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Novel mixed-method, inclusive protocol involving global key stakeholders, including carers as experts, to co-develop relevant Caregiver-Reported Outcome Domains (CRODs) in skin disease

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ABSTRACT

Introduction Ichthyoses comprise a heterogenous group of rare genetic skin disorders that involves the entire skin surface, often with additional syndromic features, and pose many clinical challenges. Without curative intervention, the mainstay of life-long symptom management is supportive in nature and can remain the responsibility of the caregiver. Although impact on the wider family is considered an important outcome of policies and services, there is a lack of caregiver consensus on what outcome domains to measure to fully assess the impact of ichthyosis on the patient and the caregiver. This project aims to identify a set of core outcome domains towards a core outcome set for ichthyosis that can measure all relevant concepts of ichthyosis in clinical practice, service delivery and research.

Methods and analysis Following the COMET (Core Outcome Measures in Effectiveness Trials) initiative, this project will employ a mixed-method study design which was developed using public and patient involvement and an international multidisciplinary expert group (clinical experts, patients and their representatives, policymakers, researchers and service providers). Experts by experience, or caregivers, will be recruited through online ichthyosis support groups. Phase one will focus on item generation and involve: (1) a systematic literature review, (2) a multimethods international qualitative study with ichthyosis caregivers and (3) co-development of items for an e-survey. Phase two, item refinement, will employ a novel four-pronged consensus approach: (1) an e-Delphi survey, (2) statistical analysis of e-Delphi survey results, (3) online qualitative feedback and (4) an online consensus discussion. All methodological considerations will be clearly linked with each Core Outcome Set-STAndards for Developing recommendation.

Ethics and dissemination Research Ethics Committee approval obtained from the School of Psychology, Ulster University (UK)(Ref:REC/20/0004). Results will be presented in published international peer-reviewed journals, at scientific meetings and support groups.

Registration COMET database (January 2019).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first robust transparent mixed-method core outcome set design proposed for use in ichthyoses, which will ultimately improve evidence synthesis in clinical practice, service delivery and research.

⇒ Protocol registered on the COMET (Core Outcome Measures in Effectiveness Trials) database and all methodological considerations (scope, stakeholder involvement and study design) are linked with each Core Outcome Set-STAndards for Developing recommendation.

⇒ The equal inclusion of international multidisciplinary professional and caregiver experts (including affected adults, grandparents and parents across all stages of the care continuum from birth to bereavement) will enable the identification of novel and caregiver-reported outcome domains.

⇒ The novel four-pronged consensus approach (an e-Delphi survey approach, statistical analysis of e-Delphi survey results, online qualitative feedback and an online consensus discussion) will additionally enable the simultaneous development and psychometric evaluation of two self-report outcome measures for ichthyosis caregivers.

⇒ Due to funding limitations and translation costs, the qualitative study, e-Delphi survey and consensus meeting will be conducted in the English language only, however, future research will endeavour to validate the core outcome set in languages other than English.

INTRODUCTION

Ichthyoses refer to a group of rare and chronic dermatological diseases characterised by abnormal keratinisation and scaling, primarily affecting the entire skin surface, nails and hair.[1] They are often associated with skin inflammation, significant morbidity and a markedly decreased ability to perspire which can lead to hyperthermia and rarely circulatory collapse.[2 3] Complications of congenital

ichthyosis can be life-threatening and require specific life-long skin and medical management,[4] similar to that of patients with moderate to severe forms of epidermolysis bullosa.[5 6] Despite the profound[7–11] and bidirectional[12 13] impact of skin disease between the caregiver and the patient, and an increase in associated resource usage and healthcare costs,[9 14] there remains an absence of caregiver-reported outcomes (CRO) that may increase our understanding of new strategies that can reduce the physiological suffering and psychosocial sequelae associated with ichthyosis in all its facets for both patient and caregiver. A limitation of chronic and rare outcomes research is the difficulty in defining which outcome domains of care are most relevant to both patient and family.[15]

