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Protocol for the development of a core outcome set for clinical trials in primary sclerosing cholangitis

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ABSTRACT

Background Primary sclerosing cholangitis (PSC) is a progressive immune-mediated liver disease, for which no medical therapy has been shown to slow disease progression. However, the horizon for new therapies is encouraging, with several innovative clinical trials in progress. Despite these advancements, there is considerable heterogeneity in the outcomes studied, with lack of consensus as to what outcomes to measure, when to measure and how to measure. Furthermore, there has been a paradigm shift in PSC treatment targets over recent years, moving from biochemistry-based endpoints to histological assessment of liver fibrosis, imaging-based biomarkers and patient-reported outcome measures. The abundance of new interventional trials and evolving endpoints pose opportunities for all stakeholders involved in evaluating novel therapies. To this effect, there is a need to harmonise measures used in clinical trials through the development of a core outcome set (COS).

Methods and analysis Synthesis of a PSC-specific COS will be conducted in four stages. Initially, a systematic literature review will be performed to identify outcomes previously used in PSC trials, followed by semistructured qualitative interviews conducted with key stakeholders. The latter may include patients, clinicians, researchers, pharmaceutical industry representatives and healthcare payers and regulatory agencies, to identify additional outcomes of importance. Using the outcomes generated from the literature review and stakeholder interviews, an international two-round Delphi survey will be conducted to prioritise outcomes for inclusion in the COS. Finally, a consensus meeting will be convened to ratify the COS and disseminate findings for application in future PSC trials.

Ethics and dissemination Ethical approval has been granted by the East Midlands—Leicester Central Research Ethics Committee (Ref: 24/EM/0126) for this study. The COS from this study will be widely disseminated including publication in peer-reviewed journals, international conferences, promotion through patient-support groups and made available on the Core Outcomes Measurement in Effectiveness Trials (COMET) database.

Trial registration number 1239.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Given the increase in clinical trial development in primary sclerosing cholangitis (PSC), the need for harmonisation is crucial. This protocol will involve an international consensus to develop a core outcome set (COS) for PSC.
⇒ The COS development will be a thorough four-stage process including a detailed systematic literature review of multiple databases.
⇒ The COS development will involve input from key stakeholders for PSC, aiming to include patients, clinicians, researchers, industry representatives and healthcare payers.
⇒ A possible limitation may be the applications of the COS for use in retrospective research as its desired target is prospective clinical trials.

BACKGROUND

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated liver disease characterised by multiple strictures that develop throughout the bile ducts.[1 2] Disease onset may be insidious, but the clinical course is progressive, leading to bile flow obstruction, cirrhosis and/or hepatobiliary cancer.[3 4] Additionally, PSC is a major risk factor for development of colorectal cancer in young people with concomitant inflammatory bowel disease (IBD).[4] Although a rare condition (prevalence 0–31 per 100 000 population),[5] PSC represents one of the greatest unmet needs in modern hepatology; given its ill-defined aetiology, significant impact on patient quality of life, poor long-term prognosis and the fact that liver transplantation remains the only lifesaving intervention for patients. Indeed, PSC accounts for 10–15% of all liver transplant activity in the UK,[6 7] emerging as a lead indication for transplantation across several European countries.[8 9]

However, the horizon for new treatments is encouraging,[10] with the advent of several innovative and ambitious therapeutic strategies.[10] The approval of new potential pharmacologic agents is reliant on efficacy assessment through randomised controlled trials (RCTs), which in recent years have increased in volume and sophistication. However, rates of clinical progression vary between individuals: although 'hard endpoints' such as cancer, need for liver transplantation or death are highly relevant to patients, providers and payers, event-free survival rates are measured in years rather than weeks or months. Therefore, clinical event-free survival rates are generally not feasible as primary endpoints in most pharmacological trials which are limited with respect to sample size and duration of follow-up.[11] To this effect, surrogate biomarkers are employed at all stages of drug development.[12]

