Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Care Interventions for People With Dementia (PWD) and their Caregivers***

I. Background and Objectives for the Systematic Review

Rising rates of dementia in the United States underscore the urgent need for a summary of the available evidence for care interventions for people with dementia (PWD) and their formal and informal caregivers. The National Institute on Aging (NIA) has commissioned such a summary from the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ) in collaboration with the National Academies of Science, Engineering, and Medicine (NASEM). The goal is to understand the evidence base for effective care interventions, and to assess the potential for broad dissemination and implementation of that evidence.

Dementia is a clinical syndrome that affects about 10 percent of older U.S. adults.[1,2] It is characterized by an acquired cognitive deficit that interferes with independence in daily activities.[3] Alzheimer's disease is the most common form of progressive dementia and—grouped with Lewy body, frontotemporal, vascular, and mixed forms—is commonly referred to as AD/ADRD (i.e., Alzheimer's disease (AD) and Alzheimer's disease related dementias (ADRD)).[4] Dementia lowers an individual's quality of life, burdens caregivers, increases institutionalization, and is costly to families and society.[5] Agitation, aggression, and other behavioral disturbances are common,[6] especially late in the disease course.

Dementia has no known cure. Although drug and nondrug interventions are available to treat symptoms, support function, and improve quality of life, nondrug interventions are recommended as first line treatments for behavioral and psychological symptoms (BPSD) over antipsychotics and other medications.[7] While nondrug interventions are generally presumed safe, few trials have reported information on their harms or other unintended consequences. (Drugs and over-the-counter supplements to treat clinical Alzheimer's-type dementia and behavioral and psychological symptoms of dementia are being addressed by a separate AHRQ systematic review; please see https://effectivehealthcare.ahrq.gov/topics/alzheimers-type-dementia/protocol for further information.)

Care for PWD is costly, and more than 83 percent of community-residing older adults who need dementia care rely on the help of family members.[8] In 2017, informal (unpaid) caregivers for PWD provided an estimated 17 billion hours of care at an economic value of $232.1 billion, and about two-thirds of informal caregivers are women.[9] The complex challenges of dementia care can be stressful and a source of physical and mental health consequences for the caregiver. Therefore, many research teams have developed and tested interventions for supporting the health and well-being of informal caregivers, such as social support, therapeutic counseling, skills training, respite, or combined approaches.[10] Additionally, many front-line paid caregivers, such as Home Health Aids in home-based settings or Certified Nursing Assistants in institutional settings, also lack adequate training and support for this difficult work. A recent NASEM report

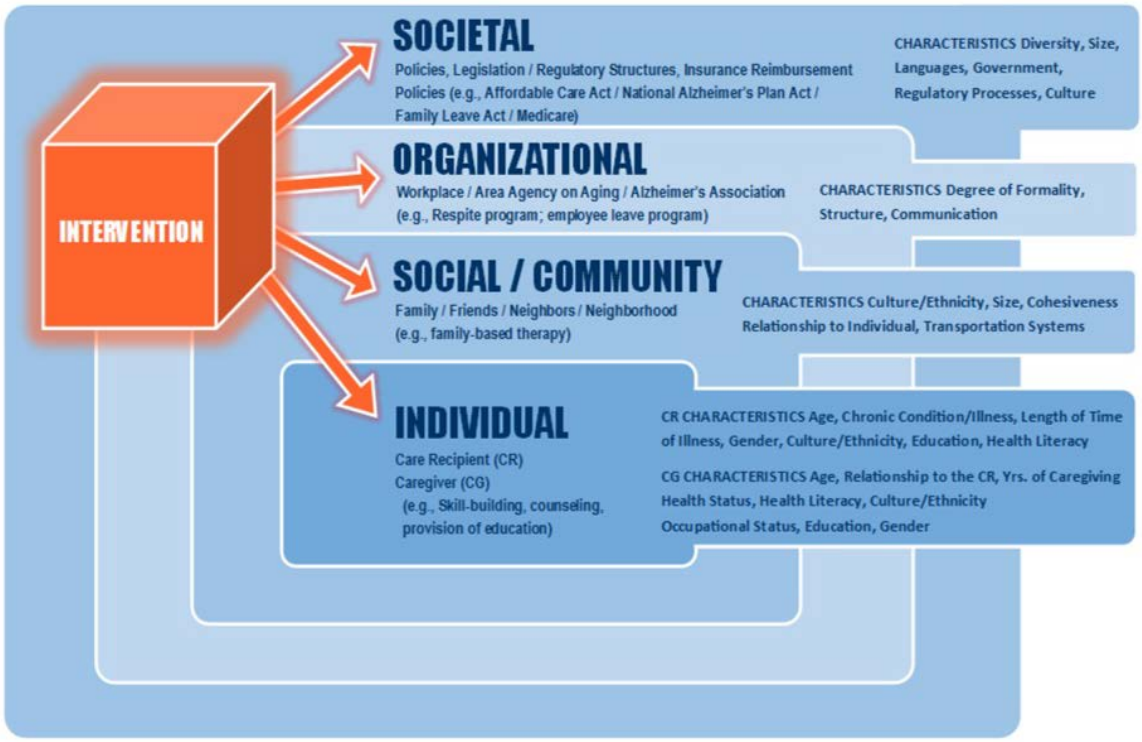
recommended an increase in federal requirements for training of direct care workers—from 75 hours to 120 hours—and an increased focus on knowledge and skills related to caring for PWD.[11]

Care for PWD encompasses a broad range of activities that support, enhance, or otherwise help PWD. Likewise, care interventions comprise an array of options that, as noted in the NASEM letter report for this review, [http://nationalacademies.org/hmd/Reports/2018/Considerations-for-the-Design-of-a-Systemati-Review-of-Care-Interventions-for-Individuals-with-Dementia-and-Their-Caregivers-Letter-Report.aspx] "contribute to a person's well-being, happiness, identity, privacy, capacity, autonomy, or authority. They can be supports, services, programs, accommodations, or practices that include behavioral, environmental, technological, and psychological methods or approaches. They may be delivered by health care, social services, and other community organizations or caregivers with the intention of having a direct impact on either a person with dementia or their caregiver or both."

