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Complete List of Authors:	Cottuli de Cothi, Elizabeth; University of Bristol Perry, Rachel; University of Bristol Kota, Rahul; University of Bristol Walker-Smith, Terrie ; University of Bristol, Bristol Heart Institute Barnes, Jonathan; North Bristol NHS Trust, Pufulete, Maria; University of Bristol Gibbison, Ben; University of Bristol, ;
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Pharmacological and non-pharmacological interventions to prevent delirium after cardiac surgery: A protocol for a systematic review and meta-analysis.

Elizabeth Cottuli de Cothi[1, 2] **gu22583@bristol.ac.uk**

Rachel Perry[1] **Rachel.perry@bristol.ac.uk**

Rahul Kota[1] **gw21656@bristol.ac.uk**

Terrie Walker-Smith **ta.smith@outlook.com**

Jon Barnes[2] **jonathan.barnes77@gmail.com**

Maria Pufulete[1] **maria.pufulete@bristol.ac.uk**

Ben Gibbison[1] **ben.gibbison@bristol.ac.uk**

1. Bristol Medical School. University of Bristol, Bristol, UK
2. North Bristol NHS Trust. Southmead Hospital Bristol. UK

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Corresponding author: Ben Gibbison. Dept of Anaesthesia. Level 7. Bristol, Royal Infirmary. Upper Maudlin St. Bristol BS2 8HW. ben.gibbison@bristol.ac.uk

Keywords: Delirium, Cardiac Surgery, Systematic Review

Patient and Public Statement: Patients and the public were not involved in the development of this protocol.

ABSTRACT

Introduction. Delirium is a syndrome characterised by a disturbance in attention, awareness, and cognition as a result of another physical condition. It occurs in up to 50% of patients after cardiac surgery and is associated with increased mortality, prolonged intensive care and hospital stay and long-term cognitive dysfunction. Identifying effective preventive interventions is important. We will therefore conduct a systematic review to identify all randomised controlled studies that have tested a pharmacological or non-pharmacological intervention to prevent delirium.

Methods and Analysis. We will search electronic databeses, as well as trial registers for randomised controlled trials (RCTs) of both pharmacological and non-pharmacological interventions designed to prevent delirium after cardiac surgery in adults. Screening of search results and data extraction from included articles will be performed by two independent reviewers using Rayyan. The primary outcome will be incidence of delirium. Secondary outcomes include: Duration of postoperative delirium, all-cause mortality, length of post-operative hospital and intensive care stay, postoperative neurological complications other than delirium, Health-related quality of life and intervention-specific adverse events. Studies will be assessed for risk of bias using the Cochrane RoB2 tool. A narrative synthesis of all included studies will be presented and meta-analysis (if appropriate network meta-analysis) will be undertaken where there are sufficient studies (3 or more) for pooling results. Results will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Ethics and dissemination. No ethical approval is required. This review will be disseminated via peer-reviewed manuscript and conferences.

Prospero registration number: CRD42022369068

Article Summary

Strengths and Limitations

- The systematic review will include a comprehensive search for both pharmacological and non-pharmacological interventions to prevent delirium after cardiac surgery in adults.
- The systematic review will include measures of both short- and long-term outcomes relevant to clinicians, providers and patients.
- The systematic review will, where possible include subgroup analysis of operative type (e.g. CABG v valve) and urgency (e.g. elective v urgent).
- The review will, where possible collect information on implementation of the intervention.

INTRODUCTION

Delirium is a frequent complication after cardiac surgery affecting between one quarter to one half of all patients (1). It is a clinical syndrome characterised by a disturbance in attention, awareness and cognition, which usually starts on post-operative days 1 to 5 and can fluctuate in severity throughout the day (2). Peak incidence is on the second post-operative day. It has been categorised as either hyperactive, hypoactive or mixed. Individuals with hyperactive delirium have heightened arousal and can be agitated and restless, whereas those with hypoactive delirium are withdrawn and lethargic. Its aetiology is multifactorial, resulting from the interaction of patient risk factors and perioperative insult. Patient risk factors include surgical risk, older age, prior neurological or psychiatric disease, and previous substance abuse. Peri-operative risk factors include length of cardiopulmonary bypass (CPB) (3)and type of surgery performed; valve surgery is associated with an increased incidence of delirium compared with coronary artery bypass grafting (CABG) surgery (4). Experiencing delirium after cardiac surgery is associated with poor outcomes, including greater risk of short and long-term mortality (1), decreased functional status (5) and increased risk of long-term cognitive dysfunction (6).

Many of the risk factors for delirium after cardiac surgery are non-modifiable (3). A number of interventions have been tried to prevent delirium after cardiac surgery. These include both pharmacologic and non-pharmacologic approaches. Pharmacological approaches include antipsychotic medications such as haloperidol and risperidone (7). Other pharmacological approaches have included different anaesthesia and post-operative regimens such as dexmedetomidine (8), avoidance of benzodiazepines (9) and use of ketamine(10). Non-pharmacological approaches include pre-operative cognitive training (11), use of sleep protocols, early mobilisation, cognitive stimulation and encouraging sensory normalisation with glasses and hearing aids (12). Many of the interventions are often used together in multi-component interventions (13), although these complex interventions are rarely fully validated and tested.

The mechanisms of action of these interventions on delirium post-cardiac surgery are complex and not fully understood. Since the biochemical changes of delirium are widespread, the interventions target a broad range of mechanisms. Non-pharmacological interventions work by encouraging sensory normalisation (e.g., giving patients their glasses and hearing aids), providing the correct environmental stimuli that people are used to (e.g., maintaining day / night orientation with adequate lighting and noise management, using calendar and clocks, getting patients out of bed as quickly as possible, and explaining to patients what is being done to them). Pharmacological interventions are centred around minimising the duration and depth of sedation (both intra-operatively and after surgery), preventing agitation and optimising physiological status (e.g., maintaining normal fluid-electrolyte balance, body temperature, oxygenation, blood sugar and blood pressure).

Individuals who experience delirium after cardiac surgery are at increased risk of short- and long-term complications, leading to a reduced quality of life and a significant economic burden. In the short-term, patients often have prolonged mechanical ventilation, prolonged length of hospital and intensive care unit stay and increased risk of hospital mortality (14). Longer term, patients are at increased risk of cognitive decline and its associated morbidity as well as increased overall long term mortality (1). Because delirium may be preventable, attention has moved to strategies to reduce its incidence. Therefore, identifying effective preventive interventions is important. A number of interventions have been investigated. However, the literature is extensive and can be conflicting, making an optimal approach unclear. As a result, the interventions used to prevent delirium vary within and between institutions and a unanimous approach is lacking.

The specific objectives are to:

1. Identify all randomised controlled trials (RCTs) investigating interventions to prevent and treat delirium after cardiac surgery.
2. Compare the effectiveness of different interventions on the incidence and duration of delirium after cardiac surgery using standard meta-analysis and, where feasible, network meta-analysis.
3. Describe the safety of the different interventions

METHODS AND ANALYSIS

This systematic review will follow guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15) and the PRISMA extension for network meta-analyses (PRISMA-NMA) (16).

Types of studies

We will include all published and unpublished randomised controlled trials (RCTs), including trials with more than two groups (e.g., comparing different interventions or different dosing regimens of the same intervention). RCTs will be included irrespective of design, and date and will not be restricted to the English language.

Types of participants

Adults (≥18 years) who are undergoing cardiac surgery – coronary artery bypass graft (CABG) surgery, heart valve surgery and thoracic aortic surgery. We will exclude patients who are emergencies (requiring surgery before the start of the next working day). Less than 1% of cardiac surgery is emergency surgery and they represent a separate cohort of patients to the majority of patients who undergo cardiac surgery. They may already be under anaesthesia or sedation, have an acute illness severity that is significantly higher and they are more likely to need prolonged ventilation and sedation than most patients undergoing cardiac surgery.

Types of interventions

We will include both pharmacologic and non-pharmacologic delirium prevention / treatment interventions delivered before, during or after the surgery.

We will include trials that compare any intervention with placebo (e.g., pharmacological) or usual care (e.g., non-pharmacological interventions) and trials that compare different interventions against each other (e.g., two pharmacological strategies, different dosing regimens of the same drug, etc.). We will also include multi-group studies that compare multiple interventions or multiple doses of an intervention against a placebo/usual care/another drug regimen. We will carefully document information about any group defined as usual care since we know that different institutions have markedly different usual care pathways in terms of intraoperative protocols, ICU sedation protocols, etc.

Types of outcome measures

Primary outcomes: Incidence of delirium (yes / no)

Secondary outcomes:

- Duration of postoperative delirium (days).
- All-cause mortality (30 days and up to 1 year).
- Length of post-operative hospital stay (days).
- Length of post-operative intensive care unit stay (days).
- Postoperative neurological complications other than delirium (e.g., seizures, stroke).
- Health-related quality of life (up to 1 year).
- Intervention-specific adverse events (AE).
- Intervention specific outcomes (e.g., pain scores for a postoperative pain prevention intervention).
- Feasibility and implementation outcomes (e.g., to what extent interventions were delivered as intended, adherence to the intervention protocols, etc.).

