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Protocol for the development of Core Outcome Sets for trials on the management of Atrial fiBrillAtion in Critically Unwell patientS (COS-ABACUS)

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Abstract

Introduction Atrial fibrillation (AF) is the most common cardiac arrhythmia in critically unwell patients. New onset atrial fibrillation (NOAF) affects 5%-11% of all admissions and up to 46% admitted with septic shock. NOAF is associated with increased morbidity, mortality, and healthcare costs. Existing trials into the prevention and management of NOAF suffer from significant heterogeneity making comparisons and inferences limited. Core outcome sets (COS) aim to standardise outcome reporting, reduce inconsistency between trials and reduce outcome reporting bias. We aim to develop an internationally agreed COS for trials of interventions on the management of NOAF during critical illness.

Methods and analysis Stakeholders including intensive care physicians, cardiologists, and patients will be recruited from national and international critical care organisations. COS development will occur in 5 stages: *1)* Outcomes included in trials, recent systematic reviews, and surveys of clinician practice and patient focus groups will be extracted. *2)* Extracted outcomes will inform a two-stage e-Delphi process and consensus meeting using GRADE methodology. *3)* Outcome measurement instruments (OMIs) will be identified from the literature and a consensus meeting held to agree OMI for core outcomes. *4)* Nominal group technique will be used in a final consensus meeting to the COS. *5)* The findings of our COS will be published in peer-reviewed journals and implemented in future guidelines and intervention trials.

Ethics and dissemination The study has been approved by the University of Liverpool ethics committee (Ref: 11256. 21/06/2022), with a formal consent waiver and assumed consent. We will disseminate the finalised COS via national and international critical care organisations and publication in peer-reviewed journals.

Strengths and limitations of this study

- A comprehensive review of the literature, drawing upon the most recent systematic reviews and an updated literature search.
- Large representative stakeholder group from the fields of cardiology and intensive care medicine.
- Patient involvement central to the development of COS-ABACUS and in accordance with the core outcome set (COS) standards of development and COMET initiative recommendations
- Steering committee comprising experts in the field of atrial fibrillation and COS development.
- A limitation of our study is that high-income countries will likely be overrepresented in our stakeholder group; we will attempt to overcome this by embedding the involvement of low-income and middle-income countries, which will increase generalisability of COS-ABACUS.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 33 million people worldwide[1]. New onset atrial fibrillation (NOAF) has been defined as AF developing in patients with no past medical history of AF. NOAF is the most common cardiac arrhythmia in critically unwell patients. NOAF affects between 5% - 11% of critically unwell patients admitted to the intensive care unit (ICU) and up to as many as 46% of patients admitted with septic shock[2,3]. The development of NOAF in critically unwell patients is associated with haemodynamic instability, higher mortality, increased ICU and hospital length of stay, thromboembolism, and the development of chronic permanent AF (PAF)[2].

Guidelines for the management of AF have been published by the National Institute of Health and Care Excellence (NICE)[4], the American College of Cardiology/American Heart Association (AHA/ACC)[5], the Canadian Cardiovascular Society[6], Asia Pacific Heart Rhythm Society[7], Japanese Circulation Society[8] and the European Society of Cardiology (ESC)[9]. However, they are not directly applicable to patients developing NOAF during critical illness and are largely based upon expert consensus[10]. In recent years a number of systematic reviews have been published with the aim of determining the optimal treatment strategy for NOAF based upon available trial data[10–13]. Despite the inclusion of over 50 studies across four systematic reviews, interpretation of the evidence is limited due to significant flaws in trial design and heterogeneity between studies. The definition of clinically relevant NOAF varied between trials, and some authors included any atrial

tachyarrhythmia as being clinically relevant. Similarly, trials differed significantly in chosen outcome measures and definitions of treatment success. Cardioversion to sinus rhythm and control of heart rate were commonly reported treatment outcomes, however, studies differed significantly in the time period used to define successful cardioversion and the magnitude of heart rate reduction considered to represent a clinically meaningful outcome. Given the morbidity and mortality associated with the development of NOAF, there is an urgent need for adequately powered randomised controlled trials. However, the lack of standardised definitions for NOAF and standardised reproducible outcomes in trials investigating NOAF hinders comparison between trials and development of new management guidelines based upon the best evidence.

Core outcome sets (COS) are agreed standard outcomes that should be reported in all clinical trials investigating specific areas of healthcare or specific healthcare conditions [14]. The use of COS aims to reduce inconsistency between trials and address the issue of outcome reporting bias[15,16]. COS define the minimum outcomes that should be measured and reported by clinical trials in a particular area of interest (e.g., disease, intervention, or condition). Previous COS for AF trials have been developed and published elsewhere[17–20]. However, these COS largely focus on AF developing as part of a chronic progressive arrhythmia spectrum rather than NOAF during acute critical illness. However, patients developing NOAF during critical illness represent a unique patient population with distinct risk factors for the development of AF and different treatment goals compared to patients that develop chronic PAF[2]. Due to these differences, there is the need for a COS that specifically addresses AF developing in critically unwell patients. Therefore, COS-ABACUS aims to achieve international consensus on a minimum dataset of outcomes for inclusion in future trials on AF in critically unwell patients.

