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Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients (Protocol)

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[Intervention Protocol]

Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness of non-pharmacological interventions designed to prevent delirium in hospitalised non-intensive care unit (ICU) patients.

BACKGROUND

Description of the condition

Delirium is a disturbance of consciousness and cognition, which usually has a rapid onset and a fluctuating course. The core features of delirium are defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, and include a "disturbance in attention, awareness and cognition, which develops over a short period of time and tends to fluctuate in severity during the course of a day. It represents an acute change from baseline and is not better explained by a pre-existing, established or evolving neurocognitive disorder or a severely reduced level of arousal such as coma. There should be evidence from history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies" (American Psychiatric Association 2013). The *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10) definition of delirium is similar, but also includes disturbance of the sleep-wake cycle and does not specify that there is a definitive underlying aetiology (World Health Organization 2016).

Delirium is highly prevalent across all inpatient hospital settings. A recent Swiss study evaluated all inpatients and found a period prevalence of 28% (Schubert 2018). The highest prevalence rates were found in patients who had experienced cardiac surgery, neurosurgery, trauma, radiotherapy and neurology (36% to 41%). However, delirium was also common in geriatric medicine, internal medicine, general surgery, reconstructive plastic surgery and

cranio-maxillo-facial surgery (22% to 29%) (Schubert 2018). A point prevalence study conducted in Ireland found that 20% of adult hospital inpatients had delirium on a single day and that age was associated with higher prevalence (5% in those under 50 years of age, versus 35% in those aged over 80) (Ryan 2013). The reported incidence of delirium during an admission to hospital spans from 3% to 29% in the published literature (Siddiqi 2006). This ranges from 11% to 14% in general medicine, 20% to 29% in geriatric medicine, 10% to 27% in stroke units, 47% in palliative care settings and 12% to 51% in orthopaedic units (Inouye 2014).

Delirium is associated with a range of serious adverse health outcomes. Factors associated with poorer outcomes after an episode of delirium include: longer duration and severity; hypoactive delirium subtype; and the presence of comorbid dementia and depression (Jackson 2016a). A meta-analysis of observational study data from older adults found those with delirium were at an increased risk of death (hazard ratio (HR) 1.95, 95% confidence interval (CI) 1.51 to 2.52), after adjusting for age, sex, comorbidity illness or illness severity and baseline dementia (Witlox 2010). Evidence indicates increased hospital length of stay is both a risk factor for developing delirium and an outcome associated with experiencing delirium (Ahmed 2014; Aitken 2017; Pendlebury 2015).

Delirium can have irreversible effects on an individual's function. A UK cohort of hospital admissions with mental health problems found only 25% of those experiencing delirium had a clinically important recovery in their activities of daily living six months after the episode (Whittamore 2013). Delirium is also associated with an increased risk in overall dependency (odds ratio (OR) 2.56, 95% CI 1.37 to 4.76) (Pendlebury 2015). This can lead to an increased risk of requiring formal institutional care (Witlox 2010), particularly for those with delirium superimposed on an existing dementia (Burton 2018).

Undiagnosed cognitive impairment and dementia are common in older adults presenting with delirium (Jackson 2016b). In adults with Alzheimer's disease, an episode of delirium was found to accelerate cognitive decline, compared to those who did not experience delirium (Fong 2009). Combined neuropathlogical and clinical cohort study data have confirmed that delirium both accelerates existing cognitive decline and is a risk factor for developing dementia (Davis 2012). Delirium symptoms experienced in early older age (60 to 69 years) are associated with poorer cognitive function after adjustment for other dementia risk factors (Tsui 2018).

An important consideration in evaluating the impact of an episode of delirium is both the duration of the episode and the severity, and validated measures are available to quantitatively assess both parameters (Vasunilashorn 2016). Persistent delirium (lasting beyond hospital discharge) is common, estimated to affect 26% (95% CI 7.9 to 43.3%) of older hospitalised patients at three months follow-up (Cole 2009). Dementia, malignancy, multimorbidity, increased delirium severity, hypoactive subtype and hypoxic illness have been independently associated with persistent delirium (Cole 2015; Dasgupta 2010).

