



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Antipsychotics for the Prevention and Treatment of Delirium: A Systematic Review.*

(Amendments Details—see Section VII)

I. Background and Objectives for the Systematic Review

Delirium is a syndrome characterized by an abrupt impairment in cognition, with a specific deficit in attention, that is generally associated with an underlying medical cause.¹ Delirium is a common and important condition in all health care settings, but is particularly prevalent in older adults and patients with critical illness. Older age is an important independent risk factor for delirium,² with a prevalence >70% in critically ill patients ≥ 60 years.^{3,4} Delirium is strongly associated with increased mortality and longer hospital stay, with an estimated cost of \$38 - 52 billion annually for patients ≥ 70 years old.⁵ Hence, preventive and therapeutic interventions for delirium are a key focus for health care researchers and clinicians.

Delirium experienced during a hospitalization is strongly associated with new or worsening long-term cognitive impairment. A large, multi-site prospective study of U.S. critically ill patients found that among 12-month survivors, ~25% had cognitive test scores similar to patients with mild Alzheimer's disease.⁶ The severity of this cognitive impairment was strongly associated with the duration of delirium in the intensive care unit (ICU). A 2018 systematic review reported that delirium duration is the modifiable factor most strongly associated with long-term cognitive impairment after critical illness.⁷ These findings are consistent with community-based epidemiological studies of older adults, demonstrating that delirium is significantly associated with incident dementia (odds ratio (OR) = 8.7) in those without pre-existing cognitive impairment⁸ and with accelerated cognitive decline⁹ in those with pre-existing dementia, with worsening dementia severity (OR = 3.1) and global function (OR = 2.8).

Preventive and therapeutic interventions are required to reduce the burden of delirium and associated long-term cognitive impairments. Currently, there are no medications approved by the Food and Drug Administration for the prevention and treatment of delirium. Recently, increasing numbers of randomized controlled trials (RCTs) have been published to study delirium prevention and treatment, with many testing pharmacologic interventions, particularly antipsychotic medications. This is important clinically as chronic use of antipsychotics in management of conditions other than delirium has been shown to increase the risk of stroke and sudden death in older adults.¹⁰⁻¹²

Previous reviews were inconclusive about benefit or harm because of a scant and heterogeneous delirium intervention literature, particularly in older adults.^{13,14} Therefore the American Geriatrics Society (AGS) is seeking a new updated systematic review to focus on evaluating both the harms and benefits of antipsychotics for delirium prevention and treatment, as well as a comparison of antipsychotics to non-pharmacologic and other interventions, particularly as it relates to older adults. This review will be used to inform an update of the AGS' Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.

II. The Key Questions

Question 1: What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **prevent** delirium?

- a. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **prevent** delirium in **persons aged 65 years or older**?
- b. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **prevent** delirium in **persons with dementia**?
- c. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **prevent** delirium in **patients in an intensive care unit**?
- d. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **prevent** delirium in **patients in a post-acute care facility**?
- e. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **prevent** delirium in **patients in palliative or hospice care**?
- f. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **prevent** delirium in **patients in post-operative care**?

Question 2: What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **treat** delirium?

- a. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **treat** delirium in **persons aged 65 years or older**?
- b. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **treat** delirium in **persons with dementia**?
- c. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **treat** delirium in **patients in an intensive care unit**?
- d. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **treat** delirium in **patients in a post-acute care facility**?
- e. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **treat** delirium in **patients in palliative or hospice care**?
- f. What are the benefits and harms for antipsychotics compared to each other, placebo, or non-drug approaches to **treat** delirium in **patients in post-operative care**?

