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Development of a core outcome set for general intensive care unit patients – a protocol.

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Abstract

Introduction Different outcomes are reported in randomised clinical trials (RCTs) in intensive care unit (ICU) patients, and no core outcome set (COS) is available for ICU patients in general. Accordingly, we aim to develop a COS for ICU patients in general.

Methods The COS will be developed in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Handbook, using a modified Delphi consensus process and semi-structured interviews involving adults who have survived acute admission to an ICU, family members, clinicians, researchers, and other stakeholders.

The modified Delphi process will include 2 steps. Step 1: conduction of a modified Delphi survey, developed and informed by combining the outputs of a literature search of outcomes in previous COSs and semi-structured interviews with key stakeholders. We plan at least two survey rounds to obtain consensus and refine the COS. Step 2: a consensus process regarding instruments or definitions to be recommended for the measurements of the outcomes selected in step 1. A 'patient and public involvement panel' consisting of a smaller group of patients, family members, clinicians and researchers will be included in the development, analysis, and interpretation of the COS.

Discussion The outlined multiple methods study will establish a COS for ICU patients in general, which may be used to increase standardisation and comparability of results of RCTs conducted in patients in the ICU setting.

Introduction

Outcome selection and prioritisation is an important part in the planning of randomised clinical trials (RCTs).[1] Variability in the selection and definition of outcomes[2] in the intensive care unit (ICU) population makes it difficult to compare and synthesise results across studies.[3] The development of core outcome sets (COSs) is generally encouraged, and several have been developed for subpopulations of critically ill patients based on primary reason for admission including those with acute respiratory failure.[4] However, a COS for the general ICU population is lacking.[5]

Patient and public involvement (PPI) is increasingly recommended and used[6,7] as it increases the likelihood that research is relevant to the target population.[3,8]

In the ICU setting, involvement of patients and family members, together with clinicians and other stakeholders, is important since patients are vulnerable[9] and rarely have the opportunity to interact during an ICU stay due to impaired consciousness and cognitive function and the stress of critical illness. Furthermore, ICU survivors often have long-term physical, psychological and cognitive impairments resulting in health and social implications.[10–12] Finally, involvement of patients and relatives in the research process increases the focus on patient-important outcomes.[6,7]

Aims

We aim to develop a non-disease-specific COS for ICU patients in general. We also aim to establish consensus on how the identified outcomes could be measured.

Methods

We have prepared this protocol in accordance with the Core Outcome Set-STAndardised Protocol (COS-STAP) statement (completed checklist available in Supplement),[13] and in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) initiative including the COMET Handbook.[3] This study has been registered in the COMET database (https://comet-initiative.org/Studies/Details/1882).

This COS will be developed using a multiple methods design including a modified Delphi process with surveys and consensus meetings and semi-structured interviews, as shown in Figure 1. The modified Delphi process approach aims to establish consensus among stakeholders while avoiding influential

individuals to markedly affect the results. Participants are only presented with aggregated responses during survey rounds.[3] The process consists of 2 steps described in further detail below:

- Step 1: item development including conceptualisation of domains item identification and consensus meeting with a finalised COS as the product, which will be reported using the Core Outcome Set – STAndards for Reporting (COS-STAR) statement.[14]
- Step 2: identification of how to measure the COS informed by step 1. This includes identifying existing instruments, quality assessment of instruments, and a consensus process for selecting instruments or definitions to be included in a core outcome measurement set (COMS).

The scope of the core outcome set:

- Health condition: critical illness requiring treatment in an ICU
- Population: adult patients (≥18 years of age) acutely admitted to an ICU
- Interventions: any form of treatment or care performed in the ICU, including pharmacological or non-pharmacological interventions or care protocols used in the ICU

Stakeholders

- Adult patients who survived acute admission to an ICU
- Adult family members (including, but not limited to, spouses, friends, close or informal caregivers or next of kin) to ICU patients regardless of patients' survival
- Clinicians (including, but not limited to, doctors and nurses) with any involvement in the care of ICU patients
- Researchers (including clinician-researchers) conducting research in the ICU setting or in adjacent populations of critically ill patients
- Other stakeholders including grant funders, patient organisations, and political and legal partners (examples included in the supplement)

We have established a *patient and public involvement panel (PPI-panel)* currently consisting of 2 patients, 2 family members, 2 nurses and 3 physicians (all clinicians with research experience, 4 of which are co-authors of this protocol) who will be included in the development, analysis and establishment of the COS. This PPI-panel is planned to be expanded by members from all regions in

Denmark. We intend to use the established PPI-panels local in their home region and together as one large PPI-panel in future research projects including the prioritisation of research questions.

