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Protocol for a meta-review of interventions to prevent and manage ICU Delirium

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Abstract

Introduction

Intensive Care Unit Delirium (ICUD) is an acute brain dysfunction that affects up to seven out of 10 patients admitted to Intensive Care Units (ICUs). Patients who develop ICUD cannot think clearly, have trouble paying attention, do not understand what is happening around them and may see or hear things that are not there. ICUD increases the time patients spend in ICUs and hospital and therefore healthcare costs. ICUD is also associated with increased mortality and dementia in the longer term. ICUD prevention and management strategies are likely to include both pharmacological and non-pharmacological components as part of a complex intervention, but it is unclear which components should be included. The objective of this meta review is to systematically map the quantity and certainty of the available evidence from reviews and meta-analyses of randomised controlled trials (RCTs) of pharmacological and non-pharmacological interventions, which will be used to design a multi-component intervention to prevent and manage ICUD.

Methods and analysis

A systematic search strategy was performed in MEDLINE (Ovid), Embase (Elsevier), Cochrane Database of Systematic Reviews, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Web of Science (from inception to 26 September 2023), as well as Epistemonikos (from inception to 19 July 2023). We will include all critically ill adults (aged ≥18 years) and any ICUD prevention or management intervention (pharmacological or non-pharmacological). For pharmacological interventions we will include reviews of RCTs. For non-pharmacological interventions we will consider reviews of RCTs, quasi-experimental and cohort studies. We will use the International Consensus Study (Del-COrS) core-outcome set for research evaluating interventions to prevent or manage ICUD and synthesise our findings using quantitative data description methods. We will involve our Patient and Public Involvement group of people who experienced ICUD to develop and comment on such aspects as the research question, methodology, and which outcomes are most important.

Ethics and dissemination

No ethical approval is required for this study. The results of this meta-review will be disseminated through peer-reviewed publications and conferences. They will also form part of an evidence map and logic model for the prevention and management of ICUD.

PROSPERO registration number CRD42023473260

Strengths and Limitations

- This systematic meta-review will provide a comprehensive overview of the evidence and evidence gaps pertaining to interventions to prevent and manage ICU Delirium.
- The meta-review will be inclusive of interventions to prevent and manage ICU Delirium – but determine the effect on each separately.
- The meta-review will help to identify potential limitations contributing to the complexity of evidence synthesis and implementation research in ICU Delirium.
- We will limit the meta-review to English-language only publications, which could miss relevant evidence.
- The meta-review will not include qualitative evidence, which we will explore separately in future work.

Introduction

Description of the condition

Intensive Care Unit Delirium (ICUD) is an acute brain dysfunction that affects up to seven out of 10 patients admitted to intensive care.[1] In the UK, this equates to over 171,000 patients developing ICUD in intensive care each year, although current diagnostic tools are suboptimal and may underestimate the true extent of ICUD. This number is set to increase as more older people and people with co-morbidities are admitted to intensive care.

Patients who develop ICUD cannot think clearly, have trouble paying attention, do not understand what is happening around them and may see or hear things that are not there. This is extremely distressing for both patients and their families. Many factors contribute to the likelihood of developing delirium, including the illness that leads to the ICU admission, comorbidities, the medications that are used in ICU (e.g., sedatives, analgesia), infections, severe pain, the brain's inability to use oxygen and withdrawal from alcohol and nicotine.

There are three subtypes of ICUD *hyperactive, hypoactive or mixed*, affecting <2%, 45% and 53%[2, 3] of patients, respectively. Patients with hyperactive delirium are aggressive and restless and may interrupt their treatment by pulling out invasive catheters and ventilation equipment. Patients with hypoactive delirium are quietly confused, non-engaged and stuporous. In mixed delirium, patients fluctuate between hyperactive and hypoactive delirium.

Why it is important to do this review

ICUD increases the time patients spend in intensive care and in hospital (hazard ratio for discharge 0.65, 95% Confidence Interval 0.55 to 0.76)[4] and therefore healthcare costs (by around £13,000 per stay).[5, 6] ICUD is also associated with increased mortality[4, 7] and dementia[8, 9] in the longer term. Assessing patients for delirium was an unmet part of the Dementia 2020 Challenge of the UK Department of Health and Social Care,[10] listed as high-priority research by NICE/Royal College of Physicians[11] and is in the top-3 priorities of the James Lind Alliance's Intensive Care Priority Setting Partnership. [12] It is therefore a shared priority for clinicians, patients and family members, and healthcare decision-makers to prevent ICUD and shorten its duration when it develops.