Advances in PSC drug development continue at pace, with several classes of agents in late phase study,[13–17] together with an increasing number of surrogate biomarkers and prognostic scoring systems. In parallel, a paradigm shift in treatment targets has occurred, with a move away from routinely collected liver biochemistry to objective measures of fibrosis; including the application of contemporary histological scores specific to biliary disease.[18–21] These shifts in the research environment have led investigators and regulatory authorities to re-evaluate the key efficacy and safety outcomes measured in PSC clinical trials.[18 20] Additionally, in recognising the need to accurately capture the patient experience, regulatory agencies have advocated for the inclusion of patient-reported outcome measures (PROMs). While a variety of PROMs have been used,[22–24] many lack international validation, or study in patient populations with diverse demographics, comorbidities and at different stages of disease. Moreover, there are limited data to show how concomitant IBD activity (which is present in up to 80% of patients) may affect the readout of a 'PSC-specific' PROM.[24]

The selection of appropriate outcomes is critical for several reasons. First, their operating properties determine trial efficiency and ultimately drive our ability to identify effective new therapies and the cost of drug development programmes. Additionally, the choice of outcomes can shape clinical practice if the selected measures are perceived as relevant to both patients and healthcare professionals. Capturing a minimum 'set standard' of outcome measures may also improve the quality of systematic reviews and meta-analyses, while allowing payers to compare safety and cost-effectiveness profiles of competing interventions.

A 'Core Outcome Set (COS)' is an agreed minimum set of outcomes that should be reported in all clinical trials for a pre-specified condition.[25–30] The expectation is that core outcomes will always be collected and reported, but the COS is not restrictive such that investigators cannot explore additional outcomes. COSs have been developed and used effectively in other disease states across gastroenterology practice such as IBD[29] and eosinophilic esophagitis,[31] with a view to standardise trial reporting, allow comparisons of new therapies, strengthen guideline recommendations and facilitate drug approval from regulatory bodies. The objective of COS application is that an agreed minimum set of outcomes are measured and reported in all clinical trials for a particular health condition. This will ensure that there are consistent outcomes being measured and reported, reduce heterogeneity between studies and allow good quality meta-analyses that inform evidence-based practice.

Herein, we present a protocol for developing a PSC-specific COS, outlining the methods to be adopted at each step and heightening awareness of this effort to encourage all stakeholders in the conduct of PSC trials to participate. This protocol follows the Core Outcome Set Standards for Development project recommendations (COS-STAD) and is registered in the non-database list of the Core Outcomes Measurement in Effectiveness Trials initiative (COMET) (https://www.comet-initiative.org).

METHODS AND ANALYSIS

The COMET initiative provides a framework for the development of a disease-specific COS, with dedicated recommendations from the COS-STAD project.[26 32] This current study will focus on developing a COS for clinical trials in adolescents and adults with PSC (age >16 years) and will consist of four stages (figure 1). The first will be to conduct a systematic review to produce a comprehensive list of outcome measures reported in clinical trials of PSC, including current interventional studies. Trials covered in existing meta-analyses, systematic reviews and Cochrane reviews will also be studied. This would generate a list of clinical, laboratory, endoscopic (gastrointestinal and biliary), radiological, histological, healthcare economic and patient-reported outcomes. Additionally, as PSC is a rare disease with limited therapeutic options, outcome measures studied in observational cohort studies (of at least one hundred patients) will also be studied. Next, the list of generated outcomes will be augmented with additional items, generated through semistructured interviews of patients, clinicians, specialist nurses, industry representatives or regulatory bodies and outcome methodologists. Thereafter, a two-round modified Delphi Process will be conducted, to grade, refine and prioritise the selected outcomes for the COS.[33] The final stage will be a consensus meeting among selected stakeholders to agree on the final COS, discuss and ratify disagreements, and support global dissemination of project findings. The process will be facilitated by the lead author (NH), with supervision from the principal investigator (PJT).

Setting the scope of a PSC COS

The scope of this COS will be intended for application in all RCTs of pharmacological therapies, cellular therapies, microbiome manipulation and medical devices used in adult patients with PSC. It will include patients without gender or sex restriction, between the ages of 16 and 80 years. Studies of exclusively paediatric populations

