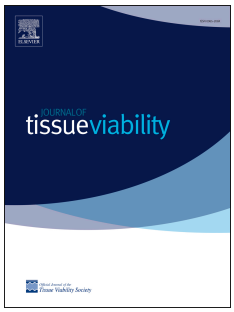

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Study Protocol for the development of a Core Outcome Set (COS) for clinical effectiveness trials of bordered foam dressings in the treatment of complex wounds

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1 Background

Wounds are an ever-growing burden as populations age and chronic diseases, particularly diabetes, spread globally. Complex wounds, in particular, account for 2-4% of total healthcare system costs in Western countries.[1] Moreover, they pose not only a significant financial burden for the healthcare system, they have major social and economic consequences as well; for example, increased hospitalisation rates and lower resources for treating other medical conditions, as well as the decrease of patients' quality of life.[2-4] Complex wounds are acute or chronic injuries that do not progress through the normal wound healing process. Wounds can be classified as complex wounds when they fulfil one or more of the following criteria; (1) extensive loss of the skin, (2) manifestation of infection, (3) compromised viability of tissue and supporting structures, and/or (4) an association with systemic pathologies that impair the normal healing process.[5,6]

The criteria that define complex wounds and their interactions in the individual patient impose a considerable challenge in treating them.[4,7,8] Bordered foam dressings may improve the treatment of complex wounds because of their specific features, such as their anti-leakage potential, their nature of adhesiveness and their stay-in-place properties. Their advantage over other dressings is that they combine several features of different dressings (e.g., exudate management, odour control, comfort for the patient due to the sealing borders that allow showering). Several benefits can be derived from these specific features, such as reduced tissue maceration and a decreased likelihood on dressing-related trauma.[4,7-11] A broad range of bordered foam dressings exist on the market. In general, they consist of at least a primary hydrophilic open-cell foam layer with high a high absorption capacity, a waterproof adhesive backing, and a margin often made of silicone that covers the peri-wound area and allows the dressing to stay in place.[12] Its relevance to clinical practice and healthcare economy is reflected in global market statistics: The global foam dressing market is estimated at USD 1.6 billion in 2020 and is expected to reach USD 2.18 billion by 2023 and USD 2.2 billion by 2027.[13] Despite their increased popularity in the treatment of complex wounds, it is difficult to evaluate their (comparative) effectiveness.[7,8,14] Therefore, outcomes to measure and assess the effect, effectiveness and/or safety of a certain intervention on the health of a given population of patients needing wound care are required.[15,16] In order to systematically compare data across clinical trials and pool results to be used in evidence-based practice, a Core Outcome Set needs to be developed.[16]

Core outcome sets (COS) can be defined as an agreed standardised set of outcomes in a specific and defined area of interest that should be measured and reported in all studies.[17] A COS provides the fundamental outcomes to facilitate synthesis of evidence and improve consistency of outcome reporting. A COS has to potential to facilitate the comparison of data across clinical trials and to pool results to be used in evidence-based health care.[16,18] The development of a COS for clinical effectiveness trials of bordered foam dressings in the treatment of complex wounds has to potential to help researchers, patients, healthcare providers, regulators and policymakers communicate with each other and gives rise to evidence-based healthcare decisions. A COS will further inform society and policymakers on how to

allocate their budgets to maximize benefits to patients and the healthcare system. Furthermore, it will provide important clinically meaningful endpoints for clinical trials in wound care.[19-21]

To date, no COS for clinical effectiveness trials of bordered foam dressings in the treatment of complex wounds exists. Therefore, our study aims to develop a COS, which recommends what outcomes should be measured and reported as a minimum, for clinical effectiveness trials of bordered foam dressings in the treatment of complex wounds. The current limited focus on bordered foam dressings as opposed to general wound dressings allows to account for the clinical indications that are characteristic to this type of dressings, as well as to features such as the anti-leakage potential, the nature of adhesiveness and the stay-in-place features which are strongly affected by the bordered foam design concept.

2 Methods

The project consists of two phases and three steps including different research methods. Phase one comprises the preparation and establishment of the background and process, and phase two comprises the development of a core outcome set. Phase two is divided into three steps: (1) the generation of a list of outcomes, including a literature review and a qualitative study, (2) a Delphi consensus study, and (3) a consensus meeting. Figure 1 provides an overview of the COS development and the phases and steps that will be completed.