Both pharmacological and non-pharmacological interventions have been used to prevent and manage ICUD. Pharmacological interventions may include avoidance of benzodiazepines, use of dexmedetomidine for sedation,[13] anti-psychotics[14] and melatonin.[15] Non-pharmacological interventions may include repeated reorientation of patients, spontaneous awakening trials, sleep protocols and use of a scheduled pain management tool. Individual interventions have been tested in numerous randomised controlled trials (RCTs). The optimal intervention is expected to include multiple components, although these have not been adequately defined and agreed by clinicians. The ABCDEF bundle[16] developed and promoted by the US Society of Critical Care Medicine (SCCM) is one example of a defined complex intervention. It has been found to improve mortality, ICU and hospital stays,[17] but barriers to its implementation include, for example, increased workload and lack of clinician engagement because of perceived lack of efficacy.[18] Some aspects of the ABCDEF bundle are difficult to apply to the UK setting due to the differences in ICU organisation, staffing structure, and case-mix between the US and UK.[19, 20]

RCTs of single pharmacological interventions have been combined in multiple systematic reviews, meta-analyses, and network meta-analyses. However, there has been no overarching review of the evidence base that also explores the conduct and reporting of findings, with potential implications for practice and research design, as well as the methodological expectations for reviews of ICUD.

Methods and analysis

Aim

To provide an overview of the evidence from systematic reviews of pharmacological and non-pharmacological interventions to prevent and manage ICUD.

Objectives

1. To identify systematic reviews of RCTs that involve single or combination pharmacological interventions or sedation protocols to prevent or manage ICUD.
2. To identify systematic reviews of RCTs or quasi-experimental and cohort studies that involve single or combination non-pharmacological interventions (with or without pharmacological components) to prevent or manage ICUD.
3. To synthesise systematic review findings against an established minimum core outcome set, as well as other important outcome measures, and assess review conduct and reporting.
4. To create an evidence map to understand the extent of the evidence on interventions for ICUD.

We will apply systematic evidence synthesis methods to the conduct of a meta-review (review of reviews, umbrella review), in alignment with guidance to produce Cochrane overviews.[21] Reporting for the protocol follows the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist[22] and is available separately (Supplement 1).

Patient and Public Involvement statement

For the duration of the review process, we will involve our Patient and Public Involvement group of people who have lived experience of ICUD to help develop and comment on such aspects as the research question, methodology, and which outcomes are most important from the patient and carer perspective.

Types of reviews

We will include all published systematic reviews in English with or without meta-analyses from 2000 to the present day. Intensive care has changed significantly since the year 2000. The number of ICU beds has increased,[23] the staffing and technology has improved, and Intensive care is now a stand-alone specialty in the UK and internationally,[24] with its own Faculty, training programme and governance structures[25]. Included primary studies published pre- and post-2000 will be recorded and discussed.

We will include reviews regardless of which country the primary research was conducted in. For pharmacological interventions we will include reviews of randomised controlled trials (RCTs), since the RCT evidence is known to be extensive. Reviews of pharmacological interventions with mixed study designs including RCTs will only be included if separate analyses are reported for RCTs. For non-pharmacological interventions, we will also consider quasi-experimental and cohort studies if there are no relevant RCTs for an intervention. We will include scoping and mapping reviews but exclude narrative reviews without systematic searches, protocols, abstract-only citations, and reviews not published in the English language. Any overviews of reviews will be recorded but excluded from data extraction and evidence mapping.

Types of participants

We will include all critically ill adults (aged ≥18 years). We define critically ill patients as those treated in a critical care or ICU of any specialty (e.g., burn, cardiac, medical, surgical, trauma) or high dependency unit (HDU). Reviews of post-operative delirium (POD) will only be considered for inclusion if they relate to the ICU setting. Reviews focused on ICU subpopulations, such as post-surgery or those receiving mechanical ventilation, will be considered as subgroups within the meta review. We will exclude those studies conducted in other intermediate care units (e.g., coronary care units, respiratory high care units). Potentially relevant reviews of mixed settings including ICU (e.g., general hospital ward and ICU) will be identified and findings synthesised and mapped only if ≥80% of included studies are reported to be conducted in the ICU. We will exclude studies of delirium related to alcohol withdrawal.

Types of interventions

Any delirium prevention, treatment, or management intervention (pharmacological or non-pharmacological). This may include single interventions, care packages / bundles or services interventions that are compared to either

another intervention, a placebo, no treatment, standard or usual care. We will include deprescribing as an intervention (e.g., avoidance of benzodiazepines). Similar interventions may be used to prevent and treat/manage delirium once it has occurred (to shorten its duration). Because we want to identify all relevant evidence, we will include all approaches and distinguish between reviews of preventative interventions and treatment or management interventions. Reviews that do not specify intervention as prophylactic, treatment, or management for ICUD will be included and this uncertainty will be recorded.

Outcomes

We will use the Del-COrS core-outcome set for research evaluating interventions to prevent or treat delirium in critically ill adults.[26] We will assess the outcomes separately for interventions designed to i) prevent and ii) treat or manage delirium.

i) Prevent - Primary Outcome

Delirium occurrence: defined as either prevalence (the number of new and/or existing cases during the reporting period) or incidence (new cases that occur during the reporting period). Although most RCTs of delirium prevention interventions are expected to use the term 'delirium incidence' as their primary outcome (the intuitive endpoint of a preventive intervention), delirium occurrence is considered more appropriate because it is difficult to establish exactly when delirium starts in any given patient. Many patients arrive in intensive care asleep or heavily sedated and current delirium diagnostic tools are unable to assess delirium unless patients are awake even though delirium may already have started. Also, delirium fluctuates (may get better, then get worse again, then get better, and so on) and it is difficult to capture the first episode.

