Meeting Report: Core outcome set for Venous leg ulceration "CoreVen"

Report from CoreVen meeting in Amsterdam 4 May 2017

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INTRODUCTION

The Core outcome set for Venous leg ulceration (CoreVen) project was established in 2016 and is registered on the COMET database (http://www.comet-initiative.org/studies/details/680). The project aims to develop a minimum list of outcomes on the effectiveness of interventions used in venous leg ulceration (VLU) and their associated measurement instruments for reporting in clinical trials. The principal investigators are Prof. Andrea Nelson (University of Leeds, UK) and Dr Georgina Gethin (NUI Galway, Ireland). Sarah Hallas is a PhD student on the project, and Mary Burke is an MSc Student. Supervision of these students is provided by Dr Susan O'Meara (University of Leeds), Prof. Andrea Nelson, and Dr Georgina Gethin. The steering group represents a range of disciplines from multiple European countries: Dr Una Adderley (Lecturer and Researcher in Community Nursing, University of Leeds, UK), Dr Jan Kottner (Scientific Director of Clinical Research for Hair and Skin Science, Department of Dermatology and Allergy, Charite-Universitatsmedizin Berlin, Berlin, Germany), Dr Mary Madden (Lecturer and Researcher in Applied Health Research, University of Leeds, UK), Dr Pauline Meskell (Senior lecturer and researcher at the Nursing and Health Research Department, University of Limerick, Ireland), Prof. Jane Nixon (Deputy Director Institute Clinical Trials Research, University of Leeds, UK), Dr Aonghus O'Loughlin (Consultant Endocrinologist, Bons Secours Hospital, Galway, Ireland and an Alliance for Research and Innovation in Wounds Steering Committee Member), Prof. Sebastian Probst (Professor of Tissue Viability and Wound Care, University of Applied Sciences Western Switzerland, Geneva, Switzerland and Council Member and Editor, EWMA), Mr Wael Tawfick (Vascular Surgeon Saolta University Health Care Group, University Hospital Galway, and the School of Medicine, National University of Ireland Galway, Ireland, and an Alliance for Research and Innovation in Wounds Steering Committee Member), and Dr Thomas Wild (General Surgeon, specialising in wound management and septic surgery, University Medical Center Hamburg-Eppendorf, Germany and Editor-in-Chief, Wound Medicine).

AIMS OF THE MEETING

The aim of the meeting was to introduce the project, its rationale, its purpose, and progress to date as well as to gain feedback on the proposed methodology. The project team members are grateful to the EWMA for facilitating this first open meeting.

ATTENDANCE AT THE MEETING

Notification of the meeting was provided in the conference programme and on the website and was therefore open to all delegates. Key opinion leaders in VLU management who were attending the conference were informed of the meeting, and pre-conference notifications were sent to contacts. A total of 52 people attended the meeting from various backgrounds, which included patient organisation representatives, vascular surgeons,

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physicians, dermatologists, podiatrists, nurses, sociologists, and researchers.

BACKGROUND

A core outcome set (COS) is a minimum set of outcomes that should be measured and reported in all clinical trials for a specific clinical area as agreed on by stakeholders in that field[1]. An outcome is any identifiable consequence of the exposure to a health care intervention, such as a drug or a dressing. An outcome must be appropriate, measurable, and meaningful to stakeholders. COS are gaining recognition as a means of improving the potential for meta-analysis within systematic reviews and ultimately synthesising results of trials that include outcomes of importance to patients and key stakeholders. A COS also reduces the risk of outcome-reporting bias[2]. For example, in the absence of these minimum requirements, the presentation of findings may be limited to outcomes with statistically significant results. The implementation of the COS for VLUs by researchers will increase the utility of trials in this field and facilitate comparison amongst different sources of evidence. Many areas of healthcare have developed a COS, such as the Outcome Measures in Rheumatology (OMERACT;[3]), the management of Otitis Media with Effusion in children with cleft palate (mOMEnt;[4]), and Harmonizing Outcome Measures for Eczema (HOME;[5]). To date, however, no standardised methods of assessment or COS exist for VLU management, and three previous systematic reviews have identified the diversity of outcomes in RCTs in this field[6,7,8].

A recent qualitative study[9] that aimed to identify the most important outcomes for complex wounds from the perspectives of patients, carers, and healthcare professionals found that most patients with VLUs, including intravenous drug users, and healthcare professionals involved in their care regarded the healing of the wound as the primary treatment goal. Patients were greatly troubled by the social consequences of having a complex wound. Thus, the CoreVen project team is working together to develop a minimum list of outcomes for VLU trials.

