**Evidence-based Practice Center Systematic Review Protocol**

**Project Title: *Interventions to Improve Care of Bereaved Persons***

## I. Background and Objectives for the Systematic Review

Bereavement – the state of having lost someone – and grief – the emotional response to the loss - are fundamental aspects of the life course and most individuals will experience the loss of someone during their lifetime.[1] In recent years, a growing number of individuals report experiencing grief and bereavement, due to both better identification of grief and grief-related needs, as well as a large aging population, the COVID-19 pandemic, and more frequent mass trauma events. Emotions related to grief can include feelings of deep sadness, longing, and shock.[2] There are a range of interventions to support individuals through their grieving process, ranging from informal supports (e.g., online resources, pamphlets, bereavement support groups) to formal supports such as individual and group therapy. Most individuals experience acute grief without formal intervention, yet a small subset of individuals develop complicated grief or grief with a high level of distress that extends 6 to 12 months following the death.[3-5] This type of grief was named prolonged grief disorder by the WHO and included in the ICD-11 in 2018[6] and classified as a formal disorder in the DSM-V TR in 2022.[7] Symptoms of prolonged grief disorder include persistent longing for the deceased person, difficulty accepting the death, emotional pain, and feelings of bitterness.[8, 9] In addition, recently bereaved individuals face higher medical risks as well, including increased risk of morbidity and mortality,[10-13] suicide,[14, 15] and lower functional status and quality of life.[10, 16]

There are a range of decisional dilemmas related to the screening, intervention, and follow-up of bereaved individuals for grief and grief-related needs over time. Broadly, there is ongoing debate about the "medicalization" of grief and its characterization as a disorder. Potential consequences of this medicalization of grief include the overdiagnosis, overtreatment, and the loss of traditional and cultural methods of adapting to the loss of a loved one.[17] Then there are important questions related to the appropriate screening of bereaved individuals, or those who may become bereaved, to identify and intervene on maladaptive grief responses, such as prolonged grief disorder. In general, mental health services for bereaved individuals, especially bereaved individuals who are caregivers to individuals at the end of life, are considered to be underutilized.[18] The public health model for bereaved individuals focuses on identifying and supporting three groups: a) the bereaved population as a whole (*universal approach*), b) individuals who may be at risk for prolonged grief disorder (*selected approach*), and c) individuals who have signs or symptoms of a grief disorder (*indicated* approach).[19] Some argue that a universal approach to screening may overlook some individuals who need more tailored support, while engaging other individuals who may not need intervention.[20] In contrast, a selected or indicated approach may overlook the opportunity to support and intervene a wider group of bereaved individuals who could benefit.

Related to approaches to identifying and supporting bereaved individuals is the timing of screening and intervention. A variety of factors are related to the grieving

processes that make it challenging to determine the most appropriate time to conduct screening. Bereavement processes are unique to each bereaved individual and the trajectory is cyclical, rather than staged.[21, 22] The type and circumstances of death (e.g., expected vs unexpected), preparation for the death, awareness of prognosis, acceptance of death, and readiness to engage in bereavement can all play a role in grief processes and timing. While proactive and early screening provides an opportunity for early intervention during the normal bereavement process, screening that comes too early in an individual's bereavement process may at best be ineffective, and at worst, create undue distress and anxiety. In contrast, screening that happens later in the course of bereavement may miss a window of opportunity for intervention.

In general, clinicians feel that bereavement screening could be useful yet there are various contextual barriers to implementation in health care settings.[23] Many bereaved individuals have time-limited contact with the healthcare system in the context of their loss and typically only if their loved one dies in a healthcare setting such as in a hospital, intensive care unit, emergency room, nursing home, or hospice. This limits opportunity for screening and intervention as well as consistent follow-up, with potential for wide variation in how screening is conducted and by whom. Numerous tools exist, but with little consensus or standardization regarding what to use when, and inconsistent implementation.[24-27]

There are several decisional dilemmas pertaining to appropriate interventions for grief. Given the cyclical and non-linear trajectory of grief, identifying the optimal time for intervention is a persistent challenge for the field. For example, could bereaved individuals experiencing "normal" or typical grief still benefit from formal interventions, and if so, what types of interventions might be most useful? When does normal grief cross a threshold into prolonged grief, and when is formal intervention likely to be most effective? And who is best suited to deliver grief interventions (e.g., health care providers such as a psychologist or psychiatrist for therapy/pharmacotherapy vs community-based practitioners such as a grief counselor or spiritual counselor)? [28-30]