Methods and analysis

This study aims to develop a COS for use in trials on the management of NOAF in critically unwell patients. Critically unwell has been variable defined but for the purposes of COS-ABACUS we will use the definition: “a state of ill health with vital organ dysfunction, a high risk of imminent death if care is not provided and the potential for reversibility.”[21] We will utilise an international group of patients, researchers, and clinicians to reach a consensus on a COS.

The COS will be developed following the methodology of the COMET initiative as set out in the COMET Handbook.[15] We will develop the COS following the standards of the Core Outcome Set-STAandards for Development (COS-STAD) and report the COS following the Core Outcome Set-STAndards for Reporting (COS-STAR) recommendations.[14,22] This study was prospectively registered on the COMET Initiative registry of COS (registration number: 2058, Accessible at https://www.comet-initiative.org/Studies/Details/2058).

Scope of COS-ABACUS

A number of core outcome sets for AF trials have been published elsewhere.[20,23] However AF includes a broad spectrum of clinical manifestations and previous COS have

been largely focussed on chronic AF or PAF rather than AF as part of critical illness. In COS-ABACUS we will limit the scope of our COS to adults over 18 years of age who develop NOAF during critical illness. Target interventions will be any pharmacological and non-pharmacological management strategies for the management of atrial fibrillation.

A detailed description of the scope of COS-ABACUS is presented (Table 1) as per COS-STAD recommendations[14].

Table 1. Scope of COS-ABASCUS presented as per COS-STAD recommendations

Domain	Standard	COS-ABACUS
Scope	Setting	Intensive care Critical care
	Condition	Atrial fibrillation 1) New onset AF 2) Pre-existing AF
	Population	Critically unwell* patients *"a state of ill health with vital organ dysfunction, a high risk of imminent death if care is not provided and the potential for reversibility"[21]
	Interventions	Any intervention including but not limited to: 1) Pharmacological anti-arrhythmic 2) Non-pharmacological anti-arrhythmic (DCCV) 3) Anticoagulation
Stakeholders involved	Users	Clinical researchers, trialists, guideline developers, policy makers
	Healthcare professionals	Doctors, nurses, pharmacists, physiologists with expertise in AF
	Patients	Patients that develop AF whilst critically unwell or have pre-existing AF admitted to intensive care, patient representative organisations (e.g. Arrhythmia Alliance)

Consensus process	Initial list of outcomes	Systematic review (Johnston et al Review of outcomes in previous systematic review (O'Bryan et al[13], Drikite et al[10], Wetterslev et al[24], Kanji). User surveys (Chean et al[25], Labbe et al[26], Wetterslev et al[27].
	a priori scoring process and consensus definition	Delphi study
	a priori criteria for inclusion/exclusion/adding outcomes	Delphi study
	Avoid ambiguity in language used in the list of outcomes	

Study oversight

A steering committee will provide expert oversight and guide all elements of the development of the COS-ABACUS. Members of the steering committee will be selected based on their expertise in the fields of critical care medicine (IW, BJ, OC), evidence and data synthesis (RH), and COS development in intensive care (BB) and cardiology (GL). The steering committee will be responsible for management and coordination of each stage of the COS development.

Stakeholders and recruitment

COMET methodology recognises that multiple stakeholders provide differing and expert insights into determining relevant outcomes.[15] To ensure that the group of stakeholders is as broad and as representative we will recruit members internationally without any geographical or time zone limitations. We will invite stakeholders from several professional groups including:

1) Clinicians primarily practicing in intensive care, anaesthetics, and cardiology specialities
2) Nurses and allied health professionals who have a primary role in critical care practice
3) Researchers and trial investigators that are primary or senior authors of research evaluating interventions for AF in critically unwell patients
4) Policy makers/funders that have been involved in funding or commissioning research into AF in critically unwell patients
5) Patients with experience of critical care and those that were treated for AF as part of being critically unwell

National and international speciality organisations will be approached by email and asked to disseminate information regarding COS-ABACUS to their membership via email lists, organisation social media, and organisation newsletters. Details of COS-ABACUS will also be disseminated via the COS-ABACUS social media account. We will target speciality groups related to intensive care medicine, cardiology and critical care research.

Potential participants interested in being involved as a stakeholder will be invited to register their details using an online form. Participants will be invited to stakeholder groups based upon expert knowledge and experience from information gathered when registering.