Electronic searches

We will search the following electronic databases using relevant keywords, subject headings (controlled vocabularies) and search syntax. We will not restrict the search by date, language or publication status.

1. CLib:CDSR (Reviews) (Issue 5, May 2022).
2. CLib:CENTRAL (Trials) (Issue 5, May 2022).
3. MEDLINE Ovid (1946 to May 23, 2022).
4. Embase Ovid (1974 to May 23, 2022).
5. PsycINFO Ovid (1806 to May Week 3 2022).

We will search the following trial registers for ongoing or unpublished trials:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; all available years).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; all available years).

Our search strategy is available in the supplementary material.

Selection of studies

Using Rayyan (17), seven review authors (BG, MP, ECdC, JB, TWS, RP, RK) will independently screen batches of titles and abstracts to identify potentially eligible studies. Each title and abstract will be screened independently by two review authors, each of whom will code it as either included, excluded or maybe. If there are any disagreements, a third review author will arbitrate. Full text papers will be retrieved for all studies deemed eligible or studies that do not provide sufficient information to exclude at the screening stage. Teams of two review authors will independently screen each full text paper; studies not meeting the inclusion criteria will be excluded and the reasons for exclusion will be recorded. Disagreements will be resolved by discussion and consensus with a third review author. The study selection process will be presented in a PRISMA flow diagram.

Data extraction and management

Two review authors will independently extract data from each included study onto a pre-specified data extraction form. Disagreements will be resolved through discussions with a third review author. The following data will be extracted from each study:

- Publication details (authors, title, date of publication, country of origin, language if not published in English, funding source, authors conflicts of interest).

- Methods: total duration of study, number of study centres, study setting, study design, withdrawals and date of study.
- Participants: demographics, inclusion and exclusion criteria, co-morbidities, number of participants randomised to each group, whether intention-to treat analysis was performed.
- Procedure characteristics: Type of surgery (e.g., CABG, valve surgery, combined CABG and valve surgery, thoracic aorta surgery), elective or urgent pathway.
- Interventions: intervention(s) and comparator. These will be intervention specific. Drug, dose, duration.
- Outcomes: Number of participants assessed for the primary and secondary outcomes specified and the time points at which they were reported.

We will contact the trial authors for information if any of the above data items are missing.

Assessment of risk of bias in included studies

Risk of bias for each included study will be assessed independently by at least two review authors. We will use The Cochrane Collaboration's new tool (RoB2) (18) for assessing risk of bias and rate the quality of each trial (low risk, high risk and some concern) in overall risk of bias. We will assess the risk of bias according to the following domains:

1. Bias arising from the randomisation process.
2. Bias due to deviations from the intended interventions
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

Blinding of participants and health care professionals in trials of non-pharmacological interventions is difficult and complete blinding may not be possible. To account for outcome-specific variation in

the bias domains affected by lack of blinding (2 and 4 above), we will group our outcomes for the purpose of risk of bias assessment for these bias domains as follows:

For the primary outcome (incidence of delirium), knowledge of intervention status, particularly for non-pharmacological interventions, may lead to deviations from the intended interventions, for example, healthcare professionals may inadvertently change aspects of care in ways that could influence the likelihood of developing delirium. Delirium diagnosis is highly likely to be subjective (if the assessor does not use the assessment instrument correctly or consistently or is influenced by knowledge of the intervention status of the patient). Therefore, we will judge a study at high risk of bias for domain 2 and 4 if healthcare professionals looking after the patients or those assessing the delirium outcome are not blinded, and some concern if this information is not provided.

All-cause mortality, hospital readmission and length of stay (ICU/hospital) are objective, easy to measure and less likely to be influenced by deviations from intended interventions or by lack of blinding of outcome assessors. These will be judged as low risk of bias for bias domains 2 and 4 regardless of whether participants, healthcare personnel or outcome assessors are blinded or not.

Health related quality of life, although a patient reported outcome that may be prone to bias if the patient is not blinded to their intervention status, will be judged at low risk of bias as patients will likely complete questionnaires after they receive the intervention and recover from delirium, so knowledge of intervention status is less likely to influence how they respond.

Assessment of bias in conducting the systematic review

We will conduct the systematic review according to the published protocol and report and deviations from it in the 'Differences between protocol and review' section of the review.

Assessment of adverse events in included studies

We will extract any additional information about adverse events that may be related to the interventions.

Measures of treatment effect

We will calculate pooled risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes (e.g., delirium, mortality, stroke). For continuous outcomes (e.g., patient reported outcomes), we will calculate pooled mean differences and 95% confidence intervals (CIs) when results are reported on the same scale (or can be converted to the same scale), or standardised mean differences and 95% CI if results are reported on different scales. Where mean and standard deviation (SD) are not reported, we will derive these from the reported test statistics (e.g., SD from standard errors (SE) or 95% CIs) or estimate them from other summary statistics (e.g., mean and SD from median and range). Some studies may report means but not SDs; in this case we will estimate SD from the mean of the SDs reported in other similar studies (assessing a similar intervention) within that treatment arm. If no appropriate data are available, then the outcome will be reported narratively. Medians and ranges will be transformed into means and SDs using the method of Hozo, Djulbegovic and Hozo (19).

Unit of analysis issue

If we identify any cluster trials, we will take into account statistical clustering in our analyses. Where trials include multiple intervention groups and a single control group, we will only use data from the intervention groups that meet our inclusion criteria. If both intervention groups are eligible for inclusion, we will divide the number randomised to the control group in half to use as a denominator for each intervention group, but we will keep the means and SDs for the control group the same.

Dealing with missing data

If the study authors do not report the required data in the publication, we will first attempt to back-calculate from data presented (e.g., numerator or denominator from percentages; standard deviation from standard error or 95% CI). If this is not possible, we will attempt to contact the study authors to request the missing data. Where this is not possible and missing data are thought to

introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis (see below).

Assessment of heterogeneity

We will assess clinical heterogeneity across studies by examining variability in the details of participants, baseline data, interventions, and outcomes to determine whether studies are similar, and visually inspecting forest plots. The I^2 statistic will be calculated to quantify and interpret statistical heterogeneity (20).

We will apply the following thresholds for the interpretation of the I^2 statistic:

- 0 to 40%, might not be important
- 30 to 60%, may represent moderate heterogeneity*
- 50 to 90%, may represent substantial heterogeneity*
- 75 to 100%, represents considerable heterogeneity*

*The importance of the observed value of the I^2 statistic depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g., P value from the Chi^2 test, or a CI for the I^2 statistic). If our I^2 statistic value indicates that heterogeneity is a possibility and either the Tau^2 is greater than zero or the P value is low (less than 0.10), heterogeneity may be due to a factor other than chance.

If we identify substantial heterogeneity (see notes on interpreting the I^2 statistic value above), we will report it and explore possible causes by prespecified subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Reporting biases

For all analyses in which treatment effects from 10 or more RCTs are synthesised, we will use funnel plots and the Egger test to examine small study bias for the primary outcomes (21).

Data synthesis

Given the array of interventions to prevent delirium after cardiac surgery, we will undertake meta-analyses only when there are 3 or more studies where the treatments, participants and underlying clinical question are similar enough for pooling to make sense. However, even with similar interventions there is likely to be substantial heterogeneity in the interventions and their delivery. Given this likely clinical heterogeneity, we will use random effects meta-analysis models for our primary analysis to pool data across trials. However, since random effect models upweight small studies which may be at higher risk of bias, we will undertake a sensitivity analysis and repeat all analyses with statistically significant results using a fixed-effects meta-analysis model. The findings from the included studies will be summarised in narrative form, following the Synthesis Without Meta-analysis (SWiM) guideline (22) if we do not find trials that are sufficiently similar to justify a meta-analysis. We will perform the data synthesis using Review Manager (Review Manager 2014) and STATA (StataCorp 2020). Draft summary of findings tables are available in the supplementary material.

Network Meta-analysis

If appropriate, we will conduct a network meta-analysis of interventions based on direct comparisons to generate indirect comparisons of interventions across trials. This will return rankings for the interventions in terms of their effectiveness.

Subgroup analyses and investigation of heterogeneity

If there is sufficient data available, we will perform the following subgroup analyses using stratified meta-analysis and/or meta regression:

1. Type of surgery – CABG vs valve vs both.
2. Intervention pathway – urgent vs elective.

Sensitivity analyses

We will use sensitivity analysis to assess the robustness of the results and for situations where it might affect the interpretation of significant results. The sensitivity analysis will allow us to evaluate the impact of including studies at risk of bias or missing data such as impact of borderline decisions. We plan to carry out the following sensitivity analyses.