Necessarily, then, interventions that address care for PWD and their caregivers can be complicated and multifaceted. Unfortunately, no consensus has been reached on classification systems for types of interventions, leaving categorization up to empirical rather than theoretical approaches. At the simplest level, interventions may be segregated into two groups: 1) **what** is provided to PWD and/or their caregivers, to improve their well-being and health, and 2) enhancing **how** the elements of care are delivered to improve effectiveness, efficiency, and/or accessibility and availability. This review will refer to interventions in the first **"what"** group as **care interventions**, and interventions in the second **"how"** group as **care delivery interventions**.

Intervention complexity stems from many sources, including the diversity of the targeted dementia populations (e.g., younger adults with Down syndrome or other genetic risk factors vs. younger adults with frontotemporal dementia vs. older adults with Alzheimer's disease) as well as different caregiver populations (e.g., spousal caregivers or adult child caregivers). Intervention designs may be multicomponent and target several levels of a system simultaneously, from a care system (whether health care or social services) to family units or caregiver/PWD dyads to individual formal or informal caregivers. (See Figure 1.) Furthermore, complexity in outcomes may arise because interventions targeting one level of a system, such as PWD, may benefit other individuals, such as caregivers, or other levels of the system, such as reduced use of heath care services for an accountable care organization.

Figure 1. Framework for care interventions



Abbreviations: CG=caregiver; CR=care recipient
Source: NASEM, 2016, *Families caring for an aging America*. p. 163.

Considering these complexities, our review focuses on which intervention characteristics are linked to effectiveness. Unfortunately, informal and formal caregivers may not always align with the levels in Figure 1; paid caregivers may be hired by family of a PWD as independent contractors, whereas unpaid volunteers may be affiliated with a larger organization. Nonetheless, understanding the relationships between patient and caregiver characteristics and outcomes will help clinicians, care providers, and other stakeholders make decisions about the best interventions fit for their specific circumstances or patients.

Assessing how ready a care intervention is for broad implementation is challenging. For this review, we will be guided by the NIH Stage Model for Behavioral Interventions.[12] The NIH stage model provides a conceptual framework of intervention research development, ranging from basic science research (stage 0) to new intervention creation (stage 1), research-setting efficacy (stage 2), "real-world" community-clinic efficacy (stage 3), broad community-based effectiveness (stage 4), to eventually dissemination and implementation research (stage 5). This model describe the stages of behavioral intervention development and are intended to promote eventual implementation. While the stages are not a direct assessment of implementation readiness, the model suggests that interventions at Stage 3 or higher will be more likely to be deemed ready for broad dissemination.

II. The Key Questions

The key questions (KQs) are structured to organize the literature by the intervention target. In response to feedback from the NASEM committee and public comment, the KQs have been modified from the preliminary version to separate informal and formal caregivers into distinct KQs, for a total of 10 instead of 8 KQs. Also based on feedback, the KQs have been edited for readability, and slight refinements to the population characteristics of interest and the organization of outcomes. These refinements have not changed the major thrust of the KQs or the intention to focus on AD/ADRD, informal and formal caregivers, and the effect of interventions on outcomes for people or systems other than the intended intervention target. The KQs are further specified by the populations, interventions, comparators, outcomes, timing, and settings (PICOTS) laid out in Table 1.

Care Interventions for Behavioral and Psychological Symptoms of Dementia (BPSD) in People With Dementia (PWD)

- KQ1: For people with dementia **(PWD),** what are the benefits and harms of care interventions aimed at treating the behavioral and psychological symptoms of dementia (BPSD) in **PWD**?
    - KQ1a: What evidence is available on how outcomes differ by **PWD** characteristics?
    - KQ1b: What evidence is available on how outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
    - KQ1c: Which intervention characteristics or components are associated with effectiveness?

- KQ2: For informal and/or formal **PWD Caregivers,** what are the benefits and harms for care interventions aimed at treating BPSD in **PWD**?
    - KQ2a: What evidence is available on how outcomes differ by **PWD** characteristics?
    - KQ2b: What evidence is available on how outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
    - KQ2c: Which intervention characteristics or components are associated with effectiveness?

Care Interventions for Quality of Life, Function, or Non-BPSD Symptoms in PWD:

- KQ3: For people with dementia **(PWD),** what are the benefits and harms for care interventions aimed at improving quality of life, function, or non-BPSD symptoms in **PWD**?
    - KQ3a: What evidence is available on how outcomes differ by **PWD** characteristics?
    - KQ3b: What evidence is available on how outcomes differ by informal and/or formal **PWD Caregiver** characteristics?

- KQ3c: Which intervention characteristics or components are associated with effectiveness?

- KQ4: For informal and/or formal **PWD Caregivers,** what are the benefits and harms for care interventions aimed at improving quality of life, function, or non-BPSD symptoms in **PWD**?
  - KQ4a: What evidence is available on how outcomes differ by **PWD** characteristics?
  - KQ4b: What evidence is available on how outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
  - KQ4c: Which intervention characteristics or components are associated with effectiveness?

Care Interventions for Quality of Life and Health Outcomes for Informal and Formal PWD Caregivers:

- KQ5: For people with dementia **(PWD),** what are the benefits and harms for care interventions aimed at supporting the quality of life and health outcomes of the informal **PWD Caregivers**?
  - KQ5a: What evidence is available on how quality of life and outcomes differ by **PWD** characteristics?
  - KQ5b: What evidence is available on how quality of life and outcomes differ by informal or formal **PWD Caregiver** characteristics?
  - KQ5c: Which intervention characteristics or components are associated with effectiveness?

- KQ6: For informal and/or formal **PWD Caregivers,** what are the benefits and harms for care interventions aimed at supporting the quality of life and health outcomes of the informal **PWD Caregivers**?
  - KQ6a: What evidence is available on how quality of life and outcomes differ by **PWD** characteristics?
  - KQ6b: What evidence is available on how quality of life and outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
  - KQ6c: Which intervention characteristics or components are associated with effectiveness?

- KQ7: For people with dementia **(PWD),** what are the benefits and harms for care interventions aimed at supporting the quality of life and health outcomes of the formal **PWD Caregivers**?
  - KQ7a: What evidence is available on how quality of life and outcomes differ by **PWD** characteristics?
  - KQ7b: What evidence is available on how quality of life and outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
  - KQ7c: Which intervention characteristics or components are associated with effectiveness?

