

Evidence-based Practice Center Systematic Review Protocol

Project Title: Non-pharmacologic Interventions for Agitation and Aggression in Dementia

I. Background and Objectives for the Systematic Review

Dementia refers to impairments in cognitive and intellectual ability, memory, language, reasoning, and judgment that interfere with everyday functioning.¹ An estimated five million Americans suffer from dementia and more than fifteen million people provide unpaid caregiving.² Dementia primarily affects older adults; approximately 14 percent of those 70 and older suffer from dementia.³ Dementia is one of the most challenging and costly to treat diseases in the United States, with \$215 billion spent on dementia care in 2010. Caregiving is the most costly aspect of dementia care; caregiving includes both informal care (i.e., unpaid care provided by family and friends) and formal care (e.g., long-term care).^{2,4} Caregivers provide assistance with functional activities (i.e., activities of daily living) and management of behavioral and psychological symptoms. Patients with behavioral or psychological symptoms may challenge caregivers; increase difficulties associated with caregiving, and in turn increase the cost of care.⁵ ⁶ For example, Beeri et al. found that managing behavioral symptoms in the community increased the cost of informal caregiving by 25 percent and formal care by 35 percent.

Up to 90 percent of those with dementia will at some stage exhibit behavioral or psychological symptoms, but these are more prevalent in advanced stages.⁷ Symptoms often occur in clusters and can include depression, psychosis, aggression, agitation, anxiety, and wandering.^{7,8,9} Behavioral and psychological symptoms cause considerable patient distress and are associated with accelerated functional and cognitive decline and are leading predictors of institutionalization.¹⁰ Behavioral and psychological symptoms also cause considerable distress to family caregivers and are associated with increases in caregiver anger, resentment (toward the patient), stress, and decreased psychological health.¹¹⁻¹³ These symptoms also challenge staff in long-term care (LTC) facilities where an estimated 80 percent of residents with dementia experience some degree of behavioral and psychological symptoms. Stressed caregivers (paid and unpaid) may be inclined to turn to antipsychotic medications to address the behavioral problems despite that such drugs are contra-indicated. To avert inappropriate use of antipsychotics, caregivers need more skill with a broader repertoire of non-pharmacological approaches.

Four theoretical frameworks have been proposed to explain the etiology of behavioral disorders in those with dementia: biologic/genetic, behavioral, reduced stress threshold, and unmet needs.¹⁴ The biologic/genetic framework posits that behavioral disturbances are due to symptoms of dementia (i.e., dementia causes changes in the brain that in turn result in problem behaviors). The behavioral model suggests that behaviors stem from a complex relationship between patients and the care environment. In this model, patients are believed to exhibit behaviors in response to a stimulus in the environment. In turn, caregivers respond to the behavior through increased attention. A cycle of behavior and attention may then develop between patients and caregivers. The reduced stress threshold model states that dementia reduces an individual's ability to experience environmental stimuli (e.g., sounds). The lower threshold to stimuli is manifested through behaviors. Finally, in the unmet needs framework, behaviors are

believed to stem from unmet needs (e.g., pain, health, and discomfort).¹⁴ Etiology frameworks are not mutually exclusive and may be specific to individuals and behaviors.

The terminology used to describe behaviors is confusing and inconsistent.¹⁵ Agitation and aggression are commonly used terms to describe many different types of behaviors and there are no uniform definitions. Agitation is often described as “excessive motor activity with a feeling of inner tension and characterized by a cluster of related symptoms including anxiety and irritability, motor restlessness and abnormal vocalization, often associated with behaviors such as pacing, wandering, aggression, shouting and nighttime disturbance.”¹⁶ Aggression is commonly described to be a subtype of agitation,¹⁷ and consists of overt harmful actions to other persons that are clearly not accidental.¹⁶ Aggressive behaviors can be physical or verbal.