- Including only trials classified as having overall low risk of bias rating
- Excluding trials with more than 20% drop out rate to assess the impact of missing data on results and conclusions
- Including only trials with >= 100 participants
- Including only published trials (not abstracts)
- Conducting fixed-effects meta-analyses for any analyses with statistically significant results using the random-effects model.

If we believe that there is large amount of missing data that will lead to serious bias, then we will explore the impact of including such studies by a sensitivity analysis (Dealing with missing data).

We will assess the overall risk of bias using The Cochrane Collaboration's new tool (RoB2) (18). Low risk of bias is defined as 'low risk of bias' in all domains for this outcome.

Summary of findings and assessment of certainty of evidence

We will use GRADEProfiler software to assess the certainty of evidence for all outcomes reported in the review (GRADEpro GDT). We will downgrade the evidence from high certainty by one level for each of the following factors: indirectness of evidence, unexplained heterogeneity, publication bias, risk of bias due to study design limitations, and imprecision of results (23).

ETHICS AND DISSEMINATION

No ethical approval is required. This review will be disseminated via peer-reviewed manuscript and conferences. We will also disseminate the study via professional networks (e.g. The Society of Cardiothoracic Surgeons of UK and Ireland) and patient groups.

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Author contributions

All authors input to designing the protocol.

RP and ECdC wrote and edited the manuscript.

BG and MP conceived the study and wrote and edited the manuscript.

JB, TWS and RK edited the manuscript.

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Competing Interest Statement

There are no declared conflicts of interest.

Supplemental Material

Appendix 1 – Search strategy

Cochrane Library, Issue 5 of 12, 2022

[Cardiac Surgery]

#1 MeSH descriptor: [Cardiovascular Surgical Procedures] explode all trees 21119

#2 MeSH descriptor: [Cardiopulmonary Bypass] this term only 2801

#3 ((thorax or thoracic) NEAR (operation* or elective* or surgery or surgeries or surgical)):ti,ab,kw 4872

#4 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or transmyocardi*) NEAR (bypass* or graft* or graR* or operation* or elective* or surgery or surgeries or surgical or procedure* or intervention* or implant* or prosthe* or transplant* or replacement* or repair* or revasculari* or re-vasculari*)):ti,ab,kw 68175

#5 (CBG or CABG):ti,ab,kw 6086

#6 (cardiomyoplast* or "maze procedure*" or pericardiectom* or pericardiocentes* or pericardiotom*):ti,ab,kw 260

#7 ((implant* NEAR/2 cardio*)):ti,ab,kw 2671

#8 MeSH descriptor: [Heart Valves] explode all trees and with qualifier(s): [surgery - SU] 752

#9 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) NEAR valv* NEAR (bypass or plasty or graft* or graR* or operat* or elective or surgery or surgeries or surgical or procedure* or intervention* or implant* or prosthe* or transplant* or replac* or repair* or revasc* or re-vasc*)):ti,ab,kw 5072

#10 (("saphenous vein" or "radial artery") NEAR harvest*):ti,ab,kw 193

#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 79424

[Delirium]

#12 MeSH descriptor: [Delirium] explode all trees 972

#13 (deliri* or deleri*):ti,ab,kw 4351

#14 ("acute brain syndrome" or "acute confusion*" or "acute organic psychosyndrom*" or "acute organic psycho-syndrom*" or "acute psycho-organic syndrom*" or "organic mental disorder*"):ti,ab,kw 47

#15 (acute NEAR cereb* NEAR insufficien*):ti,ab,kw 11

#16 ((cloud* or diminish*) NEAR/3 (state* or conscious*)):ti,ab,kw 31

#17 ((exog* or toxic*) NEAR psycho*):ti,ab,kw 122

#18 (toxic* NEAR confus*):ti,ab,kw 19

#19 obnubila*:ti,ab,kw 3

#20 (cognitive NEAR/2 (dysfunction* or declin* or fail*)):ti,ab,kw 7517

#21 ((disturbed or disturbances or disordered or abnormal* or change*) NEAR/2 (attention or "brain function" or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)):ti,ab,kw 4135

#22 (mental* NEAR (confus* or deteriorat*)):ti,ab,kw 497

#23 encephalopath*:ti,ab,kw 3623

#24 (agitat* or restless*):ti,ab,kw 7727

#25 (#12 OR #13 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) 25642

#26 (#11 AND #25) 1630

#27 (nenoat* or newborn* or infant* or child* or pediatric* or paediatric*):ti 113944

#28 #26 not #27 1521

12 Reviews, 1507 trial records

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MEDLINE(R) ALL (Ovid) <1946 to May 23, 2022>

1 exp Cardiovascular Surgical Procedures/ 433803

2 Cardiopulmonary Bypass/ 24739

3 ((thorax or thoracic) adj3 (operation? or elective? or surgery or surgeries or surgical)).mp. 42177

4 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or transmyocardi*) adj3 (bypass* or graft* or graR* or operation? or elective? or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replacement? or repair* or revasculari?ation or re-vasculari?ation)).mp. 397642

5 (CBG or CABG).tw,kf. 21911

6 (cardiomyoplast* or maze procedure? or pericardiectom* or pericardiocentes* or pericardiotom*).mp. 7775

7 (cardio* adj3 implant*).mp. 16783

8 exp Heart Valves/su [Surgery] 38967

9 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) adj5 valv* adj5 (bypass or plasty or graft* or graR* or operat* or elective or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replac* or repair* or revasc* or re-vasc*)).mp. 91169

10 ((saphenous vein or radial artery) adj3 harvest*).mp. 867

11 or/1-10 648183

12 exp delirium/ 11575

13 (deliri* or deleri*).tw,kf. 19368

14 (acute brain syndrom* or acute* confusion* or acute organic psychosyndrom* or acute organic psycho-syndrom* or acute psycho-organic syndrom* or organic mental disorder*).tw,kf. 1592

15 (acute adj3 cereb* adj3 insufficien*).tw,kf. 91

16 ((cloud* or diminish*) adj3 (state* or conscious*)).tw,kf. 889

17 ((exog* or toxic*) adj3 psycho*).tw,kf. 1366

18 (toxic* adj3 confus*).tw,kf. 104

19 obnubila*.tw,kf. 58

20 (cognitive adj2 (dysfunction* or declin* or fail*)).tw,kf. 49896

21 ((disturbed or disturbances or disordered or abnormal* or change*) adj2 (attention or "brain function" or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)).tw,kf. 24124

22 (mental* adj3 (confus* or deteriorat*)).tw,kf. 3183

23 encephalopath*.mp. 63456

24 (agitat* or restless*).tw,kf. 31887

25 or/12-24 187104

26 randomized controlled trial.pt. 568807

27 controlled clinical trial.pt. 94878

28 (randomi#ed or randomi#ation or randomi#ing).tw,kf. 744943

29 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).tw,kf. 661758

30 randomly.ab. 382757

31 placebo.tw,kf. 234784

32 clinical trials as topic.sh.199919

33 trial.ti. 262759

34 or/26-33 1551310

35 exp animals/ not humans.sh. 5009122

36 (exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/) not humans.sh. 1053254

37 34 not (35 or 36) 1427431

38 11 and 25 and 37 827

39 (exp child/ or exp infant/) not adult/ 1876597

40 ((child* or infant* or newborn* or neonat* or newborn? or p?ediatric*) not adult*).ti. 1324433

41 38 not (39 or 40) 794

An additional search for retractions and/or errata was conducted.

42 (retracted publication or "retraction of publication").pt. 22473

43 (retracted or retraction).ti. 15226

44 published erratum.pt. 116203

45 (erratum or errata).ti. 31351

46 or/42-45 147905

47 46 and (11 and 25) 8

48 47 not 41 5

****

Embase (Ovid) <1974 to 2022 May 23>

1 exp cardiovascular surgery/ 795415

2 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or transmyocardi*) adj3 (bypass* or graft* or graR* or operation? or elective? or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replacement? or repair* or revasculari?ation or re-vasculari?ation)).mp. 631659

3 (cardiomyoplast* or maze procedure? or pericardiectom* or pericardiocentes* or pericardiotom*).mp. 16076

4 extracorporeal circulation/ or cardioplegia/ or cardiopulmonary bypass/ or heart left ventricle bypass/ 73604

5 coronary artery bypass graft/ or coronary artery bypass surgery/ or coronary artery recanalization/ or coronary reperfusion/ or coronary stenting/ or heart muscle revascularization/ or off pump coronary surgery/ 135271

6 (CBG or CABG).tw,kf. 39369

7 (implant* adj3 cardio*).mp. 57669

8 heart valve surgery/ or exp heart valve prosthesis/ or exp heart valve replacement/ or exp mitral valve surgery/ or exp valvuloplasty/ 115864

9 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) adj5 valv* adj5 (bypass or plasty or graft* or graR* or operat* or elective or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replac* or repair* or revasc* or re-vasc*)).mp. 137422