- **Population(s):**
 - KQ 1: Hospitalized adults, adults in post-acute care, adults in palliative or hospice care, or adults in post-operative care
 - KQ 2: Hospitalized adults, adults in post-acute care, adults in palliative or hospice care, or adults in post-operative care who have been diagnosed with delirium using a validated instrument
- **Interventions:**
 - Antipsychotic drugs, including
 - Any first-generation agent (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine)
 - Any second-generation agent (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)
 - We will only include studies where the effects of the antipsychotic drugs can be isolated.
- **Comparators:**
 - KQ 1: Non-drug approaches to preventing delirium, placebo, active control, usual care
 - KQ 2: Non-drug approaches to treating delirium, placebo, active control, usual care
- **Outcomes:**
 - Intermediate outcomes
 - Short-term delirium symptoms
 - Delirium severity
 - Delirium-free, coma-free days alive
 - Duration of delirium
 - Patient distress
 - Use of rescue therapy
 - Use of physical restraint
 - Final health or patient-centered outcomes
 - Mortality
 - Quality of life
 - Cognitive and emotional functioning (includes functioning related to memory, communication, concentration, and understanding instructions)
 - Long-term cognitive impairment (Change in cognition after delirium that has a long-term duration or is possibly permanent)
 - Institutionalization (living in an assisted living facility or nursing home)
 - Caregiver burden/strain
 - Falls
 - Memory of patient distress
 - Resource utilization

- Re-admissions to hospital or ICU
 - Length of stay in ICU
 - Length of stay in hospital
 - Length of stay in skilled nursing facility
 - Sitter use
 - Hospice enrollment
- Adverse effects of intervention(s)
 - Sedation
 - Weight gain
 - Changes in appetite
 - Cardiac effects
 - Neurologic effects
 - Hypersensitivity reactions
 - Inappropriate continuation of antipsychotic medication
 - Swallowing difficulties
 - Aspiration pneumonia
- **Timing:**
 - Any duration of follow-up
- **Settings:**
 - Hospital setting
 - Post-acute care setting
 - Palliative care setting