There are also outstanding questions regarding the effectiveness of treatment for bereaved individuals who have been identified as having a grief disorder. Interventions to treat prolonged grief disorder include interpersonal psychotherapy, cognitive behavioral therapy, bereavement programs, peer support and group therapy. Most studies on interventions to treat bereaved individuals, however, are small pilot studies.[29] There are conflicting results related to the effectiveness of preventive interventions prior to the death, while interventions after the death have resulted in short and long-term improvements.[31] Information on their implementation and use in practice is varied, and there are inconsistencies in the extent to which current practice is substantiated by grief and loss theory. This in turn may diminish their credibility and further limit their use in practice. Innovative interventions such as narrative storytelling[32] have recently been developed to address averse emotional outcomes of grieving, but little is known about their effectiveness in clinical practice.

We know little still about how contextual factors might impact the effectiveness and even appropriateness of grief interventions.[33] The same factors that might influence the timing and appropriateness of screening likely impact the adoption and effectiveness of grief interventions such as circumstances of the death (e.g., traumatic death, anticipated death, overdose, suicide), and place of death such as the ICU, relationship to the deceased

person (e.g., child, spouse, estranged relationship), and social isolation and loneliness.[34] Comorbid mental health conditions – both pre-existing as well as new onset - may play a particularly influential role, for example the interaction between grief and comorbid depression, and how this should be integrated into intervention. Cultural preferences may influence whether a bereaved individual engages in the intervention, and what types of interventions are likely to be useful and effectives.

Finally, questions remain regarding feasible and appropriate follow-up of bereaved individuals identified as grieving and with grief-related needs. Because grief and bereavement are cyclical non-linear processes unique to each individual,[22] follow-up screening may be particularly useful to capture any new, maladaptive (or otherwise benefitting from intervention) responses to grieving. However, follow-up and longer-term screening and intervention is complicated by the various settings in which bereaved individuals may interact. For example, bereavement support might be available in the hospital following an inpatient death, but service is often discontinued once the bereaved individual returns home. Community bereavement support may be available but is often only accessed if the bereaved individual proactively seeks it out, and even then, systematic follow-up in the community is likely highly limited. Some emergency departments report bereaved family members commonly requested referral to community bereavement resources, but found that consistent follow-up was resource intensive and difficult to implement.[35] This gap between intervention and follow-up risks overlooking the potential for maladaptive grief response over the longer-term, when it may actually be more likely to develop.

### Purpose of the Review

In 2023, Congress directed The Agency for Healthcare Research and Quality (AHRQ) to establish an evidence base for what constitutes high-quality bereavement and grief care. This systematic review will inform an independent subject matter expert panel which will assess the feasibility of developing consensus-based quality standards for high quality bereavement and grief care. That panel will be convened by the Substance Abuse and Mental Health Services Administration (SAMHSA).

## II. Key Questions

The key questions proposed for the systematic review, addressing screening approach (Key Question 1), screening tools (Key Question 2), bereavement interventions (Key Question 3), and maladaptive grief-related disorder interventions (Key Question 4) were generally supported by key informants, and slightly refined following their input. We sought input from six key informants; including a patient advocate, a caregiver representative, a supportive medicine physician, a clinical psychologist, an expert in spiritual grief, and a social work representative focusing on policy. Key informants emphasized that grief is nonlinear and differs by individual person, and noted that the lack of guidance around grief and bereavement care reinforces the need for a systematic review. Major considerations or revisions recommended by key informants included 1) the importance of extending the screening and follow-up period to more than 1-year following the loss; 2) the need for clinical interview or qualitative assessment in addition to standardized screening and diagnostic tools; 3) the importance of taking spiritual,

religious, and cultural differences into account when screening, assessing, and diagnosing; and 4) the importance of considering different bereavement contexts including the type of death (e.g., illness), nature of the death (e.g., sudden death), setting of death (e.g., hospital), relationship to the deceased person (e.g., spouse), and age of the deceased person (e.g., child). Finally, key informants also noted that screening and intervention can take place in the community beyond healthcare settings; for example, facilitated through religious institutions, support groups, and online organizations.

Following the described input, the key questions are as follows:

*Key Question 1*: What is the effectiveness and harms of universally screening people for bereavement and response to loss?

a. Timing: predeath, acute, or 6-12 months post loss, and more than 1 year post loss?
b. Does effectiveness vary by patient characteristic or setting?

*Key Question 2*: How accurate are tools to identify bereaved persons at risk for or with grief disorders?