10 ((saphenous vein or radial artery) adj3 harvest*).mp. 1088

11 thorax surgery/ 36480

12 ((thorax or thoracic) adj3 (operation? or elective? or surgery or surgeries or surgical)).mp. 64808

13 or/1-12 1095198

14 exp delirium/ 36951

15 *Delirium, Dementia, Amnestic, Cognitive Disorders/ and surgery.fs. 934

16 (deliri* or deleri*).tw,kf. 29658

17 (acute brain syndrom* or acute* confusion* or acute organic psychosyndrom* or acute organic psycho-syndrom* or acute psycho-organic syndrom* or organic mental disorder*).tw,kf. 2423

18 (acute adj3 cereb* adj3 insufficien*).tw,kf. 116

19 ((cloud* or diminish*) adj3 (state* or conscious*)).tw,kf. 1177

20 ((exog* or toxic*) adj3 psycho*).tw,kf. 1211

159	21	(toxic* adj3 confus*).tw,kf.	162
160	22	obnubila*.tw,kf.	117
161	23	(cognitive adj2 (dysfunction* or declin* or fail*)).tw,kf.	75126
162	24	((disturbed or disturbances or disordered or abnormal* or change*) adj2 (attention or "brain function" or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)).tw,kf.	34869
165	25	(mental* adj3 (confus* or deteriorat*)).tw,kf.	4480
166	26	encephalopath*.mp.	103806
167	27	(agitat* or restless*).tw,kf.	50274
168	28	or/14-27	297183
169	29	intensive care/	136783
170	30	((intensive adj2 care) or ICU).tw,kf.	333077
171	31	exp Postoperative Period/	563230
172	32	postoperative complication/ or postoperative cognitive dysfunction/	372710
173	33	(postop* or post-op* or postsurg* or post-surg*).mp.	1345396
174	34	((post* or after or following) adj4 (CBG or CABG or bypass* or graft* or graR* or operation* or elective or surgery or surgeries or surgical or angioplast* or atherectom* or implant* or prosthe* or transplant* or replacement* or repair* or revasculari* or re-vasculari*)).tw,kf.	1299725
177	35	(post* adj3 complication?).tw,kf.	181976
178	36	((manag* or prevent* or reduc*) adj4 (adverse or complication*)).tw,kf. and surgery.af.	67822
180	37	((prevent* or reduc*) adj4 (adverse effect? or adverse event? or adverse outcome?)).tw,kf.	20644
182	38	(emergent or emerging).tw,kf.	411380
183	39	Adverse Drug Reaction.fs.	1305420
184	40	Drug Toxicity.fs.	572732
185	41	Side Effect.fs.	954409
186	42	or/29-41	4738846
187	43	13 and 28 and 42	7767
188	44	postoperative delirium/	3295

45	((emergent or emerging or prevent* or postop* or post-op*) adj3 (deliri* or deleri*)).tw,kf.	5137
46	exp delirium/pc	1617
47	or/44-46	6946
48	13 and 47	1598
49	43 or 48	7786
50	randomized controlled trial/	709462
51	randomization.de.	93803
52	*clinical trial/	17636
53	placebo.de.	380496
54	placebo.tw,kf.	341593
55	trial.ti.	358697
56	(randomi#ed or randomi#ation or randomi#ing).tw,kf.	1068743
57	(RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).tw,kf.	903993
58	controlled clinical trial/ and (Prevention or Rehabilitation or Therapy).fs.	110688
59	or/50-58	1876029
60	((animal or nonhuman) not (human and (animal or nonhuman))).de.	6129945
61	59 not 60	1700328
62	49 and 61	1129
63	(exp child/ or exp infant/) not adult/	2115718
64	((child* or infant* or neonat* or newborn? or p?ediatric*) not adult*).ti.	1532782
65	62 not (63 or 64)	1081

An additional search for retractions and/or errata was conducted.

66	retracted article/	11113
67	(retracted or retraction).ti.	14314
68	erratum.pt.	253441

219 69 (erratum or errata).ti. 170511

220 70 tombstone.pt. 4171

221 71 or/66-70 265614

222 72 71 and (13 and 28) 16

223 73 72 not 65 11

224

225 **********

226

227 **APA PsycInfo** (Ovid) <1806 to May Week 3 2022>

228 1 heart surgery/ 1573

229 2 exp cardiovascular disorders/ and (bypass* or graft* or graR* or operation? or elective? or
230 surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or
231 transplant* or replacement? or repair* or revasculari?ation or re-vasculari?ation).ti,id,hw.
232 5356

233 3 ((thorax or thoracic) adj3 (operation? or elective? or surgery or surgeries or
234 surgical)).tw,id,hw. 143

235 4 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or
236 transmyocardi*) adj3 (bypass* or graft* or graR* or operation? or elective? or surgery or surgeries
237 or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replacement?
238 or repair* or revasculari?ation or re-vasculari?ation)).tw,id,hw. 5085

239 5 (CBG or CABG).tw,id. 575

240 6 (cardiomyoplast* or maze procedure? or pericardiectom* or pericardiocentes* or
241 pericardiotom*).tw,id,hw. 92

242 7 (implant* adj3 cardio*).tw,id,hw. 360

243 8 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) adj3 valv*).tw,id,hw. 629

244 9 (saphenous vein or radial artery).tw,id,hw. 77

245 10 or/1-9 9729

246 11 delirium/ 3774

247 12 (deliri* or deleri*).tw,id. 8087

248 13 (acute brain syndrom* or acute* confusion* or acute organic psychosyndrom* or acute
249 organic psycho-syndrom* or acute psycho-organic syndrom* or organic mental disorder*).tw,id. 977

250 14 (cereb* adj3 insufficien*).tw,id. 247

15	((cloud* or diminish*) adj3 (state* or conscious*)).tw,id.	387
16	toxic psychoses/	220
17	((exog* or toxic*) adj3 psycho*).tw,id.	713
18	(toxic* adj3 confus*).tw,id.	38
19	obnubila*.tw,id.	17
20	(cognitive adj2 (dysfunction* or declin* or fail*)).tw,id.	25413
21	((disturbed or disturbances or disordered or abnormal* or change*) adj2 (attention or brain function or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)).tw,id.	19863
22	(mental* adj3 (confus* or deteriorat*)).tw,id.	1698
23	encephalopathies/ or toxic encephalopathies/	3544
24	encephalopath*.mp.	6926
25	distress/ or agitation/ or restlessness/	28235
26	(agitat* or restless*).tw,id.	13404
27	or/11-26	98901
28	10 and 27	664
29	clinical trials.sh.	12061
30	(randomi#ed or randomi#ation or randomi#ing).ti,ab,id.	100052
31	(RCT or at random or (random* adj3 (administ* or allocat* or assign* or class* or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or substitut* or treat*))).ti,ab,id.	116798
32	(control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw.	32527
33	((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id.	28132
34	trial.ti.	35090
35	placebo.ti,ab,id,hw.	42728
36	treatment outcome.md.	22524
37	treatment effectiveness evaluation.sh.	26706
38	or/29-37	216556
39	28 and 38	95

40	(prevent* adj3 (deliri* or deleri*)).tw,id.	353
41	10 and 40	21
42	39 or 41	111
43	((child* or infant* or newborn* or neonat* or p?ediatric*) not adult*).ti,id,hw.	555127
44	42 not 43	109

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Additional Tables

Table 1. Draft 'Summary of findings' table

Intervention compared to usual care for adults undergoing cardiac surgery

Patient or population: Adults (18 +) having cardiac surgery
Setting: hospital
Intervention: various
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with intervention**				
Incidence of post-operative delirium						
Duration of post-operative delirium			-			
All cause mortality (30 days and up to 1 year)						

Intervention compared to usual care for adults undergoing cardiac surgery

Patient or population: Adults (18 +) having cardiac surgery
Setting: hospital
Intervention: various
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with intervention**				
Health-related quality of life (up to 1 year)						
Length of post-operative hospital stay						
Total post-operative neurological complications follow up: 30 days						
Intervention-specific adverse events						
Hospital Readmission (up to 1 year)						

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Intervention compared to usual care for adults undergoing cardiac surgery

Patient or population: Adults (18 +) having cardiac surgery
Setting: hospital
Intervention: various
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with intervention**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BMJ Open

Pharmacological and non-pharmacological interventions to prevent delirium after cardiac surgery: A protocol for a systematic review and meta-analysis.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-076919.R1
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Primary Subject Heading:	Anaesthesia
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Keywords:	Cardiac surgery < SURGERY, Systematic Review, Delirium & cognitive disorders < PSYCHIATRY, Adult anaesthesia < ANAESTHETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Pharmacological and non-pharmacological interventions to prevent delirium after cardiac surgery: A protocol for a systematic review and meta-analysis.