Confusion in the definition of agitation and aggression extends to the instruments used to evaluate behaviors. For example, the Neuropsychiatric Inventory (NPI), one of the most commonly used research tools to measure behavior, combines agitation and aggression into a single domain. In contrast, the Neuropsychiatric Inventory Clinician (NPI-C), a second-generation survey designed to incorporate input from clinicians, separates agitation and aggression into two distinct domains.⁹

The difficult nature of evaluating behavioral symptoms complicates their treatment and management. More than 45 instruments are used to evaluate behavioral symptoms in dementia, and there is no gold standard.¹⁸ In part, the appropriate instrument depends on the context of care (e.g., setting, severity of disease, and whether the purpose is to identify any behavior or to identify specific behaviors) and disease severity. Instruments often document the occurrence of behavioral symptoms without identifying their source or cause. Clinical algorithms have been developed to help identify the presence and causes of symptoms in order to effectively manage behaviors.¹⁹⁻²¹ These algorithms are designed to be used alongside specific instruments to provide appropriate context to the occurrence of behaviors.

Specific instruments are based on different theoretical frameworks; designed to evaluate behaviors in a wide range of settings (e.g., in-home, hospital, or long-term care); are administered by different individuals (e.g., caregiver, nurse, or patient); and use a variety of mechanisms to obtain responses (e.g., interviews with patients or direct observation.)

Instruments for evaluating behavioral symptoms can be grouped into two broad categories: general and specific.¹⁸ General measures evaluate a host of behaviors across various domains (e.g., agitation, depression, and wandering). Most studies that report results from general measures report overall summary scores. Examples of general behavioral measurement instruments include the NPI (and its variants NPI-C, NPI-Q), the Revised Memory and Behavior Problem Check List, and the CERAD Behavior Rating Scale for Dementia. In contrast to general instruments, specific behavioral instruments evaluate a single behavioral domain (e.g., only agitation, or only depression). Examples of specific behavioral instruments that evaluate agitation and aggression include, the Agitated Behavior in Dementia Scale, the Cohen-Mansfield Agitation Inventory, and the Pittsburgh Agitation Scale.

Agitation and aggression are especially distressing to patients, caregivers, and LTC staff. The management of these behaviors has historically relied on pharmacological approaches, namely antipsychotics. Use of pharmacotherapy for behavioral symptoms is based on biological/genetic framework. However, the U.S. Food and Drug Administration has not approved any antipsychotic drug for the management of behavioral symptoms. Further, antipsychotic medications have limited evidence for efficacy and high risk for adverse effects including mortality²²⁻²⁴ and their use is associated with reduced quality of life.²⁵ The risks associated with

non-pharmacologic treatments (e.g., increased agitation), are less frequent and severe than those associated with anti-psychotic medications (e.g., mortality). Concern about these issues has led to clinical guidelines recommending non-pharmacologic interventions as first choice therapies for agitation and aggression in patients with dementia.²⁶⁻²⁹ However, non-pharmacologic interventions are rarely used in clinical practice, in part because clinicians lack knowledge regarding the use of these therapies. Establishing an evidence base for the effectiveness of non-pharmacological treatments and educating clinicians on their use could help reduce inappropriate use of antipsychotics in patients with dementia.

Many non-pharmacologic interventions have been identified for managing agitation and/or aggression in dementia. These interventions aim to: a) prevent the incidence of agitation and aggressive behaviors, b) respond to episodes of agitation and aggressive behaviors to reduce the severity and duration of the episode, and/or c) reduce caregiver distress. Non-pharmacologic interventions may be patient focused and directly intervene with patients (e.g., sensory based interventions and structured activities) or may be caregiver focused and intervene with patients indirectly through caregivers and the environment (e.g., caregiver training).¹⁴ Non-pharmacologic interventions are based on varying theoretical frameworks, and the framework(s) underpinning an intervention determine its rationale.¹⁴ Interventions may also target patient-specific behavior or serve as general strategies for managing behavioral symptoms.²⁰ General approaches can be implemented, often at the setting level. Examples include staff/caregiver education and training, structured activities, and sensory interventions (e.g., light therapy).²⁰ Improvements in behavior and mood have been reported in studies of stimulation-oriented treatments such as recreational activities; therapies involving music, art, and pets; and other programs that increase the number of pleasurable activities.³¹ Certain environmental interventions, such as environmental design and enhanced environment,¹⁴ would also be considered general approaches. Non-pharmacologic interventions are not mutually exclusive and can be used simultaneously (e.g., a care management plan may determine that a sensory intervention should be used). Targeted approaches are interventions directed at single behaviors (e.g., agitation).²⁰ These approaches typically involve a comprehensive assessment of the behavior to identify triggers and devise a plan to address the behavior by modifying exposures to triggers or and/or offering stimulating environmental distractions.²⁰ Tables 1 and 2 describe examples of important characteristics that define and classify specific interventions. These data will be abstracted from eligible studies.

