of occurred pressure ulcers, or the time until occurrence. There were also differences of the reported categories (e.g. including/excluding category 1, only category 3 and above). Some publications assessed the whole body, whereas others defined specific body areas for the assessment of pressure ulcer occurrence. Examples of the verbatim text describing the body area, which were
considered for evaluation are: “sacrum, hips and heels”, “sacrum, buttocks and heels”, “trunk and heels”, “trochanter” (see Appendix 3, nr 19). The second most commonly reported outcome domain was “costs” including outcomes which were associated with a prevention intervention in any manner, like cost savings per year, hospital costs or direct staff costs (see Appendix 3, nr. 64). Cost outcomes were reported in 73 studies. “Acceptability of intervention and comfort” was another frequent outcome domain (reported in 59 studies, nr. 59). This domain represents outcomes which were reported by patients. Other examples of listed PROs are “pain associated with pressure ulcer” (nr. 35), “pain associated with intervention” (nr. 36), “emotional well-being” (nr. 53), “patient satisfaction with intervention” (nr. 58) and “global quality of life” (nr. 56). In order to evaluate the success of a pressure ulcer prevention intervention, trials also assessed outcomes which were considered to correlate with the development of pressure ulcer occurrence, like the “interface pressure” (nr. 22), “blood perfusion” (nr. 23), “skin function” (nr. 31) or “tissue oxygenation” (nr. 24). Domains like “nutritional intake” (nr. 15) or “nutritional status” (nr. 14) are examples of intervention specific domains, which are only relevant for trials investigating nutritional supplementation.

Types of preventive interventions

In Table 2 the most frequent types of preventive interventions used in the included studies are shown. The effects of supports surfaces for the bed were reported most frequently (n = 93), followed by trials which evaluated the implementation of any kind of preventive guidelines or programs, like the implementation of educational programs or bundle of care interventions (n = 47). Other, also common interventions were the application of preventive dressings and repositioning, that were reported in more than 20 studies.

Discussion

As described in previous systematic reviews⁴,²⁶,²⁷, the reporting of pressure ulcer occurrence was heterogeneous. There was not only a difference in how the occurrence of pressure ulcers was reported, but also regarding the body sites. Even when similar body areas were evaluated for the effectiveness of pressure ulcer prevention, a great variation of the definitions exists (e.g. sacrum, buttocks, trochanter, trunk, pelvis). The use of the same terminology, classification
systems and method to calculate pressure ulcer occurrence is important to enhance the comparison of study results.\textsuperscript{36} The harmonization of capturing and reporting the identified core outcome domains will be a major task in future project steps, when it comes to developing the measurement methods. Besides the occurrence of pressure ulcers, many other outcomes showed huge variation as well. The indirect measures “interface pressure” for example, included, among others, the outcomes “maximum interface pressure”, “mean interface pressure”, “the average of highest 4 pressures”. Regarding “blood perfusion” some studies measured the “skin perfusion”, others the “capillary blood flow” or “tissue blood flow”. These examples emphasize again the difficulties that can emerge when trying to pool study results.

Our review results also indicate that there is heterogeneity between outcomes regarded as important in reviews and in primary studies. For example, ‘sleep’ was reported in primary studies, but not in any of the included reviews. On the other hand, some outcomes reported in the reviews were not applied in primary studies. This situation is similar to other fields. For example, a recently published review showed that 68\% of dermatological trial outcomes were not included as outcomes in the corresponding Cochrane Reviews and vice versa, 28\% of outcomes defined by the reviewers were not reported in any supporting trial.\textsuperscript{37} Similar observations have been made in the field of oncology\textsuperscript{38} and preterm birth prevention.\textsuperscript{39} This indicates that trialists and systematic reviewers differ in their opinions regarding relevant outcomes, which has the potential to result in research waste.\textsuperscript{40} Therefore both trialists and systematic reviewers should participate as key stakeholders in the subsequent COS consensus process.

Some of the extracted outcomes seem more appropriate for trials of treatment rather than prevention interventions. For example, the outcomes “pain associated with pressure ulcer” and “pressure ulcer status” may appear unsuitable regarding pressure ulcer prevention, as they are commonly brought into connection with ulcer treatment. However, these outcomes also fit to the concept of tertiary prevention which describes the prevention of deterioration. That is why these outcomes were also extracted when reported in pressure ulcer prevention studies. The possible overlap between prevention and treatment outcomes was observed in other COS initiatives as well.\textsuperscript{41-43} Therefore, one of the next steps is to further define the concept and levels of pressure ulcer prevention to be used in OUTPUTs. Furthermore, many intervention specific
outcomes were identified, such as “weight gain” or “nutritional status”. It must be decided whether it is more useful to develop an intervention specific COS or a generic COS that is applicable for all types of interventions. In the latter case, intervention specific outcomes are to be excluded.