- KQ8: For informal and/or formal **PWD Caregivers,** what are the benefits and harms for care interventions aimed at supporting the quality of life and health outcomes of the formal **PWD Caregivers**?
    - KQ8a: What evidence is available on how quality of life and outcomes differ by **PWD** characteristics?
    - KQ8b: What evidence is available on how quality of life and outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
    - KQ8c: Which intervention characteristics or components are associated with effectiveness?

Interventions for How Care Is Delivered:

- KQ9: For people with dementia **(PWD),** what are the benefits and harms for care delivery interventions?
    - KQ9a: What evidence is available on how outcomes differ by **PWD** characteristics?
    - KQ9b: What evidence is available on how outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
    - KQ9c: Which intervention characteristics or components are associated with effectiveness?

- KQ10: For informal and formal **PWD Caregivers,** what are the benefits and harms for care delivery interventions?
    - KQ10a: What evidence is available on how outcomes differ by **PWD** characteristics?
    - KQ10b: What evidence is available on how outcomes differ by informal and/or formal **PWD Caregiver** characteristics?
    - KQ10c: Which intervention characteristics or components are associated with effectiveness?

Dissemination and Implementation Research:

- Guiding Question 1: What is the state of the empirical evidence on implementation of interventions that have at least low-strength evidence for "real-world" benefits and harms (i.e., NIH Stage Model for Behavioral Intervention Development Stages 3-5)?

Note that in Table 1, outcomes are loosely organized to correspond with the levels shown in Figure 1. Importantly, the final organization of actual outcomes collected will depend on the individual studies and in the intentions and measures used by the study authors.

Table 1. PICOTs for care and care delivery interventions

Element	PWD	PWD Caregiver
Population	**PWD**, including individuals with possible or diagnosed AD/ADRD. PWD Subgroups: Age, sex, sexual orientation/gender identity, race/ethnicity, education, socioeconomic status, prior disability, age at diagnosis, dementia type, dementia severity [e.g. stage of dementia (early stage, moderate, or severe), level of cognitive impairment rate of cognitive decline], family/household characteristics, health insurance, geographic location (e.g. urban, rural), setting type	**Informal PWD Caregivers**, such as spouses, family, friends, and volunteers Informal PWD Caregiver Subgroups, including age, sex, sexual orientation/gender identity, race/ethnicity, family history of dementia, education, socioeconomic status, employment status, relationship with PWD, living distance from PWD, dementia care training, general health status, caregiving networks, setting type **Formal PWD Caregivers**, such as certified nursing assistants (CNAs), home health aides, auxiliary workers, personal care aides, hospice aides, promotoras or promotores, and community health workers Formal PWD Caregiver Subgroups, including age, sex, race/ethnicity, education, job position, skill, training, general health status, setting type
Intervention	KQ 1-4. Any nondrug care intervention intended to benefit PWD **except** interventions to treat conditions other than dementia, including but not limited to CPAP, and those that use supplements/natural products. (See list of example intervention types in Appendix A.) Guiding Question: Any quality improvement or implementation science study that informs the dissemination or implementation of a care intervention at least low-strength evidence for "real-world" benefits and harms (i.e., NIH Stage Model for Behavioral Intervention Development Stages 3-5)	KQ 5-6. Any care intervention intended to support informal PWD caregivers' well-being **except** interventions to treat health conditions unrelated to providing care to PWD. KQ 7-8. Any care intervention intended to support formal PWD caregivers' well-being **except** interventions to treat health conditions unrelated to providing care to PWD. KQ 9-10. Any care delivery intervention to improve how care is delivered IF the training intervention is incorporated as on-going operational procedures into the structure or processes of the organization. Interventions carried out by higher education organizations or professional organizations to provide training toward licensed professionals, and continuing education for degreed health professionals are also excluded. (See list of example intervention types in Appendix A.) Guiding Question: Any quality improvement or implementation science study that informs the dissemination or implementation of a care intervention at least low-strength evidence for "real-world" benefits and harms (i.e., NIH Stage Model for Behavioral Intervention Development 3-5)
Comparator	Inactive Comparator: No intervention, usual care, waitlist, attention control Active Comparator: Different intervention	Inactive Comparator: No intervention, usual care, waitlist, attention control Active Comparator: Different intervention

Element	PWD	PWD Caregiver
Outcomes (Generally organized to correspond with Figure 1 Framework)	Quality of life and subjective well-being Burden of care Satisfaction with care Perceived Support Expenditures/financial burden (informal caregivers) Health-related outcomes: Psychological health (e.g., depression, anxiety) Neuropsychiatric symptoms (including apathy, aggression, and agitation) Function (e.g., ADL, IADL, ability to care for one's self, ability to recreate/socialize Weight loss Sleep problems Use of restraints Use of anti-psychotics Harm reduction (e.g. driving, firearms) Palliative care/hospice outcomes: Completion of advanced directives Comfort during dying process Concordance with preferred location of death Social/Community level outcomes: Engagement in community activities, Perceived inclusion Safety/perceived safety Utilization of healthcare service outcomes: Admission to nursing home Access to care and services ICU and ER usage Hospital admission and readmission Primary, Specialty, Long-term Care usage Quality of care and services (e.g., overutilization of unnecessary antibiotics, other quality care metrics.) Societal costs, including caregiving time/time spent on activities Harms, including isolation, loneliness, perceived stigma, suicidal ideation or suicide, elder abuse (e.g., physical harm, abuse, neglect, exploitation, family violence)	Quality of life and subjective well-being Burden of care Satisfaction with care for PWD (informal caregivers) Perceived Support Expenditures/financial burden (informal caregivers) Health-related outcomes: Psychological health (e.g., depression, anxiety) Immune function (e.g., inflammation or cortisol) Sleep problems Weight loss due to stress Health behaviors (e.g., exercise, substance use) Caregiving self-efficacy Confidence to manage caregiver tasks Social/Community level outcomes (informal caregivers): Engagement in community activities, Perceived inclusion Safety/perceived safety Turnover and retention (formal caregivers) Utilization of healthcare service (e.g., physician visits, antidepressant or antianxiety medication usage) Societal costs including caregiving time/time spent on activities Harms, including isolation, loneliness, perceived stigma, caregiver PTSD
Timing	No minimum duration or followup	No minimum duration or followup
Setting	Any setting; no exclusion based on geographic location or setting. Includes home, home health care, adult day care, acute care settings, social service	Any setting; no exclusion based on geographic locations or setting. Includes home, home health care, adult day care, acute care settings, social service agencies, nursing