Delirium occurrence, prevalence or incidence may be used interchangeably in the literature, so for the purpose of our meta-review all will be classed as delirium occurrence. Where reviews report outcomes separately for occurrence, incidence, and prevalence, this will be recorded.

Prevent - Secondary Outcomes

1. ICU length of stay (days or hours as reported by the review)
2. Hospital length of stay (days or hours as reported by the review)
3. Mortality (at any timepoint reported by the review)
4. Time to delirium resolution or duration of delirium (at any timepoint reported by the review)
5. Delirium severity (measured using any scale and timing, as reported by the review)
6. Change in cognition including memory (measured using any cognitive scale and timing, as reported by the review)
7. Change in emotional distress including anxiety, depression, acute stress, or post-traumatic stress disorder* (using any symptom screening scale or diagnostic criteria at any timepoint reported by the review)
8. Change in health-related quality of life (using any scale at any timepoint reported by the review)

ii) Treat or manage - Primary Outcomes

Time to delirium resolution or duration of delirium (days or hours as reported by the review) or delirium recurrence.

Treat or manage - Secondary Outcomes

1. ICU length of stay (days or hours as reported by the review)
2. Hospital length of stay (days or hours as reported by the review)
3. Mortality (at any timepoint reported by the review)
4. Delirium severity (measured using any scale and timing, as reported by the review)
5. Change in cognition including memory (measured using any cognitive scale and timing, as reported by the review)

6. Change in emotional distress including anxiety, depression, acute stress, or post-traumatic stress disorder* (using any symptom screening scale or diagnostic criteria at any timepoint reported by the review)
7. Change in health-related quality of life (using any scale at any timepoint reported by the review)

* Post-traumatic stress disorder as a new diagnosis involves the presence of symptoms for at least one month but will be extracted where reported.

Search strategy

A systematic search strategy was performed in MEDLINE (Ovid), Embase (Elsevier), Cochrane Database of Systematic Reviews, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Web of Science (from inception to 26 September 2023), as well as Epistemonikos (from inception to 19 July 2023). The search strategy was developed and run by experienced Information Specialists (including AB) in collaboration with the review team. Our MEDLINE (Ovid) search strategy is available in Supplement 2.

Selection of reviews

This meta-review involves a team of professionals with expertise across health services research and clinical medicine. We imported search results into Excel (version 2308) for screening. Two of three reviewers (of KJ, BK, and AB) independently screened the search results at title/abstract followed by full text with removal of duplicate records. Dual, independent screening was completed against meta-review eligibility criteria for a subset of at least 20% of records at title/abstract and full text. Screening results were then aggregated by one reviewer (AB).

We will undertake further screening of all included full texts as part of data extraction by at least two of three reviewers (of KJ, BK, and AB). Any disagreements will be resolved through consensus discussion with the review team and any full texts unavailable during screening will be recorded. We will review the reference lists of excluded overviews of reviews for additional reviews not found by our initial search. We will describe included and excluded studies within a PRISMA-style flow chart during the various stages of the review and explain our reasons for excluding reviews.

Data extraction

We will perform data extraction using a standardized data extraction form in Excel, developed by the review authors and pilot-tested on at least five systematic reviews to ensure it captures all relevant data. Reviewers will extract data including the author, dates of publication (year), publication title, publishing journal, publication study design characteristics, details about the population, sample size, interventions, comparisons, outcomes, and any reported concurrent interventions not included in the comparison. Different doses and modes of intervention delivery will be extracted where reported. We will also extract information of effect or association and adverse events of the intervention, including on specific subgroups, if reported. We will (where possible, if included in the review) extract information from the review about the tools or instruments used to diagnose delirium and psychiatric diagnoses. Classification of intervention as prevention, treatment or management will be based on review author reporting.

We will identify tools or instruments used to appraise the strength of the evidence from primary research included in systematic reviews (e.g., Cochrane tool for risk of bias versions 1 and 2, Jadad scale, Newcastle-Ottawa scale or its adapted version) and any further investigations of the risk of bias through funnel plots and sensitivity analysis. Use of random or fixed effects models and I^2 assessment of heterogeneity in meta-analyses (0-100%, whereby 0-40% might not be important, 30-60% moderate heterogeneity, 50-90% substantial heterogeneity and 75-100% considerable heterogeneity[27]) will be extracted where reported. We will extract GRADE assessments of the certainty of the evidence where available. Guidance has been developed to support the consistency of such assessments in overviews, however, further assessment will not be performed for evidence mapping.[28]

Unit of analysis

The unit of analysis is the systematic review. A potential source of unit of analysis issues within systematic reviews of ICUD will be the meta-analysis of cluster and individual RCTs together. We will extract both types of RCTs from systematic reviews and, where reported, how they were handled in meta-analysis. Cross-over RCTs are not anticipated to be a research design applied to the meta-review population. The handling of multiple arm studies and multiple observations for the same outcome may be further sources of unit of analysis issues e.g., repeated measurements and recurrence of ICUD. Definitions of outcomes will be extracted where reported, including the timepoint of measurement, as well as any individual patient data (IPD) meta-analysis.