Table 1. Interventions delivered directly to patients with dementia to reduce agitated and aggressive behavior

Intervention Type	Intervention ^a	Theory of Effect (biologic/genetic, behavioral, reduced stress threshold, unmet needs)	Objective (Prevent/Respond) ^b	Implemented by (informal caregivers, formal caregivers, LTC staff, licensed professional)	Setting (Home and Community, Assisted Living, Nursing Home)	Tailored/General	Group Based or Individual	Intensity/dose (# sessions/ length of session/ frequency/duration of treatment)
Sensory Interventions	Music Therapy (listening)							
	Light Therapy							
	Pet Therapy							
	Multisensory Stimulation							
	Hearing Aids							
Active Therapy/ Structured Activities	Dancing							
	Exercise							
	Social Interaction							
	Music Therapy (playing/singing)							
	Art Therapy							
	Outdoor Walks							
Complementary Alternative Medicine	Aromatherapy							
	Reflexology							
	Massage							
	Reki							
Psychological/ Therapy	Validation Therapy							
	Reality Orientation							
	Reminiscence Therapy							
	Psychosocial Therapy							
	Cognitive Behavioral Therapy							
	Relaxation Training							
	Structured Support Groups							
Environmental	Walled in Areas,							

Intervention Type	Intervention ^a	Theory of Effect (biologic/genetic, behavioral, reduced stress threshold, unmet needs)	Objective (Prevent/Respond) ^b	Implemented by (informal caregivers, formal caregivers, LTC staff, licensed professional)	Setting (Home and Community, Assisted Living, Nursing Home)	Tailored/General	Group Based or Individual	Intensity/dose (# sessions/ length of session/ frequency/duration of treatment)
	Wandering Areas							
	Natural/Enhanced Environments (e.g., pictures on walls)							
	Reduced Stimulation Environments (e.g., quiet areas)							
Delivery of Care	Care Consultation							
	Patient Centered Care							
Patient Education	Specific Curriculum (i.e. distraction components)							

^a Examples of interventions are not mutually exclusive. For example, music therapy is considered a sensory intervention when the intervention consists of listening to music. However, music therapy is considered an active therapy when the intervention involves making music.

^b Objective of intervention describes whether the intervention aims to Prevent=prevent or reduce the incidence of behaviors; Respond=address a specific episode of agitation or aggression to reduce its duration or severity; or Both=both.

Table 2. Interventions delivered to caregivers (staff or informal caregivers) who work to reduce agitated and aggressive behaviors in persons with dementia

Intervention Type	Intervention ^a	Theory of Effect (biologic/genetic, behavioral, reduced stress threshold, unmet needs)	Objective (Prevent/Respond) ^b	Implemented by (informal caregivers, formal caregivers, LTC staff, licensed professional)	Setting (Home and Community, Assisted Living, Nursing Home)	Tailored/General	Group Based or Individual	Intensity/dose (# sessions/ length of session/ frequency/duration of treatment)
Informal Caregivers								
Support	Support Groups							
	Counseling							
	Care Respite							
Training/ Education	Specific curriculum							
	Individualized training to caregivers to care for specific behaviors							
Paid Caregivers								
Training/ Education	Specific curriculum							
	Individualized training to caregivers to care for specific behaviors							
Cultural	Guidelines							
	Payment Changes							

^a Examples of interventions are not mutually exclusive. For example, music therapy is considered a sensory intervention when the intervention consists of listening to music. However, music therapy is considered an active therapy when the intervention involves making music.