A VLU is a chronic wound that occurs below the knee and takes more than six weeks to heal[9]. A VLU is a chronic and reoccurring condition[11] that is caused by impaired venous blood flow triggered by venous hypertension. The prevalence of VLUs has been estimated at 0.29 per 1000 individuals in the UK (95% confidence interval 0.25-0.33)[12]. Estimates in the Western world suggest that 1% of the population experience VLUs, and this rate could be as high as 3% in people over the age of 65 years[13]. Venous hypertension results in damage to the valves in the legs, allowing two-way blood flow to occur instead of the normal one-way flow of blood and resulting in swelling of the leg veins, oedema, and leakage of circulatory fluid into the surrounding tissue from the capillaries in the lower legs[14]. VLU can result in pain, malodour, susceptibility to infection, and lack of mobility[15]. These issues, in turn, affects the patient's quality of life through reduction in social activity, limits on their capacity to work, and inability to perform self-care and personal hygiene activities[9,16]. In order to ensure individuals receive good quality care and treatment supported by evidence-based practice, effective treatments must be developed and rigorously tested.

The lack of consistency in clinical trial outcomes means that it is difficult to compare results of clinical trials or to perform meta-analysis[6]. This lack of consistency limits clinical judgments, as trials often have numerous and different outcomes. Often the choice of outcomes is not carefully considered as many of the outcomes are not regarded as important by patients. The use of these outcomes in clinical trials has led to waste in study resources and reporting, and these issues may be avoidable with the use of a COS[2]. Another challenge is that different trials use different measurement instruments at different time points and often with little reference to the validity and reliability of such instruments[6]. These issues underscore the need to develop COS and appropriate measurement instruments for clinical trials for VLU treatment.

While no single method of developing a COS is accepted, a multi-stage process in which all stakeholders, including patients and their carers, contribute to the final outcome set will be the most useful. Firstly, a core domain set is established. This step is followed by development of a consensus minimal set of outcomes that should be reported for any trial. Finally, consensus on how the outcomes are to be measured with respect to validity and reliability of the measurement instruments is achieved amongst the participating stakeholders.

DEVELOPMENT OF COS

IDENTIFICATION OF POTENTIAL OUTCOMES

Scoping review

The results of a scoping review, which included all outcomes identified in the Cochrane Systematic Review database that included RCTs in patients with VLU, were presented at the meeting. A scoping review enabled the concepts in a field of interest to be 'mapped' out[17] and allowed for a rapid underpinning of the key concepts[18]. The adaptation of the Arksey and O'Malley[17] five-stage methodological framework for conducting a scoping review by Levac et al.[19] was used to guide the review. Stage 1 identified the research question, which although broad, still includes the study population. In this case, the study

population included people with VLUs. Stage 2 identified the relevant studies, which were RCTs included in the Cochrane systematic reviews. Stage 3 defines the study selection. Levac et al[19] recommended that the inclusion and exclusion criteria can be applied post hoc as the researcher becomes increasingly familiar with the literature. The charting of the data (Stage 4) was designed according to the framework analysis of Ritchie and Spencer[20]. In this stage, the outcomes were organised into a structured table that facilitated the grouping of the outcomes into domains. The results were collated, summarised, and reported in Stage 5.

In total, 807 (post-deduplication) potential outcomes were extracted. Through consensus amongst the group members, these 807 outcomes were grouped into 11 domains (Table) and presented at the meeting. Domains are broad, descriptive categories that host potential groupings of several, more specific, outcomes.

Table:
Domains identified following the scoping review.

- Healing
- Patient-reported symptoms
- Clinician-reported symptoms
- Carer-reported symptoms
- Life impacts
- Clinical signs
- Clinical measurement
- Performance of the intervention
- Resource use: supplies
- Resource use: clinician time
- Adverse events

CONSENSUS METHODS DISCUSSION

The method to be used to gain consensus from stakeholders was openly discussed at the EWMA meeting. The following topics were introduced, and agreement was achieved.

- Stakeholders will include patients, carers, health professionals, policy makers, researchers, and industry representatives. Two members (Nelson and O'Meara) of the project team are editors for Cochrane Wounds Group (CWG), ensuring the involvement of a broad range of stakeholders. Other steering group members also have expertise in Cochrane Reviews. We are also likely to contact additional people who contribute to the CWG (e.g., review authors and editors) through the proposed networks.

- The Delphi method will be used via an online survey tool (Bristol Online Survey) to gain consensus on the domains. Participants will be asked to rate each domain in terms of importance on a Likert scale of 1 to 9 (1 being not important, and 9 being extremely important). Discussion with the audience suggested that most people were in favour of including two rounds for each step of the consensus process. The rationale behind this is that it is methodologically defensible. That is, with two rounds, we will be able to better identify and understand the complexities of the decision process, in agreement with processes for other COS21.