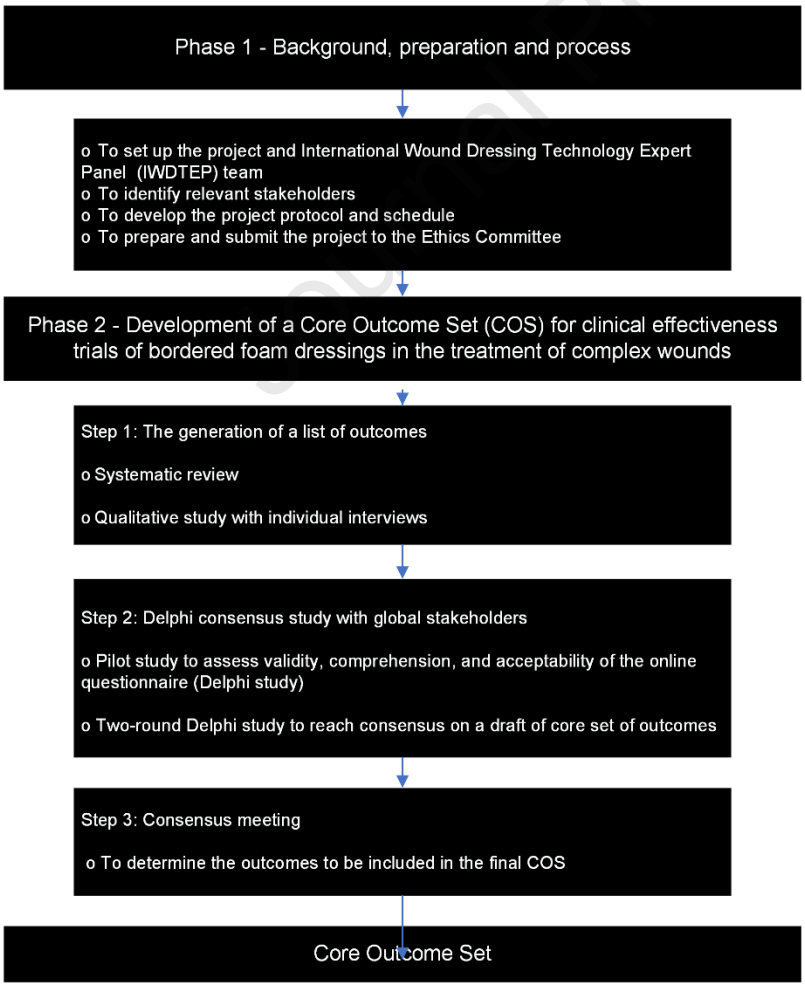

Figure 1 Project phases and steps

2.1 Phase 1: Background, preparation, and process

The project team (PT) consists of three people (C.R., D.B., J.T.) and is responsible for the design and coordination of the project and will make final decisions. The International Wound Dressing Technology Expert Panel (IWDTEP)[22] will provide guidance throughout the development of the COS.

Stakeholder involvement will be ensured throughout the process to: (1) increase the number of ideas, perspectives, and issues considered; (2) ensure credibility, relevance, and significance to diverse groups; (3) increase face validity; (4) identify concerns and barriers that otherwise would not have been considered; (5) ensure transparency; and (6) increase acceptance and dissemination of the project.[23] Stakeholders will be represented in four ways. First, the IWDTEP consists of experts in the field of dermatology, wound care, surgery, podiatry, clinical trials, biomedical engineering, and nursing who will provide guidance throughout the development of the COS. Second, a qualitative study will be conducted with individual interviews with healthcare providers, researchers, and patients to identify relevant key findings. Third, an online Delphi consensus study will be conducted with a global group of stakeholders to reach consensus on a draft set of outcomes. The stakeholders will include healthcare providers, researchers, stakeholders who are both researcher and healthcare provider, and patients. Finally, an online consensus meeting with eight of the Delphi participants will be held to determine the outcomes to be included in the final COS. Inclusion criteria for the stakeholders are included in table 1 and 2.

2.2 Phase 2: for clinical effectiveness trials of bordered foam dressings in the treatment of complex wounds

For the development of the COS three steps will be completed: (1) the generation of a list of outcomes, (2) a Delphi consensus study, and (3) a consensus meeting.