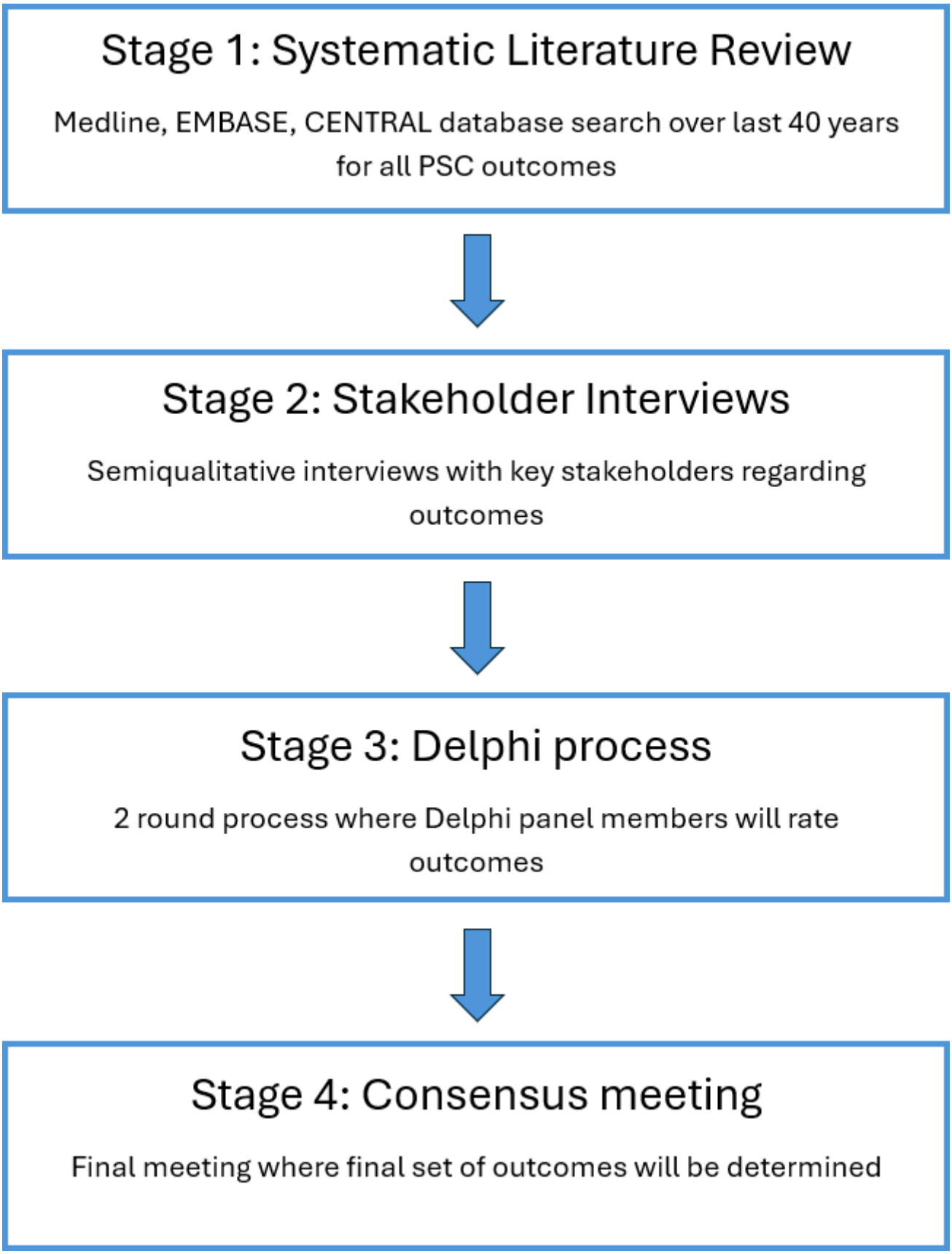

Figure 1 Flow chart demonstrating four-stage process of COS development. COS, core outcome set; PSC, primary sclerosing cholangitis.

will be excluded given differences in clinical outcomes that are relevant for children but not adults with PSC. For instance, growth, growth rate, weight gain, developmental milestones, nutritional needs, school days missed and pubertal development/development of secondary sexual characteristics. This COS will include patients with PSC with any disease extent (large duct and small duct), disease stage and severity, including those with concomitant IBD or overlapping features of autoimmune hepatitis (AIH). The COS will be applicable to all future interventional trials in PSC, including those where investigational medicinal products are given alongside preexisting bile acid, immunosuppressive and biologic therapies. This outcome set is intended for use in RCTs so may not be applicable to other trial or study designs. Surgical and endoscopic interventions will be excluded as these will require necessary alternative outcomes specific to the mode of intervention; for instance, perforation rates, postprocedure recovery length, bleeding and complication rates and time to re-intervention.