We will approach first and senior authors of trials included in the most recent systematic reviews on the management of NOAF in critically unwell patients[10–12]. The editors of speciality journals will be approached for nomination of stakeholder participants based upon previously published work in the field of AF in critically unwell patients. In addition we will conduct a search of Expertscape and SCOPUS databases to identify researchers with an interest in AF in critically unwell patients.[28,29]

Patient and public involvement

Patient involvement is an important and integral aspect in COS development.[15] We will approach national patient organisations to ensure that the group of patient stakeholders is as broad as possible and includes patients with an interest in AF or intensive care.[30,31] A full list of patient organisations that will be approached is provided in Supplementary material. Table 1. Organisations will be asked to provide information regarding COS-ABACUS to potential stakeholder participants. Potential patient stakeholders will be invited to complete an online form to register their interest in participating in COS-ABACUS. Prior to the Delphi process in stage 2 of COS-ABACUS a virtual meeting will be held with patient stakeholders during which the aims, methodology involved, and process of COS-ABACUS will be discussed. Patient stakeholders will have the opportunity to clarify any concerns or aspects of COS-ABACUS that are not clear. We will involve a patient research ambassador with experience of cardiovascular research to help ensure patient stakeholders voice are fully represented in COS-ABACUS. The patient research ambassador's role will be to guide patient stakeholders through the core outcome set process and methodology rather than take part as a stakeholder. During this initial meeting patients will be asked to discuss outcomes that they feel are important and will be asked to anonymously submit outcomes for inclusion in the list of outcomes that will be progressed to stage 1 of COS-ABACUS in preparation for the e-Delphi rounds in stage 2.

Low-income and middle-income countries

To ensure as broad and as representative as possible stakeholder group we aim to ensure that we recruit professional and patient stakeholders from low-income and middle-income countries (LMIC). During review of articles included in stage 1 we will assess relevant publications from LMIC. We will invite first and senior authors to become stakeholders in COS-ABACUS. Our co-investigator (Prof. Bronagh Blackwood) is lead of the Outcome Measures Working Group at the International Forum for Acute Care Trialists (InFACT) and will be instrumental in increasing representation from LMIC in COS-ABACUS. InFACT is a

network of investigator-led clinical research groups and academic institutions that crucially include representation from the North African Network for Intensive Care Medicine Research (NANICM Research), Latin American Critical Care Trials Investigators Network (LACCTIN), Latin American Sepsis Institute (LASI) and the Latin America Intensive Care Network (LIVEN). We will engage with and include InFACT as one of our stakeholder organisations.

We will ensure all material relating to COS-ABACUS is translated into preferred languages for stakeholders who do not speak English as a first language. We aim to conduct COS-ABACUS Delphi process and consensus meetings online to ensure that as many stakeholders can participate as possible and not be limited by geography or time zones. We will work with stakeholders from LMIC and other time zones to ensure they can attend consensus meetings online and if required conduct more than one meeting.

A full list of organisations that will be approached is provided in Supplementary material. Table 1.

Design of COS-ABACUS

COS-ABACUS will involve five stages (Figure 1):

Stage 1: Identifying potentially relevant outcomes through patient stakeholder focus group meetings, an up-to-date systematic review of clinical trials, review of previous systematic reviews and review of clinically relevant outcomes reported in survey responses from clinicians on the management of atrial fibrillation.

Stage 2: Determining core outcomes by relevant stakeholder group using an online Delphi process followed by a consensus meeting to finalise core outcome recommendations.

Stage 3: Determining measurement instruments for core outcomes through literature review and quality assessment of outcome instruments using the COMET/COSMIN guidelines and COSMIN risk of bias tool. Outcomes will be displayed using a summary of measurement properties table.

Stage 4: A final consensus meeting will take place to finalise core outcome instruments selected in stages 2 and 3.

Stage 5: COS-ABACUS will be disseminated to all stakeholders' groups, presented internationally, and published in a peer-reviewed journal.

Study status

We aim to commence the updated systematic review included in Stage 1 in June 2023. In parallel we aim to commence recruitment of participants through national and international organisations to COS-ABACUS. COS-ABACUS will run for 48 months with completion of all e-Delphi rounds, consensus meetings and COS-ABACUS finalised by June 2025.

Stage 1: Identifying potential outcomes

Systematic literature review

In stage one we will extract outcomes reported in trials included in our recently published systematic review of the management of NOAF in critically unwell adult patients. The full protocol for our systematic review and the final systematic review are published elsewhere[11,32]

In addition we will retrieve outcomes from trials included in two recently published systematic reviews by O'Bryan et al, Drikite et al and a scoping review published by Wetterslev et al.[10,24,33]

A list of trials included in each systematic review will be retrieved. Following removal of duplicates the following information will be extracted by two reviewers (BWJ, OC):

1) Definition of NOAF
2) Diagnostic criteria for NOAF
3) Any other arrhythmia reported in trials
4) All primary and secondary outcomes reported in trials
5) Definitions of primary and secondary outcomes (where provided)
6) Any patient reported outcomes (where provided)
7) Risk of Bias assessment of included trials
8) Country in which trial was conducted

We will assess all systematic reviews against the criteria described by the COSMIN and COMET initiative[34,35]. We will extract reported risk of bias assessment for individual studies and any quality assessment documented for individual studies[34,35].

To ensure a comprehensive list of outcomes we will rerun the original search strategy (Supplementary material. Table 2) used in our systematic review[11]. We will retrieve any articles published after the publication of our systematic review and assess them for inclusion based upon our systematic review inclusion and exclusion criteria (Supplementary material. Table 3) Outcomes and outcome definitions used in these trials will be extracted.