*Key Question 3*: What are the effectiveness, comparative effectiveness, and harms of interventions for people at risk for grief disorders related to bereavement?

a. Timing: predeath, acute, or 6-12 months post loss, and more than 1 year post loss?
b. Does effectiveness vary by patient characteristic or setting?

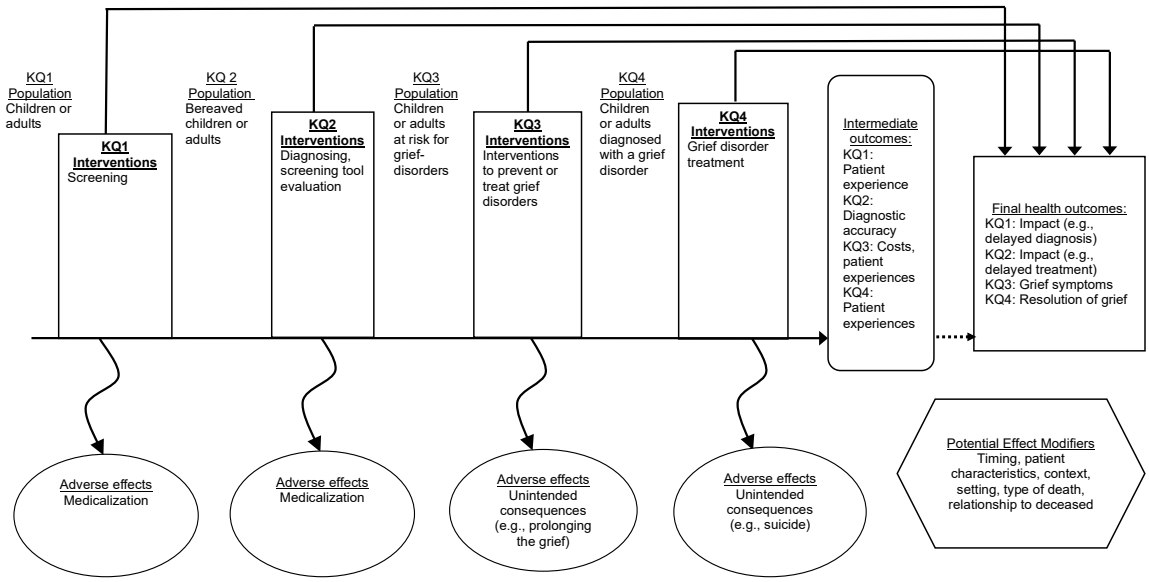
*Key Question 4*: What are the effectiveness, comparative effectiveness and harms of interventions for people diagnosed with grief-related disorders?

a. Does effectiveness vary by patient characteristic or setting?

## III. Logic Model

The analytic framework depicts the patient population, the interventions, and the outcomes that will be addressed in the evidence synthesis.

**Figure 1: Analytic Framework**




## IV. Methods

The systematic review will be guided by this systematic review protocol. We will register the review in PROSPERO, a prospective registry for systematic reviews. The project will be supported by a multidisciplinary technical expert panel. This panel is designed to provide different perspectives relevant to this complex topic. The panel will inform the final protocol and panel members will be asked to review the draft report.

### Criteria for Inclusion/Exclusion of Studies in the Review

The eligibility criteria are shown in the table.

**Table 1. Eligibility Criteria**

| Element | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| **Population** | KQ1: Children or adults<br>KQ2-3: Children or adults who have experienced a human (including in utero) death of someone close to them or will do so in the near future (e.g., in a hospice setting) and who are at risk of being diagnosed with a grief disorder.<br>KQ4: Children or adults diagnosed with a grief disorder (prolonged grief disorder, complicated grief, chronic grief disorder, persistent complex bereavement disorder) according to DSM (prolonged grief disorder) or ICD (ICD11 6B42, ICD10 F43.81, ICD9 309.0) | Studies on other forms than personal grief, such as community expressions of grief, public reactions to loss or trauma |
| **Interventions** | KQ1: Screening strategy evaluation with screening tool<br>KQ2: Diagnostic strategy evaluation, diagnostic or screening tool<br>KQ3: Interventions to prevent or treat grief disorder<br>KQ4: Interventions to treat grief disorders | KQ1: Incidental or non-systematic identification of grief or reaction to loss<br>KQ3-4: Interventions delivered by lay persons or non-healthcare professionals not |