Data synthesis

We will narratively synthesise and report quantitative findings from included reviews. We will present findings according to PICOTS (Patients, Intervention, Comparator, Outcome, Timing, Setting) reported in the included evidence. Formal meta-analysis is not planned for evidence mapping although documentation of quantitative effect sizes will be used to highlight further specific opportunities for meta-analysis and broader implications for future research. Evidence syntheses that involve network meta-analysis or pairwise meta-analysis will be presented separately with discussion of the consistency of findings.

We will begin by mapping the types of interventions included in the evidence base, the overlap of included studies, and summary characteristics of included reviews. This initial mapping will help to identify review comprehensiveness and inform the development of the synthesis strategy. Subsequently, we will create evidence tables and summaries of evidence to provide detailed overviews of the included systematic reviews and their findings.

We will create evidence maps based on included review PICOTS and the type of evidence synthesis. Separate maps are proposed for pharmacological and non-pharmacological interventions, particularly important given the different evidence thresholds being applied.

Reporting

We aim to apply approaches taken for Cochrane overviews,[21] the Preferred Reporting Items for Overviews of Reviews (PRIOR[29]) and PRISMA Extension for Scoping Reviews (PRISMA-ScR[30]) to guide and inform the reporting of this meta-review. Any deviations from the protocol will be recorded as part of the meta-review.

Discussion

This systematic meta-review will provide an overview and map of the evidence pertaining to interventions to prevent and / or manage delirium on the ICU. This map, in conjunction with surveys and qualitative research in ICUs across the UK will inform future research to establish 'the best way to tackle ICU Delirium in the UK'.

There are many systematic reviews of interventions to prevent and manage ICU Delirium. There are also two overviews of reviews[31, 32] that focus on pharmacological or non-pharmacological interventions separately, and prophylaxis across different hospital settings. This review is the first systematic meta-review that focuses on the ICU setting and aims to describe both pharmacological and non-pharmacological evidence relevant to Intensive care, producing translational clinical evidence maps.

The strengths of the review methodology are that it has been designed with a multi-disciplinary team of clinicians, methodologists and patients to provide a set of outcomes that are considered core for research, and which answer important questions regarding outcomes for patients. It complements other work packages within our programme of work, designed to provide a comprehensive picture of how patient-centred ICU Delirium research should progress within the UK. Our meta-review will help to identify potential limitations contributing to the complexity of evidence synthesis and implementation research in ICU Delirium. The review methodology has some weaknesses. For example, included evidence will be limited to English language publications due to logistical constraints, which could

miss some relevant evidence in other languages. Also, we will not include qualitative evidence in our meta-review although this will be explored separately in future work.

Ethics and dissemination

No ethical approval is required for this study and patient consent for publication is not applicable. The results of this meta-review will be disseminated through peer-reviewed publications and conferences. They will also form part of an evidence map and logic model for the prevention and management of ICUD.

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Authors' contributions

BG, MP, and AB designed the protocol and all authors contributed to initial drafts. KLJ and BK developed the methods and subsequent drafts of the protocol. AB initiated the design and performance of literature searches and is the guarantor for the meta-review. KLJ completed final editing of the protocol. All authors approved the final version of the protocol.

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Competing interests statement

KLJ: none declared
BK: none declared
AB: none declared
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MP: none declared
BG: none declared

Supplement 1. PRISMA-P 2015 checklist

Supplement 2. Search strategy

MEDLINE (Ovid)

and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations $$ Medline (Dates searched: 1946 to September 26, 2023). Number of references retrieved: 528.

1 exp confusion/
2 deliri*.ti,ab.
3 (acute adj2 (confusion* or "brain syndrome" or "brain failure" or "psycho-organic syndrome" or "organic psychosyndrome" or "organic brain syndrome")).ti,ab.
4 (terminal* adj restless*).ti,ab.
5 (toxic adj2 (confus$ or psychosis)).ti,ab.
6 metabolic encephalopathy.ti,ab.
7 clouded state.ti,ab.
8 "clouding of consciousness".ti,ab.
9 exogenous psychosis.ti,ab.
10 or/1-9
11 exp Intensive Care Units/
12 Intensive Care.ti,ab.
13 ICU.ti,ab.
14 Critical care/
15 (Critical adj2 (care or ill or illness*)).ti,ab.
16 (high dependency unit* or HDU).ti,ab.
17 or/11-16
18 (systematic review or meta-analysis).pt.
19 meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or exp technology assessment, biomedical/ or network meta-analysis/
20 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf. (331263)
21 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
22 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
23 (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
24 (handsearch* or hand search*).ti,ab,kf.
25 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
26 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
27 (meta regression* or metaregression*).ti,ab,kf.
28 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
29 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
30 (cochrane or (health adj2 technology assessment) or evidence report).jw.
31 (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
32 (outcomes research or relative effectiveness).ti,ab,kf.
33 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.