Significantly, delirium is distressing, particularly to family members who witness episodes (Finucane 2017), and also may have lasting effects on the individual patient if they recall their in-hospital experiences (Grover 2015; Partridge 2013). It can also cause distress to staff caring for these patients (Agar 2012; Partridge 2013; Waterfield 2018).

Delirium has considerable economic impact on healthcare systems and society (Leslie 2011). Estimates suggest the costs for those with delirium are two and a half times greater per day than for those without delirium (Leslie 2008). The cost effectiveness of multicomponent delirium-prevention interventions has been demonstrated using data from a non-randomised study (Akunne 2012), however there is a lack of data on cost effectiveness from randomised trials (Siddiqi 2016).

Description of the intervention

This review will assess the effectiveness of non-pharmacological interventions for preventing delirium in hospitalised patients outside the intensive care unit (ICU) setting. Non-pharmacological interventions can be broadly divided into those with a single intervention, which often target a specific risk factor, and those providing a multicomponent intervention, which target multiple risk factors for delirium. Multicomponent interventions are often based around care delivered according to specific protocols, and target risk factors such as sleep deprivation, immobility, dehydration and sensory impairment (Inouye 1999a). The National Institute for Health and Care Excellence (NICE) recommend assessing for the presence of delirium risk factors in adults aged 65 years and older; those with cognitive impairment; those with a hip fracture; and those with severe illness at the time of hospital presentation (NICE 2010). Thereafter, it recommends a multicomponent intervention tailored to needs and care setting, delivered by a multidisciplinary team (NICE 2010).

How the intervention might work

A number of risk factors for delirium have been identified (Ahmed 2014; Pendlebury 2015). While some of these are non-modifiable factors such as age and comorbidities, there are others which are potentially modifiable, including dehydration, sensory impairment and urinary catheterisation (Ahmed 2014). Predictors of incident delirium during a hospital admission include dementia, dependence in activities of daily living, and increased illness severity (O'Regan 2018). Delirium has been described as the interaction between an individual's baseline vulnerability (based on predisposing factors such as age and cognitive function) and precipitating factors or insults occurring during the hospital admission (Inouye 1996). Furthermore, it has been suggested that a combi-

nation of risk factors for delirium may interact to increase vulnerability and that susceptibility can be scored at the time of admission (Pendlebury 2017).

Why it is important to do this review

Delirium is common across all inpatient settings and, in view of the serious complications, costs and consequences arising, it is a priority for healthcare practitioners and providers. Establishing the degree to which delirium can be prevented, and identifying evidence-based strategies for prevention, will help inform evidence-based care pathways.

The previous Cochrane Review of interventions to prevent delirium (Siddiqi 2016) found heterogeneity among the multicomponent interventions studied; the number of "components" tested ranged from two (Jeffs 2013; Marcantonio 2001) to 13 (Hempenius 2013). Developing an understanding around which components are necessary and most effective would be helpful so that robust recommendations for practice can be made.

Multicomponent interventions have been shown in randomised trials to reduce the incidence of delirium by one-third (Martinez 2015; Siddiqi 2016). However, the reductions seen in delirium incidence have not demonstrated statistically significant reductions in length of stay or in longer-term sequelae, including mortality or the need for admission to long-term care (Hshieh 2015; Martinez 2015). There is uncertainty about the precision and certainty of these findings and the extent to which frailty influences outcomes (Teale 2015). Delirium and frailty (defined as '"a diminished ability to compensate for stressors") are conditions associated with poor outcomes in older people and they have been postulated to be different manifestations of "shared vulnerability to stress" (Quinlan 2011). This relationship is complex and poorly understood; recent evidence suggests that mortality risk in delirium is greatest in those with lower levels of frailty (Dani 2018), although the role of illness severity in mediating this association is not known. It would however, be helpful to identify if those with frailty are differentially affected by delirium-prevention interventions.