III. Analytic Framework

Analytic Framework

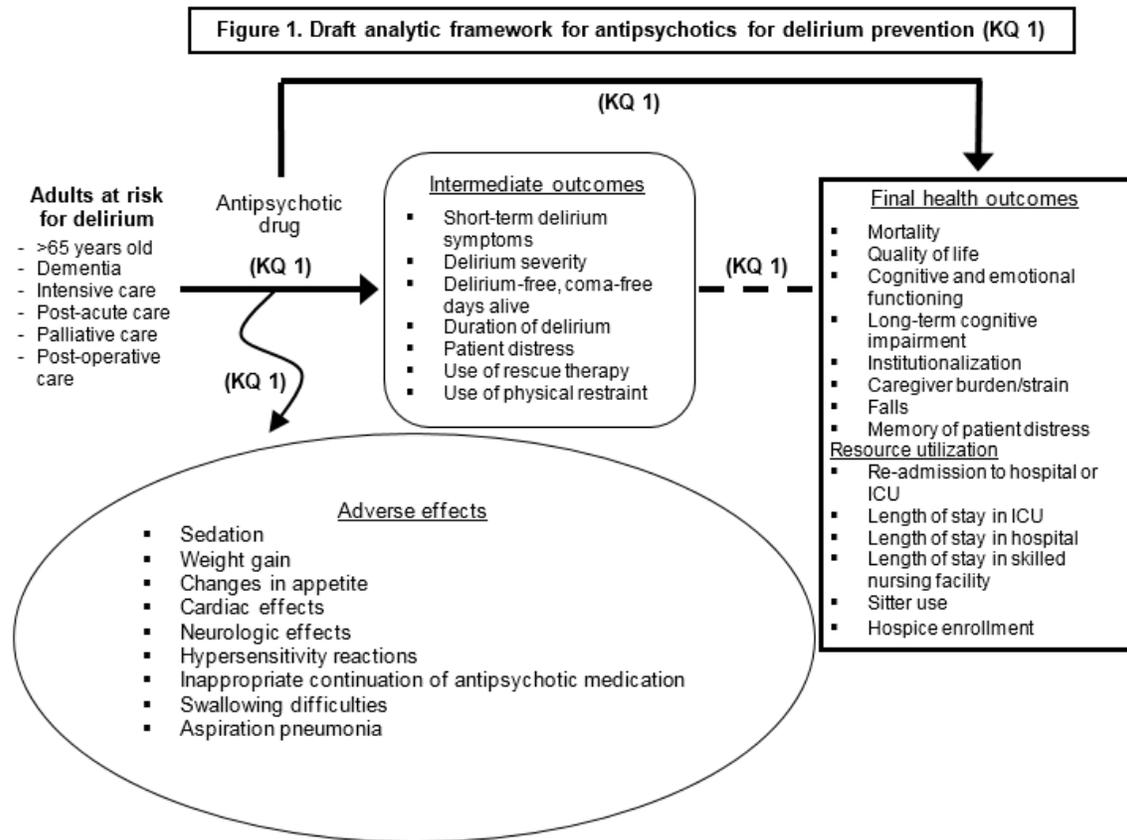
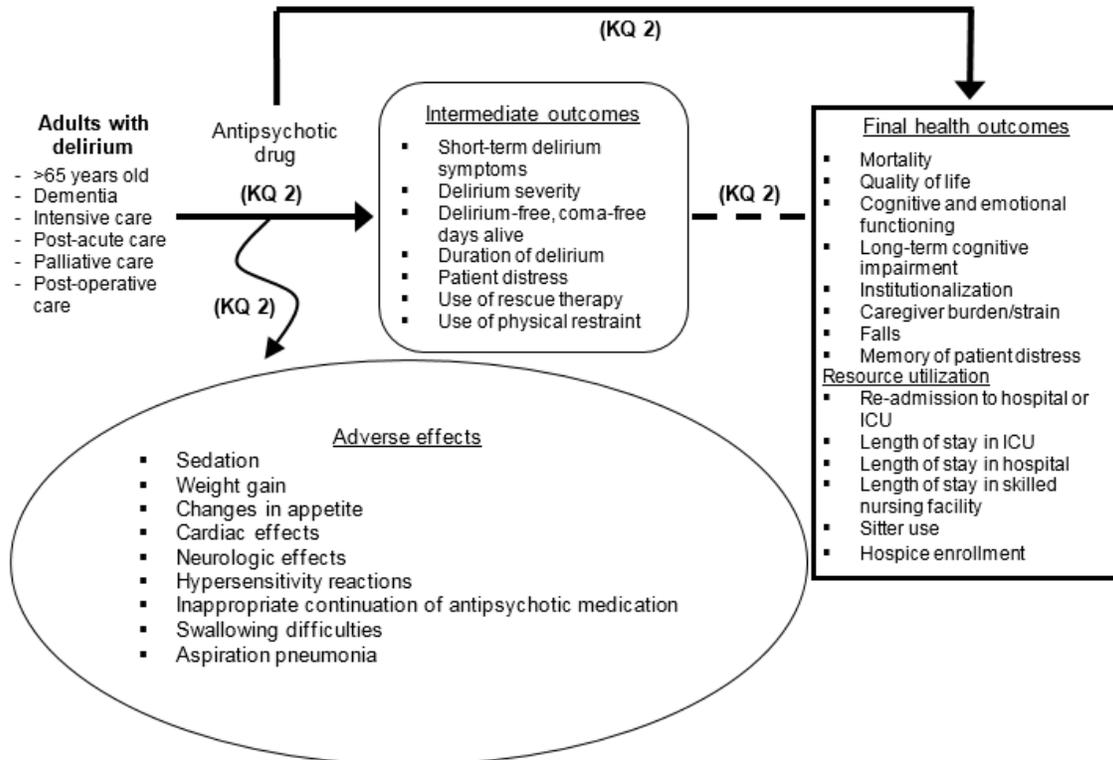