Elizabeth Cottuli de Cothi[1, 2] **gu22583@bristol.ac.uk**

Rachel Perry[1] **Rachel.perry@bristol.ac.uk**

Rahul Kota[1] **gw21656@bristol.ac.uk**

Terrie Walker-Smith **ta.smith@outlook.com**

Jon Barnes[2] **jonathan.barnes77@gmail.com**

Maria Pufulete[1] **maria.pufulete@bristol.ac.uk**

Ben Gibbison[1] **ben.gibbison@bristol.ac.uk**

1. Bristol Medical School. University of Bristol, Bristol, UK
2. North Bristol NHS Trust. Southmead Hospital Bristol. UK

Word count: 3,255

Corresponding author: Ben Gibbison. Dept of Anaesthesia. Level 7. Bristol, Royal Infirmary. Upper Maudlin St. Bristol BS2 8HW. ben.gibbison@bristol.ac.uk

Keywords: Delirium, Cardiac Surgery, Systematic Review

Patient and Public Statement: Patients and the public were not involved in the development of this protocol.

ABSTRACT

Introduction. Delirium is a syndrome characterised by a disturbance in attention, awareness, and cognition as a result of another physical condition. It occurs in up to 50% of patients after cardiac surgery and is associated with increased mortality, prolonged intensive care and hospital stay and long-term cognitive dysfunction. Identifying effective preventive interventions is important. We will therefore conduct a systematic review to identify all randomised controlled studies that have tested a pharmacological or non-pharmacological intervention to prevent delirium.

Methods and Analysis. We will search electronic databases (CDSR (Reviews), CENTRAL (Trials), MEDLINE Ovid, Embase Ovid, PsycINFO Ovid) as well as trial registers (clinicaltrials.gov and ISCRTN) for randomised controlled trials (RCTs) of both pharmacological and non-pharmacological interventions designed to prevent delirium after cardiac surgery in adults. Screening of search results and data extraction from included articles will be performed by two independent reviewers using Rayyan. The primary outcome will be incidence of delirium. Secondary outcomes include: Duration of postoperative delirium, all-cause mortality, length of post-operative hospital and intensive care stay, postoperative neurological complications other than delirium, Health-related quality of life and intervention-specific adverse events. Studies will be assessed for risk of bias using the Cochrane RoB2 tool. A narrative synthesis of all included studies will be presented and meta-analysis (if appropriate network meta-analysis) will be undertaken where there are sufficient studies (3 or more) for pooling results. Results will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Ethics and dissemination. No ethical approval is required. This review will be disseminated via peer-reviewed manuscript and conferences.

Prospero registration number: CRD42022369068

Article Summary

Strengths and Limitations

- The systematic review will include a comprehensive search of published and ongoing trials for both pharmacological and non-pharmacological interventions to prevent delirium after cardiac surgery in adults.
- The systematic review will include measures of both short- and long-term outcomes relevant to clinicians, providers and patients.
- Post cardiac surgery delirium does not have a universal method of diagnosis and therefore there may be some imprecision due to the tools used for diagnosis.
- The tools will be collected and presented for the reader to judge in the summary of included studies table.

INTRODUCTION

Delirium is a frequent complication after cardiac surgery affecting between one quarter to one half of all patients (1). It is a clinical syndrome characterised by a disturbance in attention, awareness and cognition, which usually starts on post-operative days 1 to 5 and can fluctuate in severity throughout the day (2). Peak incidence is on the second post-operative day. It has been categorised as either hyperactive, hypoactive or mixed. Individuals with hyperactive delirium have heightened arousal and can be agitated and restless, whereas those with hypoactive delirium are withdrawn and lethargic. Its aetiology is multifactorial, resulting from the interaction of patient risk factors and peri-operative insult. Patient risk factors include surgical risk, older age, prior neurological or psychiatric disease, and previous substance abuse. Peri-operative risk factors include length of cardiopulmonary bypass (CPB) (3)and type of surgery performed; valve surgery is associated with an increased incidence of delirium compared with coronary artery bypass grafting (CABG) surgery (4).

Experiencing delirium after cardiac surgery is associated with poor outcomes, including over twice the risk of short and long-term mortality (1) (1), decreased functional status (5) and increased risk of long-term cognitive dysfunction (6) . It also adds around $10, 000 to the hospital costs per patient (7)

Many of the risk factors for delirium after cardiac surgery are non-modifiable (3). A number of interventions have been tried to prevent delirium after cardiac surgery. These include both pharmacologic and non-pharmacologic approaches. Pharmacological approaches include antipsychotic medications such as haloperidol and risperidone (8). Other pharmacological approaches have included different anaesthesia and post-operative regimens such as dexmedetomidine (9), avoidance of benzodiazepines (10) and use of ketamine(11). Non-pharmacological approaches include pre-operative cognitive training (12), use of sleep protocols, early mobilisation, cognitive stimulation and encouraging sensory normalisation with glasses and hearing aids (13). Many of the interventions are often used together in multi-component interventions (14), although these complex interventions are rarely fully validated and tested.

The mechanisms of action of these interventions on delirium post-cardiac surgery are complex and not fully understood. Since the biochemical changes of delirium are widespread, the interventions target a broad range of mechanisms. Non-pharmacological interventions work by encouraging sensory normalisation (e.g., giving patients their glasses and hearing aids), providing the correct environmental stimuli that people are used to (e.g., maintaining day / night orientation with adequate lighting and noise management, using calendar and clocks, getting patients out of bed as quickly as possible, and explaining to patients what is being done to them). Pharmacological interventions are centred around minimising the duration and depth of sedation (both intra-operatively and after surgery), preventing agitation and optimising physiological status (e.g.,

maintaining normal fluid-electrolyte balance, body temperature, oxygenation, blood sugar and blood pressure).

Individuals who experience delirium after cardiac surgery are at increased risk of short- and long-term complications, leading to a reduced quality of life and a significant economic burden. In the short-term, patients often have prolonged mechanical ventilation, prolonged length of hospital and intensive care unit stay and increased risk of hospital mortality (15). Longer term, patients are at increased risk of cognitive decline and its associated morbidity as well as increased overall long term mortality (1). Because delirium may be preventable, attention has moved to strategies to reduce its incidence. Therefore, identifying effective preventive interventions is important. A number of interventions have been investigated. However, the literature is extensive and can be conflicting, making an optimal approach unclear. As a result, the interventions used to prevent delirium vary within and between institutions and a unanimous approach is lacking. This review aims to provide a comprehensive, up-to-date overview of all interventions (both pharmacological and non-pharmacological) to prevent delirium after cardiac surgery.

The specific objectives are to:

1. Identify all randomised controlled trials (RCTs) investigating interventions to prevent delirium after cardiac surgery.
2. Compare the effectiveness of different interventions on the incidence and duration of delirium after cardiac surgery using standard meta-analysis and, where feasible, network meta-analysis.
3. Describe the safety of the different interventions

METHODS AND ANALYSIS

This systematic review will follow guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16) and the PRISMA extension for network meta-analyses (PRISMA-NMA) (17).

Types of studies

We will include all published and unpublished randomised controlled trials (RCTs), including trials with more than two groups (e.g., comparing different interventions or different dosing regimens of the same intervention). RCTs will be included irrespective of design and date and will not be restricted to the English language. Non-English studies will be translated into English.

Types of participants

Adults (≥18 years) who are undergoing cardiac surgery – coronary artery bypass graft (CABG) surgery, heart valve surgery and thoracic aortic surgery. We will exclude patients who are emergencies (requiring surgery before the start of the next working day) or have pre-existing delirium. Less than 1% of cardiac surgery is emergency surgery and they represent a separate cohort of patients to the majority of patients who undergo cardiac surgery. They may already be under anaesthesia or sedation, have an acute illness severity that is significantly higher, and they are more likely to need prolonged ventilation and sedation than most patients undergoing cardiac surgery.

Types of interventions

We will include both pharmacologic and non-pharmacologic delirium prevention / treatment interventions delivered before, during or after the surgery.

We will include trials that compare any intervention with placebo (e.g., pharmacological) or usual care (e.g., non-pharmacological interventions) and trials that compare different interventions against each other (e.g., two pharmacological strategies, different dosing regimens of the same drug, etc.). We will also include multi-group studies that compare multiple interventions or multiple

doses of an intervention against a placebo/usual care/another drug regimen. We will carefully document information about any group defined as usual care since we know that different institutions have markedly different usual care pathways in terms of intraoperative protocols, ICU sedation protocols, etc.

Types of outcome measures

Whilst there are core-outcomes sets for Intensive Care Unit (ICU) Delirium, there is no core outcome set for cardiac surgery specifically. However, there is substantial cross-over between our chosen outcomes and those of the core-outcome set for ICU.

Primary outcomes:

- Incidence of delirium within 7 days of surgery

Secondary outcomes:

- Duration of postoperative delirium (days).
- All-cause mortality (30 days and up to 1 year).
- Length of post-operative hospital stay (days).
- Length of post-operative intensive care unit stay (days).
- Postoperative neurological complications other than delirium (e.g., seizures, stroke).
- Health-related quality of life (up to 1 year).
- Intervention-specific adverse events (AE).
- Intervention specific outcomes (e.g., pain scores for a postoperative pain prevention intervention).
- Feasibility and implementation outcomes (e.g., to what extent interventions were delivered as intended, adherence to the intervention protocols, etc.).

