## Towards a roadmap for COSEB: the next steps in harmonization of outcomes for epidermolysis bullosa

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Dear Editor, Epidermolysis bullosa (EB) comprises a group of rare, clinically and genetically heterogeneous genodermatoses characterized by epithelial fragility with blistering and wounding following minimal trauma.[1] EB research has advanced considerably in the past decade, leading to a range of novel and repurposed therapies being evaluated in an increasing number of clinical trials.[2] Despite the high disease burden and urgent need of targeted therapeutic approaches, there is still no uniform consensus on which aspects of EB are most relevant and clinically meaningful for assessment in clinical trials.

The Core Outcome Sets for Epidermolysis Bullosa (COSEB) initiative is an international group of stakeholders working together to establish core outcome sets (COSs) for the four major EB types (EB simplex, junctional EB, dystrophic EB and Kindler EB) by identifying the most critical outcome domains ('what' to measure) and corresponding outcome measurement instruments ('how' to measure).[3] Such COSs should be measured and reported consistently across clinical trials to ensure clinically meaningful outcomes and facilitate accurate comparison, pooling and synthesizing of data, and ultimately expedite therapy development.[4] However, the use of a COS does not preclude measuring *more*; *other* outcome domains and outcome measurement instruments can also be included in individual clinical trials to meet specific requirements.

In April 2023, the COSEB initiative was officially launched and presented to the EB community at a kick-off meeting with 104 attendees representing 24 countries and multiple key stakeholder roles.[3] Following on, 60 stakeholders joined the initiative to establish the COSEB Consortium. Consortium members subsequently organized themselves into working groups for EB simplex and dystrophic EB, and an advisory panel. Working groups for junctional and Kindler EB, both being less common,[5] will follow in future steps.

To familiarize the consortium with established COS methodology, a COSEB starting workshop was organized as a hybrid meeting in Amsterdam, the Netherlands on 15 December 2023, by the COSEB Steering Committee and the DEBRAs of Austria, France, Ireland, Spain and the UK. A total of 50 consortium members from Europe, North and South America, Australia and Asia participated in the meeting, consisting of seven patient advocates, 33 EB experts, four methodologists, three industry partners and three regulatory representatives. The workshop commenced with a presentation of the proposed COSEB protocol including the tasks and responsibilities of the involved working groups, advisory panel and Delphi panel. In addition, COS methodologists detailed the Delphi consensus procedure and granularity of outcomes. In this way, the consortium understood the value of a consensus-based standardization of outcomes, and the trade-off in granularity between *specificity* to be meaningful and *generalizability* to be feasible when defining the core outcome domains for clinical trials.

Subsequently, patient representatives emphasized the priority of clinically meaningful and patient-centred outcomes, as well as the importance of patient participation in the consensus process. They also pointed out the need for collaboration among researchers, industry and patient advocacy organizations, like DEBRAs, to secure resources for consensus initiatives such as COSEB. During the workshop, it was further concluded that COS implementation strategies,[6] broad stakeholder engagement and active involvement from the entire EB community all remain critical to the success of COSEB.

Following this, the members of the EB simplex and dystrophic EB working groups got together in two parallel break-out sessions to discuss the proposed COSEB protocol and potential challenges, including understanding the COS methodology, and managing the high workload. Moreover, the working groups initiated the development of a list of activities for the upcoming year to determine the necessary resources. The working groups continued their discussions in the weeks after the workshop, which led to invaluable input to elaborate budget plans and finalize the COSEB roadmap (Figure 1). This roadmap is based on established COS methodology of the Core Outcome Measures in Effectiveness Trials (COMET),[4] Harmonising Outcome Measures for Eczema (HOME)[7] and CHORD COUSIN Collaboration (C$^3$) initiatives.[8] Additionally, it incorporates an advisory panel representing different stakeholder groups as a unique organ in COSEB to further