We will generate tables displaying outcomes in rank order with a description of each outcome. We anticipate that studies will differ in the definition of the outcomes used, therefore we will report each definition and calculate the frequency with which different individual definitions are used. Outcomes will be grouped into domains based upon the taxonomy proposed in the COMET handbook[15]. COMET taxonomy includes the following proposed domains: (1) Mortality, (2) Physiological, (3) Infection, (4) Pain, (5) Quality of Life, (6) Mental Health, (7) Psychosocial, (8) Functional, (9) Compliance, (10) Satisfaction, (11) Resource Use, (12) Adverse events.

User surveys

To provide an insight into the setting and contextual factors that need to be considered in the development of COS-ABACUS we will review previously published surveys of clinicians practice regarding the management of atrial fibrillation in critically unwell patients[25,26,36] We will aim to identify clinically important outcomes reported by clinicians treating atrial fibrillation in critically unwell patients. We will undertake a quality assessment of any outcome measures using COSMIN checklist methodology[34].

The output from stage one of COS-ABACUS will be a comprehensive list of outcomes used in previous trials and user surveys from clinicians who manage NOAF in critically unwell patients. Outcomes will be ranked according to their frequency in published trials. We anticipate that similar outcomes will be defined differently between trials. We will include the outcome and definitions used. As part of the e-Delphi and consensus process, we will seek to determine the most used definitions and reach consensus on a definition to be reported as part of COS-ABACUS.

Stage 2: Determining core outcomes

Delphi questionnaire

We will undertake an electronic Delphi (e-Delphi) which uses a bespoke online e-management system that is maintained by the COMET initiative.[37] The e-Delphi process will be conducted in accordance with the published recommendations of the COMET initiative.[37,38]

There are no published recommendations for the optimal number of participants in Delphi rounds. We will attempt to recruit as large a panel size as possible and will aim for at least 5 – 10 participants from each group of stakeholders. (Supplementary material. Table 1).

To limit attrition between e-Delphi rounds we will send personalised email invitations with a clear study outline with timelines for each e-Delphi round. Each e-Delphi questionnaire will be open for 14 days with an automated email reminder distributed on day 7. We will conduct the second e-Delphi round not more than four weeks following completion of round 1.

When participants agree to take part in the e-Delphi process they will receive study documents that outline the importance of completing all rounds, a summary of time required and plain language summaries. We aim to conduct two e-Delphi rounds followed by one consensus meeting.

Delphi rounds

In round one of the e-Delphi process we will present outcomes extracted from systematic reviews, user surveys, and patient focus groups, in stage one.

To limit presentation bias, we will present outcomes in alphabetical order and provide a plain language definition of each outcome. Participants will be asked to score each outcome

on a Likert scale of 1-9 as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale.[39] The GRADE scale categorises scores between 1-3 as 'not that important', between 4-6 as 'important but not critical' and scores between 7-9 as 'critically important.'[39] During round one participants will also be asked to provide up to 5 additional outcomes they feel are important but are missing from the outcomes list. Participants will also have the opportunity to highlight if they would like to modify existing outcomes. New outcomes suggested during rounds 1 and/or 2 will be coded and added into the list of outcomes in alphabetical position. Where uncertainty exists, outcomes will be reviewed by the steering committee.

To help define the composition of the e-Delphi panel we will collect demographic data for each participant that will be stored on a separate database. Demographic data will include, age, country, years of experience, field of practice, current position, and organisation that participants are affiliated with. Patient participants will also be asked if they are an ICU survivor, have been diagnosed with NOAF or AF or are affiliated with a particular national or international organisation. Each participant will be provided with a unique identifier to ensure answers and summary reports are anonymised. Completion of the e-Delphi survey will assume implied consent. If participants wish to withdraw their responses, they may do so within one week. After one week we will anonymise the responses and disaggregate them from participant identifiable information therefore it will not be possible to responses to be withdrawn for individuals.

A summary report of round 1 of the e-Delphi will be prepared. Outcomes for which 70% or more of participants score 7-9 on the Likert scale and 30% or less score 1-3 on the Likert scale will be retained and presented in round 2[15]. New outcomes suggested in round 1 will be presented and participants will again be asked to score each outcome on a Likert scale of 1-9 as per GRADE scale.[39]

We anticipate the potential for a significant number of outcomes to be derived during stage one of COS-ABACUS and during round 1 of the e-Delphi. Following publication of the results of e-Delphi round 1 we will hold a feedback session before e-Delphi round 2. Participants will be provided the opportunity to discuss the results of e-Delphi round 1 and will have the opportunity to discuss the outcomes. Patient stakeholders will also be given the opportunity to discuss the results and will be supported by the patient stakeholder ambassador throughout the process. At the end of the feedback session participants will be provided a summary of the discussion prior to taking part in e-Delphi round 2.

During e-Delphi round 2 participants will receive a summary of their own responses, responses by stakeholder group and summary of the feedback session. Participants will be invited to re-review their e-Delphi round 1 rating and provide e-Delphi round 2 ratings for new outcomes.