^b Objective of intervention describes whether the intervention aims to Prevent=prevent or reduce the incidence of behaviors; Respond=address a specific episode of agitation or aggression to reduce its duration or severity; or Both=both.

Evidence synthesis on the efficacy and comparative effectiveness of interventions specifically for agitated and aggressive behaviors in patients with dementia could potentially reduce the frequency and severity of aggressive and agitated behaviors; improve functioning; and improve levels of distress among persons with dementia and reduce or delay residential long-term care. Examples of validated instruments used to measure these agitation and aggression in persons with dementia include the Cohen-Mansfield Agitation Inventory,³² the Agitated Behavior Scale,³³ and the Pittsburgh Agitation Scale.³⁴ Interventions may also reduce antipsychotic use. Results from this review will inform guidelines on management of agitation and aggressive behaviors in persons with dementia.

II. The Key Questions

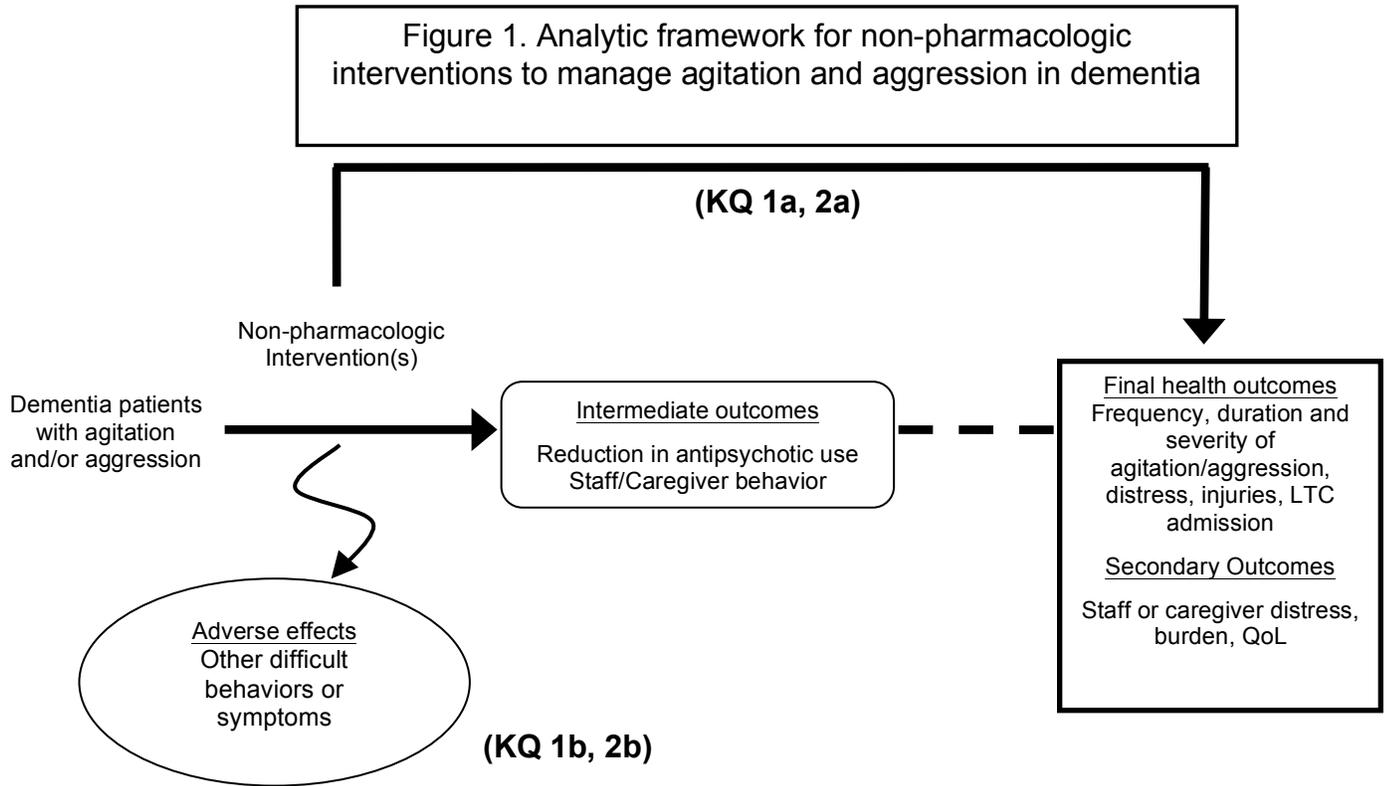
Question 1a: What is the comparative effectiveness of non-pharmacologic interventions in preventing and responding to agitated and aggressive behaviors among dementia patients in long-term care settings on staff outcomes and in managing caregiver burden, distress, and quality of life?