Some of the risk factors for delirium - including nutrition, hydration, restraint use, and iatrogenic events - can be seen as measures of the quality of hospital care. The occurrence of delirium has been linked to the quality of care delivered to inpatients, which can highlight areas for improvement (Inouye 1999b). The associations between delirium and dementia mean that interventions to prevent delirium are of interest to the wider public health agenda of dementia prevention (Fong 2015).

Over the past decade there has been a rapid increase in the number of randomised trials of delirium-prevention interventions. In 2007, the original version of this Cochrane Review identified six trials evaluating six interventions, only one of which was a non-pharmacological intervention (Siddiqi 2007). The 2016 update identified 39 trials of 22 interventions, which included seven trials of multicomponent interventions and two other non-pharmacological interventions (Siddiqi 2016). Focusing on non-pharmacological interventions will allow a synthesis of the most contemporaneous specific evidence to inform and improve clinical practice.

OBJECTIVES

To assess the effectiveness of non-pharmacological interventions designed to prevent delirium in hospitalised non-intensive care unit (ICU) patients.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), including cluster-RCTs.

Types of participants

We will include studies of adult participants (aged 18 years and over) who are admitted to general-hospital settings. This will include acute and rehabilitation hospitals and sub-acute care provided in hospital. We will exclude studies conducted in community settings, such as long-term care or nursing homes, as these are considered in a separate Cochrane Review (Clegg 2014). If settings are mixed, we will only include the study if data can be extracted specifically for the hospitalised patients.

We will exclude studies of delirium associated with psychoactive substance misuse or withdrawal, as these presentations are clinically distinct. We will exclude studies conducted in intensive care unit (ICU) and high dependency unit (HDU) settings, due to the different populations and interventions likely to be found in such environments. ICU settings, also known as Level 3 settings, are those where patients require either respiratory support alone, or support of a minimum of two organs (Intensive Care Society 2009). HDU settings, also known as Level 2 settings, are those where patients either receive single-organ support or are stepping down from Level 3 care; need pre-operative optimisation using invasive monitoring; or need extended postoperative care (Intensive Care Society 2009).

We will consider studies of delirium prevention in patients receiving only in-hospital specialist palliative care, and include them as a separate subgroup analysis within this review. Delirium prevalence in specialist palliative care settings can be very high (approximately

42% of admissions to specialist palliative care units) and the goals of care may be different in this context (Bush 2017).

Types of interventions

We will only include non-pharmacological interventions which have been designed and implemented to prevent delirium. Studies targeting those with "geriatric syndromes", rather than delirium specifically, will not be eligible for inclusion. We will exclude studies administering pharmacological interventions as a means of delirium prevention. Specifically, this includes tablets, infusions, injectable medications, inhaled medications, or anaesthetic gases, given to all participants in active treatment arms with the intention of preventing delirium. Studies that include correction of abnormal physiology using a pharmacological intervention as part of a multicomponent intervention, e.g. administration of oxygen in presence of low oxygen saturations, will be eligible for inclusion. Eligible trials include those of multicomponent interventions or single-component interventions targeting a specific risk factor (e.g. sleep, hydration, re-orientation). These may include trials of an intervention compared to the usual care available or to an active control intervention. Interventions may be implemented at the level of the ward or department providing care, or at the individual level.

Types of outcome measures

We will include all studies which report any of the primary or secondary outcomes. We have prespecified clinically important secondary outcomes and adverse outcomes which are relevant to patients, families and healthcare providers.

Primary outcomes

1. Incidence of delirium, using a validated diagnostic method (studies using only a positive screening test in the absence of a formal diagnosis will be excluded).
2. Mortality as an inpatient, between one and three months, six and 12 months, and beyond 12 months from randomisation.
3. New diagnosis of dementia, made between one and three months, six and 12 months, and beyond 12 months from randomisation.