Recruitment of participants

- Invitation for participation to the COS development study will be promoted in the outpatient clinics of the participating hospitals and ICUs.
- Information and invitation to the COS development study will be given to patients and family members, when delayed consent is obtained for participation in RCTs or at long-term follow-up in RCTs originating from the Collaboration of Research in Intensive Care (CRIC; www.cric.nu) in Denmark.
- Patients not participating in these RCTs will be visited in the general ward before discharge for information and invitation or when participating in ICU patient cafes.
- Information and invitation to participate will be available as handouts in the participating hospitals and relevant charities and support organisations.
- Clinicians will be identified in the authors' affiliations and invited by e-mail, interdisciplinary meetings and by phone calls.
- Researchers will be identified by the authors' affiliations and research networks (e.g. CRIC) and invited by e-mail.

In Table 1 we have listed participants' characteristics to be obtained; we will strive for balanced distribution of these among the participating stakeholders.

We plan to start the modified Delphi process and semi-structured interviews at the end of 2021, and we expect to finalise the first Delphi round in the summer of 2022, the second round at the end of 2022, and to obtain final consensus in the spring of 2023. The final version of the COS is estimated to be completed at the end of 2023.

Step 1, part 1: Developing the COS

We are developing a survey by condensation of the existing literature, complemented with knowledge gained from semi-structured interviews. The survey will be distributed and answered online using the

DelphiManager software (COMET Initiative, Liverpool, UK). We will ensure internal validity of the survey prior to commencing the formal modified Delphi process with a pilot test in accordance with the COMET Handbook.[3]

Existing literature will be summarised according to a systematic literature review, using a search string from a previous systematic review of COS for critical illness and recovery, developed by a librarian (Supplement).[5]

We searched PubMed and Embase on 1 May 2021 without any filters. We also searched the COMET database for relevant COS with assistance from the COMET group. Two authors independently and in duplicate screened results for COS (MNK and SED).

Subsequently, two research teams (MNK, PS, MOC, GKV and SED, LMP, CBM) independently followed the recommended process described in the COMET Handbook,[3] and classified outcomes in categories describing similar outcomes, followed by division into sub-domains, where all categories were placed and reconsidered before deciding on the final number of domains. These domains will be discussed with the involved stakeholders and serve as the fundament for the Delphi survey along with the additional knowledge gained from the semi-structured interviews.

We will invite relevant stakeholders to the semi-structured interviews, in parallel with the modified Delphi process, by quota sampling to ensure balanced distributions of the characteristics shown in Table 2. Interviewed respondents will be invited to the modified Delphi process.

The semi-structured interviews will provide us with experiential knowledge of what constitutes patient-important outcomes. We will construct an interview guide based on the domains identified from the literature and from the categorisation of outcomes to ensure rigorous interviews, and to elaborate thoughts and considerations regarding admission to an ICU with critical illness and sequelae.

The survey will be pilot tested by the PPI-panel and revised as necessary (Supplement).

Step 1, part 2: Delphi round 1: consensus on core outcomes

At the start of Delphi round 1 we will collect baseline variables for the included stakeholders (variables listed in Table 1). Other stakeholders will answer on behalf of their organisations and not individually, and the results will be tabulated separately.

The round 1 survey will be structured so outcomes common to all stages of the ICU admission will be listed first, followed by outcomes that are specific to specific time points during the ICU admission. Within this structure, the order of outcomes will initially be randomised individually for all participants. For each outcome, participants will be able to provide free-text comments and suggest additional outcomes.

Participants will score the importance of each outcome as outlined in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach,[15] using a Likert scale ranging from 1 to 9 in terms of importance for inclusion in the final COS. The same rating for multiple outcomes is allowed. Scores of 1-3 are defined as 'not important' for inclusion, 4 -6 as 'important but not critical', and 7-9 as 'critical' for inclusion. The survey will also include an item "unable to score" to reduce the number of incomplete answers.