Responses during e-Delphi round 2 will be analysed as for round 1. At the end of round 2 outcomes considered of ranked 7-9 (critical importance) by 70% of participants will be included in the list of candidate outcomes that will be progressed to the consensus meeting. If there is significant disagreement or significant numbers of new outcomes suggested between e-Delphi rounds we will consider holding more than two e-Delphi processes.

Consensus meeting

Following the e-Delphi process the steering committee will discuss the list of outcomes generated and consider whether a consensus meeting is required. If the list of outcomes is small and there is significant consensus between stakeholders, then a consensus meeting may not be necessary. We will therefore progress to stage 3 of COS-ABACUS.

Participants that complete the two e-Delphi rounds will be invited to participate in the consensus meeting. We will hold two virtual consensus meetings to allow participants from different time zone localities to participant. The Nominal Group Technique will be utilised to finalise and develop the COS.[15,40,41] In the consensus meeting we will present the outcomes included following the second e-Delphi round. Outcomes will be presented by stakeholder group and identify any differences between groups. We will ensure that each participant is happy with the definition and understanding of the outcome through group discussion and allowing all participants the opportunity to discuss their views. Following discussion, participants will be asked to vote 'yes' or 'no' anonymously for inclusion in the final list of outcomes for inclusion in the COS. Outcomes will be classified as 'critical,' 'important but not critical' and 'not that important.' Further rounds of voting my take place until all participants reach consensus.[15,40,41] For inclusion in the COS >70% of participants will be required to vote 'yes' for inclusion of that outcome.

Stage 3: Determining how to measure core outcomes

Stage 3 of COS-ABACUS will be concerned with establishing how to define and measure the core outcomes and outcome measurement instruments (OMI's) agreed by consensus in stage 2. We will follow the recommendations by COSMIN and COMET for selected OMI's for outcomes included in COS-ABACUS.[34] The joint initiative by COSMIN and COMET describe the selection of OMI's involving four main steps:

(1) Conceptual considerations, during which the outcome and target population will be defined. Target populations will be defined taking into consideration relevant subgroups such as age and gender. The context of use will also be considered (e.g., in hospital, ambulatory or in the community) [15,34].
(2) Finding existing OMI's in the literature,
(3) Quality assessing the OMI's by evaluating the measurement properties and feasibility of the OMI's and
(4) Generic recommendation on the selection of OMI's[15,34]

Data on OMI's will be extracted by two reviewers (BWJ and OC) from the trials retrieved and included in stage 1 of COS-ABACUS. The SPIRIT 2013 criteria will be used as a framework for extracting data on how outcomes are measures. Outcome data will include (1) the specific name of the variable, (2) analysis metric of the variable (e.g. change from baseline, time to event), (3) method of aggregation (e.g. median, proportion), and (4) timepoint for the outcome[42]. For patient reported outcomes we will use the SPIRIT12-PRO Extension and SPIRIT13-PRO Extension to guide data extraction.[42,43]

OMI's utilised in NOAF trials will be identified during Stage 1 of COS-ABACUS. We will report the frequency and definition of each OMI. Outcome measures will also be extracted from previous outcome parameters established for ambulatory/chronic atrial fibrillation trials.[20,23] We will quality assess the evidence of included OMI's as described by COSMIN[44]. Each OMI will be assigned a quality rating of high, moderate, low, very low or unknown as described by COSMIN and in agreement with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[35,39]

Stage 4: Finalising core outcome set for atrial fibrillation

Participants involved in the previous e-Delphi rounds will be invited to participate in a second consensus meeting. We will hold two consensus meetings to allow participants in different time zones to participate. The aim of the second consensus meeting will be to establish how best to measure the core outcomes and finalise COS-ABACUS. We will rank OMI's for inclusion in the COS based on the findings of stage 3 of COS-ABACUS. We will present the core outcomes, OMIs and quality of the evidence to key stakeholders during virtual consensus meeting. Using Nominal Group Technique stakeholders will have the opportunity to discuss the OMIs following which they will be asked to vote on OMIs that will be included in COS-ABACUS[41]. We aim to include only one OMI for each core outcome. OMI's will only be included in the final COS if >70% of participants vote 'yes' for their inclusion.

Ethics and dissemination

We obtained ethics approval and formal consent waiver and assumed consent from the University of Liverpool ethics committee (Ref: 11256. 21/06/2022). All answers during the e-Delphi rounds and consensus meetings will be anonymised and only group results will be presented to participants. Agreement to partake in the e-Delphi rounds and consensus meetings will be taken as assumed consent.

A dissemination plan for COS-ABACUS will be agreed by the steering committee. National and International organisations that nominated a stakeholder will be provided with a two-page infographic and copy of the findings agreed COS of COS-ABASCUS. COS-ABACUS will be reported in a peer-reviewed journal. Findings will also be presented at national and international conferences in the fields of intensive care medicine and cardiology. We will also present COS-ABACUS via social media and invite stakeholder organisations to disseminate the COS to interested parties.