This protocol focuses on identifying a set of core outcome domains, defined as the broader aspects of a disease indicating 'what to measure', as currently established for health-related quality of life or clinical signs.[16] Fostering consensus among professional and caregiver experts, we aim to develop a core outcome set (COS), defined as an agreed-upon minimum standardised set of outcome domains that should be measured and reported in all studies for this specific health condition and population.[17] At the time of study registration on the COMET (Core Outcome Measures in Effectiveness Trials) database,[18] a platform that maintains a registry of COS development studies and supports COS methodological research, there were no registered COS development studies for ichthyosis. Given that Cochrane editors emphasise that the availability of COS would strengthen the evidence base for healthcare decision-making by using outcomes relevant to all stakeholders and improve the comparability of interventions,[19–22] it is crucial to optimise the development of a candidate list of meaningful and relevant outcome domains for ichthyosis. Furthermore, the results of recent systematic reviews indicate that the validity and reliability of dermatological outcome measures are not supported with sufficient evidence,[23] leading to poor COS uptake.[15 24] To address these issues, the COMET initiative,[25] the Cochrane Skin Group-Core Outcome Set Initiative,[26] Core Outcome Set-STAndards for Developing (COS-STAD)[27] and the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) group[28] recommend greater family inclusion in the identification and consensus of outcome domains.

METHODS

Project design will be guided by the Harmonising Outcomes for Eczema (HOME) 'roadmap',[29] the COMET initiative[2 5] and the Outcome Measures for Arthritis Clinical Trials (OMERACT) Filter 2.0.[30] The project started in September 2019. Study one was completed in October 2020. The planned end date for this project is December 2023.

Ethics and dissemination

Research Ethics Committee approval has been obtained from the School of Psychology, Ulster University (UK) (Ref:REC/20/0004). Informed written consent will be obtained from all participants prior to participating. Participants will receive written information and will provide informed written consent prior to any data collection. Separate online consent forms will be sent to participants prior to the qualitative study and e-Delphi survey. All transcripts will be confidential and will be labelled with a code. Model consent forms are provided in online supplemental file 1. Publication of Caregiver-Reported Outcome Domains (CRODs) in an international journal for rare disease will serve as the primary medium for result dissemination. Ongoing dissemination will continue via relevant online support groups, poster and oral presentations at conferences.

Methodological frameworks suggest a two-staged approach for COS development: (1) the what to measure (core outcome domains) and (2) the how to measure (measurement tools). This protocol focuses on the first stage and will be completed in three phases:

Phase 1: identification of candidate outcome domains by means of

- Study 1: Systematic literature review to identify outcome domains in psychosocial measurement tools validated for use with dermatological caregivers.
- Study 2: International multi-methods qualitative study with ichthyosis caregivers to identify clinical and service relevant endpoints.
- Study 3: Co-development of evidence-based caregiver reported items.

Phase 2: reaching domain consensus by means of

- Study 4: Refinement of items using an e-Delphi consensus process that uniquely views diverse expert opinions (healthcare professional experts and experts by experience) as equally valid.
- Study 5: Statistical analysis of e-Delphi survey results, qualitative feedback and online consensus discussion to reach final consensus on core outcome domains.

Phase 3: publication and dissemination of CRODs by means of

- Email summaries to patients and caregivers.
- Publication in peer-reviewed international medical journals.
- Scientific meetings (oral and poster presentations).

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist was used to improve the quality of reporting of the content of this protocol (online supplemental file 2).[31] To ensure rigour, methodological considerations (scope, stakeholder involvement and study design) will be clearly linked with each COS-STAD recommendation in this protocol.[27]

Scope specification

COS-STAD 1

This COS is intended to inform outcome selection in clinical practice, service delivery and research.

COS-STAD 2

It aims to be relevant for patients (child and adult) and their caregivers living with both syndromic and non-syndromic forms of ichthyosis.

COS-STAD 3

Outcome domains will target both patient and caregivers internationally and be relevant across all life stages and/or ages.

COS-STAD 4

This COS will be used to assess outcomes at both the need and support level to inform the targeted delivery of healthcare and services.

Stakeholder involvement

COS-STAD 5

An international professional multidisciplinary expert group will be composed of those who will use the COS in research, including consultant dermatologists who both lead and run trials, but who are also practicing clinicians.