We will also explore the outcomes with semi-structured interviews in parallel with the first survey round. Additional outcomes identified in the interviews will be included in the second round. Further details regarding the semi-structured interviews (including the pre-planned framework analysis) are presented in the Supplement.

Step 1, part 3: Consensus process after 1st survey round

In-person or online consensus meetings will be held to confirm the final COS contents or undertake any additional voting if the number of included outcomes in the COS is perceived as excessive, and to ensure that participants of the meetings do not disregard the results from the first survey round. The COS Management Committee (MC; consisting of all authors of this protocol), will review the findings of the first survey to determine the structure, format, and content of the consensus meeting. For the consensus meeting, the PPI-panel will take part, representing relevant stakeholders.[3]

Modified Delphi consensus definition

Consensus for inclusion of an outcome is defined for every particular group of stakeholders as ≥70% of responses rating the outcome as "critical" (a score ≥7, and ≤15% of responses rating the outcome "not important", i.e. a score ≤3).[3] Participants will be asked to complete survey rounds within 7 days of receipt; non-respondents will receive reminders for survey completion during an overall survey window of 3 weeks from the original e-mail.

Step 1, part 4: Additional Delphi rounds

Outcomes from round 1 that have reached consensus on "not important for inclusion" will be removed to maximise efficiency by avoiding re-scoring of redundant outcomes. Remaining outcomes and new outcomes identified from round 1 will be carried forward to round 2.

Participants will be shown their own scores from round 1 and summarised scores from each of the three participant groups when re-scoring the outcomes.[16] Participants can report reasons to change any scores.

Participants will repeat scoring for three planned rounds, with possible addition of further rounds, if consensus is not reached but seems obtainable with further rounds.[15]

Step 2, part 1: Establishing the COMS

To determine how to measure the outcomes, we will follow the guideline from The Classroom Observation Schedule to Measure Intentional Communication (COSMIC) initiative for selecting instruments for a COS.[17] We also aim to narrow down a suggested measurement time point/period.

The COSMIC guideline contains 4 steps independent from the modified Delphi process. In the first step, a COS for the target population will be defined. In the second step, all existing outcome measurement instruments will be sought by a systematic literature search for all core outcomes. In the third step, quality of measurement instruments will be measured. In the fourth step, a generic COMS with suggestions for one primary instrument/definition for each outcome will be established.[17]

There is an ongoing scoping review concerning patient-important outcomes other than mortality[18] which will provide us with insight into the most used instruments and the methodological issues around these. Decisions on suggested instruments will be based on methodologic quality assessments using the Consensus-based Standards for the selection of health Measurement Instrument (COSMIN).[19] We do not expect patients and family members to possess academic skills for the COSMIN assessment, and this assessment will thus be conducted by the MC.

Step 2, part 2: Modified Delphi Consensus process

Findings of the consensus process for determining measurement instruments will be similarly reviewed by the PPI-panel and the MC. Consensus meetings may be conducted as described in Step 1. Involvement of the PPI-panel is important for the consensus process when deciding between instruments with equal COSMIN assessment to agree on instruments that are manageable.

Analysis

Attrition bias between rounds

Attrition bias between rounds may occur if non-respondents have different views from those continuing to participate and may lead to missed outcomes or overstated importance of certain outcomes.[20] We aim to limit attrition by pilot testing the survey for intelligibility and face validity by observing how the survey is received. We will display the number of respondents in the completed rounds to ensure transparency as outlined in Table S1 (Supplement).

In case of more than 5% attrition we will use simple imputation for patients not responding in round 2 (or 3) by 'Last Observation Carried Forward' (LOCF) of the previously rated items. We will display both results including imputed values (considered the primary results) and results including completed cases only.

In case of more than 20% attrition in any round but the first for each stakeholder group, we will pragmatically assess whether attrition may introduce bias[3] by calculating medians with inter-quartile ranges (IQR) for each outcome in the previous round for all non-respondents, and compare those responses with the medians and IQRs calculated for participants responding to the current round. If median values appear substantially different (assessed without format statistical comparison) attrition

bias will be considered likely. Regardless of whether attrition bias is considered likely, we will consider the imputed analyses as the primary with the complete case analyses presented in the supplementary materials.