Electronic searches

We will search the following electronic databases using relevant keywords, subject headings (controlled vocabularies) and search syntax. We will not restrict the search by date, language or publication status.

1. CLib:CDSR (Reviews) (Issue 5, May 2022).
2. CLib:CENTRAL (Trials) (Issue 5, May 2022).
3. MEDLINE Ovid (1946 to May 23, 2022).
4. Embase Ovid (1974 to May 23, 2022).
5. PsycINFO Ovid (1806 to May Week 3 2022).

We will search the following trial registers for ongoing or unpublished trials:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; all available years).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; all available years).

Our search strategy is available in the additional material(18).

Selection of studies

Using Rayyan (19), seven review authors (BG, MP, ECdC, JB, TWS, RP, RK) will independently screen batches of titles and abstracts to identify potentially eligible studies. Each title and abstract will be screened independently by two review authors, each of whom will code it as either included, excluded or maybe. If there are any disagreements, a third review author will arbitrate. Full text papers will be retrieved for all studies deemed eligible or studies that do not provide sufficient

information to exclude at the screening stage. Teams of two review authors will independently screen each full text paper; studies not meeting the inclusion criteria will be excluded and the reasons for exclusion will be recorded. Disagreements will be resolved by discussion and consensus with a third review author. The study selection process will be presented in a PRISMA flow diagram.

Data extraction and management

Two review authors will independently extract data from each included study onto a pre-specified data extraction form. Disagreements will be resolved through discussions with a third review author. The following data will be extracted from each study:

- Publication details (authors, title, date of publication, country of origin, language if not published in English, funding source, authors conflicts of interest).
- Methods: total duration of study, number of study centres, study setting, study design, withdrawals and date of study.
- Participants: demographics, inclusion and exclusion criteria, co-morbidities, number of participants randomised to each group, whether intention-to treat analysis was performed.
- Procedure characteristics: Type of surgery (e.g., CABG, valve surgery, combined CABG and valve surgery, thoracic aorta surgery), elective or urgent pathway.
- Interventions: intervention(s) and comparator. These will be intervention specific. Drug, dose, duration.
- Outcomes: Number of participants assessed for the primary and secondary outcomes specified and the time points at which they were reported. The procedure for diagnosing delirium and the instrument used for diagnosis will also be collected.

We will contact the trial authors for information if any of the above data items are missing.

Assessment of risk of bias in included studies

Risk of bias for each included study will be assessed independently by at least two review authors. We will use The Cochrane Collaboration's new tool (RoB2) (20) for assessing risk of bias and rate the quality of each trial (low risk, high risk and some concern) in overall risk of bias. We will assess the risk of bias according to the following domains:

1. Bias arising from the randomisation process.
2. Bias due to deviations from the intended interventions
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

Blinding of participants and health care professionals in trials of non-pharmacological interventions is difficult and complete blinding may not be possible. To account for outcome-specific variation in the bias domains affected by lack of blinding (2 and 4 above), we will group our outcomes for the purpose of risk of bias assessment for these bias domains as follows:

For the primary outcome (incidence of delirium), knowledge of intervention status, particularly for non-pharmacological interventions, may lead to deviations from the intended interventions, for example, healthcare professionals may inadvertently change aspects of care in ways that could influence the likelihood of developing delirium. Delirium diagnosis is highly likely to be subjective (if the assessor does not use the assessment instrument correctly or consistently or is influenced by knowledge of the intervention status of the patient). Therefore, we will judge a study at high risk of bias for domain 2 and 4 if healthcare professionals looking after the patients or those assessing the delirium outcome are not blinded, and some concern if this information is not provided.

All-cause mortality, hospital readmission and length of stay (ICU/hospital) are objective, easy to measure and less likely to be influenced by deviations from intended interventions or by lack of

blinding of outcome assessors. These will be judged as low risk of bias for bias domains 2 and 4 regardless of whether participants, healthcare personnel or outcome assessors are blinded or not.

Health related quality of life, although a patient reported outcome that may be prone to bias if the patient is not blinded to their intervention status, will be judged at low risk of bias as patients will likely complete questionnaires after they receive the intervention and recover from delirium, so knowledge of intervention status is less likely to influence how they respond.

Assessment of bias in conducting the systematic review

We will conduct the systematic review according to the published protocol and report and deviations from it in the 'Differences between protocol and review' section of the review.

Assessment of adverse events in included studies

We will extract any additional information about adverse events that may be related to the interventions.

Measures of treatment effect

We will calculate pooled risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes (e.g., delirium, mortality, stroke). For continuous outcomes (e.g., patient reported outcomes), we will calculate pooled mean differences and 95% confidence intervals (CIs) when results are reported on the same scale (or can be converted to the same scale), or standardised mean differences and 95% CI if results are reported on different scales. Where mean and standard deviation (SD) are not reported, we will derive these from the reported test statistics (e.g., SD from standard errors (SE) or 95% CIs) or estimate them from other summary statistics (e.g., mean and SD from median and range). Some studies may report means but not SDs; in this case we will estimate SD from the mean of the SDs reported in other similar studies (assessing a similar intervention) within that treatment arm. If no appropriate data are available, then the outcome will be reported narratively. Medians and ranges will be transformed into means and SDs using the method of Hozo, Djulbegovic and Hozo (21).

Unit of analysis issue

If we identify any cluster trials, we will take into account statistical clustering in our analyses. Where trials include multiple intervention groups and a single control group, we will only use data from the intervention groups that meet our inclusion criteria. If both intervention groups are eligible for inclusion, we will divide the number randomised to the control group in half to use as a denominator for each intervention group, but we will keep the means and SDs for the control group the same.

Dealing with missing data

If the study authors do not report the required data in the publication, we will first attempt to back-calculate from data presented (e.g., numerator or denominator from percentages; standard deviation from standard error or 95% CI). If this is not possible, we will attempt to contact the study authors to request the missing data. Where this is not possible and missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis (see below).

Assessment of heterogeneity

We will assess clinical heterogeneity across studies by examining variability in the details of participants, baseline data, interventions, and outcomes to determine whether studies are similar, and visually inspecting forest plots. The I2 statistic will be calculated to quantify and interpret statistical heterogeneity (22).

We will apply the following thresholds for the interpretation of the I2 statistic:

- 0 to 40%, might not be important
- 30 to 60%, may represent moderate heterogeneity*
- 50 to 90%, may represent substantial heterogeneity*
- 75 to 100%, represents considerable heterogeneity*

*The importance of the observed value of the I^2 statistic depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g., P value from the Chi^2 test, or a CI for the I^2 statistic). If our I^2 statistic value indicates that heterogeneity is a possibility and either the Tau^2 is greater than zero or the P value is low (less than 0.10), heterogeneity may be due to a factor other than chance.

If we identify substantial heterogeneity (see notes on interpreting the I^2 statistic value above), we will report it and explore possible causes by prespecified subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Reporting biases

For all analyses in which treatment effects from 10 or more RCTs are synthesised, we will use funnel plots and the Egger test to examine small study bias for the primary outcomes (23).

Data synthesis

Given the array of interventions to prevent delirium after cardiac surgery, we will undertake meta-analyses only when there are 3 or more studies where the treatments, participants and underlying clinical question are similar enough for pooling to make sense. However, even with similar interventions there is likely to be substantial heterogeneity in the interventions and their delivery. Given this likely clinical heterogeneity, we will use random effects meta-analysis models for our primary analysis to pool data across trials. However, since random effect models upweight small studies which may be at higher risk of bias, we will undertake a sensitivity analysis and repeat all analyses with statistically significant results using a fixed-effects meta-analysis model. The findings from the included studies will be summarised in narrative form, following the Synthesis Without Meta-analysis (SWiM) guideline (24) if we do not find trials that are sufficiently similar to justify a meta-analysis. We will perform the data synthesis using Review Manager (Review Manager 2014)

and STATA (StataCorp 2020). Draft summary of findings tables are available in the additional tables (18).

Network Meta-analysis

If appropriate, we will conduct a network meta-analysis of interventions based on direct comparisons to generate indirect comparisons of interventions across trials. This will return rankings for the interventions in terms of their effectiveness.

Subgroup analyses and investigation of heterogeneity

If there is sufficient data available, we will perform the following subgroup analyses using stratified meta-analysis and/or meta regression:

1. Type of surgery – CABG vs valve vs both.
2. Intervention pathway – urgent vs elective (Urgent surgery – surgery performed as an inpatient, usually after a precipitating event e.g. acute coronary syndrome. Elective Surgery – surgery performed at a time to suit both the patient and the surgeon)

Sensitivity analyses

We will use sensitivity analysis to assess the robustness of the results and for situations where it might affect the interpretation of significant results. The sensitivity analysis will allow us to evaluate the impact of including studies at risk of bias or missing data such as impact of borderline decisions. We plan to carry out the following sensitivity analyses.