COS-STAD 6

Those healthcare professionals who have experience with patients with ichthyosis. Experts will be identified from personal networks, hospitals, academia, healthcare policy, and organisations relevant to stakeholder groups.

COS-STAD 7

An international caregiver group will include representatives of patients with Autosomal Recessive Congential Ichthyosis (ARCI) and non-ARCI, including parents, guardians and grandparents. Caregivers may also be affected adults themselves.

Patient and public involvement

Study 2

In response to the increasing need for patient and public involvement (PPI) in public health matters,[32] the rarity of disease and the international design focus of the research, caregivers will be recruited from two online ichthyosis support groups (Ichthyosis Support Group in England and the Foundation of Ichthyosis and Related Skin Types in America) who have given written support of this project. Both groups will post the online research notice, which will contain an embedded Participant Information Sheet and consent form (created using Qualtrics). Eligible caregivers will include those aged 18 years old or older, fluent in English and who either provided daily care for a child (of any age) at the time of advertising, or within the previous 15 years, diagnosed with any subtype of ichthyosis. Care will be defined as 'any care over and beyond what is considered normal for a typically developing child'. Informal caregivers will include parents, foster parents, guardians, grandparents or adoptive parents of children with ichthyosis (no age restrictions). To maximise recruitment of a balanced caregiver sample, caregivers will be asked to complete an online sociodemographic section once informed consent is provided. A semi-structured interview schedule will be emailed to caregivers 1 week in advance of the data collection. Caregivers will be recruited in batches until no new themes are identified in the data. At least four focus groups and four interviews are planned.

Study 3

In terms of caregiver recruitment, this study will adopt the same strategy previously outlined for Study 2. Professional multidisciplinary experts will be identified from personal networks, hospitals, academia, healthcare policy, web-based searches and organisations relevant to stakeholder groups. These contacts will be emailed individually and invited to develop and refine CRODs. We hope to achieve an interdisciplinary expert panel consisting of 50% caregivers (n=15) and 50% professionals (n=15). The estimated total sample size for this descriptive study is n=30. Once online informed consent has been obtained, the initial draft of the survey will be individually emailed to each participant for feedback via return email.

Study 4

We aim to achieve an interdisciplinary expert panel consisting of caregivers (n=30) and professionals (n=15). In terms of caregiver recruitment, this study will adopt the same strategy outlined in Study 2. All professional experts recruited to Study 3 will be individually emailed, thanked and asked to contribute again to this study. Once informed online consent is obtained, participants will receive an email for each round containing the e-survey link, created using the software Qualtrics. To reduce caregiver burden, the consent form will ask caregivers to provide informed consent to be included in each round. Participants will be asked to reflect over the duration of their caregiving experience and have 2 weeks to complete each round, a reminder email will be sent 1 week in advance of the deadline.

Study 5

As this study is an extension in terms of analysis of the data collected in Study 4, no further recruitment will be needed.

STUDY DESIGN

Phase 1: identification of potential outcomes and domains considered important by both expert groups (COS-STAD 8)

Study 1: systematic literature review to identify outcome domains in psychosocial measurement tools validated for use with dermatological caregivers.[23]

Objective

To review available and useful psychosocial needs assessment tools to identify relevant items and domains to

promote caregiver health outcomes and evidence-based decisions within clinical practice and service delivery. Depending on similarities among included articles, we aimed to additionally provide an overview of methodological analysis of the included instruments using Both *et al*'s criteria.[33] This appraisal tool was previously employed in comparable systematic reviews of dermatological outcome measures and the authors felt that actual yields of wielding the COSMIN's risk of bias tool[28] would be negatively influenced by the lack of the author's skills, knowledge, experience and training. The protocol is published with the PROSPERO database (CRD42019159956), registered on the COMET database and was conducted according to the recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement[34] and the Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statement.[35]

Inclusion criteria

Studies that involved adult caregivers (age 18 years and over), caring for a child (no age limit) with any form of any skin condition that were published in English between 2000 and 2021 were included. Given a lack of consensus in the literature on the use of the term 'psychosocial', we did not define this term to allow inclusion of a diverse range of tools (cognitive, social and emotional). Patient outcome measures, generic quality of life (QoL) measurement tools not validated for use with dermatological caregivers, studies that only included child or spousal caregivers and/or have poor overall quality were excluded from this review.