| Element | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| | | applicable to a healthcare setting |
| **Comparators** | KQ1: No screening approach, usual care, or an alternative screening approach<br>KQ2: No tool, an alternative tool, concordance with grief disorder diagnosis<br>KQ3: No intervention, usual care, or an alternative intervention<br>KQ4: Usual care or an alternative intervention | KQ1: No reference standard or method to detect the impact of screening<br>KQ2: No reference standard to determine the accuracy of the diagnostic tool<br>KQ3-4: No concurrent comparator |
| **Outcomes** | KQ1: Immediate experience (patient experience, medicalizing grief, abnormalizing grief, feeling of pathologizing a normal process), screening accuracy (e.g., correctly diagnosed with grief disorder), and impact (e.g., delayed diagnosis, underdiagnosis, overdiagnosis, delayed treatment, undertreatment due to missed diagnosis, overtreatment)<br>KQ2: Diagnostic accuracy (e.g., sensitivity, specificity, accuracy, area under the curve, positive predictive value, negative predictive value, false positives, false negatives, grief disorder identification) or impact (e.g., delayed diagnosis, underdiagnosis, overdiagnosis, effects of false positive test results, delayed treatment, undertreatment due to missed diagnosis, overtreatment)<br>KQ3: Grief symptoms, incidence of grief disorder, severity of grief disorder, any adverse events or unintended consequences of the intervention<br>KQ4: Grief symptoms, resolution of grief disorder diagnosis, physical or mental health, quality of life, functional status, patient experience, costs, any adverse events or unintended consequences of the intervention | Clinician or organizational barriers to, opinions on, preferences to, or uptake of screening, diagnosing, or treatment of grief |
| **Timing** | Any, no restrictions regarding the timing of the intervention or follow up | |
| **Setting** | Any setting. | |
| **Study Design** | KQ1-2: Screening and diagnosis impact analyses and diagnostic accuracy studies<br>KQ3-4: Randomized controlled trials (RCTs), clinical trials comparing two or more interventions, observational cohort studies comparing two or more intervention cohorts, controlled post-only studies, and case-control studies | KQ1-2: Descriptions without information on the impact or accuracy of the screening approach or tool performance<br>KQ3-4: Studies without control group or concurrent group that does not receive the intervention or that receives a different intervention |
| **Other limiters** | Data published in English-language journal manuscript or trial records; relevant literature reviews will be retained for reference mining | Data only reported in abbreviated format (e.g., conference abstracts) and/or data only reported in non-English outlets |

Notes: DSM Diagnostic and Statistical Manual of Mental Disorders, ICD international classification of diseases, KQ key question

The review will explicitly include children and adults given that there is a need for more information for both populations. The review is not limited to persons who have recently lost someone given that late effects can occur with a considerable delay. We will also include grieving populations where the death is imminent but has not yet occurred, for

example, to capture interventions for relatives of a palliative care patient. Rather than restricting to a set of known or currently/clinically indicated interventions, this review is designed to identify all available approaches that have been evaluated in research studies. This will allow us to identify novel and only recently established bereavement interventions which may offer valuable options for bereaved persons. Based on scoping searches to inform this protocol, we note that authors have used many different outcome measures. Hence, we will apply a broad outcome eligibility criterion to select studies that are eligible for this review.

We will include a range of study designs, but studies will need to report on a comparator. For screening and diagnostic studies, we will include screening and diagnostic analyses that assess the impact of the approach as well as diagnostic accuracy studies. For treatment studies, eligible study designs include concurrently controlled studies such as randomized controlled trials (RCTs), clinical trials comparing two intervention arms, observational cohort studies comparing two intervention cohorts, controlled post-only studies, and case-control studies. The other limiters domain clarifies that we will include studies published in a scientific outlet (journal or research record). However, studies published in abbreviated form (e.g., conference abstracts) will be excluded because these will provide insufficient detail for detailed analyses. The review is restricted to primary research studies, but relevant scoping reviews, systematic reviews, evidence maps, and meta-analyses will be retained for reference mining.

There are no publication date restrictions. Studies with data exclusively published in non-English language publications will be excluded to ensure transparency. We will obtain all published reports providing data on a study (a study is defined by the included participants), including trial records and multiple publications, and consolidate the information into one study record.

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

For primary research studies we will search PubMed (biomedical literature), EMBASE (pharmacology emphasis), CINAHL (allied nursing), PsycINFO (psychological literature), Social Work Abstracts (social work), and Dimensions (linked research data platform). Addressing bereavement is multidisciplinary, and multiple sources reduce the chances of missing relevant studies. Many different treatments have been suggested for bereaved people and many known interventions are not specific to addressing grief, such as psychotherapy. Hence, broader searches will capture relevant and/or novel approaches. The search combines search terms for bereavement with broad diagnostic and treatment terms (rather than only a set of known tools or interventions). The draft search strategy is shown in the appendix. For quality assurance, the search strategy will be peer reviewed.