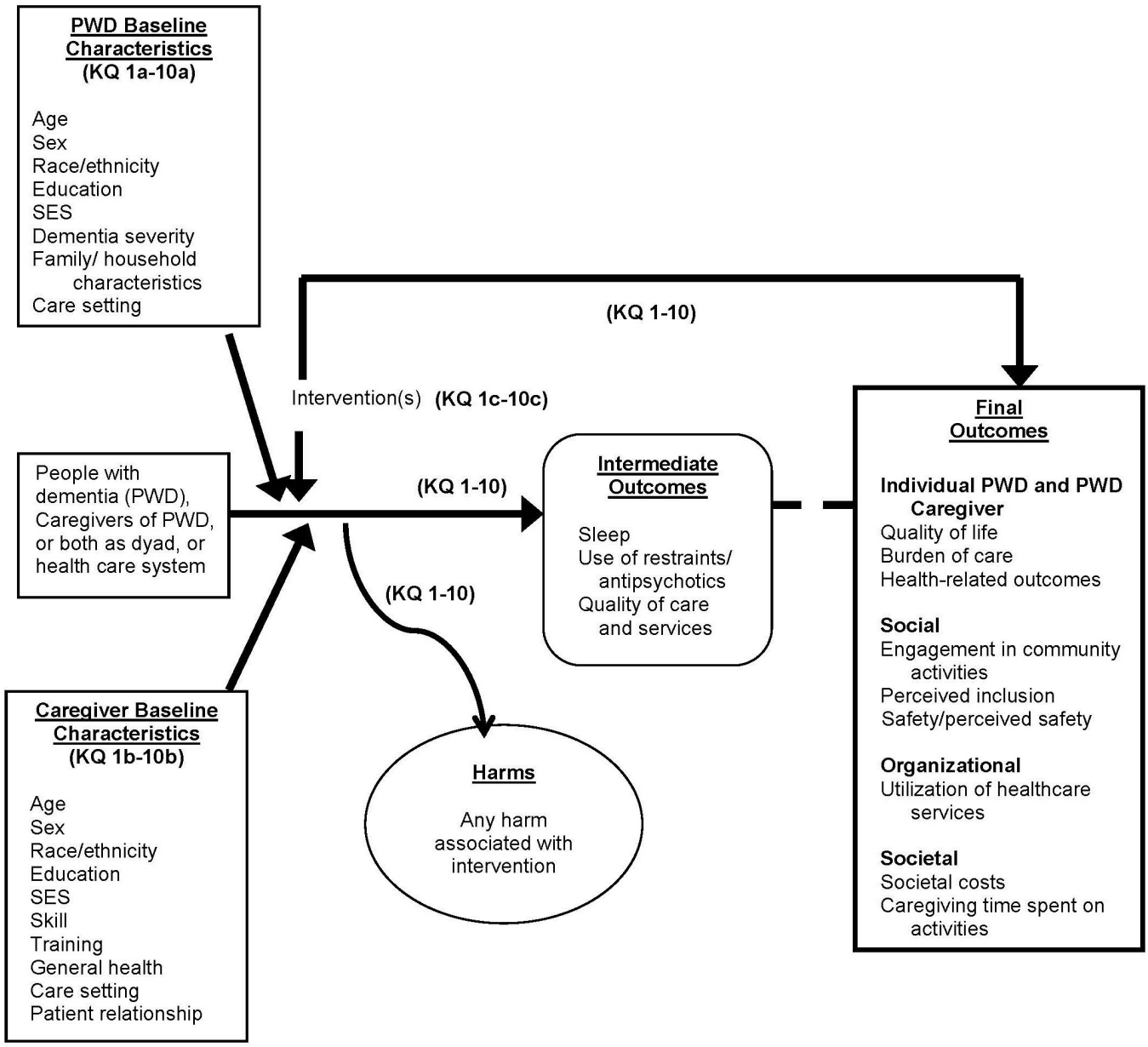
Element	PWD	PWD Caregiver
	agencies, nursing homes, assisted living, memory care units, hospice, rehabilitation centers/ skilled nursing facilities, long-distance caregiving, and nonplace-based settings	homes, assisted living, memory care units, hospice, rehabilitation centers/ skilled nursing facilities, long-distance caregiving, and nonplace-based settings

Abbreviations: ADL=activities of daily living; CPAP = continuous positive airway pressure; IADL=instrumental activities of daily living; ICU = intensive care unit; ER = emergency room; KQ = key questions; PICOTS = populations, intervention, comparator, outcome, timing, setting; PTSD = post-traumatic stress disorder; PWD = people with dementia

III. Analytic Frameworks

Figure 2 is a traditional analytic framework, illustrating the relationship of interventions and outcomes. Due to limited space, not all baseline characteristics or outcomes listed in Table 1 are specifically listed in the Figures.

Figure 2. Analytic Framework



Abbreviations: KQ=key question; PWD=people with dementia; SES=socioeconomic status

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the review based on the PICOTS framework outlined above in Table 1 and the study-specific inclusion criteria described in Table 2.

Table 2. Study inclusion criteria

Category	Criteria for Inclusion
Study Enrollment	Adults with possible or diagnosed AD/ADRD. No age requirement is made, e.g., early onset disease that may be experienced by people with Down syndrome or other genetic risk factors are included. Study populations may include adults with mild cognitive impairment (MCI) if 15% or less of total sample, or must report results for dementia population separately.