Discussion

COS-ABACUS will be the first COS designed for use in observational and interventional trials of NOAF in critically unwell patients. Previous AF related COS have been designed for use in trials investigating chronic AF or PAF. Typically, the goals of treatment and management aims in chronic AF compared to NOAF and this is often reflected in the design and outcomes of research trials. Existing trials investigating NOAF in critically unwell patients have been

difficult to interpret given the heterogeneity between what was defined as NOAF, how NOAF was identified and the trials primary and secondary outcomes. It remains unclear how best to manage NOAF, whether a rate control strategy or rhythm control strategy should be employed, what is defined as optimal rate control and whether anticoagulation is required for episodes of NOAF during critical illness. There is an urgent need for adequately powered well designed studies to address these questions. By developing a comprehensive COS, it will be possible to compare studies investigating different management strategies for NOAF.

Strengths and limitations

We believe our study is the first aiming to develop a core outcome set for NOAF in critically unwell patients. Existing core outcome sets have focused on AF as part of a chronic arrhythmia spectrum. A limitation of our study may be that there will be considerable overlap in core outcomes generated in our study and those of existing core outcome sets. Despite this we believe it is important to highlight common areas of concern to patients and stakeholders between NOAF in critically unwell patient and those with pre-existing AF. We also believe that as patients recover from their critical illness core outcomes important in the long-term management of AF will become more prevalent and important to individual patients and stakeholders. This is important to recognise as long-term outcomes is an area of increasing interest in survivors of critical illness. We aim to include a broad a group of stakeholders as possible. We hope to include LMIC and have factored in translation costs, meetings online and more than one meeting to allow as many stakeholders in different geographical areas as possible to contribute. Despite this we are limited in stage 1 of COS-ABACUS to those studies that are already published in the literature and anticipate that the majority of studies will be English language and lack input from LMIC. Whilst this is an obvious limitation, we hope that COS-ABACUS will highlight the importance of LMIC in future clinical trials investigating the management of NOAF.

Contributors

BWJ, IW, RH and BB conceived COS-ABACUS based upon a previous systematic review. All authors (BWJ, RH, BB, IW, and GL contributed to the study design, and drafting of the manuscript. BB and RH provided significant input into COS methodology and will provide expert oversight of all aspect of COS-ABACUS. BWJ, and IW will be involved with data extraction, analysis and interpretation for our updated systematic review. All authors have read and approved the manuscript.

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Completing interests

The authors have no competing interests to declare.

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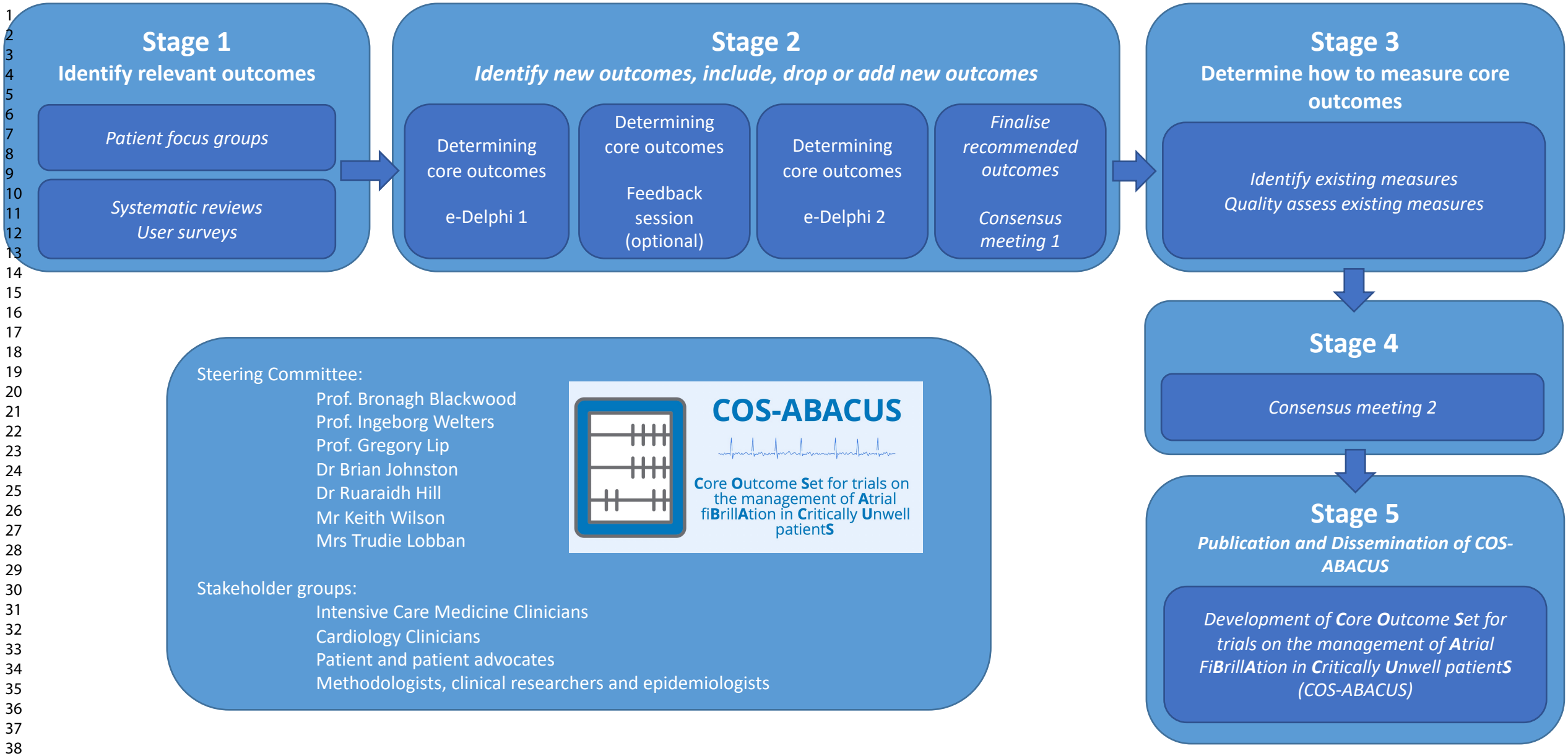
Figure title:

Figure 1. Diagrammatic representation of the stages involved in COS-ABACUS


Stage 1
Identify relevant outcomes
Patient focus groups
Systematic reviews
User surveys
Stage 2
Identify new outcomes, include, drop or add new outcomes
Determining core outcomes
e-Delphi 1
Determining core outcomes
Feedback session (optional)
Determining core outcomes
e-Delphi 2
Finalise recommended outcomes
Consensus meeting 1
Stage 3
Determine how to measure core outcomes
Identify existing measures
Quality assess existing measures
Stage 4
Consensus meeting 2
Stage 5
Publication and Dissemination of COS-ABACUS
Development of Core Outcome Set for trials on the management of Atrial FiBrillAtion in Critically Unwell patientS (COS-ABACUS)
Steering Committee:
Prof. Bronagh Blackwood
Prof. Ingeborg Welters
Prof. Gregory Lip
Dr Brian Johnston
Dr Ruaraidh Hill
Mr Keith Wilson
Mrs Trudie Lobban
COS-ABACUS
Core Outcome Set for trials on the management of Atrial fiBrillAtion in Critically Unwell patientS
Stakeholder groups:
Intensive Care Medicine Clinicians
Cardiology Clinicians
Patient and patient advocates
Methodologists, clinical researchers and epidemiologists

Supplementary Material Table 1

STAKERHOLDER GROUPS INCLUDED IN COS-ABACUS	
STAKEHOLDER GROUP	Organisation
(1) INTERNATIONAL AND NATIONAL INTENSIVE CARE ORGANISATIONS	Intensive Care Society (UK)
	Faculty of Intensive Care Medicine (UK)
	Royal College of Anaesthetists (UK)
	Intensive Care Society of Ireland (Ireland)
	British Association of Critical Care Nurses
	European Federation of Critical Care Nursing Associations (Europe)
	European Society of Anaesthesiologist's (Europe)
	European Society of Intensive Care Medicine (Europe)
	Society of Critical Care Medicine (USA)
	Critical Care Societies Collaborative (USA)
	American College of Chest Physicians (USA)
	American Thoracic Society (USA)
	American Association of Critical Care Nurses (USA)
	Canadian Critical Care Society (Canada)
	Australian and New Zealand Intensive Care Research Centre (Australia, New Zealand)
	Australian College of Critical Care Nurses (Australia)
	Australia and New Zealand Intensive Care Society (Australia, New Zealand)
	Chinese Society of Critical Care Medicine (China)
	Japanese Society of Intensive Care Medicine (Japan)
	World Federation of Intensive and Critical Care
(2) INTERNATIONAL AND NATIONAL CARDIOLOGY ORGANISATIONS	British Heart Foundation (UK)
	British Cardiovascular Society (UK)
	European Society of Cardiology (Europe)
	Canadian Cardiovascular Society (Canada)
	American College of Cardiology (USA)
	American Heart Association (USA)
	Cardiology Society of Australia and New Zealand (Australia and New Zealand)
	Chinese Society of Cardiology (China)
	Japanese Circulation Society (Japan)
	Korean Society of Cardiology (Korea)
	South African Heart Association (South Africa)
(3) PATIENT REPRESENTATIVE GROUPS	Arrhythmia Alliance
	AF Association
	ICUSteps
	COMET PoPPIE working group
(4) ACADEMIC AND	National Association of Academic Anaesthetists

RESEARCH / MIXED STAKEHOLDER GROUP	Intensive Care National Audit and Research Centre
	National Institute for Health and Care Research
	United Kingdom Critical Care Research Group (UK)
	China Critical Care Clinical Trial Group (China)
	Canadian Critical Care Trials Group (Canada)
(5) JOURNAL EDITORS	Journal of the American College of Cardiology
	Circulation
	Journal of the American Heart Association
	JAMA Cardiology
	Circulation Research
	European Heart Journal
	International Journal of Cardiology
	Nature Reviews Cardiology
	Heart Rhythm
	American Heart Journal
	American Journal of Respiratory and Critical Care Medicine
	Intensive Care Medicine
	Critical Care Medicine
	Critical Care
	Chest
	Annals of Intensive Care
	European Heart Journal: Acute Cardiovascular Care
	Journal of Intensive Care
	Journal of Intensive Care Medicine
	Journal of Critical Care
(6) LMIC SPECIFIC STAKEHOLDER GROUPS	
	Outcome Measures Working Group of International Forum for Acute Care Trialists (InFACT)
	North African Network for Intensive Care Medicine Research (NANICM Research)
	Latin American Critical Care Trials Investigators Network (LACCTIN)
	Latin American Sepsis Institute (LASI)
	Latin American Intensive Care Network (LIVEN)
	Jaffna University, Sri Lanka

Supplementary material Table 2.