- Including only trials classified as having overall low risk of bias rating
- Excluding trials with more than 20% drop out rate to assess the impact of missing data on results and conclusions
- Including only trials with >= 100 participants
- Including only published trials (not abstracts)

- Conducting fixed-effects meta-analyses for any analyses with statistically significant results using the random-effects model.

If we believe that there is large amount of missing data that will lead to serious bias, then we will explore the impact of including such studies by a sensitivity analysis (Dealing with missing data).

We will assess the overall risk of bias using The Cochrane Collaboration's new tool (RoB2) (20). Low risk of bias is defined as 'low risk of bias' in all domains for this outcome.

Summary of findings and assessment of certainty of evidence

We will use GRADEProfiler software to assess the certainty of evidence for all outcomes reported in the review (GRADEpro GDT). We will downgrade the evidence from high certainty by one level for each of the following factors: indirectness of evidence, unexplained heterogeneity, publication bias, risk of bias due to study design limitations, and imprecision of results (25).

ETHICS AND DISSEMINATION

No ethical approval is required. This review will be disseminated via peer-reviewed manuscript and conferences. We will also disseminate the study via professional networks (e.g. The Society of Cardiothoracic Surgeons of UK and Ireland) and patient groups.

Author contributions

All authors input to designing the protocol.

RP and ECdC wrote and edited the manuscript.

BG and MP conceived the study and wrote and edited the manuscript and are guarantors of the review

JB, TWS and RK edited the manuscript.

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Competing Interest Statement

There are no declared conflicts of interest.

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Additional Tables

Table 1. Draft 'Summary of findings' table

Intervention compared to usual care for adults undergoing cardiac surgery

Patient or population: Adults (18 +) having cardiac surgery
Setting: hospital
Intervention: various
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with intervention**				
Incidence of post-operative delirium						
Duration of post-operative delirium			-			
All cause mortality (30 days and up to 1 year)						
Health-related quality of life (up to 1 year)						
Length of post-operative hospital stay						

Intervention compared to usual care for adults undergoing cardiac surgery

Patient or population: Adults (18 +) having cardiac surgery
Setting: hospital
Intervention: various
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with intervention**				
Total post-operative neurological complications follow up: 30 days						
Intervention-specific adverse events						
Hospital Readmission (up to 1 year)						

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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Supplemental Material

Appendix 1 – Search strategy

Cochrane Library, Issue 5 of 12, 2022

[Cardiac Surgery]

#1 MeSH descriptor: [Cardiovascular Surgical Procedures] explode all trees 21119

#2 MeSH descriptor: [Cardiopulmonary Bypass] this term only 2801

#3 ((thorax or thoracic) NEAR (operation* or elective* or surgery or surgeries or surgical)):ti,ab,kw 4872

#4 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or transmyocardi*) NEAR (bypass* or graft* or graR* or operation* or elective* or surgery or surgeries or surgical or procedure* or intervention* or implant* or prosthe* or transplant* or replacement* or repair* or revasculari* or re-vasculari*)):ti,ab,kw 68175

#5 (CBG or CABG):ti,ab,kw 6086

#6 (cardiomyoplast* or "maze procedure*" or pericardiectom* or pericardiocentes* or pericardiotom*):ti,ab,kw 260

#7 ((implant* NEAR/2 cardio*)):ti,ab,kw 2671

#8 MeSH descriptor: [Heart Valves] explode all trees and with qualifier(s): [surgery - SU] 752

#9 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) NEAR valv* NEAR (bypass or plasty or graft* or graR* or operat* or elective or surgery or surgeries or surgical or procedure* or intervention* or implant* or prosthe* or transplant* or replac* or repair* or revasc* or re-vasc*)):ti,ab,kw 5072

#10 (("saphenous vein" or "radial artery") NEAR harvest*):ti,ab,kw 193

#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 79424

[Delirium]

#12 MeSH descriptor: [Delirium] explode all trees 972

#13 (deliri* or deleri*):ti,ab,kw 4351

#14 ("acute brain syndrome" or "acute confusion*" or "acute organic psychosyndrom*" or "acute organic psycho-syndrom*" or "acute psycho-organic syndrom*" or "organic mental disorder*"):ti,ab,kw 47

#15 (acute NEAR cereb* NEAR insufficien*):ti,ab,kw 11

#16 ((cloud* or diminish*) NEAR/3 (state* or conscious*)):ti,ab,kw 31

#17 ((exog* or toxic*) NEAR psycho*):ti,ab,kw 122

#18 (toxic* NEAR confus*):ti,ab,kw 19

#19 obnubila*:ti,ab,kw 3

#20 (cognitive NEAR/2 (dysfunction* or declin* or fail*)):ti,ab,kw 7517

#21 ((disturbed or disturbances or disordered or abnormal* or change*) NEAR/2 (attention or "brain function" or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)):ti,ab,kw 4135

#22 (mental* NEAR (confus* or deteriorat*)):ti,ab,kw 497

#23 encephalopath*:ti,ab,kw 3623

#24 (agitat* or restless*):ti,ab,kw 7727

#25 (#12 OR #13 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) 25642

#26 (#11 AND #25) 1630

#27 (nenoat* or newborn* or infant* or child* or pediatric* or paediatric*):ti 113944

#28 #26 not #27 1521

12 Reviews, 1507 trial records

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MEDLINE(R) ALL (Ovid) <1946 to May 23, 2022>

1 exp Cardiovascular Surgical Procedures/ 433803

2 Cardiopulmonary Bypass/ 24739

3 ((thorax or thoracic) adj3 (operation? or elective? or surgery or surgeries or surgical)).mp. 42177

4 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or transmyocardi*) adj3 (bypass* or graft* or graR* or operation? or elective? or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replacement? or repair* or revasculari?ation or re-vasculari?ation)).mp. 397642

5 (CBG or CABG).tw,kf. 21911

6 (cardiomyoplast* or maze procedure? or pericardiectom* or pericardiocentes* or pericardiotom*).mp. 7775

7 (cardio* adj3 implant*).mp. 16783

8 exp Heart Valves/su [Surgery] 38967

9 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) adj5 valv* adj5 (bypass or plasty or graft* or graR* or operat* or elective or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replac* or repair* or revasc* or re-vasc*)).mp. 91169

10 ((saphenous vein or radial artery) adj3 harvest*).mp. 867

11 or/1-10 648183

12 exp delirium/ 11575

13 (deliri* or deleri*).tw,kf. 19368

14 (acute brain syndrom* or acute* confusion* or acute organic psychosyndrom* or acute organic psycho-syndrom* or acute psycho-organic syndrom* or organic mental disorder*).tw,kf. 1592

15 (acute adj3 cereb* adj3 insufficien*).tw,kf. 91

16 ((cloud* or diminish*) adj3 (state* or conscious*)).tw,kf. 889

17 ((exog* or toxic*) adj3 psycho*).tw,kf. 1366

18 (toxic* adj3 confus*).tw,kf. 104

19 obnubila*.tw,kf. 58

20 (cognitive adj2 (dysfunction* or declin* or fail*)).tw,kf. 49896

21 ((disturbed or disturbances or disordered or abnormal* or change*) adj2 (attention or "brain function" or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)).tw,kf. 24124

22 (mental* adj3 (confus* or deteriorat*)).tw,kf. 3183

23 encephalopath*.mp. 63456

24 (agitat* or restless*).tw,kf. 31887

25 or/12-24 187104

26 randomized controlled trial.pt. 568807

27 controlled clinical trial.pt. 94878

28 (randomi#ed or randomi#ation or randomi#ing).tw,kf. 744943

29 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).tw,kf. 661758

30 randomly.ab. 382757

31 placebo.tw,kf. 234784

32 clinical trials as topic.sh. 199919

33 trial.ti. 262759

34 or/26-33 1551310

35 exp animals/ not humans.sh. 5009122

36 (exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/) not humans.sh. 1053254

37 34 not (35 or 36) 1427431

38 11 and 25 and 37 827

39 (exp child/ or exp infant/) not adult/ 1876597

40 ((child* or infant* or newborn* or neonat* or newborn? or p?ediatric*) not adult*).ti. 1324433

41 38 not (39 or 40) 794

An additional search for retractions and/or errata was conducted.