Study Objective	KQ 1-3: Evaluate benefits and harms of care interventions for BPSD symptoms in PWD KQ 3-4: Evaluate benefits and harms of care interventions for quality of life, function, or non-BPSD symptoms in PWD KQ 5-6: Evaluate benefits and harms of care interventions for quality of life and health outcomes of informal caregivers for PWD KQ 7-8: Evaluate benefits and harms of care interventions for quality of life and health outcomes of formal caregivers for PWD KQ 9-10: Evaluate benefits and harms of care delivery interventions that address how care is delivered KQ subquestions: Evaluate possible effect modifiers of intervention benefits and harms
Study Design	RCTs, and prospective studies with concurrent comparator arms, and at least 10 participants per arm at study analysis.* Interrupted time series with at least 3 measures both pre- and post-intervention.
Outcomes	Outcomes listed in Table 1. Actual outcome measures will be defined by study authors. Common measures are provided in Appendix B. We will only include studies with immune function, turnover, or retention of caregivers if the study also includes another PWD or quality outcomes; that is, we will not include the study if it only examines turnover or retention as an intermediate outcome in isolation.
Publication type	Published in peer-reviewed journals and grey literature with full text available (if sufficient information to assess eligibility and risk of bias are provided). Letters and abstracts are excluded due to the inability of such short publications to provide the information needed to fully describe the interventions.
Language of Publication	English only, due to resource limitations

*We will exclude studies with N <10 per arm, since these small studies are often lower in quality, inadequately powered on their own, and inappropriate to pool. Without pooling, studies of this size cannot reject null hypotheses even when true associations are large (i.e. Cohen's D = 1.2 for N=24 at 80% power). Regarding appropriateness for pooling, small studies are prone to overestimate the magnitude of an association, potentially exaggerating the accuracy and harms of diagnostic testing, and biasing the pooled estimates.

RCTs= Randomized controlled trials

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

The following discussion about review search processes is organized by type of research question—first the key questions, then the guiding question.

For the key questions, we will search Ovid Medline, Ovid PsycInfo, Ovid Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify studies published and indexed in bibliographic databases. The search algorithm will include relevant controlled vocabulary and natural language terms for the concepts of Alzheimer's disease and dementia (Appendix C).We will supplement our search strategies with backward and forward citation searches of other recent relevant systematic reviews.

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. 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 that inclusion criteria are applied consistently.

We will conduct additional grey literature searching to identify relevant completed and ongoing studies that meet the study design inclusion criteria noted in Table 2. 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. We will also track, using ClinicalTrials.gov, ongoing trials that have yet to publish results, emphasizing their contributions to a potential research agenda.

For the guiding question, we will search Medline, combining the AD and ADRD terms with specific filters to identify quality improvement and implementation studies to identify relevant literature from the bibliographic databases. We will also do forward citation searching of studies with low to moderate strength of evidence for companion articles describing implementation processes.

Lastly, to provide resources for care interventions which may not have been empirically studied using included study designs, we will search websites of relevant governmental agencies, professional associations, and AD or ADRD nongovernmental groups for curated resources listing known interventions. An example list of organizations is provided in Appendix D.

We will update searches while the draft report is under public/peer review.

Data Abstraction and Data Management

Studies meeting inclusion criteria will be distributed among investigators for data extraction. These data fields will include author, year of publication, population (including a granular checklist of patient and caregiver characteristics) of interest, intervention, comparison, outcomes cited, intervention duration and study followup, setting, risk of bias elements, and NIH stage model assessment.

For the key questions, additional data will be extracted from NIH Stage 3 to 5 studies assessed as having low to moderate risk of bias. These fields include subject inclusion and exclusion criteria, intervention and comparison characteristics, descriptions and results of included outcomes and harms, and study funding source. Intervention characteristics will include theory base, components and activities, timing, frequency, duration, use of technology, training, delivery approach (prescriptive or manualized vs tailored), other delivery modalities, and use of cultural adaptations or modifications. We will note the point on the disease continuum (or stage of dementia) the intervention is intended and methods for targeting the interventions to the PWD and/or caregivers and their identified goals and priorities.

For the guiding question, we will extract further information related to implementation readiness criteria such as feasibility, acceptability, and expenditures and costs of the intervention. Acknowledging the NIH Stage Model recognizes that intervention development may not be perfectly linear, we may include information from studies identified for the key questions that were conducted as NIH stages 0 to 2 if they are pertinent to a particular study identified for the guiding question. For example, an NIH Stage 1 study may examine a refinement of a component of previously tested in an NIH Stage 3 or 4 intervention.

Relevant data will be extracted into Microsoft Excel. Evidence tables will be reviewed and verified for accuracy by a second investigator. Data will be extracted to

evidence and outcomes tables by one investigator and reviewed and verified for accuracy by a second investigator. Given the expected number of included studies, we will not be contacting study authors for missing data.

Assessment of Methodological Risk of Bias and NIH Stage of Individual Studies

Based on AHRQ guidance,[13] Two investigators will independently assess risk of bias for all eligible studies. Investigators will consult to reconcile discrepancies in overall risk of bias. Overall risk of bias assessments for each study will be classified as low, moderate, or high based on the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations. However, the approach will differ based on the KQ and study NIH Stage model. We will begin with an initial sorting into NIH Stages 1-2 versus NIH Stages 3-5 by simple examination of the study aims.

For KQ1-8: For individual care intervention studies, risk of bias will be rated using modified Cochrane risk of bias tools as high, medium, or low for each of the following domains: (1) Selection bias (adequacy of randomization method [RCTs], accounting for imbalance in prognostic variables [observational studies]); (2) attrition bias (differentiated by mortality versus loss to followup); (3) detection bias (outcome measurement quality, outcome assessor masking); (4) performance bias (intention to treat or test analysis, adjustment for potential confounding variables, participant masking to treatment assignment); (5) reporting bias (selective reporting of outcomes). While we are not expressly looking for studies identified as quality improvement interventions, we recognize that complex care delivery interventions will use multicomponent approaches similar to QI interventions. For these complex interventions, risk of bias will include domains similar to those outlined in a risk of bias tool for quality improvement, such as fidelity to the program.[14] For studies associated with at least low-strength evidence findings in KQ1-8, we will differentiate between more challenging designs that may blur the lines between tightly controlled RCTs and other studies that approximate pragmatic designs or use pragmatic design elements.

For KQ9-10: We anticipate that care delivery studies will generally fall in the range of NIH Stage 3 to 4 effectiveness trials, with the possibility that one or a few may be carried out as quality improvement and thus stage 5. Since the NIH Stage Model is explicitly designed to balance, or trade off, internal and external validity, we will approach risk of bias assessment as a threshold requirement rather than a continuum for these studies. We will assess whether a study is below the threshold of high risk of bias based on selection bias, level of attrition, and fidelity to the intervention. If a study is determined to be below the threshold, the study will then be assessed for NIH stage. We will use a modified PRECIS-2 tool. Since the PRECIS-2 tool was developed to use during the design phase of a study, this novel use of the tool requires prototyping and testing during the review process. Appendix E provides a draft version of the modified tool. The final established process will be fully reported in the EPC report. During the development phase, included studies will be assessed individually by all team members and then domain and overall ratings will be determined by consensus. Team consensus will continue to be used until an acceptable level of rating consistency is determined, at which point two investigators will independently assess the stage.