Question 1b: What are the comparative harms of non-pharmacologic interventions in preventing and responding to agitated and aggressive behaviors among dementia patients in long-term care settings?

Question 2a: What is the comparative effectiveness of non-pharmacologic interventions in preventing and responding to agitated and aggressive behaviors among community-dwelling dementia patients on caregiver outcomes and in managing caregiver burden, distress, and quality of life?

Question 2b: What are the comparative harms of non-pharmacologic interventions in preventing and responding to agitated and aggressive behaviors among community-dwelling dementia patients?

Analytic Framework



PICOTS

Population(s)

KQ1: Individuals with dementia and symptoms of agitation and aggression (not attributable to pain, delirium, or psychosis); stratified by dementia disease stage, symptom severity, type of dementia and staff of long-term care facilities.

KQ2: Individuals with dementia and symptoms of agitation and aggression (not attributable to pain, delirium, or psychosis); stratified by dementia disease stage, symptom severity, type of dementia and formal and informal caregivers.

Interventions (KQ1 & KQ2)

Interventions aimed at preventing/responding to aggressive and agitated behaviors
(Tables 1&2)

Comparators (KQ1 & KQ2)

- Usual care
- Other non-pharmacologic intervention
- Pharmacologic intervention

Outcomes

Intermediate

- Staff/Caregiver behavior change
- Reduction in antipsychotic use

Final Health Outcomes

- Frequency, duration, and severity of agitated behaviors
- Frequency, duration and severity of aggressive behaviors
- Patient distress
- Admission to LTC facility/hospital
- Injuries to patients, staff, caregivers

Secondary Outcomes

- Staff distress, burden, QoL
- Caregiver distress, burden, QoL

Adverse effects of intervention(s)

- Increase in other difficult behaviors
- Increase in other symptoms

Timing

Any duration of follow-up

Setting

LTC facilities and community

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the review based on the PICOTS framework outlined above and the study-specific inclusion criteria described in Table 3.

Table 3. Study inclusion criteria

Category	Criteria for Inclusion
Study Enrollment	Studies that enroll persons diagnosed with dementia (any type) and experiencing behavioral symptoms of agitation and aggression.
Study Objective	Intervention aiming to prevent and/or decrease agitation and aggression associated with dementia.
Study Design	Systematic reviews, RCTs, nonrandomized controlled trials, and prospective cohort studies will be included for study design. Prospective studies must include a comparator and appropriate methods to correct for selection bias. Studies specifically addressing treatment harms may also include retrospective cohort studies. Systematic reviews must include risk of bias assessment with validated tools.
Time of Publication	Literature published from 1994 forward (reflects interventions used today).
Publication type	Published in peer reviewed journals.
Language of Publication	English

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will search Ovid Medline, Ovid PsycInfo, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials and nonrandomized controlled trials published and indexed in bibliographic databases. Our search strategy included relevant medical subject headings and natural language terms for concepts of dementia, behavioral symptoms, and the various intervention types. These concepts were combined with filters to select trials.

