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BMJ Open Alpha 2 agonists for sedation to produce better outcomes from critical illness (A2B trial): protocol for a mixed-methods process evaluation of a randomised controlled trial

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ABSTRACT

Introduction An association between deep sedation and adverse short-term outcomes has been demonstrated although this evidence has been inconsistent. The A2B (alpha-2 agonists for sedation in critical care) sedation trial is designed to determine whether the alpha-2 agonists clonidine and dexmedetomidine, compared with usual care, are clinically and cost-effective. The A2B intervention is a complex intervention conducted in 39 intensive care units (ICUs) in the UK. Multicentre organisational factors, variable cultures, perceptions and practices and the involvement of multiple members of the healthcare team add to the complexity of the A2B trial. From our pretrial contextual exploration it was apparent that routine practices such as type and frequency of pain, agitation and delirium assessment, as well as the common sedative agents used, varied widely across the UK. Anticipated challenges in implementing A2B focused on the impact of usual practice, perceptions of risk, ICU culture, structure and the presence of equipoise. Given this complexity, a process evaluation has been embedded in the A2B trial to uncover factors that could impact successful delivery and explore their impact on intervention delivery and interpretation of outcomes.

Methods and analysis This is a mixed-methods process evaluation guided by the A2B intervention logic model. It includes two phases of data collection conducted during and at the end of trial. Data will be collected using a combination of questionnaires, stakeholder interviews and routinely collected trial data. A framework approach will be used to analyse qualitative data with synthesis of data within and across the phases. The nature of the relationship between delivery of the A2B intervention and the trial primary and secondary outcomes will be explored.

Ethics and dissemination All elements of the A2B trial, including the process evaluation, are approved by Scotland A Research Ethics Committee (Ref. 18/SS/0085). Dissemination will be via publications, presentations and media engagement.

Trial registration number NCT03653832.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The use of mixed-methods process evaluation will enhance the completeness of the overall trial explanations and provide a more comprehensive evaluation than either qualitative or quantitative data alone.
- ⇒ We will sample widely across sites given the potential for contextual variation and gather data from multiple members of the research and clinical teams across the entire trial trajectory.
- ⇒ This process evaluation uses a validated framework and is underpinned by a predefined logic model.
- ⇒ Due to the implications of the COVID-19 pandemic, we are limited to remote data collection through interviews and surveys rather than being able to undertake observation as an element of the process evaluation.

INTRODUCTION

The alpha 2 agonists for sedation to produce better outcomes from critical illness (A2B) multisite open-label randomised controlled trial is funded as a National Institute of Healthcare Research Health Technology Assessment Agency commissioned trial (16/93 ‘alpha-2 agonists for sedation in critical care’, 2017; grant reference number: 16/93/01). The trial (registered on ClinicalTrials.gov (NCT03653832); EudraCT (No. 2018-001650-98)) is designed to determine whether intravenous sedation using either of the alpha-2 agonist agents, dexmedetomidine or clonidine, can decrease the time to successful extubation from mechanical ventilation in adult critically ill patients. The trial commenced patient recruitment throughout the UK in December 2018, although progress was significantly impacted by the COVID-19 pandemic through much of 2020–2021.

Recruitment of patients concluded on 27 October 2023, with patient follow-up to complete in December 2023. Process evaluation data collection will conclude in December 2023.

The A2B sedation trial involves using different sedative agents according to a sedation management guideline, where dosing is adapted to the needs and safety of each participant during their period of mechanical ventilation in the intensive care units (ICUs). As such, although a comparison of different sedative agents, the trial is an evaluation of a complex healthcare intervention. It is also delivered to patients in multiple ICUs across the UK, which may vary in terms of staffing, local culture and service design. Trials that test complex interventions are subject to variation in how they are implemented within and between sites. This can pose challenges in understanding the effect of the intervention overall, as well as understanding the influence of variation in intervention delivery.^{1,2} Sedation of the critically ill patient involves multiple members of the healthcare team with a range of perceptions about important elements of practice interacting to assess and deliver multiple agents using a series of interdependent and interrelated activities.^{3,4} There is also evidence that sedation practices vary across sites.⁵