Data Synthesis

We will summarize results in evidence tables and synthesize evidence for each unique population, comparison, and outcome or harm. The evidence tables will be organized by intervention targets, interventions, comparators, and PWD, caregiver, or other system-level outcomes. Because we have not identified an agreed-upon taxonomy of interventions by general purpose, we will categorize interventions empirically by intervention and comparator pairs, and classify them by our assessment (unless specifically noted by study authors) of the study's appropriate NIH stage model. Subgroups, where possible, will be examined in separate tables.

We anticipate that few studies will report most of the patient and caregiver characteristics of interest. We will capture and summarize in tables which and how many studies both captured and used in analyses the characteristics of interest. If our expectations are incorrect and sufficient numbers of studies can be aggregated on particular patient or caregiver characteristics, we will amend the protocol to further address synthesis approaches.

For the key questions, we will assess the efficacy and comparative effectiveness of outcomes using minimal important differences when they are well established, but for many outcomes this will not be the case. For outcomes measured with instruments that lack established thresholds to measure improvement, we will calculate standard effect sizes and require a small effect size (for example, Cohen's d>0.2) to conclude benefit.

If certain comparisons can be pooled, we will meta-analyze the data using random effects models. We will calculate risk ratios and absolute risk differences with the corresponding 95 percent confidence intervals for binary primary outcomes. Weighted mean differences and/or standardized mean differences with the corresponding 95 percent confidence intervals 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.[15] We will assess statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic.[16]

For interventions with at least low-strength evidence, we will explore the possibility of conducting network meta-analysis to investigate the relative contribution of intervention characteristics to a specific subset of critical benefits and harms. If we determine there are sufficient similar studies for a given intervention/comparison pair to allow this level of aggregation, we will file a protocol amendment with specific actions. The statistician who will conduct the meta-analysis will not be involved in the screening or abstracting processes prior to this decision to maintain some objectivity. That being said, any results from a network meta-analysis will be viewed and presented as hypothesis-generating analyses, not tests of hypotheses. Alternatively but similarly, if we find a sufficient set of similar studies to allow for qualitative comparative analysis techniques, we will file an amendment for that set of activities. At minimum, a qualitative narrative synthesis using matrix table approaches will be used.

Grading the Strength of Evidence for Major Comparisons and Outcomes

The overall strength of evidence for select outcomes for KQs 1 through 10 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.[17] 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 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:

- **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 confident 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.

An overall rating of high strength of evidence would imply that the included studies were randomized controlled trials with a low risk of bias, with consistent, direct, and precise domains. We will assess strength of evidence for key final health outcomes measured with validated scales.

Assessing Applicability

Applicability of studies is generally 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.[18] These applicability issues are present in the synthesis frameworks and sensitivity analyses described in more detail in the data synthesis section. In particular, we will also approach applicability of findings for interventions with at least low-strength evidence by adapting the PRECIS-2 tool.

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VI. Definition of Terms

AD– Alzheimer's disease
ADRD – Alzheimer's disease related dementias (i.e., frontotemporal dementia, Lewy body dementia, and vascular cognitive impairment/dementia)
PWD – person with dementia

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
State 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. Explain what the change aims to accomplish.

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.

Because of the overall design from our National Institute on Aging (NIA) sponsor, this project is following a unique model. The role of the Key Informants was filled by the NASEM committee that will use the report to help develop its own report on the state of knowledge on the efficacy, comparative effectiveness, and harms of interventions to protect cognitive health and prevent cognitive decline and dementia. Because the NASEM panel would not see the draft key questions, PICOTS, and analytic framework until the key questions were posted for public comment, a panel of content experts from federal agencies acted as a proxy Key Informants. Federal content experts were drawn from the National Institute on Aging, the Veterans Administration, The Department of Defense, and the Center for Disease Control and Prevention, the Office of the Assistant Secretary for Planning and Evaluation and the Administration for Community Living within the Department of Health and Human Services. There was not a separate, independent Key Informant panel.

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.

Because of the overall design from our NIA sponsor, this project is following a unique model. The role of the Technical Experts will be filled by the NASEM committee that will use the report to help develop its own report on the state of knowledge on the efficacy, comparative effectiveness and harms of interventions to protect cognitive health and prevent cognitive decline and dementia. There will not be a separate, independent Technical Expert Panel.

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

The topic for this project was nominated by the National Institute on Aging and funded under Contract No. HHSA290201500008I 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.

XIV. Registration

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

Appendix A. Examples of included interventions

Essentially, interventions are automatically included unless *specifically* stated as excluded. Note that the list is *not* divided by KQs 1-10. Some interventions may be aimed at both PWD and PWD Caregivers; some may be aimed at one or the other. The list is not intended to be exhaustive, and is a simple categorization based on what may be a more likely classification. The actual distinction between whether an intervention is examining **what** care is delivered or **how** to deliver care would be determined by the study purpose.

- Memory evaluation
- Driving evaluation or encouraging driving cessation
- Meaningful activities
- Advance care planning
- Behavior management
- ADL support
- Home modifications
- Wandering and fall risk management
- Palliative care
- Caregiver support and support groups
- Sensory-based interventions
- Changing the physical environment/environmental modification across settings (e.g., in hospitals, in people's homes)
- Mindfulness training
- Interventions focused on the development of Dementia Friendly Training (e.g., training of police officers in local communities)
- Wandering and Wayfinding
- Reminiscence Therapy
- Prompts and Multicomponent Interventions
- Engagement Interventions
- Exercise Interventions
- Psychoeducational
- Art therapy
- Dance movement therapy
- Music therapy
- Cognitive behavior therapy
- Counseling/care management (including emotionally focused couples therapy)
- General support
- Respite
- Training of PWD
- Psychosocial interventions/studies
- Caregiver support groups
- Therapeutic counseling
- Support interventions, including involving informal caregiver social network to support the primary caregiver