Figure 2. Draft analytic framework for antipsychotics for delirium treatment (KQ 2)



IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review - The inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria

PICOTS	Inclusion criteria	Exclusion criteria
Population	<ul style="list-style-type: none"> • For KQ 1, we will include hospitalized adults who are at risk of delirium. • For KQ 2, we will include hospitalized adults with delirium. 	<ul style="list-style-type: none"> • For KQ 2, we will exclude studies that did not use a validated instrument to diagnose delirium.¹⁵ • We will exclude studies conducted in children.
Intervention	<ul style="list-style-type: none"> • We will include studies that evaluate an antipsychotic drug, including: <ul style="list-style-type: none"> ○ Any first-generation agent (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine) ○ Any second-generation agent (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) 	<ul style="list-style-type: none"> • We will exclude studies where the effects of the antipsychotic drugs cannot be isolated.

Comparison	<ul style="list-style-type: none"> For KQ 1, we will include non-drug approaches to preventing delirium, including placebo, active control, and usual care. For KQ 2, we will include non-drug approaches to treating delirium, including placebo, active control, and usual care. 	<ul style="list-style-type: none"> For outcomes other than adverse events, we will exclude studies that do not have a comparison group.
Outcomes	<ul style="list-style-type: none"> We will include studies addressing the following outcomes: <ul style="list-style-type: none"> Intermediate outcomes (short-term delirium symptoms; delirium severity; delirium-free, coma-free days alive; duration of delirium; patient distress; use of rescue therapy; use of physical restraint) Final health or patient-centered outcomes (mortality; quality of life; cognitive and emotional functioning; long-term cognitive impairment; institutionalization; caregiver burden/strain; falls; memory of patient distress) Resource utilization (readmission to the hospital or ICU; length of stay in ICU; length of stay in hospital; length of stay in skilled nursing facility; sitter use; hospice enrollment) Adverse effects (sedation; weight gain; changes in appetite; cardiac effects; neurologic effects; paradoxical reactions; hypersensitivity reactions; inappropriate continuation of antipsychotic medication; swallowing difficulties; aspiration pneumonia) 	
Type of study	<ul style="list-style-type: none"> For all outcomes except adverse events, we will include only randomized controlled trials. For adverse events, we will include randomized controlled trials, non-randomized controlled trials, and prospective cohort studies with and without a comparison group. We will include studies regardless of language. 	<ul style="list-style-type: none"> We will exclude studies with no original data. We will exclude meeting abstracts.
Timing and setting	<ul style="list-style-type: none"> We will include studies regardless of the length of followup. 	

ICU = intensive care unit; KQ = key question

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions – We will search the following databases for primary studies through June 2018: MEDLINE®, Embase™, the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL®), and PsycINFO®. We will develop

a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text words identified a priori. Our search strategy is presented in Table 2. Our search will be peer-reviewed by a medical librarian with experience in developing literature searches in the field of delirium. We will hand search the reference lists of included articles and relevant reviews. We will also hand search the references included in several delirium-specific bibliographic repositories.¹⁶⁻¹⁸ We will update the search during the peer review process.