Retention strategy

During the modified Delphi survey rounds, strategies for facilitating retention of participants will be implemented including personal invitations and reminders about the survey completion, provision of contact details for the research team, regular checks to verify and update contact details, and optimising elements of the online survey including interface, conciseness and speed of completion. One author will be assigned to each group of stakeholders to facilitate survey completion.

Sample size

We will include a sample of 30 interviews with patients, family members, and other stakeholders each (i.e., 90 interviews in total). The planned sample size for the semi-structured interviews was selected using the concept of information power considering a vied aim, not use of theory, small population, weak dialogue, and transverse analysis.[21] The interviews will be conducted by phone and analysis strategy with the ambition of investigating the ICU admission trajectory for acutely admitted patients.[21]

The optimal sample size to achieve valid consensus in studies using modified Delphi methods is undetermined and influenced by aspects of practicality, and scope of the question.[3] We estimate that 100 patients, 100 family members and 200 clinicians, researchers and other stakeholders are needed. To minimize attrition bias, which may lead to overestimations of the degree of consensus in the final results, only participants responding favourably to the primary invitation to participate will be recruited.[22]

Statistics

We will use simple descriptive statistics to describe the populations and Delphi responses, i.e. number of respondents, numbers and percentages for categorical data and medians with IQRs for numeric data for the characteristics of participants. Attrition bias will be assessed according to the COMET Handbook as described above.

Software used

All Delphi survey rounds will be delivered electronically using the web-based COMET DelphiManager (COMET Initiative, Liverpool, UK), (www.comet-initiative.org/delphimanager).

To support qualitative analysis of the semi-structured interviews we will use NVivo computer software version 12 (QSR International, Melbourne, Australia). For statistics we will use R (R Foundation for Statistical Computing, Vienna, Austria) and SAS (SAS Institute, North Carolina, US).

We will send the survey link to all eligible patients through a digitally secure electronic mail system (e-Boks) and for other stakeholders, including family members, via e-mail after obtaining their consent. For patients or family members not able to enter data in the web-based survey system, we will invite them to receive a conventional letter containing a hard copy of the survey and a pre-paid envelope to return the survey.

Ethics and dissemination

Participants being interviewed will provide written informed consent, survey participants will consent by ticking 'confirming consent' in the survey, after being advised that participation is voluntary and before any additional responses are collected. Data will be handled confidentially and anonymously, and all participants will be able to withdraw their consent to participate at any time. We seek approval for all participating hospitals and the Danish Data Protection Agency and ensure compliance with General Data Protection Regulation (GDPR). The Ethical Committee for the Capital Region of Denmark has waived the need for ethical approval (H-21010116).

Subject confidentiality is secured by the participating investigators, research staff, and the sponsoring institution. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the MC.

For the COMET Delphi Manager tool, anonymity of all participants will be ensured by individual unique identifiers and data will be stored at a secure location.

We will report the COS in accordance with the COS-STAR checklist.[14] All results will be published in peer-reviewed journals and presented at international conferences.

Discussion

The outlined multiple-methods study will develop a general COS for ICU patients.

Strengths of the study include planned inclusion of a high number of stakeholders in the modified Delphi process and the use of semi-structured interviews. Furthermore, we will adhere to the recommendations by the COMET Handbook and, have prepared this protocol in accordance with relevant recommendations (COS-STAP).[3]

The outlined study comes with limitations too. Primarily, we plan to only include Danish-speaking stakeholders in our modified Delphi process and semi-structured interviews. However, we expect the Danish population, health care system, and society to be generally comparable to other Scandinavian countries[23–26] and probably also other European countries with caution for cultural diversity. Our literature search for outcomes might not be fully comprehensive as we only use two databases, but it was done pragmatically with an existing search used previously for a review.[5] Inspite of only acutely admitted ICU patients being included, we assume that outcomes in the final COS will be relevant for elective ICU patients.[27]

Conclusion

The outlined multiple methods study will develop a COS for general ICU patients which will help outcome selection and prioritisation in future trials conducted in the ICU and simplify comparison and pooling of individual trial results.