Secondary outcomes

1. Duration of delirium episode, measured in days.
2. Peak severity of delirium, measured using validated instruments including the Memorial Delirium Assessment Scale (MDAS) (Breitbart 1997), Delirium Rating Scale (DRS) (Trzepacz 1988), and Delirium Rating Scale Revised 1998 (DRS-R-98) (Trzepacz 2001).
3. Length of hospital admission, measured in days.
4. Use of new psychotropic medication during hospital admission.
5. Activities of daily living, measured using a validated instrument including the Barthel Index (Mahoney 1965) and Katz Index (Katz 1963), between one and three months, six and 12 months, and beyond 12 months from randomisation.
6. Quality of life, measured using a validated patient reported measure, between one and three months, six and 12 months, and beyond 12 months from randomisation.
7. Carer's quality of life, using a validated carer-reported measure, between one and three months, six and 12 months, and beyond 12 months from randomisation.
8. Withdrawal from protocol by participants.

Adverse outcomes

1. Readmission to hospital within 30 days of discharge.
2. Progression of existing dementia, measured using a validated instrument, between one and three months, six and 12 months, and beyond 12 months from randomisation.
3. New care-home admission at discharge and between one and three months, six and 12 months, and beyond 12 months from randomisation.
4. Falls.
5. Pressure ulcers.

We will use GRADEpro Guideline Development Tool software (GRADEpro 2014) to determine the overall quality of the evidence and to generate a 'Summary of findings' table for the outcomes: incidence of delirium, inpatient mortality, new diagnosis of dementia, duration of delirium, peak delirium severity, length of hospital admission, and discharge to new long-term care placement.

Search methods for identification of studies

Electronic searches

We will search the specialised register of the Cochrane Dementia and Cognitive Impairment Group (ALOIS) (www.medicine.ox.ac.uk/alois). We will search for all RCTs of non-pharmacological interventions for preventing delirium. The Information Specialists of the Cochrane Dementia and Cognitive Impairment Group maintain ALOIS, which contains studies about dementia and cognitive impairment identified from the following.

1. Monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACs.
2. Monthly searches of a number of trials registers: the metaRegister of Controlled Trials, the Umin Japan Trial Register, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal (which covers

ClinicalTrials.gov, ISRCTN Registry, the Chinese Clinical Trials Register, the German Clinical Trials Register, the Iranian Registry of Clinical Trials and The Netherlands Clinical Trials Register, plus others).

3. Quarterly searches of the Cochrane Library's Central Register of Controlled Trials (CENTRAL).

4. Monthly searches of the grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched for ALOIS, please visit the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement trials, can be viewed on the Cochrane Dementia and Cognitive Improvement Group's website: https://dementia.cochrane.org/searches.

We will run additional searches in MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov and the WHO ICTRP portal to ensure that the searches are as comprehensive and as up-to-date as possible. We have presented the search strategy that will be used for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) in Appendix 1. There will be no time or language restrictions on literature searches.

Searching other resources

We will examine reference lists from identified articles and relevant systematic reviews to identify any additional potential trials to review for eligibility. We will search the ClinicalTrials.gov database, to identify any relevant ongoing trials. We will compare the trials that meet our review inclusion criteria with the trials register to identify any trials where results have been unpublished. We will contact the lead author of any unpublished trials, to ask if they are prepared to share their results (we will examine these against the published protocols to ensure they have been consistently analysed).

Data collection and analysis

Selection of studies

We will directly import the results of the literature searches into Covidence software (Covidence 2017). This will automatically remove direct duplicate records. Thereafter, two review authors, with experience in conducting systematic reviews, will independently screen the titles and abstracts of all identified articles and remove irrelevant results. We will resolve any disagreements by discussion, involving a third review author if necessary. Two review authors will then independently examine the full-text articles of potentially relevant articles against the review eligibility criteria. We will resolve any disagreements by consensus with a third review author. If we are unable to determine eligibility based on the available information, for example if only an abstract is identified, we will contact the study authors for clarification and additional data as necessary. We will list all articles excluded after full-text assessment in the 'Characteristics of excluded studies' table, with reasons for exclusion. We will present a PRISMA diagram to summarise the study selection process.