34 (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
35 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
36 umbrella review*.ti,ab,kf.
37 (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
38 (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
39 (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
40 or/18-39
41 and/10,17,40

*Lines 18 to 39 are taken from the CADTH SR/MA/HTA/ITC - MEDLINE, Embase, PsycInfo search filter, adapted for Ovid Medline.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review **Yes**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **Not applicable**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **Yes**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **Yes**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **Yes**
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 **Not applicable**
Support:		
Sources	5a	Indicate sources of financial or other support for the review **Yes**
Sponsor	5b	Provide name for the review funder and/or sponsor **Yes**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **Yes**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **Yes**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **Yes**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **Yes**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage **Yes**
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 **Yes**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **Yes**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **Yes**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **Yes**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications **Yes**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **Yes**
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 **Yes**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **Yes**
	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 (such as I^2, Kendall's τ) **Yes**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **Yes**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **Yes**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **Yes**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **Yes**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Protocol for a meta-review of interventions to prevent and manage ICU Delirium

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Protocol for a meta-review of interventions to prevent and manage ICU delirium

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Abstract

Introduction

Intensive Care Unit delirium is an acute brain dysfunction that affects up to seven out of 10 patients admitted to Intensive Care Units (ICUs). Patients who develop ICU delirium cannot think clearly, have trouble paying attention, do not understand what is happening around them and may see or hear things that are not there. ICU delirium increases the time patients spend in ICUs and hospital and therefore healthcare costs. ICU delirium is also associated with increased mortality and dementia in the longer term. ICU delirium prevention and management strategies are likely to include both pharmacological and non-pharmacological components as part of a complex intervention, but it is unclear which components should be included. The objective of this meta review is to systematically map the quantity and certainty of the available evidence from reviews and meta-analyses of randomised controlled trials (RCTs) of pharmacological and non-pharmacological interventions, which will be used to design a multi-component intervention to prevent and manage ICU delirium.

Methods and analysis

A systematic search strategy was performed in MEDLINE (Ovid), Embase (Elsevier), Cochrane Database of Systematic Reviews, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Web of Science (from inception to 26 September 2023), as well as Epistemonikos (from inception to 19 July 2023). We will include all critically ill adults (aged ≥18 years) and any ICU delirium prevention or management intervention (pharmacological or non-pharmacological). For pharmacological interventions we will include reviews of RCTs. For non-pharmacological interventions we will consider reviews of RCTs, quasi-experimental and cohort studies. We will use the International Consensus Study (Del-COrS) core-outcome set for research evaluating interventions to prevent or manage ICU delirium and synthesise our findings using quantitative data description methods. We will involve our Patient and Public Involvement group of people who experienced ICU delirium to develop and comment on such aspects as the research question, methodology, and which outcomes are most important.

Ethics and dissemination

No ethical approval is required for this study. The results of this meta-review will be disseminated through peer-reviewed publications and conferences. They will also form part of an evidence map and logic model for the prevention and management of ICU delirium.

PROSPERO registration number CRD42023473260

Strengths and Limitations

- This systematic meta-review will provide a comprehensive overview of the evidence and evidence gaps pertaining to interventions to prevent and manage ICU delirium.
- The meta-review will be inclusive of interventions to prevent and manage ICU delirium – but determine the effect on each separately.
- The meta-review will help to identify potential limitations contributing to the complexity of evidence synthesis and implementation research in ICU delirium.
- We will limit the meta-review to English-language only publications, which could miss relevant evidence.
- The meta-review will not include qualitative evidence, which we will explore separately in future work.

Introduction

Description of the condition

Intensive Care Unit delirium is an acute brain dysfunction that affects up to seven out of 10 patients admitted to intensive care.[1] In the UK, this equates to over 171,000 patients developing ICU delirium in intensive care each year, although current diagnostic tools are suboptimal and may underestimate the true extent of ICU delirium. This number is set to increase as more older people and people with co-morbidities are admitted to intensive care.

Patients who develop ICU delirium cannot think clearly, have trouble paying attention, do not understand what is happening around them and may see or hear things that are not there. This is extremely distressing for both patients and their families. Many factors contribute to the likelihood of developing delirium, including the illness that leads to the ICU admission, comorbidities, the medications that are used in ICU (e.g., sedatives, analgesia), infections, severe pain, the brain's inability to use oxygen and withdrawal from alcohol and nicotine.

There are three broad, clinical manifestations of ICU delirium; *hyperactive, hypoactive or mixed*, affecting <2%, 45% and 53%[2, 3] of patients, respectively. Patients with hyperactive delirium are aggressive and restless and may interrupt their treatment by pulling out invasive catheters and ventilation equipment. Patients with hypoactive delirium are inattentive, non-engaged and stuporous. In mixed delirium, patients fluctuate between hyperactive and hypoactive delirium.

Why it is important to do this review

ICU delirium increases the time patients spend in intensive care and in hospital (hazard ratio for discharge 0.65, 95% Confidence Interval 0.55 to 0.76)[4] and therefore healthcare costs (by around £13,000 per stay).[5, 6] ICU delirium is also associated with increased mortality[4, 7] and dementia[8, 9] in the longer term. Assessing patients for delirium was an unmet part of the Dementia 2020 Challenge of the UK Department of Health and Social Care,[10] listed as high-priority research by NICE/Royal College of Physicians[11] and is in the top-3 priorities of the James Lind Alliance's Intensive Care Priority Setting Partnership. [12] It is therefore a shared priority for clinicians, patients and family members, and healthcare decision-makers to prevent ICU delirium and shorten its duration when it develops.