Identifying existing knowledge

No PSC-specific COS currently exists. However, the International PSC Study Group undertook a consensus process published in 2016, critically reviewing and subsequently setting out recommendations on ideal surrogate endpoints likely to predict clinical benefit in PSC. They focused on five surrogate endpoints, with three showing 'promise' with regards to assessing disease progression (histology, serum alkaline phosphatase and transient elastography). This consensus process is valuable in informing the clinical trial design and crucial endpoints that measure disease activity, but its limitations include a lack of focus on endpoints that measure the burden of symptoms or quality of life measures.[12]

A second article published in collaboration with the United States Food and Drug Administration highlighted the challenges in clinical trial design for a disease where differing phenotypes affect disease progression and survival, as well as the confounding impact comorbidities such as IBD can have on PROMs and health-related quality of life. There is also an exploration of disease complications that may have a transient effect on biomarkers, particularly the rise seen in liver biochemistry parameters during acute episodes of bacterial cholangitis. Increased risk of malignancy, namely colorectal cancer and cholangiocarcinoma are additional factors that need to be accounted for in clinical trial design in PSC.[18] The benefit of either co-primary or composite endpoints was also highlighted, alongside the need for long-term symptom assessment. It is precisely these factors and complexities within PSC that can lead to heterogeneity, and highlight the need for selecting a core series of outcomes that allow comparability in future clinical trials.[18]

The above work is useful in recommending surrogate outcomes that inform PSC progression, but this is very different to the objective of a COS. The focus of a PSC-specific COS is to ensure the homogeneity among clinical trials, ensuring the minimum set of outcomes to be reported to allow clear and meaningful future systematic review and meta-analysis.

Stage 1—systematic literature review

A list of all possible outcomes will be identified by a comprehensive systematic literature search of the following databases: Medline, EMBASE and Cochrane Library. This will be conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[34] Studies published in English and from the last 40 years (January 1983 to January 2024) will be included, to ensure that the data captured reflects both historic and contemporary knowledge about PSC. This review is registered with PROPERO (ID No: CRD42024441848, Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024441848).

The following inclusion criteria will be applied:

a. RCTs.
b. Open-label clinical trials.
c. Observational cohort and case–control studies with a minimum of 100 patients.
d. Participants aged 16 or older.
e. Articles on PSC specifically, including platform and basket trials that include other diseases.
f. Small and large duct PSC, with and without overlap features of AIH.
g. PSC with and without concomitant IBD.
h. Outcomes are specifically stated and are clear and measurable.

Exclusion criteria

a. Articles that exclusively study the paediatric PSC population (<16 years of age).
b. Case reports, book chapters, conference abstracts.
c. Studies of <4 weeks of participant follow-up, after day 1 of the intervention.
d. Studies exclusively evaluating liver transplant recipients.
e. Studies where multiple liver diseases are studied, and in which results specific to individuals with PSC cannot be separated or quantified.

In addition to this literature review, there will be a search on clinicaltrials.gov and the International Standard Randomised Controlled Trial Number registry to identify outcomes used in current phase II and phase III trials. Reviewers will develop a list of all possible outcomes via completing a data collection form. This list of outcomes will then be grouped into separate domains appropriate for PSC, and this will then be taken forward to the Delphi process.

Stage 2—stakeholder interviews

A minimum of 20 respondents will be invited for the stakeholder interviews, comprising a diverse pool which will include; patients with PSC (minimum n=4), hepatologists (minimum n=4), gastroenterologists with a specialist interest in IBD (minimum n=2), gastrointestinal and hepatopancreatobiliary radiologists (minimum n=2),

patient-support group representatives (minimum n=2), industry representatives (minimum n=2), regulators (minimum n=2) and methodologists (minimum n=2). The minimum requirement for clinician participation will also include expertise in PSC and/or IBD trial conduct or outcome assessment, as reflected by metrics of at least 20 publications related to PSC or IBD, or the involvement in at least two PSC clinical trials (either as an investigator or through input into the trial design); or clinical expertise demonstrated by being the medical or surgical leads of a dedicated PSC centre. Participant selection will be via invitation, and we will aim to ensure representation from different demographics, patients with varying disease extent and clinical expertise. The interview design will be semiqualitative and conducted either face to face or online. Interviews will be estimated to last between 30 and 60 min. The interviews will focus on (1) patient experiences of having PSC and their expectation from clinical trials; (2) suggested outcomes felt by the stakeholders to be important to include in this COS; (3) recommended measurement tools for suggested outcomes and (4) feedback and opinion of outcomes obtained from the systematic review. The interviews will be recorded and transcribed verbatim. These will be imported into qualitative data analysis software to generate a list of the key themes and points.[35]