Data extraction and management

We will create a data extraction tool, adapted from the version used in the previous update of this review. Two authors will extract data using this tool. Two authors will discuss any disagreements regarding data extraction, involving a third author if necessary.

For our component-based analysis we will extract the information provided on the description of the components of the interventions in as much detail as possible. In the previous version of the review, these were tabulated into 20 categories, providing an overview of included components (Siddiqi 2016). Ideally, components should be defined at a level that clinical recommendations could be based on, for example, they should include a measure of duration and intensity as well as the nature of the intervention delivered to participants. However, we appreciate that this may not be possible given the descriptions available. In the event that such detail is lacking, we will correspond with study authors to try to obtain the required information.

If it is not possible to define components at such a level, we will define components at broader levels, possibly based on the type of intervention or intensity or risk factor it is targeting, or a combination of these. Such grouping will only occur following consultation of clinical expertise from two review authors who agree the classification has clinical validity.

We will conduct sensitivity analyses where there is uncertainty over the optimal way to define components by defining alternative component definitions, repeating the analysis and assessing the robustness of results to such changes. Similarly, where a component is only given to a fraction of a trial arm, we will explore changes in classification definitions via sensitivity analysis.

We will use Review Manager 5 to produce tables which document the characteristics of included, excluded and ongoing trials (Review Manager 2014). We will create 'Summary of findings' tables using GRADEPro GDT (GRADEpro 2014) software. If there are multiple publications reporting the findings of a single study, we will extract these onto a single data extraction form.

Assessment of risk of bias in included studies

Two review authors will independently perform a 'Risk of bias' assessment at the time of data extraction. We will evaluate each study using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2018). We will assess trials for the domains of: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due

to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result.

Cluster-RCTs are subject to additional biases: recruitment bias (recruitment of individual study participants after randomisation of clusters), chance between-cluster baseline imbalances due to a small number of clusters, loss of clusters (e.g. withdrawal of a study site), not accounting for clustering during the analysis (incorrect unit of analysis issues), or bias introduced through combining data from cluster-randomised and individually-randomised trials in meta analyses (risk of underestimation of treatment effects).

We will judge each of these domains as being at either high, low or unclear risk of bias in each study. We will resolve any disagreements by discussion between the two review authors, involving a third author if necessary. We will produce summary tables and figures of the 'Risk of bias' assessment, with justification, in Review Manager 5 (Review Manager 2014).

Measures of treatment effect

We anticipate the outcome data to include continuous and dichotomous measures. For continuous outcomes we will calculate between-group (intervention versus control) mean differences with 95% confidence intervals (CIs). If an identified study does not report data to calculate the primary outcome, we will contact the authors directly to ask them to share these data.

Unit of analysis issues

We expect some included studies to use a cluster-randomised design. Where these studies have analysed data using statistical methods that account for clustering, we will extract the adjusted effect measures (risk ratio or hazard ratio) and their 95% CIs. If an included study has performed unadjusted analyses we will approximate corrected analyses by extracting data on the number of clusters, mean size of each cluster, primary outcome data and estimates of intra-cluster correlation coefficient (ICC). If approximately corrected analyses are not possible, then we will extract the primary data and calculate risk ratios with 95% CIs.

Dealing with missing data

We will report missing data for each included study, including reporting the number of participants included in the final analysis as a proportion of all participants in the study. We will perform available case analysis, including data on those whose outcomes are known. We will contact study authors to try to obtain data not reported in the publication. We will report incomplete outcome assessment in the 'Risk of bias' table for each study, including an assessment of the potential impact of missing data on the results.

Assessment of heterogeneity

It is anticipated that the identified trials will be both clinically and methodologically heterogeneous. We will describe clinical heterogeneity. If the data are considered appropriate for quantitative synthesis, we will calculate statistical heterogeneity and describe it using the I^2 statistic (Higgins 2002). Interpretation of the I^2 statistic will be in accordance with guidance in the Cochrane Handbook (Deeks 2019).