Both pharmacological and non-pharmacological interventions have been used to prevent and manage ICU delirium. Pharmacological interventions may include avoidance of benzodiazepines, use of dexmedetomidine for sedation,[13] anti-psychotics[14] and melatonin.[15] Non-pharmacological interventions may include repeated reorientation of patients, mobilisation, sleep protocols and use of a scheduled pain management tool. Individual interventions have been tested in numerous randomised controlled trials (RCTs). The optimal intervention is expected to include multiple components, although these have not been adequately defined and agreed by clinicians. The ABCDEF bundle[16] developed and promoted by the US Society of Critical Care Medicine (SCCM) is one example of a defined complex intervention. It has been found to improve mortality, ICU and hospital stays,[17] but barriers to its implementation include, for example, increased workload and lack of clinician engagement because of perceived lack of efficacy.[18] Some aspects of the ABCDEF bundle are difficult to apply to the UK setting due to the differences in ICU organisation, staffing structure, and case-mix between the US and UK.[19, 20]

RCTs of single pharmacological interventions have been combined in multiple systematic reviews, meta-analyses, and network meta-analyses. However, there has been no overarching review of the evidence base that also explores the conduct and reporting of findings, with potential implications for practice and research design, as well as the methodological expectations for reviews of ICU delirium.

Methods and analysis

Aim

To provide an overview of the evidence from systematic reviews of pharmacological and non-pharmacological interventions to prevent and manage ICU delirium.

Objectives

1. To identify systematic reviews of RCTs that involve single or combination pharmacological interventions or sedation protocols to prevent or manage ICU delirium.
2. To identify systematic reviews of RCTs or quasi-experimental and cohort studies that involve single or combination non-pharmacological interventions (with or without pharmacological components) to prevent or manage ICU delirium.
3. To synthesise systematic review findings against an established minimum core outcome set, as well as other important outcome measures, and assess review conduct and reporting.
4. To create an evidence map to understand the extent of the evidence on interventions for ICU delirium.

We will apply systematic evidence synthesis methods to the conduct of a meta-review (review of reviews, umbrella review), in alignment with guidance to produce Cochrane overviews.[21] Reporting for the protocol follows the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist[22] and is available separately (Supplement 1).

Patient and Public Involvement statement

For the duration of the review process, we will involve our Patient and Public Involvement group of people who have lived experience of ICU delirium to help develop and comment on such aspects as the research question, methodology, and which outcomes are most important from the patient and carer perspective.

Types of reviews

We will include all published systematic reviews in English with or without meta-analyses from 2000 to the present day. Intensive care has changed significantly since the year 2000. The number of ICU beds has increased,[23] the staffing and technology has improved, and Intensive care is now a stand-alone specialty in the UK and internationally,[24] with its own Faculty, training programme and governance structures[25]. Included primary studies published pre- and post-2000 will be recorded and discussed.

We will include reviews regardless of which country the primary research was conducted in. For pharmacological interventions we will include reviews of randomised controlled trials (RCTs), since the RCT evidence is known to be extensive. Reviews of pharmacological interventions with mixed study designs including RCTs will only be included if separate analyses are reported for RCTs. For non-pharmacological interventions, we will also consider quasi-experimental and cohort studies if there are no relevant RCTs for an intervention. We will include scoping and mapping reviews but exclude narrative reviews without systematic searches, protocols, abstract-only citations, and reviews not published in the English language. Integrative reviews will be considered if they have relevant included study designs. Any overviews of reviews will be recorded but excluded from data extraction and evidence mapping.

Types of participants

We will include all critically ill adults (aged ≥18 years). We define critically ill patients as those treated in a critical care or ICU of any specialty (e.g., burn, cardiac, medical, surgical, trauma) or high dependency unit (HDU). Reviews of post-operative delirium (POD) will only be considered for inclusion if they relate to the ICU setting. Reviews focused on ICU subpopulations, such as post-surgery or those receiving mechanical ventilation, will be considered as subgroups within the meta review. We will exclude those studies conducted in other intermediate care units (e.g., coronary care units, respiratory high care units). Potentially relevant reviews of mixed settings including ICU (e.g., general hospital ward and ICU) will be identified and findings synthesised and mapped only if ≥80% of included studies are reported to be conducted in the ICU. We will exclude studies of delirium related to alcohol withdrawal.

Types of interventions

Any delirium prevention, treatment, or management intervention (pharmacological or non-pharmacological). This may include single interventions, care packages / bundles or services interventions that are compared to either another intervention, a placebo, no treatment, standard or usual care. We will include deprescribing as an intervention (e.g., spontaneous awakening trials and avoidance of benzodiazepines)[26]. Similar interventions may be used to prevent and treat/manage delirium once it has occurred (to shorten its duration). Because we want to identify all relevant evidence, we will include all approaches and distinguish between reviews of preventative interventions and treatment or management interventions. Reviews that do not specify intervention as prophylactic, treatment, or management for ICU delirium will be included and this uncertainty will be recorded.