Table 2. Search strategy

#	String
1	Confusion[mh] OR delirium*[tiab] OR delirium*[tiab] OR deliria*[tiab] OR delirious[tiab] OR delirious[tiab] OR confusion*[tiab] OR "agitated emergence"[tiab] OR "altered consciousness"[tiab] OR "dis orientation"[tiab] OR "dis oriented"[tiab] OR "dis orientations"[tiab] OR "emergence agitation"[tiab] OR "emergence excitement"[tiab] OR "postanaesthetic excitement"[tiab] OR "postanesthetic excitement"[tiab] OR disorient*[tiab] OR hallucinate*[tiab] OR illusion*[tiab] OR illuser*[tiab]
2	Antipsychotic agents[mh] OR antipsychotic*[tiab]
3	Chlorpromazine[mh] OR chlorpromazine*[tiab] OR Droperidol[mh] OR droperidol*[tiab] OR Fluphenazine[mh] OR fluphenazine*[tiab] OR Haloperidol[mh] OR haloperidol*[tiab] OR Loxapine[mh] OR loxapine*[tiab] OR Molindone[mh] OR molindone*[tiab] OR Perphenazine[mh] OR perphenazine*[tiab] OR Pimozide[mh] OR pimozide*[tiab] OR Prochlorperazine[mh] OR prochlorperazine*[tiab] OR Thiothixene[mh] OR thiothixene*[tiab] OR tiotixene*[tiab] OR Thioridazine[mh] OR thioridazine*[tiab] OR Trifluoperazine[mh] OR trifluoperazine*[tiab]
4	Aripiprazole[mh] OR aripiprazole*[tiab] OR Asenapine[nm] OR asenapine*[tiab] OR Brexpiprazole[nm] OR brexpiprazole*[tiab] OR Cariprazine[nm] OR cariprazine*[tiab] OR Clozapine[mh] OR clozapine*[tiab] OR loperidone[nm] OR iloperidone*[tiab] OR Lurasidone hydrochloride[mh] OR lurasidone*[tiab] OR Olanzapine[nm] OR olanzapine*[tiab] OR Paliperidone palmitate[mh] OR paliperidone*[tiab] OR Quetiapine fumarate[mh] OR quetiapine*[tiab] OR Risperidone[mh] OR risperidone*[tiab] OR Ziprasidone[nm] OR ziprasidone*[tiab]
5	#1 AND (#2 OR #3 OR #4)
6	Animals[mh] NOT humans[mh]
7	#5 NOT #6

We will conduct grey literature searches to identify data and studies not reported in the published literature, to assess for publication and reporting bias, and to inform future research needs. Studies identified through grey literature searches will be considered for inclusion into the review under two conditions: 1) if they are a source of a unique study that meets inclusion criteria and provides enough methodologic detail to assess risk of bias or 2) if they can be matched to an original publication that has been included into the review when the abstract or presentation reports data on an outcome that was not reported in the original publication. The team will search ClinicalTrials.gov to identify any relevant registered trials. We will update the ClinicalTrials.gov literature search during the peer review process. We will review any material that is submitted through the Supplemental Evidence and Data for Systematic Reviews (SEADS) portal and the Federal Register.

Two independent reviewers will screen each abstract. Both reviewers will need to agree that the article meets at least one of the exclusion criteria to be excluded (see Table 1 for the list of inclusion/exclusion criteria). We will track and resolve differences between reviewers regarding abstract inclusion or exclusion through consensus adjudication.

Articles promoted on the basis of the abstract screen will undergo another independent screen by two reviewers using the full-text. We will track and resolve differences between reviewers regarding article inclusion or exclusion through consensus adjudication.

Data Abstraction and Data Management – We will use a systematic approach to extract all data to minimize the risk of bias in this process. We will create standardized forms for data extraction and pilot test them.

Each article will undergo double review by the study investigators for data abstraction. The second reviewer will confirm the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles to ensure consistency in the data abstraction of the articles. Reviewers will not be masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers will extract information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., population, age, sex, presence of dementia, setting, presence of substance use, presence of hypertension), interventions (e.g., dose, administration, frequency of use, and duration of use), comparisons, the method of ascertainment of outcomes, and the outcome results, including measures of variability. Non-drug interventions will be categorized following the scheme developed by Oh and colleagues.¹⁹

All information from the article review process will be entered into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada) by the reviewer. Reviewers will enter comments into the system whenever applicable. The DistillerSR database will be used to maintain the data and to create detailed evidence tables and summary tables. We may contact the authors of the included studies for additional data, if necessary. Data will later be uploaded into the Systematic Review Data Repository.