Given the complexity of ICU sedation practice and the evidence that usual sedation practice does not always reflect current practice guidelines,⁶ it is essential to develop a detailed understanding of how the A2B trial intervention is operationalised in individual sites to uncover the nature of the relationship between intervention delivery and trial outcomes. This will be achieved by undertaking detailed context assessment prior to commencing the trial, and by conducting a process evaluation embedded within the A2B sedation trial. Guidance from the UK Medical Research Council on process evaluation will be followed.⁷ In the situation that the intervention is proven effective, the findings from the process evaluation can be used to guide implementation into practice beyond the trial. Conversely, if the intervention shows no effect, the process evaluation findings can help understand whether the lack of demonstrated benefit was due to a lack of adequate protocol implementation or a lack of intervention effect.

The following aims guide the A2B process evaluation:

1. To establish the degree to which the A2B intervention is delivered as intended, over time and between ICUs, specifically in relation to fidelity, dose and reach across patients and staff.
2. To understand factors that impact on successful delivery of both the A2B intervention and trial, over time and between ICUs, in relation to attitudes, perceptions and context, including standard care.
3. To explore the nature of the relationship between A2B intervention delivery and trial primary outcome, considering the level of intervention adherence.

METHODS AND ANALYSIS

Pretrial contextual data of the participating ICUs

To assist with the planning of both the A2B trial and the embedded process evaluation, extensive exploration of the current UK critical care setting was undertaken. Contextual data were collected via structured survey and team conversations from 38 ICUs planning to participate in A2B between 7 February 2019 and 12 January 2023, with 28 (74%) of those conversations occurring before the end of 2019. These ICUs varied in size from 7 to 46 beds, annual admission rates from 150 to 3300 patients, 31–450 nurses, 1–9 research nurses, 4–26 medical consultants, 5–45 junior doctors and 1–4 pharmacists.

Sedation assessment and management

Sedation, analgesia and delirium practice varied across the sites, although with some common patterns. A detailed description can be found in online supplemental file 1. Sedation assessment was most frequently conducted using the Richmond Agitation-Sedation Scale (RASS)⁸ between 1 and 4 hourly. Processes used to implement sedation practices were highly variable, with some units using formal sedation targets and clear multidisciplinary team meetings or review. Depth of sedation was also found to be highly variable, with agreement that patients were generally more heavily sedated overnight in response to concerns about patient safety. Propofol was used as the usual first-line approach to sedation, with midazolam, clonidine and dexmedetomidine all being used as secondary agents.

Pain and delirium assessment and management

Continuous opioid infusions are administered routinely in ICU alongside sedative agents.⁹ Most ICUs planning to participate in A2B assessed pain using a validated pain assessment tool 2–4 hourly, with alfentanil, fentanyl, remifentanyl and morphine being used most frequently as opioid analgesics. Almost all ICUs planning to participate in A2B screened patients for delirium using the Confusion Assessment Method for the ICU,¹⁰ usually on each shift.

Clinicians' attitudes and perceptions

We recognised, a priori, that successful implementation of the A2B trial would be dependent on addressing clinicians' attitudes and perceptions that might influence operationalisation. Four key themes that could potentially affect implementation were identified in the pretrial preparation: the impact of usual practice, perceptions of risk, ICU culture and structure, and equipoise.

Impact of usual practice

Use of dexmedetomidine or clonidine as both a sole sedative, and as a first-line approach to sedation, was considered a significant challenge. Usual practice was that these sedatives were second or third-line sedatives and used as an adjunct to propofol. Concerns included uncertainty related to dexmedetomidine's utility as a first-line sedative, use of alpha-2 agonists as a sole sedative agent, the

altered depth of sedation being targeted and the preparation of dexmedetomidine in usual practice being different to the A2B protocol.

Concerns related to the use of clonidine focused on it being ordinarily used at a lower dose and given as a bolus. Despite this, there was a perception that clinical staff would be more comfortable with patients on clonidine than dexmedetomidine in A2B as they used it more frequently in usual practice and it presented less practice change.