Outcomes

We will use the Del-COrS core-outcome set for research evaluating interventions to prevent or treat delirium in critically ill adults.[27] We will assess the outcomes separately for interventions designed to i) prevent and ii) treat or manage delirium.

i) Prevent - Primary Outcome

Delirium occurrence: defined as either prevalence (the number of new and/or existing cases during the reporting period) or incidence (new cases that occur during the reporting period). Although most RCTs of delirium prevention interventions are expected to use the term 'delirium incidence' as their primary outcome (the intuitive endpoint of a preventive intervention), delirium occurrence is considered more appropriate because it is difficult to establish exactly when delirium starts in any given patient. Many patients arrive in intensive care asleep or heavily sedated and current delirium diagnostic tools are unable to assess delirium unless patients are awake even though delirium may already have started. Also, delirium fluctuates (may get better, then get worse again, then get better, and so on) and it is difficult to capture the first episode.

Delirium occurrence, prevalence or incidence may be used interchangeably in the literature, so for the purpose of our meta-review all will be classed as delirium occurrence. Where reviews report outcomes separately for occurrence, incidence, and prevalence, this will be recorded.

Prevent - Secondary Outcomes

1. ICU length of stay (days or hours as reported by the review)
2. Hospital length of stay (days or hours as reported by the review)
3. Mortality (at any timepoint reported by the review)
4. Time to delirium resolution or duration of delirium (at any timepoint reported by the review)
5. Delirium severity (measured using any scale and timing, as reported by the review)
6. Change in cognition including memory (measured using any cognitive scale and timing, as reported by the review)
7. Change in emotional distress including anxiety, depression, acute stress, or post-traumatic stress disorder* (using any symptom screening scale or diagnostic criteria at any timepoint reported by the review)
8. Change in health-related quality of life (using any scale at any timepoint reported by the review)

ii) Treat or manage - Primary Outcomes

Time to delirium resolution or duration of delirium (days or hours as reported by the review) or delirium recurrence.

Treat or manage - Secondary Outcomes

1. ICU length of stay (days or hours as reported by the review)
2. Hospital length of stay (days or hours as reported by the review)
3. Mortality (at any timepoint reported by the review)
4. Delirium severity (measured using any scale and timing, as reported by the review)

5. Change in cognition including memory (measured using any cognitive scale and timing, as reported by the review)
6. Change in emotional distress including anxiety, depression, acute stress, or post-traumatic stress disorder* (using any symptom screening scale or diagnostic criteria at any timepoint reported by the review)
7. Change in health-related quality of life (using any scale at any timepoint reported by the review)

* Post-traumatic stress disorder as a new diagnosis involves the presence of symptoms for at least one month but will be extracted where reported.

Search strategy

A systematic search strategy was performed in MEDLINE (Ovid), Embase (Elsevier), Cochrane Database of Systematic Reviews, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Web of Science (from inception to 26 September 2023), as well as Epistemonikos (from inception to 19 July 2023). The search strategy was developed and run by experienced Information Specialists (including AB) in collaboration with the review team. Our MEDLINE (Ovid) search strategy is available in Supplement 2.

Selection of reviews

This meta-review involves a team of professionals with expertise across health services research and clinical medicine. We imported search results into Excel for screening. Two of three reviewers (of KJ, BK, and AB) independently screened the search results at title/abstract followed by full text with removal of duplicate records. Dual, independent screening was completed against meta-review eligibility criteria for a subset of at least 20% of records at title/abstract and full text. Screening results were then aggregated by one reviewer (AB).

We will undertake further screening of all included full texts as part of data extraction by at least two of three reviewers (of KJ, BK, and AB). Any disagreements will be resolved through consensus discussion with the review team and any full texts unavailable during screening will be recorded. We will review the reference lists of excluded overviews of reviews for additional reviews not found by our initial search. We will describe included and excluded studies within a PRISMA-style flow chart during the various stages of the review and explain our reasons for excluding reviews.

Data extraction

We will perform data extraction using a standardized data extraction form in Excel, developed by the review authors and pilot-tested on at least five systematic reviews to ensure it captures all relevant data. Reviewers will extract data including the author, dates of publication (year), publication title, publishing journal, publication study design characteristics, details about the population, sample size, interventions, comparisons, outcomes (including composite delirium outcomes e.g., delirium- and coma-free days), and any reported concurrent interventions not included in the comparison. Different doses and modes of intervention delivery will be extracted where reported. We will also extract information of effect or association and adverse events of the intervention, including on specific subgroups, if reported. We will (where possible, if included in the review) extract information from the review about the tools or instruments used to diagnose delirium and psychiatric diagnoses. Classification of intervention as prevention, treatment or management will be based on review author reporting.