Stage 3—Delphi process

A Delphi panel will be created consisting of representatives from all the stakeholder groups listed earlier. The panel will be diverse representing a broad range of clinical, professional and patient experience. We aim to have a broad geographical representation, including members from Europe, North America, South America and the Asia-Pacific Region. We estimate a sample size of 30–40 panel members. All potential participants will be sent an invitation letter via email. This invitation will set out the aim and methods of this study and emphasise the importance of participation throughout the complete Delphi process. Each panel member will be assigned a unique participant number and blinded to other participants. Only the lead author (NH) and principal investigator (PJT) will have access to the matched panel members and their participant numbers.

This process will consist of two rounds and follow the COMET recommendations to form a list of outcomes to be taken to the consensus meeting.[32] In round 1, each panel member will complete a data collection form comprising of their professional background, clinical and research experience and the stakeholder group they belong to. They will be presented with a list of all the outcomes developed from the literature review and stakeholder interviews. Panel members must then rate each outcome on a 9-point Likert scale based on Grading of Recommendations Assessment, Development and Evaluation definitions.[36] A score of 1–3 is considered 'not important', 4–6 is important and a score of 7–9 is considered critically important for inclusion. There will be a free-text option provided where participants will be able to provide a justification should they feel the need to, as well as provide feedback or any suggestion for additional outcomes they feel should be included. Following a review of free-text commentary, any additional outcomes suggested will be included with the original list of outcomes to be presented to the panel members in round 2 of the Delphi process.

In round 2, all participants will be shown their original rating alongside the aggregated rating based on the overall ratings from all members. Participants will then be asked to rate each outcome again between 1 and 9, and specifically to note if the outcome should be included in the COS. Descriptive statistics will then be used to analyse these final ratings. Outcomes to be considered having met the criteria for inclusion will need to have >70% of panel members scoring the outcome 7–9 and <15% giving that outcome a score of 1–3. Conversely, outcomes for exclusion will be those that received >70% of panel members giving the outcome a rating of 1–3 and <15% scoring it 7–9. The outcomes not meeting these criteria will be grouped as 'no consensus'.

Stage 4—consensus meeting

The consensus meeting will follow the Nominal Group Technique and will be held in a hybrid manner (in person and virtually) and all Delphi members will be invited to participate. There will be a discussion with the final objective of formalising the COS. First, the outcomes that meet the criteria to be included and those for exclusion from the Delphi process will be ratified. Second, those outcomes which had 'no consensus' will be discussed, followed by anonymously voting for each outcome to be included or excluded from the final COS.

Once the COS has been determined, the participating members will discuss how the selected outcomes should be measured, and subsequently make recommendations of validated methods.

ETHICS AND DISSEMINATION

Ethical approval

Ethical approval has been granted with respect to participation in stakeholder interviews, Delphi process and the consensus meetings for this study. This was granted by the East Midlands—Leicester Central Research Ethics Committee (Ref: 24/EM/0126) on 28 May 2024. All participants will be asked to provide informed consent.

Dissemination

The developed COS from this study will be widely disseminated. This will include publication in peer-reviewed journals, presentation at international conferences and regulatory agencies and promotion through patient-support group communications. The COS will also be made available on the COMET database along with a lay summary.

DISCUSSION

Evaluations, comparisons and reviews of clinical trials are of paramount importance. However, to be able to do

this reliably there needs to be a consistent measuring and reporting of outcomes in studies that look at the same disease. PSC remains an area of ongoing and heightened research to try and improve survival, slow progression, manage symptoms and develop a cure. This will impact clinical guidelines, but the development of this COS will help create the standardisation needed for high-quality meta-analyses to inform these. Following the guidance from the COMET initiative will ensure that the COS developed will be essential and relevant to the stakeholders for this condition.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

This study protocol was developed in collaboration with members of the patient organisation PSC Support and members of the Centre for Patient Reported Outcomes Research, University of Birmingham. These representatives are co-authored in the protocol and will be involved during the conduct of all steps of COS development.

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Contributors NH and PJT were involved in study conception and manuscript drafting and editing. MW and PH reviewed the manuscript. CM, MV, KK, AB, CP, CL, DA, CS, CB, MT, VJ, OLA and GH reviewed the manuscript and provided edits through to finalisation. All authors approved the final draft.

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