Assessment of Methodological Risk of Bias of Individual Studies - We will assess article quality differently for RCTs and observational or nonrandomized studies. For RCTs, we will base the dual, independent review of article quality on the Cochrane Collaboration's Risk of Bias Tool.²⁰ For observational studies, we will use the Cochrane Collaboration's Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.²¹

Two reviewers will independently evaluate the risk of bias of each study. Differences between reviewers will be resolved by consensus adjudication.

Data Synthesis – We will organize the report by Key Question and then by outcome. For each Key Question, we will create a set of detailed evidence tables containing all information extracted from eligible studies. We will conduct meta-analyses when there are sufficient data (at least three studies) and studies are sufficiently

homogenous with respect to key variables (population characteristics, study duration, and treatment).

For the subquestion regarding persons aged 65 years or older, we will include any study that has at least 50% of the population over the age of 65 years.

We will combine studies of any antipsychotic when reporting outcomes. If we see substantial heterogeneity (I-squared > 50%) in pooled estimates for any outcome, we will explore whether this is due to pooling studies of unique medications. We will then stratify studies by medication and repeat the pooled analyses and measures of heterogeneity.

Heterogeneity among the trials for each outcome we consider appropriate for quantitative pooling will be tested using a standard chi-squared test using a significance level of alpha less than or equal to 0.10. We also will examine heterogeneity among studies with an I-squared statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance. A value greater than 50 percent will be considered to indicate substantial heterogeneity.²²

For continuous outcomes, we will calculate a standardized mean difference by using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity²³ or with appropriate analyses when there is higher heterogeneity.²⁴ For dichotomous outcomes, we will calculate a pooled effect estimate of the relative risk between the trial arms of RCTs, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance in settings of low heterogeneity²³ or with appropriate analyses when there is higher heterogeneity.²⁴

Publication bias will be examined by using Begg's test and Egger's test, including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted and there are at least 10 studies.^{25, 26} Publication bias will also be qualitatively considered as part of the strength of evidence determination.

STATA statistical software (Intercooled, version 12.1, StataCorp, College Station, TX) will be used for all meta-analyses.

Studies that are not amenable to pooling will be summarized qualitatively.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

At the completion of our review, we will grade the strength of evidence addressing the Key Questions by adapting an evidence grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews.²⁷ We will apply evidence grades to the bodies of evidence about each comparison for each critical outcome.

Critical outcomes will be determined separately for each sub-population. We will ask the Key Informants and the Technical Experts to select the 5 outcomes that are most

important for each of the patient groups, with at least 1 outcome being a potential adverse effect. Importance will be defined as those outcomes that have the greatest relevance in making decisions about the use of antipsychotics for the prevention or treatment of delirium in the specific patient group.

We will assess the limitations to individual study quality (using individual risk of bias assessments), consistency, directness, precision, and reporting bias. We will classify evidence pertaining to the Key Questions into four categories: (1) “high” grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion).

Assessing Applicability – We will discuss the applicability of studies in terms of the degree to which the study population (e.g., age, sex, co-morbid conditions, stage of dementia), interventions (e.g., dose, frequency, rescue therapy, duration of exposure), outcomes (e.g., outcome definition and reporting), and settings are typical of the treatment of individuals who are at risk or who have been diagnosed with delirium.

V. References

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VI. Definition of Terms

ICU = intensive care unit

OR = odds ratio

RCT = randomized controlled trial

AGS = American Geriatric Society

KQ = Key Question

MeSH = medical subject heading

SEADS = Supplemental Evidence and Data for Systematic Reviews

ROBINS-I = Risk of Bias in Non-Randomized Studies of Interventions

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as “because the AE/TOO/TEP/Peer reviewer told us to” but explain what the change hopes to accomplish.

(NOTE THE FOLLOWING PROTOCOL ELEMENTS ARE STANDARD SECTIONS TO BE ADDED TO ALL PROTOCOLS)

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the key questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

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XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).