Abbreviations:

COMET: Core Outcome Measures in Effectiveness Trials

COMS: core outcome measurement set

COS: core outcome set

COS-STAP: Core Outcome Set – STAndardised Protocol items

COS-STAR: Core Outcome Set – STAndards for Reporting

COSMIC: The Classroom Observation Schedule to Measure Intentional Communication

CRIC: Collaboration of Research in Intensive Care

GDPR: General Data Protection Regulation

GRADE: Grading of Recommendations Assessment, Development, and Evaluation approach

ICU: intensive care unit

IQR: inter-quartile range

MC: management committee

PPI: patient and public involvement

RCT: randomised clinical trial

SMS-ICU: Simplified Mortality Score for the Intensive Care Unit

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Conflict of interest: The Department of Intensive Care at Rigshospitalet (MNK, AG, GVK, PS, CRLB, MHM, EB, MBM, IE, AP and MOC) has received funding for other projects from The Novo Nordisk Foundation, Pfizer, Ferring Pharmaceuticals and Fresenius Kabi, and conducts contract research for AM-Pharma (the REVIVAL trial). The Department of Anaesthesiology, Zealand University Hospital in Køge (SE, CBM and LMK) has received funding for other projects from The Novo Nordisk Foundation and conducts contract research for AM-Pharma (the REVIVAL trial). The Department of Anaesthesia and Intensive Care at Aalborg University Hospital (BSR and SRV) has received funding for other projects from The Novo Nordisk Foundation, Ministry of Higher Education and Science, and conducts contract research for AM-Pharma (the REVIVAL trial). Aarhus University Hospital, Department of Intensive Care (SC) conducts contract research for AM-Pharma (the REVIVAL trial).

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Table 1. Characteristics of all stakeholders who accepted to participate in the Delphi survey round 1

	Patients	Family members	Clinicians	Researchers[i]
Characteristics	# (# to #)	# (# to #)	# (# to #)	# (# to #)
Age(years)[a]				
Sex (female)[b]	# (#%)	# (#%)	# (#%)	# (#%)
Region of residence:				
-Capital Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Region Zealand[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Central Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Northern Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Southern Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
Origins				
- Danish[c]	# (#%)	# (#%)	# (#%)	# (#%)
- Other than Danish[d]	# (#%)	# (#%)	# (#%)	# (#%)
Admission type				
- Surgical[b]	# (#%)			
- Medical[b]	# (#%)			
SMS-ICU[d] at ICU admission[a]	# (# to #)			
- Low <17 point[b,f]	# (#%)			
- High ≥17 point[b,f]	# (#%)			
Self-reported critical illness severity[a,g]	# (# to #)			
ICU length of stay (days)[a]	# (# to #)			

Time since ICU admission (months)[a,h]	# (# to #)			
Family to a deceased patient[b]		# (#%)		
Clinical experience (years)[a]			# (# to #)	# (# to #)
Employed in ICU (experience in years)[a]			# (# to #)	# (# to #)
Professional group				
- Doctor[b]			# (#%)	
- Nurse[b]			# (#%)	
- Physiotherapist[b]			# (#%)	
- Occupational therapist[b]			# (#%)	
- Other[b,j]			# (#%)	
Research experience (years)[a]			# (# to #)	# (# to #)
- Doctor[b]			# (#%)	# (#%)
- Nurse[b]			# (#%)	# (#%)
- Physiotherapist[b]			# (#%)	# (#%)
- Occupational therapist[b]			# (#%)	# (#%)
- Other[b,k]			# (#%)	# (#%)
Time doing research				
- Full-time[b]			# (#%)	# (#%)
- Part-time[b]			# (#%)	# (#%)
- Free-time[b]			# (#%)	# (#%)
Highest obtained academic degree				
- Bachelor			# (#%)	# (#%)
- Master[b]			# (#%)	# (#%)
- PhD or higher[b]			# (#%)	# (#%)

Employment				
- University hospital[b]				# (#%)
- Non-university hospital[b]				# (#%)
- University[b]				# (#%)
- Other[b]				# (#%)

[a] Median (Interquartile (IQR) range).

[b] N (%).

[c] Danish origin has at least one parent born in Denmark with Danish citizenship, (Statistics Denmark, www.dst.dk).