We will search for systematic reviews published since 2004. We anticipate that older treatments may be covered by prior reviews. (See Risk of Bias section below for discussion of quality assessments of systematic reviews.) We will also search for RCTs, nonrandomized controlled trials, and prospective cohort studies published since 1994. We will supplement this search strategy with backward and forward citation searches of recent relevant systematic reviews. We will update searches while the draft report is under public/peer review.

We will review bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. Search results will be downloaded to EndNote. Titles and abstracts will be reviewed by two independent investigators to identify studies meeting PICOTS framework and inclusion/exclusion criteria. All studies identified as relevant by either investigator will undergo full-text screening. We will track the number of non-English studies that appear eligible based upon English title and abstract to assess the magnitude of studies excluded for language. Two investigators will

independently perform full-text screening to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator. We will document the inclusion and exclusion status of citations undergoing full-text screening. Throughout the screening process, team members will meet regularly to discuss training material and issues as they arise to ensure consistency of inclusion criteria application.

We will conduct additional grey literature searching to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and funded research databases. We will search ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for ongoing studies. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs.

C. Data Abstraction and Data Management

We will explore the possibility of including relevant systematic reviews determined to have fair or good quality to replace de novo extraction for specific population/treatment/outcome comparisons. Only systematic reviews that assessed and reported individual study risk of bias will be assessed for quality. We will reassess risk of bias of included studies for comparison purposes. We will extract author, year of publication, eligibility criteria, relevant synthesis results and strength of evidence assessment. We will use data provided by the systematic review to assess strength of evidence for results without strength of evidence assessments. Studies in included systematic reviews will be tracked for contribution to unique population/treatment/outcome comparisons to avoid double-counting study results.

Studies meeting inclusion criteria will be distributed among investigators for data extraction. Data fields to be extracted will be determined based upon proposed summary analysis. These fields will include author, year of publication; setting, subject inclusion and exclusion criteria, intervention and control characteristics (intervention components, timing, frequency, and duration), follow-up duration, participant baseline demographics, comorbidities; method of diagnosis, enrollment, and severity, descriptions and results of primary outcomes and adverse effects, and study funding source. Relevant data will be extracted into web-based extraction forms created in Microsoft Excel. Data will be analyzed in RevMan 5.21³⁵ software. Evidence tables will be reviewed and verified for accuracy by a second investigator.

D. Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias of eligible studies will be assessed using instruments specific to study design. For RCTs, questionnaires developed from the Cochrane Risk of Bias tool will be used. The seven domains included in this tool include sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (i.e., was incomplete outcome data adequately addressed), selective reporting, and other sources of bias (i.e., problems not covered by other domains). Study power will be assessed in 'other sources of bias in studies with data that is not eligible for pooling. For behavioral health trials, the presence of treatment fidelity, that is, treatment definition and implementation will also be evaluated. Outcome

measurement issues inherent in the psychometric properties of the questionnaires used to measure outcomes and assessment methods used to detect change in those questionnaire results will be specifically evaluated for detection bias. Specific study methodology or conduct will be used to judge potential risk of bias with respect to each domain following guidance in the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0.³⁶

We will develop an instrument for assessing risk of bias for observational studies based on the RTI Observational Studies Risk of Bias and Precision Item Bank.³⁷ We selected items most relevant in assessing risk of bias for this topic, including participant selection; attrition, ascertainment, and appropriateness of analytic methods. Study power will be assessed in other sources of bias in studies with data that is not eligible for pooling. The form will be tested by investigators using an initial sample of included studies and will be finalized by full team input.