The challenge of achieving optimal (usually light) sedation in the propofol arm of A2B was noted. This is particularly related to nurses being accustomed to sedating patients heavily on propofol (RASS -3 or deeper), the challenge for nurses to achieve optimal sedation consistently and regularly on propofol (identified in audits), and propofol viewed as an ICU-wide 'cultural safety net'.

Perceptions of risk

ICU clinicians reported an awareness that patients were likely to be more lightly sedated in A2B than in usual practice. This raised safety concerns about adverse events such as unplanned device removal; this concern was heightened for patients in individual rooms.

Other concerns included that patients may not be manageable on alpha-2 agonists alone due to not being able to achieve deep enough sedation for perceived clinical need, being unable to adequately control agitation, cardiovascular instability or side effects. A reticence to use dexmedetomidine in certain subgroups of patients (≤ 65 years) based on the publication of the SPICE (Sedation Practice in Intensive Care Evaluation) III results¹¹ and subsequent secondary analysis¹² was also expressed. A perception that a RASS of +1 would not be considered an acceptable target so nurses would not comfortably keep patients at this RASS level, and that family members are not always comfortable with light sedation and the potential for restlessness or agitation, was expressed – this would pose a challenge to the bedside nurse when visitors were present. These concerns were sometimes linked to historical patient safety events such as ventilator disconnections by agitated patients.

ICU culture and structure

Attitudinal and organisational factors were identified as potential barriers or enablers to implementing the A2B trial. Barriers included difficulty engaging clinical staff exacerbated by junior doctors on short-term rotations and poor awareness of current research, particularly by staff nurses. This latter issue was considered particularly problematic for A2B where the intervention is predominantly nurse led. Multidisciplinary clinicians at a majority of participating ICUs described a positive research culture and good research profile within their units, suggesting a general willingness to implement clinical research.

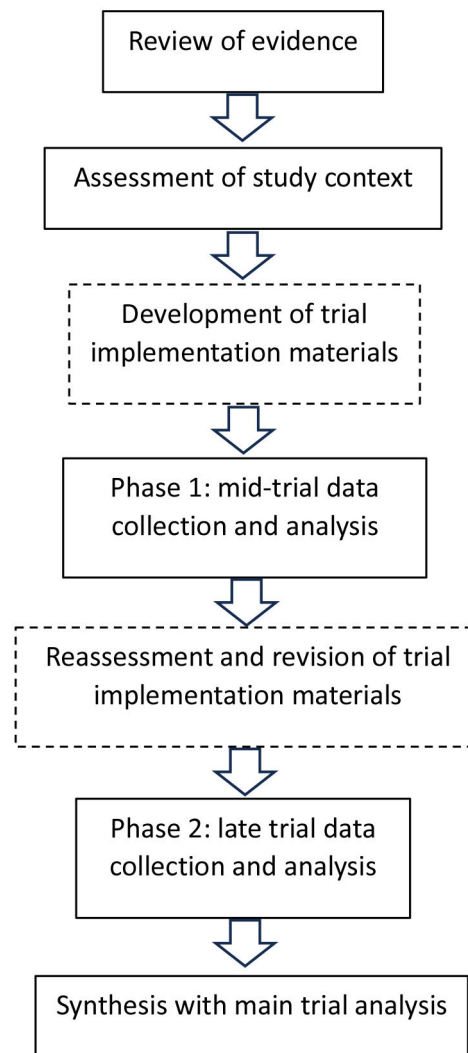


Figure 1 A2B (Alpha-2 agonists for sedation in critical care) process evaluation.

Equipoise

Most ICUs considered they had equipoise on an overall basis, although noted it was affected by both the current evidence and previous experience with dexmedetomidine and clonidine. Equipoise was affected by the publication of the SPICE III trial¹¹ and subsequent secondary analysis,¹² where increased mortality in patients ≤ 65 years was reported. Previous negative experiences with dexmedetomidine and clonidine were noted to impact equipoise, with some clinicians considering these agents ineffective as sedatives. These opinions differed between individuals, but generally, equipoise was considered to exist on ICUs as a whole.

These variations in practice related to assessment of the elements of anxiety, pain and delirium, as well as how deeply patients are sedated, informed the development of implementation strategies for the A2B trial¹³ (figure 1).