2.2.1 Step 1: Generation of a list of outcomes

A systematic review will be carried out to identify a list of outcomes. The process of this systematic review will be recorded in PROSPERO. To identify articles, the electronic databases MEDLINE (PubMed interface), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE and The Cochrane Library will be searched using a various combinations of key terms including complex wounds, bordered foam dressing, and treatment. Additionally, relevant articles will be provided by members of the IWDTEP. The following inclusion criteria will be applied: (1) study sample includes an adult population, (2) intervention includes the treatment of complex wounds with a bordered foam dressing as a primary dressing, (3) retrieved from the original research, and (4) articles published no earlier than 2000 (or published between 2000 and 2022). There will be no limitations regarding language (IWDTEP members are fluent in Spanish, Flemish, Portuguese and Hebrew in addition to English) or study design. Studies will be excluded if they primarily focus on prevention. The results of the database search will be independently screened by three expert reviewers, and disagreements will be resolved by consensus. In case of discrepancies, a fourth expert will be consulted. Data on the author/s, year of publication, study design, setting, country, study sample, wound type, period of dressing use, outcome domains,

outcomes, instruments, time points, and outcome measurement will be extracted in tables. The OMERACT Filter 2.0 will be used as the conceptual framework to extract outcomes.[23]

Next, a qualitative study will be conducted that will include a minimum of 15 individual semi-structured interviews with healthcare providers (n=5), healthcare researchers (n=5), and patients (n=5) in the wound care area to prioritise outcomes of importance in the treatment of complex wounds with bordered foam dressings. Informed consent will be obtained prior to the interview assuring confidentiality. A thematic analysis, as described by Braun and Clark[24], will be conducted. The participants will be recruited through the network of IWDTEP and the PT. Inclusion criteria for the participants are included in table 1. To minimise bias, all interviews will be conducted by the same researcher (C.R.) experienced in qualitative research. Decisions regarding sampling, data collection, and data analysis will be discussed with the IWDTEP members and recorded in an audit trail. Variation sampling will be assured by interviewing 3 different stakeholder groups to facilitate a broad range of perspectives and to guarantee that a variety of meanings will be represented in the sample.

Table 1 Inclusion criteria interview participants

Stakeholder group	**Inclusion criteria**
Healthcare providers	- Adults (≥18 years) - Minimum 3 years of experience treating patients with complex wounds such as DFU VLU, etc - Used a bordered foam dressing to treat complex wounds at least once - Able to give informed consent - Speak and understand English
Healthcare researchers	- Adults (≥18 years) - Research background in wound care and wound dressings - Took part in/conducted a clinical trial - Able to give informed consent - Speak and understand English
Patients	- Adults (≥18 years) - Able to give informed consent - Able to communicate verbally - Have/had one or more complex wound(s) - Treated with a bordered foam dressing at least once - Speak and understand English

Final, the results from the systematic review and interviews will generate a long list of outcomes to be used in the questionnaire of the Delphi consensus study.

2.2.2 Step 2: Delphi consensus study with global stakeholders

Prior to the Delphi consensus study, the questionnaire will be tested to assess validity, comprehension, and acceptability (pilot test). From the network of the PT, eight individuals will be contacted by email to participate in the pilot test (3 patients, 3 healthcare providers, 2 researchers). Upon confirmation they will receive an e-mail containing the informed consent and the Delphi study. The questionnaire starts with signing the informed consent. They will be asked to complete the questionnaire within 10 days after receiving the email. After the evaluation and possible adjustment of the questionnaire a two-round Delphi

study will be conducted with a global stakeholder group. The global stakeholder group will consist of four groups; (1) healthcare providers, (2) researchers, (3) stakeholders who are both researcher and healthcare provider, and (4) patients (Table 2). All participants will be adults (18 years or older) and able to complete an online survey in English. A minimum of 60 participants will be invited to accomplish a minimum of 50 experts completing the two rounds of the Delphi study, considering a 80% response rate. A 9-point Likert scale will be used which is recommended by the Grading of Recommendation Assessment, Development and Evaluation (GRADE) and was reported to be advantageous in the specific context of wound care clinical research by De Meyer et al. (2019).[16,25]

Table 2 Stakeholder groups Delphi study

Stakeholder group	Group characteristics	Number of participants
Healthcare providers	This group is composed of healthcare professionals and health care providers (facilities) who have experience treating complex wounds with bordered foam dressings	Minimum 15
Healthcare researchers	This group is composed of professionals working in all areas of clinical research relevant to complex wound care, as well as methodologists or statisticians currently working only as researchers	Minimum 20
Patients	This group is composed of individuals who have/had at least one complex wound	Minimum 5
Healthcare researchers and providers	A separate category is created for these professionals who are involved in both healthcare and research, as they may have different perspectives on key outcomes than professionals who are involved in only one of the two activities	Minimum 20

First round

Participants will be emailed to complete the online Delphi survey within two weeks. At the beginning of the survey, participants will receive information about the study and how to complete the questionnaire. The questionnaires will be created and sent in an online format, using Qualtrics.

At the beginning of the survey, participants will be asked to indicate which of the four stakeholder groups they belong to. A unique code will be generated for each participant. The demographic information that will be collected for each stakeholder group is provided in Table 3.