[d] Other than Danish origins covers 'immigrants' born abroad and neither of the parents is a Danish citizen or born in Denmark and 'descendants' born in Denmark and neither of the parents is a Danish citizen or born in Denmark (Statistics Denmark, www.dst.dk).

[e] The Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)[28] is a severity score that predicts 90-day mortality with higher points meaning higher risk of mortality. The range of points is 0-42.

[f] To assure a balanced distribution of patients with higher mortality risk ≥17 (predicted 90-day mortality risk of 25.3% and above) vs. lower risk <17 (predicted 90-day mortality risk of 22.8% and below).[28]

[g] Self-reported severity of illness assessed on a numeric score (0-10 where 0 is non-critical and 10 is most critical).

[h] From either the patients' view or from the view of family members to ICU patients.

[i] Researchers (including clinician-researchers) conducting research in the ICU setting or in adjacent populations of critically ill patients.

[j] Other professional backgrounds will be specified in the footnote.

[k] Other research experience than listed will be described.

Table 2. Characteristics of all stakeholders who accepted to participate in the semi-structured interviews

Characteristics	Patients	Family members	Clinicians	Researchers[i]
Age(years)[a]	# (# to #)	# (# to #)	# (# to #)	# (# to #)
Sex (female)[b]	# (#%)	# (#%)	# (#%)	# (#%)
Region of residence:				
-Capital Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Region Zealand[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Central Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Northern Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
-Southern Region[b]	# (#%)	# (#%)	# (#%)	# (#%)
Origins				
- Danish[c]	# (#%)	# (#%)	# (#%)	# (#%)
- Other than Danish[d]	# (#%)	# (#%)	# (#%)	# (#%)
Admission type				
- Surgical [b]	# (#%)			
- Medical [b]	# (#%)			
SMS-ICU[d] at ICU admission[a]	# (# to #)			
- Low <17 point[b,f]	# (#%)			
- High ≥17 point[b,f]	# (#%)			
Self-reported critical illness severity[a,g]	# (# to #)			
ICU length of stay (days)[a]	# (# to #)			

Time since ICU admission (months)[a,h]	# (# to #)			
Family to a deceased patient[b]		# (#%)		
Clinical experience (years)[a]			# (# to #)	# (# to #)
Employed in ICU (experience in years)[a]			# (# to #)	# (# to #)
Professional group				
- Doctor[b]			# (#%)	
- Nurse[b]			# (#%)	
- Physiotherapist[b]			# (#%)	
- Occupational therapist[b]			# (#%)	
- Other[b,j]			# (#%)	
Research experience (years)[a]			# (# to #)	# (# to #)
- Doctor[b]			# (#%)	# (#%)
- Nurse[b]			# (#%)	# (#%)
- Physiotherapist[b]			# (#%)	# (#%)
- Occupational therapist[b]			# (#%)	# (#%)
- Other[b,k]			# (#%)	# (#%)
Time doing research				
- Full-time[b]			# (#%)	# (#%)
- Part-time[b]			# (#%)	# (#%)
- Free-time[b]			# (#%)	# (#%)
Highest obtained academic degree				
- Bachelor			# (#%)	# (#%)
- Master[b]			# (#%)	# (#%)
- PhD or higher[b]			# (#%)	# (#%)

Employment				
- University hospital[b]				# (#%)
- Non-university hospital[b]				# (#%)
- University[b]				# (#%)
- Other[b]				# (#%)

[a] Median (Interquartile (IQR) range).

[b] N (%).

[c] Danish origin has at least one parent born in Denmark with Danish citizenship, (Statistics Denmark, www.dst.dk).

[d] Other than Danish origins covers 'immigrants' born abroad and neither of the parents is a Danish citizen or born in Denmark and 'descendants' born in Denmark and neither of the parents is a Danish citizen or born in Denmark (Statistics Denmark, www.dst.dk).

[e] The Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)[28] is a severity score that predicts 90-day mortality with higher points meaning higher risk of mortality. The range of points is 0-42.

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[g] Self-reported severity of illness assessed on a numeric score (0-10 where 0 is non-critical and 10 is most critical).

[h] From either the patients' view or from the view of family members to ICU patients.

[i] Researchers (including clinician-researchers) conducting research in the ICU setting or in adjacent populations of critically ill patients.