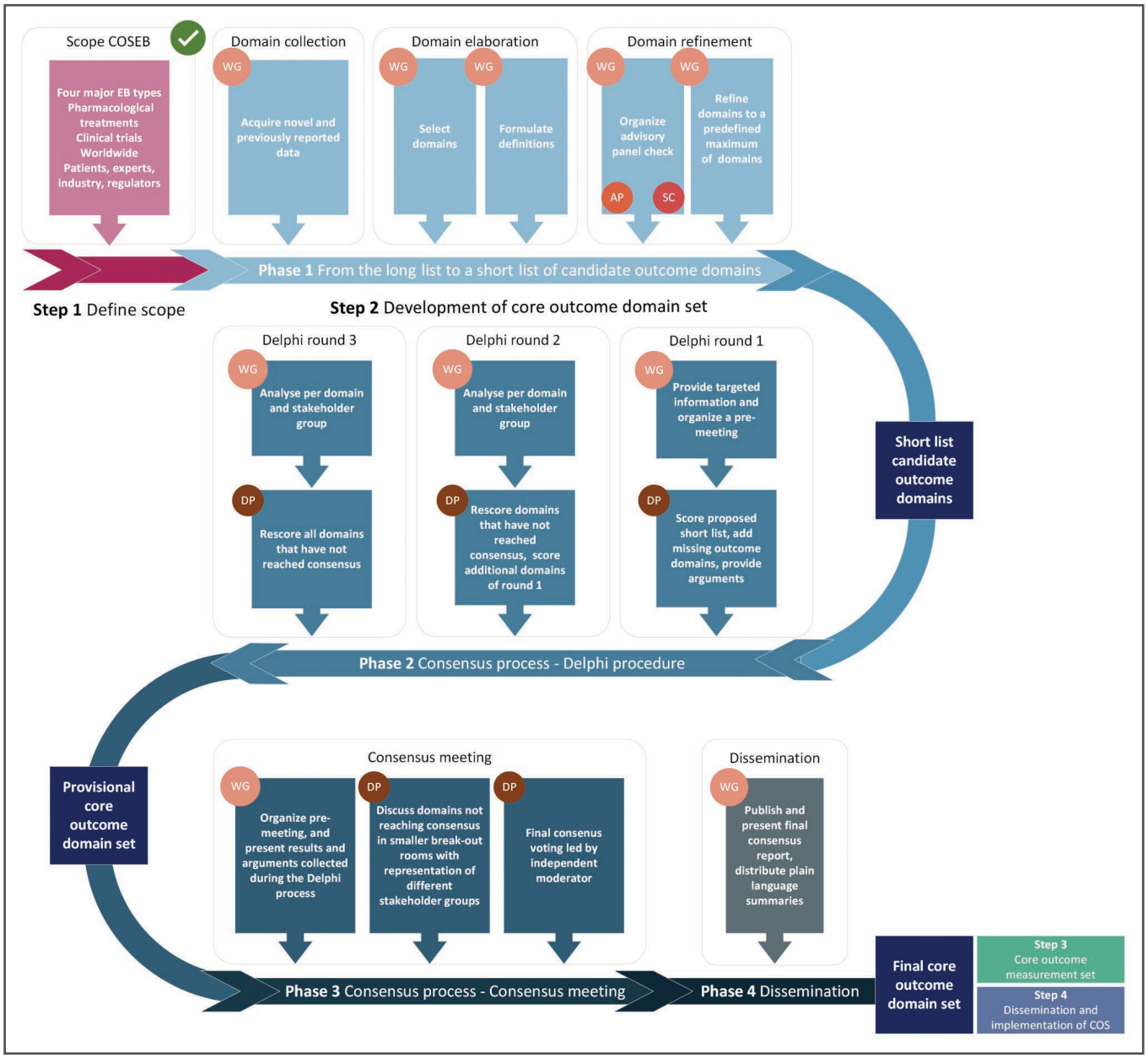


**Figure 1** The COSEB roadmap to reach consensus on the core outcome domain sets for the four major epidermolysis bullosa types separately. AP, advisory panel; COS, core outcome set; COSEB, Core Outcome Sets for Epidermolysis Bullosa; DP, Delphi panel; EB, epidermolysis bullosa; SC, steering committee; WG, working group

strengthen the consensus procedure. The roadmap will now serve as the basis for refinement of the COSEB protocol to develop core outcome domain sets for the major EB types, which is intended to be published during 2024. The COSEB Consortium continues to welcome participation and therefore invites interested stakeholders to contact us (coseb@umcg.nl).

The COSEB roadmap defines the following phases of the COSEB initiative: (1) start-up of the working group activities towards refined short lists of candidate outcome domains, (2) Delphi procedures and (3) stakeholder agreement on the core outcome domain sets for the major EB types in final consensus meetings. Following this, recommendations will be developed on the optimal outcome measurement instruments to measure the selected core outcome domains ('how' to measure). Ultimately, this should result in COSs for all major EB types and thereby enhance clinical translation of therapeutic strategies worldwide.

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The full membership of the COSEB Consortium is provided in Supplementary Appendix S1.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

**Appendix S1** Full membership of the COSEB Consortium.

**Appendix S2** Full conflicts of interest statement for all authors.

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