Two investigators will independently assess risk of bias for all included studies. Investigators will consult to reconcile any discrepancies in overall risk of bias assessments. Overall summary risk of bias assessments for each study will be classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations. When the two investigators disagree, a third party will be consulted to reconcile the summary judgment. Systematic review quality will be assessed using AMSTAR criteria.³⁸

E. Data Synthesis

We will summarize the results in evidence tables and synthesize evidence for each unique population, comparison, and outcome combination. When a comparison is adequately addressed by a previous systematic review of acceptable quality (fair or high quality according to AMSTAR) and no new studies are available, we will reiterate the conclusions drawn from that review. When new trials are available, previous systematic review data will be synthesized with data from the additional trials when possible. We will analyze included studies in these systematic reviews to assess the balance of publication dates and study-level risk of bias relative to the original research we include. We will summarize study characteristics of eligible studies in evidence tables developed. We will attempt to identify established minimum important differences (MIDs) for key outcomes measurement instruments using targeted literature searches of instruments identified in targeted literature searches and TEP input. We do not anticipate the ability to pool data, but instead plan qualitative synthesis. We will try to use MIDs to assess the efficacy and comparative effectiveness of outcomes with well-established MIDs, but many of our outcomes are not likely to have established minimum important differences.

If certain comparisons can be pooled, we will meta-analyze the data using a random effects model. We will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary primary outcomes. Weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs will be calculated for continuous outcomes. We will assess the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.³⁹ We will assess statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic.³⁹

Results will be organized by setting (i.e. long-term care, community-dwelling). We will explore whether data allows the evidence to be stratified by dementia stage, type, and/or severity.

We will assess harms as dichotomous variables to acknowledge the inherent difficulties of assessing harms, and also to simplify analysis. There are various ways to assess harms; each has problems. One can use RCT and controlled cohort data, but they generally have small samples and short follow-ups. One can use case series, but they have no controls and may overestimate the rate of “adverse events” since the rate of “adverse events” among persons getting placebos is high.⁴⁰ One can use case-control studies, but they are subject to recall bias. One can examine adverse events with the intervention in other patient populations, but this does not exclude the possibility that persons with dementia and agitation and/or aggression have different susceptibilities. The non-pharmacologic interventions addressed in this review have a low incidence of harms. We will use reported harms from RCTs, and prospective and retrospective cohort studies in persons with dementia.

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

The overall strength of evidence for primary outcomes of KQ1 within each comparison will be evaluated based on five required domains: (1) study limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); (4) precision (degree of certainty around an estimate); and (5) reporting bias.⁴¹ Based on study design and risk of bias, study limitations will be rated as low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study) based on the whether intervention effects are similar in direction and magnitude, and statistical significance of all studies. Directness will be rated as either direct or indirect based on the need for indirect comparisons when inference requires observations across studies. That is, more than one step is needed to reach the conclusion. Precision will be rated as precise or imprecise based on the degree of certainty surrounding each effect estimate or qualitative finding. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For outcomes found to have at least moderate or high strength of evidence, reporting bias will be evaluated by the potential for publication bias, selective outcome reporting bias, and selective analysis reporting bias by comparing reported results with those mentioned in the methods section and an assessment of the grey literature to assess potentially unpublished studies. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association.

Based on these factors, the overall strength of evidence for each outcome will be rated as:⁴¹

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.

- **Moderate:** Moderately confidence that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

We will assess strength of evidence for published systematic reviews replacing de novo review processes that did not provide a strength of evidence assessment based on a GRADE or GRADE-equivalent method and incorporating all relevant articles, including new articles identified in bridge searches. For prior systematic reviews that did provide acceptable strength of evidence, strength of evidence domains will be extracted to assess impact of new articles on the overall body of evidence will take into consideration the differences in strength of evidence domains and the relative contributions of the prior review and the new articles.

We will assess strength of evidence for key final health outcomes measured with validated scales.

G. Assessing Applicability

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the population from which the study participants are enrolled, diagnostic assessment processes, narrow eligibility criteria, and patient and intervention characteristics different than those described by population studies behavioral symptoms in dementia.⁴² These applicability issues are present in the synthesis frameworks and sensitivity analyses described in more detail in the data synthesis section.

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VI. Definition of Terms

Not applicable.

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.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The 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 \$10,000 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 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 health 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 recommend 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 \$10,000 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 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 \$10,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers may not have any financial conflict of interest greater than \$10,000. 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

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.