Medline and Embase search strategies that will be used in systematic review.

Databases	Date searched	No. retrieved
MEDLINE (Ovid), Epub ahead of print and MEDLINE In-Process (Ovid)	11/12/2018	662
EMBASE (Ovid)	11/12/2018	1298

Search strategies

Database: Medline

Strategy used:

1	Atrial Fibrillation/	48328
2	(Atrial* adj2 (Fibrillat* or flutter)).tw.	63328
3	AF.tw.	34240
4	(tachycardia or tachyarrhythmia or arrhythmia or supraventricular).tw.	87656
5	1 or 2 or 3 or 4	160116
6	((new* or recent*) adj1 diagno*).tw.	63298
7	(onset* or new*).tw.	3048950
8	6 or 7	3053023
9	Critical Care/	47996
10	Critical Illness/	24797
11	((critical* or intensiv*) adj4 (care or ill*)).tw.	176778
12	((critical* or intensiv*) adj4 (care or ill* or unwell*)).tw.	176812
13	9 or 10 or 11 or 12	198998
14	5 and 8 and 13	662

Database: Embase

Strategy used:

1	Atrial Fibrillation/	41928
2	(Atrial* adj2 (Fibrillat* or flutter)).tw.	109441
3	AF.tw.	65045
4	(tachycardia or tachyarrhythmia or arrhythmia or supraventricular).tw.	121780
5	1 or 2 or 3 or 4	240819
6	((new* or recent*) adj1 diagno*).tw.	107104
7	(onset* or new*).tw.	3689424
8	6 or 7	3695973
9	Critical Care/	88512
10	Critical Illness/	26890
11	((critical* or intensiv*) adj4 (care or ill*)).tw.	254629
12	((critical* or intensiv*) adj4 (care or ill* or unwell*)).tw.	254703
13	9 or 10 or 11 or 12	295857
14	5 and 8 and 13	1399
15	limit 14 to medline	91
16	14 not 15	1308
17	remove duplicates from 16	1298

Supplementary Material. Table 3.

Table 3. Eligibility criteria for systematic review.

Inclusion criteria (if all of the following met)	Exclusion criteria (if any of the following met)
1. Population comprised adults admitted to a critical care setting (ICU, HDU, A+E, AMU) who have developed or develop NOAF including paroxysmal AF (rhythm classification by continuous ECG monitoring or 12 lead ECG)	1. Population includes patients younger than 18 years, pregnant women, patients with known AF or a history of previous episodes of AF, patients who have undergone or are scheduled to undergo cardiac surgery, permanent pacemaker insertion or surgical ablation, or patients post cardiac/thoracic surgery
2. Intervention was any anti-arrhythmic or rate control medication (including but not limited to beta antagonists, calcium channel antagonists, Digoxin, Amiodarone, Magnesium), DCCV, or any combination of these interventions	2. Case reports and studies with no original data presented (e.g., design/protocol paper, [systematic] review, meta-analysis, commentary/editorial)
3. Comparator was any of the interventions above, placebo, standard care or no comparator	4. Insufficient information (e.g., study only available as a conference proceeding/abstract)
4. 1. Primary outcome measures included achievement of heart rhythm control/cardioversion to sinus rhythm or achievement of heart rate control (defined as heart rate less than 110 bpm); 2. Secondary outcomes included: a. development of permanent atrial fibrillation, b. development of recurrent paroxysmal atrial fibrillation that terminates within 48 h as defined by the ESC, c. any thromboembolic events (such as stroke pulmonary embolism, deep vein thrombosis, left atrial thrombus) during critical care admission, d. development of major bleeding events after administration of therapeutic anticoagulation as recommended in NICE guidelines, e. any complication documented secondary to the intervention, f. last reported mortality, g. ICU mortality, h. length of stay in critical care and length of hospital stay	
5. RCTs, quasi-RCTs and prospective or retrospective observational studies published in peer-reviewed journals	

NOAF defined as AF occurring during admission in a patient with no history of chronic AF. We also included studies of new-onset supraventricular arrhythmias (SVAs) where AF was the dominant arrhythmias

AF=atrial fibrillation; ECG= electrocardiogram; ESC= European Society of Cardiology; HDU=high dependency unit; ICU=intensive care unit; A+E=emergency department; AMU=acute medical unit; NICE=National Institute of Health and Care Excellence; NOAF=new onset atrial fibrillation; RCT=randomised controlled trial; DCCV=direct current cardioversion