Search methods for identification of studies

The databases MEDLINE, PsycINFO and EMBASE using the OVID interface and CINAHL (Cumulative Index to Nursing and Allied Health Literature) EBSCO were searched. Grey literature, bibliographies, online databases of QoL tools and trial registers were also searched. Each search strategy was tailored to the specifications of each of the databases searched and developed in collaboration with a subject-specific librarian and expert group. Each keyword was individually mapped to appropriate subject headings (MeSH) in each database, where available, to ensure a broad and thorough search. Each concept was taken individually and/or MeSH with the keyword(s). Date and language limits were then applied. After the search was run, inclusion/exclusion criteria were applied.

Data collection and analysis

Title, abstract, full-text screening and data abstraction were conducted independently in duplicate by two reviewers (CW and GL) according to the eligibility criteria. Consensus discussions resolved any discrepancies, including the risk of bias, at the full-text screening stage. Study-specific (name of tool, country of origin, disease of affected patient, sample sizes and study setting), questionnaire-specific (domains, subscales, number of items, recall period, scoring system and administration time) and adequacy of measurement properties (transferability, reliability, validity, structural and interpretability) for all included tools were recorded on purposively created data abstraction forms. Narrative synthesis was used to present the findings. A list of published ichthyosis-specific domains were developed for presentation in Study 3. Study 1 has now been completed.[23]

Study 2: international multimethods qualitative study involving a broad range of ichthyosis caregivers to identify clinical and service relevant outcomes

Objective

To identify and interpret common ichthyosis-specific themes of need using experts by experience.

Design

To complement the outcomes identified from Study 1, an inclusive, holistic and explorative qualitative design will now be used with experts by experience to identify CRODs through focus group discussions and interviews. This study will consider different caregiver experiences and contexts, as it is concerned with learning from individual cases and situations. A multimethods approach is planned due to the time frame of the project and to optimise the number and variety of caregivers participating from geographically diverse locations. Focus groups will help in identifying gaps in coverage of domains or items in literature, while interviews will allow a more in-depth questioning of emergent themes.[36] The semi-structured interview schedule (online supplemental file 3) will be created based on findings from a literature review and Cochrane reviews and contain items relating to the positives of caregiving, caregiver role and responsibilities, coping strategies, supportive care needs, transitions in care continuum, supports, expectations and hopes.[37]

Data analysis

Data collection will be audio-recorded, transcribed verbatim and double coded (first two focus groups); NVivo (V.10) will facilitate the coding process. To address the desired outcome of the study and offer a more transparent approach, framework analysis will be used and a coding frame and inductive reasoning will assist in categorising feedback into themes and subcodes.[38] Themes included in the final analysis will be raised by more than one caregiver in a single group and, ideally, by caregivers in more than one group. Simple counts of frequency, member checking and peer debriefing will be conducted to assess the quality of research findings. To ensure anonymity, transcribed data will not be linked to caregiver information and the study will closely adhere to the Consolidated Criteria for Reporting Qualitative studies.[39]

Study 3: co-development of evidence-based caregiver reported items for e-Delphi survey using two distinct expert groups

Objective

To co-develop evidence-based practice-relevant items with two distinct expert groups (professional multidisciplinary stakeholders and caregivers).

Design

An online survey will be developed de novo using a hybrid of literature and caregiver feedback. Both expert groups will be given the opportunity to develop the survey in terms of the need for each proposed domain and candidate items within the field of their daily practice. There will be an opportunity to name additional items or domains that were not reported in Study 1 or 2. Once the initial survey draft has been developed, experts will be asked to evaluate the face validity of the items by considering: (1) the wording in terms of feasibility and acceptability; (2) the content coverage of the survey to ensure inclusion of all relevant concepts; (3) the clarity of each item; (4) comprehensiveness and relevance of each item; and (5) appropriateness of the response scales, recall period, response options and format. To ensure anonymity among experts is maintained, all qualitative feedback will be collected via individual email for this descriptive study.