This review included not only clinical trials and reviews, but also other study designs. Especially the inclusion of qualitative studies is considered important, because they are a relevant source in identifying potential outcomes important for patients. Including other evidence sources in addition to published clinical trials increases the review and data extraction workload, but in this review it allowed us to identify the following eight outcome domains that would otherwise have been missed: “appetite”, “patient’s balance”, “injuries reported as adverse event”, “disorientation/confusion reported as adverse event”, “muscle tonus”, “self-consciousness & self-esteem”, “privacy”, “time investment by patient”. Finding an optimal balance between more sensitive or more specific literature searches for long-list creation in COS development is challenging, but we support the statement that looking at published clinical trials only is insufficient.

The results of this review provide the basis for the next steps of the OUTPUTs initiative, whose main objective is to reduce this long list down to a consensus agreed list of essential outcome domains. Although the project group follows latest methodological guidance, there are a number of methodological challenges in this new field, such as how best to involve patients in the development of a COS without overstraining them. Involving patients as participants in an e-Delphi survey might be difficult due to the complex question which needs a deeper understanding of the concept of COS. To ensure meaningful involvement of patients, it is essential to provide assistance and guidance. In addition, it is crucial that all outcome domains are presented with clear definitions, so that all participants understand its meaning and are able to rate its importance. Further, it is also not settled yet, how to address the issue of timing. Variations in time periods over which studies are conducted are challenging regarding the interpretation of trial results. Timing is therefore also a factor that might be considered in sorting out the heterogeneity of trial results. Whatever form this may take, it will probably be necessary to distinguish between timing in terms of indirect outcomes of pressure (e.g. blood
perfusion, tissue oxygenation, interface pressure) and direct outcomes of prevention (pressure ulcer development regarding the whole body/regarding defined body sites/device related).

Limitations

Only papers in English language were included, which may be regarded as a language bias. Although the literature search was conducted in most relevant electronic databases, there might be publications which were not identified. Qualitative studies were included to capture the views of patients and service users. Nevertheless, additional ways are needed to identify possibly missing outcomes, such as direct interviews with patients. The review was completed in 2016. Because data saturation was reached, it is unlikely that new outcomes were introduced in the literature since then.

Conclusions

Pressure ulcer occurrence is the most often reported outcome in pressure ulcer prevention research, but there is also a wide range of other outcomes. So far, there has not been a harmonization regarding the relevance of the single outcomes. OUTPUTs will help to prioritize and standardize the outcome selection in future pressure ulcer prevention trials.

Acknowledgements

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References


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34. COMET Initiative Outcome Classification [Available from: http://www.comet-initiative.org/OutcomeClassification.


Supporting Information

Appendix 1 Example of search strategy

Appendix 2 Eligibility criteria

Appendix 3 Extracted outcomes and corresponding outcome domains

Figure Legends

Figure 1 Conceptual scheme of pressure ulcer prevention

Figure 2 Flowchart of the screening and eligibility assessment process
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Table 2 Types of preventive interventions reported in included studies

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<th>Reported in other primary studies (n)</th>
<th>Reported in reviews (n)</th>
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<td>Support surface – bed</td>
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Indirect preventive interventions
Activities to facilitate the adoption, implementation and sustainability of direct preventive interventions in clinical practice

Direct prevention process in individual patients

Assessment of pressure ulcer risk (including skin assessment) → Patient information and shared decision-making → Preventive interventions

Reducing the magnitude & duration of mechanical load (pressure, shear and friction)
- Repositioning
- Mobility promotion
- Support surfaces
- Off-loading
- Prophylactic dressings
- Friction reducing textiles
- Monitoring medical devices

Enhancing tissue tolerance
- Preventive skin care
- Nutrition (systemic intervention)
- Electrical stimulation
- Modulating heat & moisture

Effect of intervention
Publications identified for screening  
\( n = 4490 \)

Publications screened (title and abstract)  
\( n = 2754 \)

Irrelevant publications removed  
\( n = 2166 \)

Publications excluded  
\( n = 311 \)
- Not evaluating HIV prevention efficacy/interventions: 86
- Duplicate: 75
- Not exploring/evaluating/PRD regarding HIV prevention: 23
- Not a MOET or systematic review fulfilling the entry criteria: 58
- Inadequate study population (healthy volunteers only; study population age of 15 or younger; study endpoint not prevention): 20
- Language: 3
- Dispersed paper; no paper accessible: 12
- Other reason: e.g. article containing insufficient information, no English language: 20

Publications included for data extraction  
\( n = 357 \)

Publications removed  
\( n = 314 \)

Publications screened (full text)  
\( n = 688 \)

Publications excluded  
\( n = 311 \)
- Not evaluating HIV prevention efficacy/interventions: 86
- Duplicate: 75
- Not exploring/evaluating/PRD regarding HIV prevention: 23
- Not a MOET or systematic review fulfilling the entry criteria: 58
- Inadequate study population (healthy volunteers only; study population age of 15 or younger; study endpoint not prevention): 20
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Publications included for data extraction  
\( n = 357 \)