We will also search US and international research registries (clinicaltrials.gov, ICTRP) to capture all relevant data regardless of the publication status. We will identify existing reviews and use these for reference-mining. We will search the same databases used for primary research plus the Cochrane Database of Systematic Reviews and PROSPERO to systematically identify existing research syntheses. We will also systematically search for existing clinical practice guidelines, using the ECRI repository, G-I-N, MagicApp, and

ClinicalKey. The guidelines will be used to inform context and current clinical practice and as a further check that all relevant research studies have been identified. The identified systematic reviews and existing guidelines collection will be an additional resource as part of the review.

We will leverage key informant, technical expert panel, and AHRQ partner knowledge to identify relevant data sources and research studies. We will provide a list of included studies, together with all associated publications, and a list of excluded studies to facilitate this process. Finally, AHRQ will set up a portal for submissions of Supplemental Evidence And Data for Systematic Reviews (SEADS) and publish a notice on the Federal Register to encourage SEADS submissions. The searches will be updated during public review of the draft report.

**Data Abstraction and Data Management**

The data abstraction will capture detailed information about eligible studies. We will document the screening approach and targeted population for screening approaches. We will document the triggers or decision rules prompting the screen, categorize populations (universal, selected, or indicated screening approach), and abstract reported participant characteristics. We will document clinical setting, format, timing, and personnel involved. We will abstract tool characteristics (format, questions or items, answer mode, known psychometric characteristics), employed analysis, and the observed prognostic/diagnostic performance to address diagnostic tools. The information will be collected together with clinical context variables (e.g., clinical setting, geographic region, cultural characteristics), recruitment strategy (e.g., routine care visit), and characteristics of participants (e.g., ethnicity, cultural identity) that may influence the performance of the tool.

The data abstraction for bereavement interventions will include the setting and clinical context of the evaluation. We will abstract sufficient detail to be able to distinguish patient samples, including selection criteria for entering the research sample, demographics and other patient characteristics (e.g., comorbidity), relationship to the deceased person, type of death (e.g., unexpected), and timing of the intervention in the grieving process. We established a taxonomy of interventions based on identified interventions with input from the technical expert panel. The review will differentiate psychotherapy, pharmacotherapy, expert-facilitated support groups, peer support groups, non-psychotherapy / spiritual counseling, self-help interventions, and other interventions. We will standardize the reporting format of the interventions to help facilitate comparisons across studies. Detailed evidence tables will describe the intervention category (e.g., counselling, antidepressants), focus (individual or family target), intervention components (in particular for complex intervention), format (e.g., individual or group), involved personnel (e.g., psychiatrist, spiritual counselor), the timing relative to the experienced death, and the duration of the intervention. As important as the description of the intervention will be the description of the comparator, i.e., what is the intervention compared against to determine its effects. We will abstract the outcome measure and what the observed results were. For prolonged grief disorder treatment, we will document the eligibility criteria of the study and the included patients in the research

sample. This will include abstracting any definitions used in the study (e.g., complicated grief), given that there is little shared understanding and established terminology. We will abstract the treatment approach in detail together with the study design, analysis, and any framework for conceptualizing grief and measuring the effects of the intervention.

**Assessment of Methodological Risk of Bias of Individual Studies**

The review addressed different domains (screening, diagnosis, treatment) and different study designs will be eligible across and within domains. We will tailor the risk of bias assessment to the question the study is used to answers. It is important that studies can still be compared across, and we will apply a set of evaluation criteria that focuses on the underlying risk of biases, rather than applying dozens of different study design-specific tools. Studies will be assessed with criteria consistent with domains assessed in QUIPS (Quality in Prognosis Studies), QUADAS 2 (Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies), and RoB 2 (Risk of Bias 2).[36-38]

For screening and diagnostic studies contributing to key question 1 and 2, we will evaluate four domains:

- *Patients*: This domain will address whether the selection of patients could have introduced bias, taking into account, for example, whether the study enrolled a consecutive or random sample, whether the data are not based on a retrospective case-control design, and whether the study avoided inappropriate or problematic exclusions from the patient pool.
- *Tool*: The domain will evaluate whether the conduct or interpretation of the applied tool could have introduced bias, taking into account whether the results of the screening approach or diagnostic test were interpreted without knowledge of the results of the reference standard and whether any thresholds or cut-offs were pre-specified (e.g., instead of determined in the study to maximize diagnostic performance).
- *Reference standard*: The domain will evaluate whether the reference standard, its conduct, or its interpretation may have introduced bias, taking into account the quality of the reference standard in correctly classifying the condition (e.g., a gold standard may not exist) and whether the reference standard results were interpreted without knowledge of the results of the index test approach or tool.
- *Design*: The domain will evaluate whether the conduct of the study may have introduced bias. The assessment will take into account whether the interval between the tool and the reference standard was appropriate, whether the diagnosis of all patients is known, whether all patients were included in the analysis, and whether there were any additional confounders.