Assessment of reporting biases

We will compare the studies included in our review with clinical trial registries, to identify trials with unpublished results. We will compare the protocols of published studies included in the review against their protocols to check adherence.

Data synthesis

Where it is appropriate, we will undertake meta-analysis of extracted data using Review Manager 5 (Review Manager 2014). We will perform meta-analyses using a random-effects model. We will calculate pooled risk ratios with 95% CIs for dichotomous outcomes (intervention versus control), and pooled mean differences with 95% CIs for continuous outcomes. If studies use different instruments to measure the same continuous outcome, we will calculate the standardised mean difference. We will synthesise outcomes from appropriately adjusted cluster-RCTs. We will measure statistical heterogeneity using the I^2 statistic (Higgins 2002). We will perform data synthesis only where it is considered that the identified studies are clinically homogenous, such that pooling of data is appropriate and valid comparisons can be made. If the clinical heterogeneity is significant, we will report a narrative evidence synthesis.

In addition to the standard meta-analysis, if the available data permit it, we will fit a component level network meta-analysis model to the data to explore and estimate the effectiveness of individual components of the interventions (Welton 2009). The National Institute for Health Research Complex Review Support Unit will perform this analysis. Such an analysis attempts to decompose the estimates of effect in multicomponent interventions so that the effectiveness of individual components can be estimated. As well as providing clinical insight, the optimum combination of components can also be considered. With modest numbers of trials, an additive model often has to be used, which assumes the effects of components add together directly when combined, and no interactions between components affect their effectiveness. With more data, the additive assumption can be relaxed and interaction terms included in the model. When fitting different models is possible, clinical plausibility and statistical goodness-of-fit of the models will dictate which model is used in the final analysis. Irrespective of whether multiple models are fit, how well the model fits the data will be examined and reported via goodness-of-fit statistics. The WinBUGS software will be used for this analysis (WinBUGS).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for participants in trials conducted in medical versus surgical inpatient settings; those receiving palliative care only versus those receiving other medical or surgical treatment; those with and without a diagnosis of dementia (measured using a validated diagnostic instrument); and those who are considered to have frailty versus those who are not (measured using a validated instrument).

Sensitivity analysis

We will perform a sensitivity analysis where appropriate following assessment of the risk of methodological bias in the included studies.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. Delirium/

2. deliri*.mp.

3. “acute confusion*”.ti,ab.

4. “acute organic psychosyndrome”.ti,ab.

5. “acute brain syndrome”.ti,ab.

6. “metabolic encephalopathy”.ti,ab.

7. “acute psycho-organic syndrome”.ti,ab.

8. “clouded state”.ti,ab.

9. “clouding of consciousness”.ti,ab.

10. “exogenous psychosis”.ti,ab.

11. “toxic psychosis”.ti,ab.

12. “toxic confusion”.ti,ab.

13. Delirium, Dementia, Amnestic, Cognitive Disorders/su [Surgery]

14. obnubilat*.ti,ab.

15. or/1-14

16. Primary Prevention/

17. prevent*.mp.

18. reduc*.ti,ab.

19. stop*.ti,ab.

20. taper*.ti,ab.

21. avoid*.ti,ab.

22. “cut* down”.ti,ab.

23. or/16-22

24. 15 and 23

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomi?ed.ab.

28. placebo.ab.

29. drug therapy.fs.

30. randomly.ab.

31. trial.ab.

32. groups.ab.

33. or/25-32

34. (animals not (humans and animals)).sh.

35. 33 not 34
36. 35 and 24

CONTRIBUTIONS OF AUTHORS

JKB developed and drafted the protocol and co-ordinated comments from the other protocol authors.

NS, EAT & AJB provided comments and critical review of the manuscript.

AS contributed to the statistical analysis methods.

All protocol authors approved the manuscript.

DECLARATIONS OF INTEREST

JKB has no known conflicts of interest.

NS has no known conflicts of interest.

EAT has no known conflicts of interest.

AJB has no known conflicts of interest.

AS has no known conflicts of interest.

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