Logic model

In accordance with the MRC's recommendations for process evaluations of complex interventions,⁷ a logic

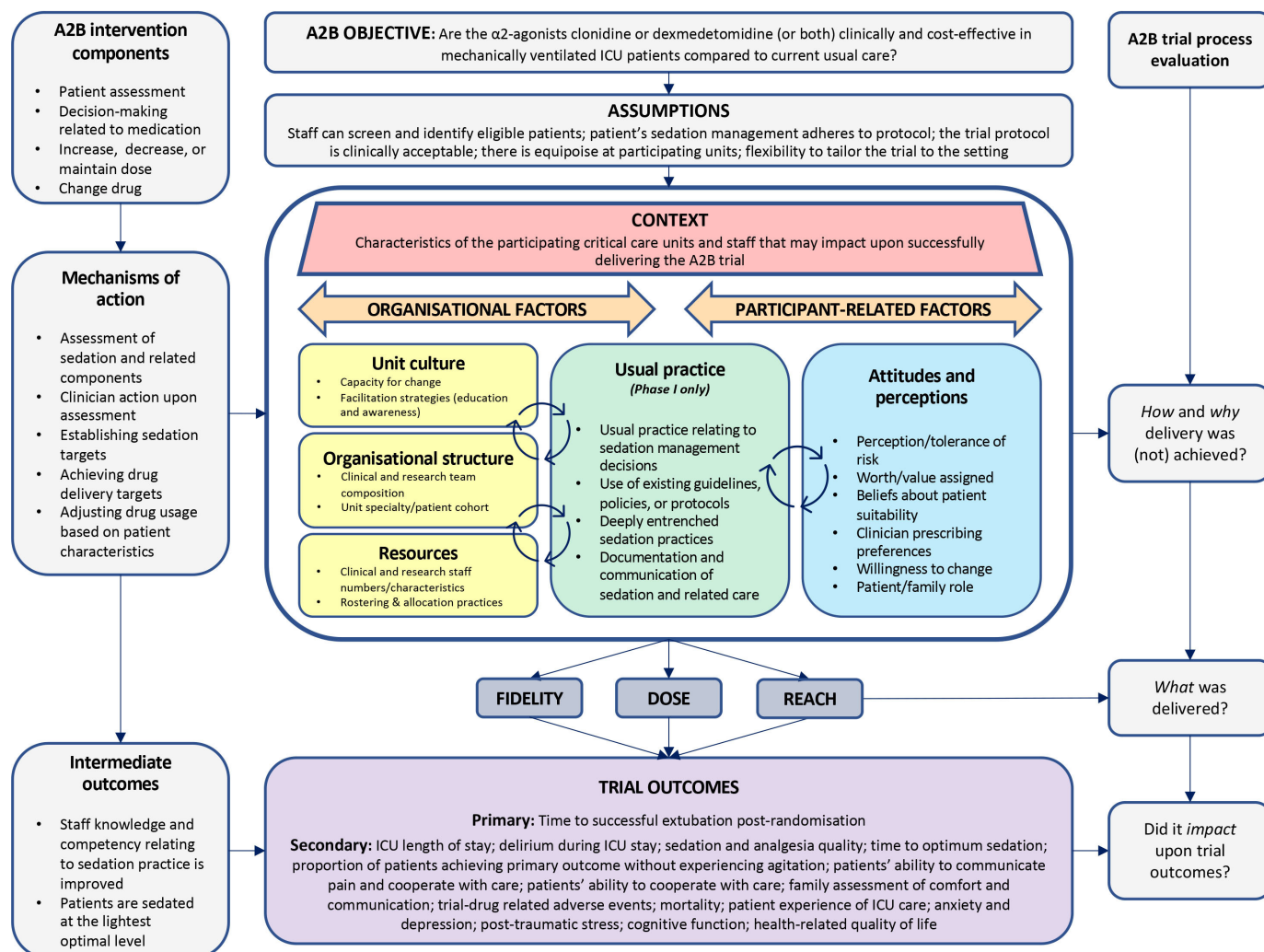


Figure 2 A2B (alpha-2 agonists for sedation in critical care) logic model; ICU, intensive care unit.

model was incorporated into the study to enable development of a clear definition of the intervention and clarify the theory of how the intervention is intended to work. Logic models are a visual depiction of the statement of activities required to bring about change¹⁴ and assist with identifying potential risk points, that is, potential for a break in the intervention delivery pathway or deviation from the model.