Table 3 Demographic information Delphi study

Stakeholder group	Demographic information
Healthcare providers	Age, gender, country, type of clinical practice, years of experience in clinical practice
Healthcare researchers	Age, gender, country, type of clinical research activity, years of clinical research activity

Patients	Age, gender, country, wound information (type, location, status)
Researchers and healthcare providers	Age, gender, country, function, type of specialty in clinical practice and research, years of experience in clinical practice and research

For an outcome to be included in the COS, a majority is required for the outcome to be considered as critically important and a minority for the outcome to be considered as not important. In the first round, participants will be asked to evaluate whether each potential core outcome is important enough to be included in this COS using a nine-point Likert scale. A score of 7 to 9 means the outcomes are of critical importance, and a score of 4 to 6 means they are important but not critical. Outcomes with a score of 1 to 3 are considered to be of low importance.[16] Participants will have the chance to propose outcomes that not have been included in the first round, but these will not be rated. The suggested outcomes will be considered for inclusion into the second round if, as judged by the PT, the outcome does not reflect nor is similar to an outcome included in the first round. To prevent possible weighting of the results by the order results will be presented alphabetically.

Second round

Only participants who completed the first round of the Delphi study will be invited to the second round (3 weeks after ending round one). All items will be carried forward from the first to the second Delphi rounds, and results will be displayed along with the anonymised feedback from the four stakeholder groups from the first round. The cumulative ratings for each outcome will be provided for each stakeholder group's and individual participants will be asked to rate the outcomes again on the same nine-point Likert scale. Through this process, participants will have the opportunity to provide an updated evaluation regarding each point in light of the collected feedback. ~~They will have the possibility to keep or change their original rating.~~ Additionally, they will have the opportunity to explain their reasons if they change a rating.

Data processing

Outcomes are categorized as 'in', 'out', or 'no consensus'. Consensus on the inclusion of an outcome (consensus in) is defined as ≥ 70% rating the item 7 to 9 and 15% rating it 1 to 3. Consensus on not including an outcome (consensus out) is defined as ≤ 15% rating the item 7 to 9 and ≥ 70% rating it 1 to 3. Any other outcome is defined as 'no consensus'.[16] This will be done for each stakeholder group. Outcomes categorized as "no consensus" in the Delphi survey by all stakeholder groups and the final number of outcomes will be discussed at the consensus meeting (step 3). Descriptive statistics will be used for each round to summarize all responses. The number of participants who completed each round of the survey will be documented and attrition will be assessed. The unique identification number will allow calculation of the dropout rate between rounds.

2.2.3 Step 3: consensus meeting

An online consensus meeting will be held with the PT to determine the outcomes to be included in the final COS. To ensure meaningful input from all stakeholder groups, eight Delphi participants will be invited to this meeting. All participants who signed up for the Delphi survey and completed both rounds will be asked (at the end of round 2) if they would like to participate in an online consensus meeting involving healthcare providers, healthcare researchers, and patients. Because the sample size of Delphi study is large, we will randomly select eight participants to participate in the meeting. Patients, healthcare providers, healthcare researchers, and/or professionals combining both will be recruited in a 2:1:1 ratio.

3 Ethics

Study procedures were reviewed and approved by the Ethical Committee of Ghent University Hospital (BC-11258). Participation will be voluntarily recruited after the provision of written information about the theoretical purposes of the project and how participation will strengthen evidence-based decision making, and improved methodology of complex wound care. Written informed consent will be obtained from all participants. Furthermore, participants will be able to withdraw from the study at any point in time.

4 Dissemination

The COS for clinical effectiveness trials of bordered foam dressings in the treatment of complex wounds will be disseminated via international journal publications. Presentations at relevant conferences will further promote the acceptance and implementation of this COS. The results of the study will be reported using the Core Outcome set-Standards for Reporting (COSTAR).[26] The development of this COS aims to reduce reporting bias and heterogeneity. Additionally, it aims to improve quality of clinical trials in complex wound care, enhance data synthesis, which can stimulate the production of systematic reviews, meta-analyses and evidence-based guidelines.

5 Discussion and conclusions

Although bordered foam dressings have become increasingly popular in the treatment of complex wounds and a substantial number of studies with bordered foam dressings have been performed[4,7,8], there is a noticeable heterogeneity and low data comparability between studies. This inevitably poses a challenge to compare and pool data between studies and thus constrain clinical decision-making. In this project a core outcome set for clinical effectiveness trials of bordered foam dressings in the treatment of complex wounds will be developed. The use of this COS will enhance the comparability of study results worldwide, facilitate data synthesis, decrease possible outcome reporting bias, and stimulate evidence-based practice and decision-making.

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Conflict of interest

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