Data analysis

Analysis of the emailed descriptive feedback will be presented for discussion with the research team and conducted with the help of Excel.

Phase 2: reaching consensus on the domains of the COS, whereby a scoring process and consensus definition were described a priori (COS-STAD 9)

Study 4: refinement of items using an e-Delphi consensus process that uniquely views diverse expert opinions as equally valid

Objective

Using all identified domains, a comprehensive e-Delphi survey will be distributed to two distinct groups of experts (professionals and experts by experience) to determine the degree of item consensus.

Delphi procedure

The design of the e-Delphi study will be guided by the COMET Handbook,[25] and is registered in the COMET database. The Delphi method allows input from diverse stakeholders and remote predefined consensus to be reached on items which reflect the construct to be measured, ensuring that CRODs will be relevant and acceptable. This study will facilitate a consensus process by using a series of sequential surveys to collect data from diverse international expert groups. It is anticipated that the survey will contain four sections: (1) sociodemographic; (2) screening variables; (3) severity scale of impactful disease parameters; and (4) needs and support scale. The estimated duration of this study is 4 months.

Data collection and analysis

The first round of the e-Delphi survey will contain all items identified from literature and caregiver feedback. In accordance with recommendations on the development of outcome measures, participants will be asked to rate each caregiver-related concept in the final section as a whole first before rating each suggested intervention so that they can be measured appropriately in order to fully identify the value of any future interventions.[40] Participants will first rate the relevance of a need on a 4-point Likert scale (‘extremely important’, ‘very important’, ‘moderately important’, ‘not important’) and then rate the perceived helpfulness of each suggested support using a different 4-point Likert scale (‘very often helpful’, ‘often helpful’, ‘sometimes helpful’, ‘rarely/not helpful’).

To view diverse expert opinions as equally valid and avoid power differences, each response will be converted into a percentage per respective group.[41] For ease of analysis, it is planned to dichotomise the responses for each respective group and to use the average of these dichotomised group percentages as the final consensus rating for each item ((‘extremely important’ or ‘very important’ vs ‘moderately important’ or ‘not important’) and (‘very often helpful’ or ‘often helpful’ vs ‘sometimes helpful’ or ‘rarely/not helpful’)). Table 1 provides an overview of the proposed consensus classification. All items reaching positive consensus (dichotomised group consensus ratings >69%) will be automatically included in the final domain set. Items reaching negative consensus (dichotomised group consensus ratings <40%) will be excluded from the next round, whereas only those items which fail to reach positive or negative consensus (dichotomised group consensus ratings 40–69%) will be redistributed in subsequent rounds. Only those who are involved in Round 1 will be invited to complete Round

Table 1 Overview on the consensus classification for the Delphi procedure

Consensus	Description	Definition
Positive consensus	Consensus that item should be included in the final core outcome set	Dichotomised group consensus ratings *more than* 69% for items relating to VOH/OH.
Negative consensus	Consensus that the item should be eliminated	Dichotomised group consensus ratings *less than* 40% for items relating to VOH/OH.
No consensus	Uncertainty about the importance of the item so retain/amalgamate/reword for next round	Dichotomised group consensus ratings between 40% and 69% for items relating to VOH/OH.

OH, often helpful; VOH, very often helpful.

2. All responses will be forced to avoid inputting missing cases for each round.

Study 5: statistical analyses of e-Delphi results and online consensus discussion to inform final consensus on core outcome domains

Objective

To provide an objective insight into the total number of outcome domains represented and explore the underlying structure of and relationships between constructs that caregivers consider meaningful.