- Cognitive reframing (changing caregivers' maladaptive behaviors or beliefs)
- Web-based multimedia intervention
- Caregiver-therapist e-mail support
- Educational and peer-support website
- Bereavement support
- Improving acute care systems
- Skill training, including for CNAs, home health aides, and/or informal caregivers
- Training for CNAs, home health aides, and/or informal caregivers
- Improving care transitions
- Care coordination
- Multicomponent interventions

Appendix B. Common Outcome Measures

Test Name	Domain	Data Source	Reference
BEHAVE-AD	General behavior scales & global BPSD		Reisberg et al. 1987
Neuropsychiatric Inventory (NPI)	General behavior scales & global BPSD	informant	Cummings et al 1994
Cohen-Mansfield Agitation Inventory (CMAI)	Agitation/ aggression	informant	Cohen-Mansfield, 1986
Cornell Scale	Depression	patient or informant	Alexopoulos et al. 1988
Patient Health Questionnaire (PHQ-9)	Depression	patient	Spitzer et al., 1999
Geriatric Depression Scale (GDS) 30-item	Depression	patient	Yesavage et al. 1983
Geriatric Depression Scale (GDS) 15-item	Depression	patient	
Montgomery Asberg Depression Rating Scale (MADRS)	Depression		Montgomery & Asberg, 1979
Hamilton Depression Rating Scale (HDRS)	Depression	patient	Hamilton, 1960
Beck Anxiety Inventory (BAI)	Anxiety	patient	
Brief Psychiatric Rating Scale (BPRS)	Mood; Psychosis	clinician administered interview	Overall 1962; Beller 1984
Schedule for Affective Disorders and Schizophrenia (SADS)	Mood; Psychosis	clinician administered interview	Endicott 1978
Schedule for Affective Disorders and Schizophrenia -Lifetime version (SADS-L)	Mood; Psychosis	clinician administered interview	Endicott 1978
Schedule for Affective Disorders and Schizophrenia -Change version (SADS-C)	Mood; Psychosis	clinician administered interview	Endicott 1978
Behavioral Syndromes Scale for Dementia (BSSD)	General behavior scales & global BPSD	informant	Devanand 1992
Barthel index	ADLs	informant	Mahoney and Barthel, 1965
Bristol Activities of Daily Living Scale (BADLS)			Bucks et al. 1996
Direct Assessment of Functional Status	ADLs + IADLs	performance-based	Loewenstein, Amigo, & Duara, 1989
Disability Assessment for Dementia (DAD) Scale		informant	
Functional Activities Questionnaire (FAQ)		informant	Pfeffer et al 1982
Functional Independence Measure (FIM)	ADLs + (social, cogn, etc)	informant	Keith et al. 1987
Health Assessment Questionnaire (HAQ)			
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)		informant	Jorm and Jacomb,1989
Instrumental Activities of Daily Living scale	IADLs		Lawton and Brody, 1969
Katz Index of Independence in ADLs	ADLs		Katz et al. 1963
Modified Health Assessment Questionnaire (MHAQ)			
Older Americans Resources and Services (OARS)	ADLs + IADLs	self-report	George & Fillenbaum, 1985
Physical Self-Maintenance Scale (PSMS)	ADLs		Lawton and Brody, 1969
Minimum Data Set (MDS)-ADL Self Performance Scale	ADLs		
Progressive Deterioration Scale (PDS)	ADLs + IADLs	informant	DeJong 1989

AD-related Quality of Life scale (QoL-AD)		patient or informant	Logsdon et al. 1999
DEMQOL		patient	Smith et al. 2007
DEMQOL		informant	Smith et al. 2007
EuroQol measure		patient or informant	EuroQol Group, 1990
Short Form-36 (SF-36)		patient	Ware & Sherbourne, 1992
General Health Questionnaire (GHQ)	Global Distress		Goldberg & Williams 1988
Zarit Burden Interview	Caregiver Burden		Zarit et al. 1980
Neuropsychiatric Inventory – Distress Scale	Caregiver Distress		Cummings et al 1994
Revised Memory and Behavior Problem Checklist (RMBPC)		informant	Terie et al 1992

Appendix C. Search algorithms for selected databases

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 06, 2018>
Search Strategy:

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1 exp Alzheimer Disease/ (83289)
2 Dementia/ (45164)
3 (dementia or alzheimer*).ti. (97725)
4 1 or 2 or 3 (139036)
5 limit 4 to "therapy (best balance of sensitivity and specificity)" (6136)
6 limit 5 to english language (5766)
7 limit 6 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or comparative study or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or evaluation studies or "expression of concern" or festschrift or government publications or guideline or historical article or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or observational study or patient education handout or periodical index or personal narratives or portraits or "review" or "scientific integrity review" or validation studies or video-audio media or webcasts) (2140)
8 limit 7 to (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or randomized controlled trial) (587)
9 6 not 7 (3626)
10 8 or 9 (4213)
11 limit 10 to ("all child (0 to 18 years)" (372)
12 limit 11 to ("middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (337)
13 10 not 11 (3841)
14 12 or 13 (4178)

Database: Embase Classic+Embase <1947 to 2018 June 08>
Search Strategy:

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1 exp *Alzheimer disease/ (103967)
2 *dementia/ (50978)
3 (alzheimer* or dementia*).ti. (136009)
4 1 or 2 or 3 (165774)
5 limit 4 to english language (149043)
6 limit 5 to "therapy (best balance of sensitivity and specificity)" (11249)
7 limit 6 to "reviews (best balance of sensitivity and specificity)" (2742)
8 6 not 7 (8507)
9 limit 8 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (58)
10 limit 9 to (adult <18 to 64 years> or aged <65+ years>) (38)

11 8 not 9 (8449)
12 10 or 11 (8487)
13 limit 12 to (book or book series or conference proceeding or trade journal) (94)
14 12 not 13 (8393)
15 limit 14 to conference abstracts (2173)
16 14 not 15 (6220)
17 limit 16 to (abstract report or books or "book review" or chapter or conference abstract or "conference review" or editorial or letter or note or patent or reports or "review" or short survey or tombstone) (472)
18 16 not 17 (5748)
19 limit 18 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine) (355)
20 18 not 19 (5393)