The A2B trial logic model (figure 2) was developed as a representation of the intervention theory outlining its context, mechanisms of action and anticipated outcomes. The process evaluation team drafted a 'pathway map' showing how they envisaged the planned intervention being delivered from the beginning through to the trial outcomes.¹⁵ They also considered assumptions about intervention delivery (clinical acceptability; protocol adherence) and external factors that could impact on intervention delivery (drug cost and availability).¹⁶ Through iterative discussions with the wider research team, we gained agreement on the necessary components for the A2B logic model. The logic model helped identify the factors that will require exploration in this process evaluation. Although this model captures the 'big picture'

it is not an exact representation of everything that goes on, nor can it predict unintended consequences. It simplifies reality but contains enough information and the key components for demonstrating, and evaluating, how the intervention is intended to work.¹⁷ The logic model has been used to guide data collection and development of data collection tools.

Patient and public involvement

Former ICU patients and their relatives were consulted during development of the funding application for this trial. A former ICU patient is a coapplicant on the grant and a coinvestigator on the trial and an independent lay person is a member of the trial steering group. The patient and public involvement group is being consulted at regular intervals throughout the trial regarding the importance of the study question and various design elements including data collection patterns and processes.

Process evaluation data collection

The following two phases of the process evaluation incorporate the mid-trial and end-of-trial data collection:

Phase I: mid-trial

Data collection during this phase is specifically designed to address aims 1 and 2, that is, to understand the degree to which the A2B intervention is delivered as intended and the factors that impact on that. During the trial, online/telephone semistructured interviews (online supplemental file 2) will be conducted with stakeholders from participating sites. We will employ maximum variation sampling to select 15–20 sites. The selection of sites will be determined using a sampling matrix (online supplemental file 3) to select sites with different characteristics. Sampling characteristics include ICU size, participant recruitment rate, pretrial routine sedation practice and research infrastructure. Interviews will be conducted with stakeholders at least 3 months after the ICU commences patient recruitment. Semistructured interview guides have been designed with the logic model in mind, to explore the assumptions and external factors, and to identify breaks/barriers in the chain of anticipated intervention delivery. Specifically, interviews will explore contextual detail relating to (1) staff attitudes and perceptions of implementing the A2B trial; (2) challenges and factors influencing ease and process of implementing A2B protocol; (3) factors influencing participant recruitment; (4) staff perceptions of A2B protocol adherence and strategies used to optimise intervention delivery and (5) the impact of COVID-19 on conducting the A2B trial.

Phase II: end of trial

Data collection during this phase is targeted at addressing all aims of the process evaluation, with an emphasis on aim 3. Within the last 6 months of the trial, online/telephone semistructured interviews will be conducted with participants (outlined below) to examine issues that arose during the course of the trial related to implementation and/or intervention delivery (online supplemental file 2). Similar to the sampling of sites undertaken in phase 1, we will employ maximum variation sampling to select a further 15–20 sites (they may be the same or different to those selected in phase 1) using a sampling matrix (online supplemental file 3). Only sites that have enrolled patients into A2B within the past 3 months will be selected to optimise their recall of factors related to intervention delivery. Within sites we will use purposive sampling to obtain a range of participants according to profession, role and grade/experience as well as number of participants recruited into the study, and recruitment numbers in the final 6 months. Interview data will be collected to understand the degree to which the A2B intervention was delivered as intended, and understand factors that impacted on successful delivery of both the A2B interventions and trial.

The process evaluation will draw on routinely collected trial data such as recruitment rates, reasons for not recruiting eligible patients and intervention adherence data. These data will assist the evaluation of recruitment patterns and intervention compliance. These data are inputted by research nurses into the study database and

will be provided to the process evaluation team by the clinical trials unit overseeing the trial.