- An audience member highlighted the fact that an online format has methodological limitations and may be limited in its ability to reach the patient group. This challenge was discussed and acknowledged by the team. Because of funding restraints, however, it will not be possible to send out paper copies of the survey. Paper formats are also much more time consuming. The survey will benefit from the 'snowball' effect, in that the number of people that have the opportunity to participate will be increased via links from wound care organisations and all other known networks with an interest in VLU research; however, individuals will not be contacted by their National Health Service (NHS) UK use or employment. Ethical approval for this step has been sought from the University of Leeds, UK.

- It was suggested that ulcer recurrence should be considered an outcome. The initial response from the team was that ulcer recurrence was not included in this COS initiative, as the focus of the COS was the treatment of open VLUs. Following an in-depth discussion, the group concluded that ulcer recurrence will not be included as a domain or outcome. Unfortunately, the scope of this project cannot cover all aspects of VLU management, especially in light of the fact that the scoping review of open ulceration has revealed that this by itself is a significant endeavour.

- An audience member asked whether there will be representation from the healthcare industry. Following an in-depth discussion after the meeting at EWMA, it was decided that healthcare industry representatives will be part of the stakeholder group.

- Additional issues that will not be addressed within the scope of the project were addressed. The CoreVen project aims to develop the COS only and will not be advising on the conduct and reporting of trials; however, we highlight the need for future research on the conduct and reporting in VLU trials. The following issues were discussed:

- The idea that the COS should include recommendations about duration of follow-up was suggested. This idea was discussed based on the criticisms raised in the systematic review by Hodgson et al.[22], in which a median follow-up of 12 weeks was suggested for trials evaluating treatments for chronic wounds. A later comment reiterated that recommendation for a minimum follow-up time for assessment of both healing and recurrence within that period would be useful. Our group, however, will not be recommending a minimum follow-up time; however, we do emphasise that future research on the minimum follow-up time is needed.

- Members of the audience suggested that trials should report baseline prognostic variables per group. While the COS will not cover such recommendations, the COS, once established, can be implemented alongside tools, such as CONSORT (Consolidated Standards of Reporting Trials, 23), which includes recommendations on the reporting of baseline variables, to address this issue.

- A question was posed regarding whether the COS would provide guidance on the target number of trial participants. The team responded by stating the COS will recommend outcomes on which estimations of statistical power would be based but would not recommend a target number for trial participants directly as this number depends on the individual trial aims.

- Members of the audience questioned how the steering group decided on a 70% level of consensus (as opposed to other values). The team responded that this decision was based on methods used by other COS initiatives, such as OMERACT[24], which developed COS in rheumatology; Kirkham et al.[25], who developed the COS-STAR (Core Outcome Set-STAndards for Reporting) statement; McNair et al.[26], who developed COS in colorectal cancer surgery; and Millar et al.[21], who developed COS in prescribing for older adults in care homes.

- The core outcome(s) may vary according to trial endpoint and the treatment being evaluated. The team responded to this point by stating that the aim of the initiative is to identify core outcomes for all VLU trials and that trialists can certainly add other outcomes. The core outcome may be a secondary outcome within a study and does not necessarily have to be a primary outcome.

- An audience member also said that researchers involved in future studies should be able to justify the reasons that outcomes from the COS were not reported in the trial.

CONCLUSION

The meeting was successful as the audience raised valuable questions and provided helpful comments during the meeting to facilitate the development of the COS. In conclusion, industry stakeholders will be accessed through their identified networks. Researchers will be able to include additional outcomes in their studies, will be able to decide which of the COS are primary and secondary in their trials, and will be able to omit some outcomes as long as they provide justification. As with all initiatives, some issues will not be covered by the scope of the project because the CoreVen project aims to develop the COS only and will not be advising on the conduct and reporting of trials. The team, however, emphasises the need for future research on conduct and reporting in VLU trials. This includes recommendations on the minimum follow-up time, baseline prognostic variables, and number of trial participants. A two round online survey that will soon be launched will seek to gain consensus on the domains listed (see Table). Following this survey which is to gain consensus on the domains, an additional online survey will be completed in two rounds to gain consensus on the specific outcomes that fall within the domains that were voted as important in the previous online survey.

WHAT IS NEXT?

The online survey will be launched in September/October 2017, and the team aims to complete the two rounds of data gathering by December 2017. The findings will be ready for presentation in early 2018. A second meeting will be held in 2018 to discuss the findings and finalise the method for the second Delphi study on the core outcomes. The full protocol will be published and made readily available.

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Nonstandard abbreviations

CONSORT Consolidated Standards of Reporting Trials
CoreVen Core outcome set for Venous leg ulceration
COS Core Outcome Set
COS-STAR Core Outcome Set- STAndards for Reporting
CWG Cochrane Wounds Group
EWMA European Wound Management Association
HOME Harmonizing Outcome Measures for Eczema
mOMEnt management of Otitis Media with Effusion in children with cleft palate
NHS National Health Service
OMERACT Outcome Measures in Rheumatology
RCT Randomised Control Trial
VLU Venous Leg Ulceration

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