Design

To further improve the reorganisation and/or condensing of items into more meaningful domains, control the quality of items generated and improve interpretation of the underlying constructs, descriptive (mean, median, SD, percentages) and inferential statistics (independent samples t-test, analysis of variance (ANOVA) and tests of correlations) will be additionally employed in this study. An online anonymous consensus discussion with both expert groups will further improve the consensus process by deciding if some domains need to be excluded, retained, reworded and/or amalgamated. In line with recommendations from the COMET initiative, pre-consensus discussion information will be individually emailed to consenting participants. Participants will be provided with the finalised e-Delphi results, anonymised online qualitative feedback and a list of those domains which are significantly associated with severity and/or need. Participants will be asked to email which domains should be considered 'core' in the final COS, and which domains should be excluded. Microsoft Excel and SPSS will be used in this study.

Data analysis

Given the potential to change clinical practice in a way that leads to improved caregiver outcomes, inter-rater reliability (per cent agreement) will be explored between the professional and caregiver group for each candidate outcome domain.[42] To address the lack of available validated caregiver self-report severity and needs assessment tools, as identified by the systematic review, this study will additionally use inferential statistics to simultaneously evaluate the preliminary psychometric properties of a caregiver self-report perceived (1) Severity Scale and (2) Needs Scale. Due to the aim of this protocol, Study 5 only tests two of the six measurement properties (internal consistency and construct validity) required for these scales to be recommended for use, as outlined by the COSMIN group.[28] However, we plan to conduct add-on studies involving larger sample sizes in the future, to additionally provide evidence of the structural validity, test–retest reliability, measurement error and responsiveness of the scales.

Both scales will be assessed for item variability and internal consistency, using Cronbach's α coefficient.[10] Inter-item correlations will examine the degree to which individual disease parameter scores are related to scores on all other items in the Severity Scale. Total mean severity and need scores will be calculated for each of these scales. Corrected item-total correlations, and correlations between each candidate outcome domain and (1) total need score and (2) total severity score will be calculated. Similarly, corrected item-total correlations, and correlations between individual disease parameters and (1) overall perceived severity and (2) total severity score will be calculated. Relationships between (1) outcome domains, (2) screening variables and (3) disease parameters and total need and/or severity scores will be explored using independent samples t-tests, ANOVAs and tests of correlations. Correlation tests will explore the strength and direction of relationships between continuous variables and will determine correlation between total need score and total severity score. A cut-off total-item correlation value of 0.4 will be adopted for this study.[43] Where relevant, Cohen's d will be used to calculate the magnitude of the differences in the means or effect size.[44] Known group validity with total need and/or severity will be explored for: (1) severity (using two disease category groupings called ARCI and non-ARCI), (2) patient age (under 7 years old vs 7 years and older), (3) patient sex (girls vs boys) and (4) caregiver overall perceived severity rating (none/mild vs moderate/severe).

COS-STAD 10

Criteria for including/dropping/adding outcomes were defined a priori.

This recommendation will be achieved by individually emailing a general summary of results to each participant at the end of each round to tell them their own count, overall percentage of members in each group who rated the relevance of each item and the overall average score. They will also be provided with their own rating for items in that round and be able to change their original ratings if they so wish based on anonymous group feedback. Space will be provided at the end of the survey for qualitative feedback and/or additional items which they feel should be included. This process will continue until the criteria is met for the convergence of ratings, which will signal the cessation of voting. Descriptive and statistical analysis will be performed on the results with the help of Microsoft Excel and SPSS.

COS-STAD 11

Care was taken to avoid ambiguity of language used in the list of outcomes. This recommendation will be achieved by using online, anonymous qualitative feedback to review the content of the e-Delphi survey items and inform decisions around whether items need to be reworded, amalgamated or retained. All outcomes will be clearly defined.

Phase 3: publication and dissemination of CRODs

Publication of CRODs in an international journal for rare disease will serve as the primary medium for result dissemination. Ongoing dissemination will continue via

relevant online support groups, poster and oral presentations at conferences.

DISCUSSION

Although CROs have been identified as imperative in advancing patient care, they remain neglected aspects of quality healthcare and lacking in literature. Recognising that COSs are lacking for ichthyosis in clinical practice and service delivery, this is the first protocol aimed at establishing international content validity evidence for an agreed co-developed set of CRODs. Guided by methodological frameworks, including COMET,[25] HOME[29] and OMERACT,[30] a literature review and an international Delphi procedure involving diverse expert collaboration will be conducted.