42 (retracted publication or "retraction of publication").pt. 22473

43 (retracted or retraction).ti. 15226

44 published erratum.pt. 116203

45 (erratum or errata).ti. 31351

46 or/42-45 147905

47 46 and (11 and 25) 8

48 47 not 41 5

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Embase (Ovid) <1974 to 2022 May 23>

1 exp cardiovascular surgery/ 795415

2 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or transmyocardi*) adj3 (bypass* or graft* or graR* or operation? or elective? or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replacement? or repair* or revasculari?ation or re-vasculari?ation)).mp. 631659

3 (cardiomyoplast* or maze procedure? or pericardiectom* or pericardiocentes* or pericardiotom*).mp. 16076

4 extracorporeal circulation/ or cardioplegia/ or cardiopulmonary bypass/ or heart left ventricle bypass/ 73604

5 coronary artery bypass graft/ or coronary artery bypass surgery/ or coronary artery recanalization/ or coronary reperfusion/ or coronary stenting/ or heart muscle revascularization/ or off pump coronary surgery/ 135271

6 (CBG or CABG).tw,kf. 39369

7 (implant* adj3 cardio*).mp. 57669

8 heart valve surgery/ or exp heart valve prosthesis/ or exp heart valve replacement/ or exp mitral valve surgery/ or exp valvuloplasty/ 115864

9 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) adj5 valv* adj5 (bypass or plasty or graft* or graR* or operat* or elective or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replac* or repair* or revasc* or re-vasc*)).mp. 137422

10 ((saphenous vein or radial artery) adj3 harvest*).mp. 1088

11 thorax surgery/ 36480

12 ((thorax or thoracic) adj3 (operation? or elective? or surgery or surgeries or surgical)).mp. 64808

13 or/1-12 1095198

14 exp delirium/ 36951

15 *Delirium, Dementia, Amnestic, Cognitive Disorders/ and surgery.fs. 934

16 (deliri* or deleri*).tw,kf. 29658

17 (acute brain syndrom* or acute* confusion* or acute organic psychosyndrom* or acute organic psycho-syndrom* or acute psycho-organic syndrom* or organic mental disorder*).tw,kf. 2423

18 (acute adj3 cereb* adj3 insufficien*).tw,kf. 116

19 ((cloud* or diminish*) adj3 (state* or conscious*)).tw,kf. 1177

20 ((exog* or toxic*) adj3 psycho*).tw,kf. 1211

21 (toxic* adj3 confus*).tw,kf. 162

22 obnubila*.tw,kf. 117

23 (cognitive adj2 (dysfunction* or declin* or fail*)).tw,kf. 75126

24 ((disturbed or disturbances or disordered or abnormal* or change*) adj2 (attention or "brain function" or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)).tw,kf. 34869

25 (mental* adj3 (confus* or deteriorat*)).tw,kf. 4480

26 encephalopath*.mp. 103806

27 (agitat* or restless*).tw,kf. 50274

28 or/14-27 297183

29 intensive care/ 136783

30 ((intensive adj2 care) or ICU).tw,kf. 333077

31 exp Postoperative Period/ 563230

32 postoperative complication/ or postoperative cognitive dysfunction/ 372710

33 (postop* or post-op* or postsurg* or post-surg*).mp. 1345396

34 ((post* or after or following) adj4 (CBG or CABG or bypass* or graft* or graR* or operation* or elective or surgery or surgeries or surgical or angioplast* or atherectom* or implant* or prosthe* or transplant* or replacement* or repair* or revasculari* or re-vasculari*)).tw,kf. 1299725

35 (post* adj3 complication?).tw,kf. 181976

36 ((manag* or prevent* or reduc*) adj4 (adverse or complication*)).tw,kf. and surgery.af. 67822

37 ((prevent* or reduc*) adj4 (adverse effect? or adverse event? or adverse outcome?)).tw,kf. 20644

38 (emergent or emerging).tw,kf. 411380

39 Adverse Drug Reaction.fs. 1305420

40 Drug Toxicity.fs. 572732

41 Side Effect.fs. 954409

42 or/29-41 4738846

43 13 and 28 and 42 7767

44 postoperative delirium/ 3295

45 ((emergent or emerging or prevent* or postop* or post-op*) adj3 (deliri* or deleri*)).tw,kf. 5137

46 exp delirium/pc 1617

47 or/44-46 6946

48 13 and 47 1598

49 43 or 48 7786

50 randomized controlled trial/ 709462

51 randomization.de. 93803

52 *clinical trial/ 17636

53 placebo.de. 380496

54 placebo.tw,kf. 341593

55 trial.ti. 358697

56 (randomi#ed or randomi#ation or randomi#ing).tw,kf. 1068743

57 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).tw,kf. 903993

58 controlled clinical trial/ and (Prevention or Rehabilitation or Therapy).fs. 110688

59 or/50-58 1876029

60 ((animal or nonhuman) not (human and (animal or nonhuman))).de. 6129945

61 59 not 60 1700328

62 49 and 61 1129

63 (exp child/ or exp infant/) not adult/ 2115718

64 ((child* or infant* or neonat* or newborn? or p?ediatric*) not adult*).ti. 1532782

65 62 not (63 or 64) 1081

An additional search for retractions and/or errata was conducted.

66 retracted article/ 11113

67 (retracted or retraction).ti. 14314

68 erratum.pt. 253441

69 (erratum or errata).ti. 170511

70 tombstone.pt. 4171

71 or/66-70 265614

72 71 and (13 and 28) 16

73 72 not 65 11

****

APA PsycInfo (Ovid) <1806 to May Week 3 2022>

1 heart surgery/ 1573

2 exp cardiovascular disorders/ and (bypass* or graft* or graR* or operation? or elective? or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replacement? or repair* or revasculari?ation or re-vasculari?ation).ti,id,hw. 5356

3 ((thorax or thoracic) adj3 (operation? or elective? or surgery or surgeries or surgical)).tw,id,hw. 143

4 ((cardiac or cardio* or coronary or heart or epicardi* or myocardi* or pericardi* or transmyocardi*) adj3 (bypass* or graft* or graR* or operation? or elective? or surgery or surgeries or surgical or procedure? or intervention? or implant* or prosthe* or transplant* or replacement? or repair* or revasculari?ation or re-vasculari?ation)).tw,id,hw. 5085

5 (CBG or CABG).tw,id. 575

6 (cardiomyoplast* or maze procedure? or pericardiectom* or pericardiocentes* or pericardiotom*).tw,id,hw. 92

7 (implant* adj3 cardio*).tw,id,hw. 360

8 ((cardi* or heart* or aortic* or mitral* or pulmonary or tricuspid) adj3 valv*).tw,id,hw. 629

9 (saphenous vein or radial artery).tw,id,hw. 77

10 or/1-9 9729

11 delirium/ 3774

12 (deliri* or deleri*).tw,id. 8087

13 (acute brain syndrom* or acute* confusion* or acute organic psychosyndrom* or acute organic psycho-syndrom* or acute psycho-organic syndrom* or organic mental disorder*).tw,id. 977

14 (cereb* adj3 insufficien*).tw,id. 247

15 ((cloud* or diminish*) adj3 (state* or conscious*)).tw,id. 387

16 toxic psychoses/ 220

17 ((exog* or toxic*) adj3 psycho*).tw,id. 713

18 (toxic* adj3 confus*).tw,id. 38

19 obnubila*.tw,id. 17

20 (cognitive adj2 (dysfunction* or declin* or fail*)).tw,id. 25413

21 ((disturbed or disturbances or disordered or abnormal* or change*) adj2 (attention or brain function or cognition or cognitive or consciousness or neurobehavi* or neuro-behavi* or perception*)).tw,id. 19863

22 (mental* adj3 (confus* or deteriorat*)).tw,id. 1698

23 encephalopathies/ or toxic encephalopathies/ 3544

24 encephalopath*.mp. 6926

25 distress/ or agitation/ or restlessness/ 28235

26 (agitat* or restless*).tw,id. 13404

27 or/11-26 98901

28 10 and 27 664

29 clinical trials.sh. 12061

30 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. 100052

31 (RCT or at random or (random* adj3 (administ* or allocat* or assign* or class* or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or substitut* or treat*))).ti,ab,id. 116798

32 (control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. 32527

33 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. 28132

34 trial.ti. 35090

35 placebo.ti,ab,id,hw. 42728

36 treatment outcome.md. 22524

37 treatment effectiveness evaluation.sh. 26706

38 or/29-37 216556

39 28 and 38 95

40	(prevent* adj3 (deliri* or deleri*)).tw,id.	353
41	10 and 40	21
42	39 or 41	111
43	((child* or infant* or newborn* or neonat* or p?ediatric*) not adult*).ti,id,hw.	555127
44	42 not 43	109

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	x		1/2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	x		NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	x		42
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x		11, 12, 14, 15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x		438 and below
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	x		NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	x		444
Sponsor	5b	Provide name for the review funder and/or sponsor	x		444
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	x		444
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	x		50-116
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	x		118 and below
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	x☐	☐	130 and below
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	x☐	☐	176 and below
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	x☐	☐	Supplementary material
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x☐	☐	204 and below
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	x☐	☐	205 and below
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	x☐	☐	204 and below
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	x☐	☐	208 and below
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	x☐	☐	160 and below
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	x☐	☐	224 and below
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	x☐	☐	307 and below
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	x☐	☐	307 and below
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	x☐	☐	321 and below
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x☐	☐	321 and below
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	x☐	☐	304 and below
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	x☐	☐	350 and below