For each domain, we will assess the potential risk of bias in the study in order to identify high-risk of bias and low risk of bias studies. Consistent with QUADAS-2,[37] the critical appraisal will evaluate for each study and appraisal domain whether there are concerns regarding the applicability of the study results to the review question. This encompassed whether the patients included in the studies do not match the review question; whether the tool or approach, the conduct, or interpretation differ from the review question; or whether the target condition as defined by the reference standard does not fully match the review question.

For grief interventions and interventions for prolonged grief disorder, we will adapt the RoB 2 and assess the following domains:

- *Selection bias*: For selection bias, we will assess the randomization sequence and allocation concealment in RCTs as well as baseline differences and potential confounders in all studies.
- *Performance bias*: Performance bias will evaluate whether patient- or caregiver knowledge of the intervention allocation or circumstances such as the trial context may have affected the outcome, and whether any deviations from intended interventions were balanced between groups.
- *Attrition bias*: Attrition bias will consider the number of dropouts, any imbalances across study arms, and whether missing values may have affected the reported outcomes.
- *Detection bias*: Detection bias will assess whether outcome assessors were aware of the intervention allocation, whether this knowledge could have influenced the outcome measurement, and whether the outcome ascertainment could differ between arms.
- *Reporting bias*: Reporting bias assessment will include an evaluation of whether a pre-specified analysis plan exists (e.g., a published protocol), whether the numerical results likely have been selected on the basis of the results, and whether key outcomes were not reported (e.g., an obvious effectiveness indicator is missing) or inadequately reported (e.g., anecdotal adverse event reporting).
- *Other sources of bias*: In addition to the types of bias listed above, we will assess other potential sources of bias such as early termination of studies, inadequate reporting of intervention details, and lack of intention-to-treat analyses.

Because we are including experimental as well as observational studies, assessing confounding variables will be of particular importance. Throughout, the critical appraisal will be focused on how study design features may have affected the reported results. One goal of the appraisal will be to identify high risk of bias studies for sensitivity analysis (e.g., to determine whether effects are primarily based on low-quality studies) as well as finding low-risk studies that can strengthen evidence statements through confirmation of results in strong studies. We will incorporate the risk of bias results into the strength of evidence assessment and downgrade our confidence in evidence summaries in the presence of study limitations.

**Data Synthesis**

We will answer each key question with the available evidence. The evidence tables resulting from the data abstraction will provide a comprehensive overview of every included study. Concise summary of findings tables will summarize the findings across studies.

We will use meta-analysis as a data-aggregation technique with appropriate meta-analysis models[39] which is in particular important given the many small studies that have been published to date. We will report point estimates together with 95 percent confidence intervals. Where studies cannot be combined statistically, we will convert to measure-independent effect estimates (standardized mean differences, relative risk) and convert

absolute numbers to rates and proportions to facilitate comparisons across studies. We will test for heterogeneity across reported results using graphical displays and the I-squared statistics. We will explore potential sources of heterogeneity through subgroup analyses while recognizing that the ability of statistical methods to detect heterogeneity may be limited.[40] We will assess the effectiveness and any adverse events as well as the comparative effectiveness and safety of different interventions. For this, we will evaluate any direct evidence from head-to-head comparisons of tools and treatments, and we will explore indirect evidence through indirect analysis across studies using meta-regression. For the interpretation of findings, we will take into account whether effects appear to be study design-independent (i.e., are shown in studies that allow strong evidence statements such as RCTs where available), and robust (e.g., effects are still shown after excluding high risk of bias studies). We will assess the potential for publication bias for all key outcomes using the Begg and the Egger test.[41, 42] The trim and fill method will be used to provide alternative estimates where evidence of publication bias will be detected.[43]

Discussions with key informants and content experts determined the following a priori subgroups: timing, patient characteristics, and settings. Regarding timing, we will differentiate predeath, acute, or 6-12 months post loss, and more than 1 year post loss. Regarding patient characteristics, we will distinguish between children and adults. For settings, we will distinguish between healthcare and community settings. In addition, we will explore the potential effect of the relationship of study participants to the deceased, the type of death (e.g., expected or unexpected), and other setting characteristics (e.g., type of provider using the tool or implementing the treatment).