Although COS development should be concerned about raising the standards of measurement tools,[45] recent systematic reviews consistently highlight that most existing tools do not meet modern standards in terms of content, face and structural validity.[23] The US Food and Drug Administration[46] and OMERACT[30] reinforce that content validity should be demonstrated before any measurement tool is recommended for a core domain. With increasing recognition of the unreliability of Patient-Reported Outcome Measures (PROMs) for paediatric patients due to patient age and/or developmental challenges,[47] caregiver feedback is often needed. In recognition that informal caregivers are integral to patients' health outcomes and to address the forementioned limitations, this is the first protocol to focus on the development of a set of CRODs towards a COS for any disease.

This protocol differs from existing COS frameworks in several aspects to improve the content validation process and ensure that identified CRODs become dependable outcomes for accurately measuring significant symptom indicators, needs and interventions for both patient and caregiver. This will be the first dermatological COS to be informed using a multimethods qualitative study involving international experts by experience, which will increase our understanding of caregiver and child variables, potentially enabling more timely identification of vulnerable caregivers and informing the development of therapeutic and psychoeducational interventions while maximising benefits across service settings.[48] The inclusion of caregivers as equal research partners may address the recognised failure of objective measures to account for psychological burden[49] and empirical evidence highlighting the exclusion of recommended core areas in COS, such as 'resource use/economic impact'.[25] It may also prove valuable considering an increase in disease severity does not always mean an increase in all disease parameters.[49] The intentional, strategic and equal inclusion of experts by experience throughout this project, while not congruent with the usual tenets of COS development, will address a significant limitation of existing COS,[50] by establishing the appropriateness of items and domains and providing evidence that the identified CRODs evaluate relevant concepts of interest.

Similarly, this has the potential to contribute towards the first dermatological COS whereby items have been systematically and objectively refined using both the Delphi technique and statistical analyses. It is anticipated that this refinement process may simultaneously facilitate the psychometric evaluation of two subsections of the e-Delphi survey: a severity scale and a needs scale. The international, anonymous and iterative approach of the e-Delphi study will allow for investigation and interspersed discussion into diverse expert consensus on items of relevance and representation. Although the 9-point response scale is most often used in COS studies to measure agreement between Delphi study participants,[51] the decision rules are under scrutiny with the use of 3-point and 4-point response scales identifying identical consensus items in comparable studies.[52] With no reference standards existing for conducting Delphi methods and for consensus definitions,[53] this protocol uses the consensus definition based on previous findings from OMERACT meetings[30] and adopts the use of a 4-point Likert scale. To ensure that no group of experts could steer evidence towards any fixed preconceptions, established consensus methods will be used.[23] This will include the maintenance of response anonymity among diverse international stakeholder representation, inclusive of affected patients, caregivers, consultant dermatologists, nurses, health policy advisors, support group representatives and academics recruited from Europe, the USA and India. Scientists from the pharmaceutical industry will be excluded due to documented negative affect outcomes in terms of influencing the inclusion of disease parameters.[45] Due to the lack of evidence on the results of face-to-face consensus meetings,[25] documented recruitment difficulties for face-to-face meetings with stakeholders[54] and the proposed geographical reach of the project, this protocol proposes online consensus discussions only.

In contrast to existing PROMs for paediatric patients which generally focus only on physical and mental health parameters,[55] it is planned that this set of CRODs will include a more comprehensive range of disease parameters, based on the WHO's definition of health.[56] This will prove valuable for informal caregivers, who in spite of demonstrating their ability to accurately assess the severity of their child's dermatological disease,[57] remain unable to report perceived severity with any of the existing validated ichthyosis severity scales[58 59] that were developed as visual clinician scales and do not reflect disease parameters included in the ichthyosis management guidelines.[4] The International Psoriasis Council concur that 'any system of disease classification must go beyond strict assessor-driven cut-offs' as they are associated with downgraded disease severity and restricted access to therapies.[49] Potential limitations include the exclusion of items or domains due to the proposed inclusion criteria for the literature review, recruitment, retention and response rate challenges and/or the lack of face-to-face consensus discussions.

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Collaborators N/A.

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