[j] Other professional backgrounds will be specified in the footnote.

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Figure 1

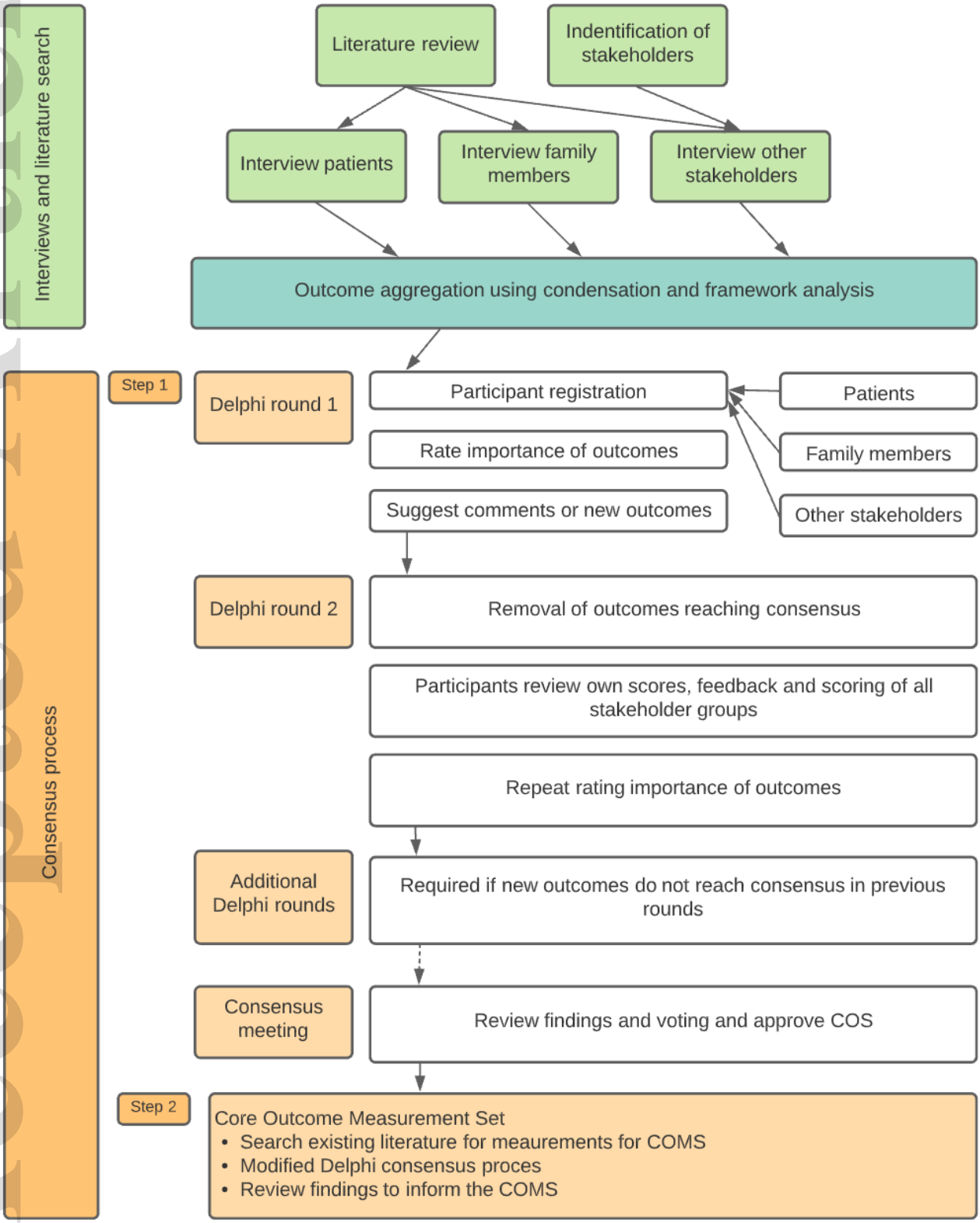

Figure 1. Flow diagram outlining the core outcome set (COS) development. Steps required for consensus for the COS and core outcome measurement set (COMS) instruments are summarised. Dashed lines (----) indicate specific requirements for a consensus meeting determined on completion of the modified Delphi consensus process.