The synthesis will order findings by screening, diagnostic, treatment of grief, and treatment of prolonged grief disorder. For each approach, we will further organize by comparators, and then within these comparisons, by outcome domain. We prioritized outcomes for the review synthesis with the help of the TEP to ensure a concise summary of findings. Selected as key outcomes were the following outcomes:

- KQ1: *Any information on the clinical impact of the screening process, patient experience (e.g., impression of medicalizing, abnormalizing, or pathologizing grief; or feeling understood), any information on the validity and diagnostic accuracy of the screening tool or approach; adverse events associated with the screening procedure; administrative time; inter-rater reliability;*
- KQ2: *Patient experience; impression of medicalizing, abnormalizing, or pathologizing grief; test-retest reliability; most often reported diagnostic accuracy measure; any information on the clinical impact of a correct or incorrect diagnosis;*
- KQ3: *Incidence of grief disorder; severity of grief disorder; grief symptoms; quality of life; loneliness; suicidal ideation, attempted suicide, suicide completion; adverse health behaviors, unintended consequences of the intervention*
- KQ4: *Grief symptoms; severity of grief disorder; continued meeting grief disorder criteria; depression symptoms; quality of life; loneliness; suicidal ideation, attempted suicide, suicide completion; substance use*

In addition, we will provide a structured gap analysis that uses the analytic framework and the eligibility criteria dimensions to make detailed recommendations and guide future research.

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

We will apply the EPC strength of evidence criteria to evaluate the body of evidence, informed by GRADE guidance for prognostic, diagnostic, and treatment studies.[44] The strength of evidence assessment will clearly document uncertainty, outline the reasons for insufficient evidence where appropriate, and communicate our confidence in the findings.

The strength of evidence for each body of evidence (based on the Key Question, diagnostic and treatment approach, comparator, and outcome) will be initially assessed by one researcher with experience in determining strength of evidence for each primary clinical outcome by following the principles for adapting GRADE (Grading of Recommendations Assessment, Development and Evaluation), outlined in the AHRQ methods guide.[45] The initial assessment will be discussed in the team.

We will formulate evidence statements for all identified key outcomes. We will differentiate effectiveness and safety (compared to passive comparators such as no screening strategy, diagnostic test, or bereavement intervention) versus comparative effectiveness and safety (comparing two alternative strategies, tests, or interventions). In determining the strength of a body of evidence, the following domains will be evaluated:

- *Study limitations*: The extent to which studies reporting on a particular outcome are likely to be protected from bias. The aggregate risk of bias across individual studies reporting an outcome is considered; graded as low, medium, or high level of study limitations.
- *Consistency*: The extent to which studies report the same direction or magnitude of effect for a particular outcome; graded as consistent, inconsistent, or unknown (in the case of a single study or no identified studies).
- *Directness*: Describes whether the intervention (approach, test, or treatment) and the comparator were directly compared (i.e., in head-to-head trials) or indirectly (e.g., through meta-regressions across studies). In addition, indirectness reflects whether the outcome is directly or indirectly related to health outcomes of interest of the key question. The domain is graded as direct or indirect.
- *Precision*: Describes the level of certainty of the estimate of effect for a particular outcome, where a precise estimate is one that allows a clinically useful conclusion. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies will be considered. The domain is graded as precise or imprecise.
- *Reporting bias*: Occurs when publication or reporting of findings is based on their direction or magnitude of effect. Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. Reporting bias is difficult to assess as systematic identification of unpublished evidence is challenging. If sufficient numbers of RCTs are available, we will review Begg and Egger tests and evaluate the trim and fill method derived estimate.