Database: PsycINFO <1806 to June Week 1 2018>
Search Strategy:
---
1 exp *ALZHEIMER'S DISEASE/ (37834)
2 *dementia/ (26693)
3 (dementia* or alzheimer*).ti. (51716)
4 1 or 2 or 3 (64340)
5 limit 4 to "therapy (best balance of sensitivity and specificity)" (8415)
6 limit 5 to (childhood <birth to 12 years> or adolescence <13 to 17 years>) (56)
7 limit 6 to adulthood <18+ years> (46)
8 5 not 6 (8359)
9 7 or 8 (8405)
10 limit 9 to animal (765)
11 9 not 10 (7640)
12 limit 11 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs> or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs>) (377)
13 limit 12 to (360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>" or "390 very old <age 85 yrs and older>") (345)
14 11 not 12 (7263)
15 13 or 14 (7608)
16 limit 15 to (abstract collection or bibliography or chapter or clarification or "column/opinion" or "comment/reply" or dissertation or editorial or encyclopedia entry or interview or letter or obituary or poetry or publication information or review-book or review-media or review-software & other or reviews) (661)
17 15 not 16 (6947)
18 limit 17 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (13)
19 17 not 18 (6934)
20 limit 19 to english language (6617)

21 limit 20 to "therapy (maximizes specificity)" (1068)

Appendix D. Examples of sources for grey literature

The Administration for Community Living

AARP

Benjamin Rose Institute on Aging (resource list not yet released to public)

Bright Focus Foundation

Centers for Medicare and Medicaid Services

Family Caregiver Alliance

HCBS Clearinghouse

Mayo Clinic (Glen Smith)

National Alzheimer's and Dementia Resource Center (NADRC)

National Alzheimer's Caregiver Power Research Network

Office of the Assistant Secretary for Planning and Evaluation,

Patient-Centered Outcomes Research Institute

Rosalynn Carter Institute for Caregiving

Salzburg Global Health Seminar Dementia Initiative

Substance Abuse and Mental Health Services Administration

Appendix E. NIH Stage Assessment Tool

Table: PRECIS-2 scores for trial domains, with modification for Care Delivery Intervention literature

Domain	Score (1-5)	Rationale for score	Modified prompts, with examples
Eligibility criteria			To what extent are trial participants similar to PWD who would receive the intervention as part of usual care? [5= identical to usual care; 1=many exclusions (highly selected sample, uncommon tests used, exclude noncompliant or non-responders, etc.)] Example considerations: PWD: Other comorbidities allowed? Health or behavior restrictions? Mobility or language restrictions? Dementia severity range? Insurance restrictions? Participant had to opt in? Caregiver: Level of mobility/health/cognition necessary? How much time/work loss required?
Recruitment path			How much extra effort is required to recruit participants over usual care? [5=pragmatic, usual care (appt. or clinic); 1=targeted invitation letters, public media announcements, incentives] Example possible scores: 5: Invited during routine clinic visit 4: Invitation letter/call from doctor 3: Identified PWD via diagnosis/billing code(s)→sent letter 2: Incentive(s) for participation 1: Worker hired to find participants (clinic, health plan)
Setting			How different is the trial setting from usual care for PWD? [5=identical to usual care; 1=single center, special trial or academic center, etc.] Example considerations (*if setting not part of study question*): Urban only, or likely available in rural settings? Multiple settings included (private group practice, academic, HMO) Components: training for PWD/Caregiver on-site, but implemented at home via case manager?
Intervention organization			How different are intervention resources, provider expertise, and care organization from those available in usual care? How easy to implement without major changes (new staff, funding, policy)? Example possible scores: 4: Multicomponent + requires community partners 3: Multicomponent + requires new software 2-4: Requires new staff and funding (some) 1-2: Requires new or proprietary software (1+ sites), policy change, major new staff and funding
Flexibility of intervention: delivery			How different is flexibility of intervention delivery from usual care for PWD? Example possible scores: 5: Suggested services obtained based on ability to pay

Domain	Score (1-5)	Rationale for score	Modified prompts, with examples
			4-5: Care manager calls/care coordination per care manager/participant discretion 2-3: short training required of PWD/Caregiver (at clinic) 1: lengthy/intensive training required of PWD/Caregiver, or at academic center 2-3: Scheduled calls from case manager (1-2 if frequent; 1 if frequent + case manager calls when needed)
Flexibility of intervention: adherence			How different is the flexibility of intervention adherence requirement from usual care? How rigorous are measures to increase adherence? (Note: rate adherence studies too) <u>Example possible scores:</u> 5: usual encouragement; 1-2: prompts/measures to improve adherence
Follow-up			How different is trial follow-up or measurement intensity from usual care? Does trial follow-up (frequency, intensity, content) result in care that differs from usual care? <u>Example possible scores</u> 5: measurement from usual follow up. 3-4: in home assessment every 6 months by case manager 1: extensive data collection, longer/more frequent clinic visits, event(s) triggered visits
Primary outcome			To what extent is the primary outcome relevant to participants? [5=obviously important; 1=intermediate or physiologic outcome, requires expert assessment, outcome timing/measure differs from usual care] <u>Example possible scores:</u> 5: important to PWD and routinely assessed in usual care 4-5: important to PWD and longer term 3-4: composite primary outcome, some elements unimportant to PWD 2-3: important to PWD but measured earlier than usual care/short-term 1-2: assessment expertise differs from usual care; surrogate, intermediate outcomes.
Primary analysis			To what extent are all data included in the analysis of the primary outcome? <u>Example possible scores:</u> 4-5: ITT or modified ITT 1-2: exclude PWD with low intervention adherence (when adherence ≠ an outcome) 1-2: post hoc-derived subgroup analysis; secondary endpoints 1-2: data merged from > 1 study 1: compliant completer analysis
MN EPC			
Applicability			Population: PWD and/or PWD Caregivers: -narrow or broadly generalizable for PWD?
Qualifier(s)			Setting/implementation: -urban setting, practices with linked electronic health records -health plan level with trained case managers

Domain	Score (1-5)	Rationale for score	Modified prompts, with examples
			-modest vs. intensive electronic health record data extraction required? -needs proprietary software -costs not reported but startup likely intensive -costs not reported but likely feasible addition to usual care -not likely feasible in US health system -not likely feasible in (some) rural areas