We will identify tools or instruments used to appraise the strength of the evidence from primary research included in systematic reviews (e.g., Cochrane tool for risk of bias versions 1 and 2, Jadad scale, Newcastle-Ottawa scale or its adapted version) and any further investigations of the risk of bias through funnel plots and sensitivity analysis. Use of random or fixed effects models and I^2 assessment of heterogeneity in meta-analyses (0-100%, whereby 0-40% might not be important, 30-60% moderate heterogeneity, 50-90% substantial heterogeneity and 75-100% considerable heterogeneity[28]) will be extracted where reported. We will extract GRADE assessments of the certainty of the

evidence where available. Guidance has been developed to support the consistency of such assessments in overviews, however, further assessment will not be performed for evidence mapping.[29]

Unit of analysis

The unit of analysis is the systematic review. A potential source of unit of analysis issues within systematic reviews of ICU delirium will be the meta-analysis of cluster and individual RCTs together. We will extract both types of RCTs from systematic reviews and, where reported, how they were handled in meta-analysis. Cross-over RCTs are not anticipated to be a research design applied to the meta-review population. The handling of multiple arm studies and multiple observations for the same outcome may be further sources of unit of analysis issues e.g., repeated measurements and recurrence of ICU delirium. Definitions of outcomes will be extracted where reported, including the timepoint of measurement, as well as any individual patient data (IPD) meta-analysis.

Data synthesis

We will narratively synthesise and report quantitative findings from included reviews. We will present findings according to PICOTS (Patients, Intervention, Comparator, Outcome, Timing, Setting) reported in the included evidence. Formal meta-analysis is not planned for evidence mapping although documentation of quantitative effect sizes will be used to highlight further specific opportunities for meta-analysis and broader implications for future research. Evidence syntheses that involve network meta-analysis or pairwise meta-analysis will be presented separately with discussion of the consistency of findings.

We will begin by mapping the types of interventions included in the evidence base, the overlap of included studies, and summary characteristics of included reviews. This initial mapping will help to identify review comprehensiveness and inform the development of the synthesis strategy. Subsequently, we will create evidence tables and summaries of evidence to provide detailed overviews of the included systematic reviews and their findings.

We will create evidence maps based on included review PICOTS and the type of evidence synthesis. Separate maps are proposed for pharmacological and non-pharmacological interventions, particularly important given the different evidence thresholds being applied.

Reporting

We aim to apply approaches taken for Cochrane overviews,[21] the Preferred Reporting Items for Overviews of Reviews (PRIOR[30]) and PRISMA Extension for Scoping Reviews (PRISMA-ScR[31]) to guide and inform the reporting of this meta-review. Any deviations from the protocol will be recorded as part of the meta-review.

Discussion

This systematic meta-review will provide an overview and map of the evidence pertaining to interventions to prevent and / or manage delirium on the ICU. This map, in conjunction with surveys and qualitative research in ICUs across the UK will inform future research to establish 'the best way to tackle ICU delirium in the UK'.

There are many systematic reviews of interventions to prevent and manage ICU delirium. There are also two overviews including systematic reviews[32, 33] that focus on pharmacological or non-pharmacological interventions separately, and prophylaxis across different hospital settings. This review is the first systematic meta-review that focuses on the ICU setting and aims to describe both pharmacological and non-pharmacological evidence relevant to Intensive care, producing translational clinical evidence maps.

The strengths of the review methodology are that it has been designed with a multi-disciplinary team of clinicians, methodologists and patients to provide a set of outcomes that are considered core for research, and which answer important questions regarding outcomes for patients. It complements other work packages within our programme of work, designed to provide a comprehensive picture of how patient-centred ICU delirium research should progress

within the UK. Our meta-review will help to identify potential limitations contributing to the complexity of evidence synthesis and implementation research in ICU delirium. The review methodology has some weaknesses. For example, included evidence will be limited to English language publications due to logistical constraints, which could miss some relevant evidence in other languages. Also, we will not include qualitative evidence in our meta-review although this will be explored separately in future work.

Ethics and dissemination

No ethical approval is required for this study and patient consent for publication is not applicable. The results of this meta-review will be disseminated through peer-reviewed publications and conferences. They will also form part of an evidence map and logic model for the prevention and management of ICU delirium.

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Authors' contributions

BG, MP, and AB designed the protocol and all authors contributed to initial drafts. KLJ and BK developed the methods and subsequent drafts of the protocol. AB initiated the design and performance of literature searches and is the guarantor for the meta-review. KLJ completed final editing of the protocol. All authors approved the final version of the protocol.

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Competing interests statement
KLJ: none declared
BK: none declared
AB: none declared
EG: none declared
MP: none declared
BG: none declared

Supplement 1. PRISMA-P 2015 checklist

Supplement 2. Search strategy

MEDLINE (Ovid)
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1 exp confusion/
2 deliri*.ti,ab.
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17 or/11-16
18 (systematic review or meta-analysis).pt.
19 meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or exp technology assessment, biomedical/ or network meta-analysis/
20 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf. (331263)
21 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review **Yes**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **Not applicable**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **Yes**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **Yes**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **Yes**
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 **Not applicable**
Support:		
Sources	5a	Indicate sources of financial or other support for the review **Yes**
Sponsor	5b	Provide name for the review funder and/or sponsor **Yes**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **Yes**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **Yes**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **Yes**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **Yes**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage **Yes**
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 **Yes**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **Yes**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **Yes**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **Yes**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications **Yes**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **Yes**
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 **Yes**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **Yes**
	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 (such as I^2, Kendall's τ) **Yes**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **Yes**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **Yes**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **Yes**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **Yes**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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