Bodies of evidence consisting of RCTs are initially considered as high strength, while bodies of comparative observational studies begin as low-strength evidence. However, the screening and diagnostic strategies will unlikely include RCTs. In order to avoid ceiling effects, we will use prospective studies starting as high strength of evidence rather than random assignment to tests or interventions. The strength of the evidence may be downgraded based on the limitations described above. There are also situations where observational evidence may be upgraded (e.g., large magnitude of effect, presence of dose-response relationship or existence of plausible unmeasured confounders) as described in the AHRQ Methods guides.[45]

A final strength of evidence grade will be assigned by evaluating and weighing the combined results of the above domains. To ensure consistency and validity of the evaluation, the grades will be reviewed by the team of investigators. The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale:

- *High*: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
- *Moderate*: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- *Low*: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- *Insufficient*: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Summary tables will include ratings for individual strength of evidence domains (i.e., risk of bias, consistency, precision, directness) based on the underlying evidence. The systematic review will not make any recommendations for practice, acknowledging that practice guidelines have to take more aspects into account than the research evidence base. Instead, we will provide a clear overview of the existing evidence base to date. We will work closely with partners to ensure that we provide evidence statements that align with the areas of interest for the planned standard of care and guideline recommendations.

**Assessing Applicability**

Applicability will be assessed in accordance with the AHRQ's Methods Guide. Factors that may affect applicability, which we have identified *a priori*, include type of loss, patient characteristics, intervention features, settings, and study design features. We will address whether outcomes are different across studies that recruit different populations (e.g., age groups) or use different methods to implement the interventions of interest. We will use this information to evaluate the applicability to clinical practice, paying special attention to the following: study eligibility criteria; demographic features of the enrolled

population in comparison to the target population; characteristics of the intervention used (including the intervention personnel) in comparison with care models currently in use; and clinical relevance and timing of the outcome measures. We will assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

### Use of Artificial Intelligence and/or Machine Learning

All citations retrieved by the literature searches will be screened by at least one human literature reviewer and a DistillerSR software machine learning algorithm trained by the human reviewers to ensure that no relevant citation will be missed. Any citations identified as potentially relevant by the algorithm that have not been selected for full text publication review will be rescreened for relevance by an independent literature reviewer.

### Peer Review and Public Comment

Prior to publication of the final evidence report, EPCs will seek input from independent peer reviewers without financial conflicts of interest. The draft report will also be publicly posted to elicit input from the public. Comments received from peer reviewers and the public review will be addressed in the final evidence report.

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## VI. Definition of Terms

None

## VII. Summary of Protocol Amendments

None

## VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing of the public comments and seeking 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 the decisional dilemmas and help keep the focus on Key Questions that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for the 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. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

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

## X. Technical Experts

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

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

## XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can 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. Direct financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify an EPC core team investigator.

## XIII. Role of the Funder

This project was commissioned and funded by the Patient-Centered Outcomes Research Institute (PCORI) and executed under Contract No. 75Q80120D00009 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ 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 PCORI, 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. Search strategies

**PubMed**

#1
("bereavement"[MeSH Terms] OR "bereavement"[Title/Abstract] OR "bereavements"[Title/Abstract] OR "bereaved"[Title/Abstract] OR "bereaving"[Title/Abstract] OR "grief"[Title/Abstract] OR "grieving"[Title/Abstract] OR "mourning") AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])

#2
(bereavement[MESH] OR bereavement[Title/Abstract] OR bereavements[Title/Abstract] OR bereaved[Title/Abstract] OR bereaving[Title/Abstract] OR persistent complex bereavement disorder[Title/Abstract] OR grief[Title/Abstract] OR grieving[Title/Abstract] OR mourning[Title/Abstract]) AND (prospective OR cohort OR controlled study OR comparative study OR controlled post-only OR concurrent comparator OR comparative effectiveness OR case control OR case-control OR prospective studies[MeSH] OR controlled trial)

#3
(bereavement[MESH] OR bereavement[Title/Abstract] OR bereavements[Title/Abstract] OR bereaved[Title/Abstract] OR bereaving[Title/Abstract] OR grieving[Title/Abstract] OR mourning[Title/Abstract] OR grief disorder[Title/Abstract] OR grief disorders[Title/Abstract] OR complex grief[Title/Abstract] OR complicated grief[Title/Abstract] OR abnormal grief[Title/Abstract] OR pathological grief[Title/Abstract] OR traumatic grief[Title/Abstract] OR unresolved grief[Title/Abstract] OR disenfranchised grief[Title/Abstract] OR unanticipated grief[Title/Abstract] OR grief distress[Title/Abstract] OR chronic grief[Title/Abstract] OR cumulative grief[Title/Abstract]) AND (Screening[Title/Abstract] OR identification tool[Title/Abstract] OR identification tools[Title/Abstract] OR diagnosis[Title/Abstract] OR diagnosing[Title/Abstract] OR diagnostic[Title/Abstract] OR sensitivity[Title/Abstract] OR specificity[Title/Abstract] OR assessment[Title/Abstract] OR diagnosis[MeSH])

#4
#1 OR #2 OR #3