An intervention adherence grading algorithm will be developed during this phase to facilitate measurement of ICU overall intervention adherence to assist with interpretation of the main trial analysis findings.

Interviews and focus groups

All interviews in both phases will be conducted remotely and it is anticipated they will last for 45–60 min each. Ideally, interviews will be conducted as a focus group with participants from each clinical site, although if individual interviews are required to capture all participants this will be undertaken. Interviews will be recorded using either an encrypted recorder or the record function of online conferencing facilities and transcribed verbatim by a transcription company approved by the study sponsor.

Participants

Participants in both phases of data collection will be those who were integral to the implementation and delivery of the A2B trial. Inclusion criteria are as follows:

- ▶ The principal investigators for A2B at each clinical site.
- ▶ Research nurses responsible for coordinating A2B implementation—one or more research nurses involved in A2B at each site.
- ▶ Clinical staff responsible for delivering the A2B trial to patients—2–4 clinical staff at each site.

The principal investigator and lead research nurse for each site will be contacted via email by the study research fellow to arrange data collection. The principal investigator and research nurse will then be responsible for recruiting other members of the clinical and research staff and negotiating a suitable time for the interview.

Data analysis

A seven-step framework analysis will be used to analyse qualitative data.¹⁸ This involves audiorecording and transcribing the interviews, and coding the data. A deductive analytical framework will be developed which allows for themes emerging from the data to be used as indexing categories. The analytical framework will be applied to a sample of transcripts, and a second member of the research team will review the thematic framework as it is applied to the data. Data are then mapped into the framework. Unallocated data will be examined inductively, and the framework revised iteratively until all data can be allocated to a theme/domain. The research team will discuss the codes and themes to achieve consensus and develop a codebook. Interpretation of the data will be reviewed by the research team, to construct overall explanations. An advantage of the framework approach is that researchers' interpretations of participants' experiences are transparent.¹⁹ It is particularly useful when managing large datasets, such as process evaluation transcript data, because the framework provides an intuitively structured overview of all the summarised data.¹⁸



This will enable themes identified a priori to be combined with those that emerge de novo to be captured in the final analysis framework. This analysis will be conducted within each phase and across the phases to identify barriers and facilitators of implementing the A2B intervention. Barriers and facilitators identified during the mid-trial phase will be used to refine implementation resources to support the fidelity of the study. The data will be used to explore the nature of the relationship between delivery of the A2B intervention and the trial primary outcome. This will be based on the intervention grading algorithm that will be developed in phase I and will facilitate ICU overall intervention adherence to be used in informing interpretation of the main trial analysis findings on the primary and secondary outcomes.

ETHICS AND DISSEMINATION

All elements of the A2B trial, including the process evaluation, are approved by Scotland A Research Ethics Committee (Ref. 18/SS/0085). Written informed consent for each element of the process evaluation will be sought from all clinicians and researchers being interviewed, and written consent to review routinely collected study data will be incorporated into the main trial consent processes. Anonymity of all participants will be preserved in the presentation of all study results. During the conduct of the study, data will be stored in potentially reidentifiable form in City, University of London files which are accessible only to those with appropriate password access. On completion of the study, data will be archived in accordance with ethics and sponsor guidance. Dissemination of the results will be via publications, conference presentations and engagement with the media.

Current status

The trial recruited its first patient in December 2018. Recruitment was severely affected by the COVID-19 pandemic, with many sites closed for much of 2020–2021. The trial reopened in late 2020, but recruitment was affected by ICU pressures and diminished research capacity during 2021–2022. Recruitment of patients concluded on 27 October 2023, with patient follow-up continuing through to late December 2023. It is anticipated that the database will be locked in February 2024 with analysis commencing after that. Phase 2 process evaluation data collection is currently underway and will conclude in December 2023.

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Contributors LMA and LE led the design of the process evaluation, with contribution from BB, KK and TW. LMA, LE, KK, BB, BC-B, NL, CAM, MR, CW, MPW and TW reviewed and refined the protocol. LMA drafted the manuscript; LMA, LE, KK, BB, BC-B, NL, CAM, MR, CW, MPW and TW read, edited and approved the final manuscript prior to submission.

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