Protocol for a systematic review on interventions for caregivers of persons with mild cognitive impairment and early dementia: does early stage intervention improve caregiver well-being and ability to provide care?

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ABSTRACT

Introduction Caregivers of persons with dementia and mild cognitive impairment (MCI) are at risk of decreased well-being. While many interventions for caregivers exist, evidence is sparse regarding intervention timing and effectiveness at an early stage of cognitive decline. Our systematic review aims to answer the following questions: (1) Do interventions for caregivers of persons with early stage dementia or MCI affect their well-being and ability to provide care? (2) Are particular types of caregiver interventions most effective during early stage cognitive decline? (3) How does effectiveness differ when early and later interventions are directly compared? (4) Do effects of early stage caregiver intervention vary based on care recipient and caregiver characteristics (eg, sex, type of dementia)?

Methods and analysis The databases MEDLINE, EMBASE, PSYCINFO and CINAHL, as well as grey literature databases, will be searched for English language studies using search terms related to caregiver interventions and dementia/MCI. Abstracts and full texts will be screened by two independent reviewers; included studies must assess the effects of an intervention for caregivers of persons with early stage dementia or MCI on caregiver well-being or ability to provide care. Intervention, study and participant characteristics will be extracted by two independent reviewers, along with outcome data. Risk of bias will be assessed using the Cochrane risk of bias tool (for controlled trials with and without randomisation). Interventions will be grouped by type (eg, psychoeducational) and a narrative synthesis is planned due to expected heterogeneity, but a meta-analysis will be performed where possible. The Grading of Recommendations, Assessment, Development and Evaluations approach will be used to inform conclusions regarding the quality of evidence for each type of intervention.

Ethics and dissemination Findings from this review will be disseminated via conferences and peer-reviewed publication, and a summary will be provided to the Alzheimer Society.

Strengths and limitations of this study

- This work addresses intervention timing and the effectiveness of early stage intervention for caregivers of persons with dementia, which is a meaningful gap in this body of literature.
- This review will involve a rigorous search and screening process, to maximise comprehensiveness and minimise bias.
- Many different types of caregiver interventions will be included for review, and significant heterogeneity may limit our ability to conduct statistical meta-analyses of effects.
- A strength of this review will be the consideration of findings in relation to assessment of bias and evidence Grading of Recommendations, Assessment, Development and Evaluation; this will help inform conclusions about the state of evidence for the effectiveness of early stage intervention on included outcomes.

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INTRODUCTION

Informal caregivers are relatives, partners, friends or neighbours who have a personal relationship with a person with a chronic or disabling condition, and provide various types of assistance to that person. The majority of care recipients with dementia receive assistance (such as with basic and instrumental activities of daily living and general supervision) from multiple informal caregivers, with one person assuming a primary caregiver role. A recent review suggests that informal caregivers of persons with Alzheimer’s disease provide an average of 56 hours of assistance per week. Informal caregivers spend
significantly more time providing care when they are a spouse/partner of the care recipient, and when the care recipient’s functional status is worse or their dementia is more severe.3, 4

Psychological issues such as general distress, depression and anxiety are common among family caregivers of persons with dementia.4–6 Moreover, a growing body of research suggests that caregiving to a person with dementia negatively affects the caregiver’s sleep quality, cognitive functioning and physiological health (particularly in relation to markers of immune function, cellular ageing and cardiovascular risk factors).7 It is also well established in the literature that informal caregivers of persons with dementia are at risk of experiencing caregiver burden.8, 9 Caregiver burden may be best understood as a multidimensional construct reflecting caregiver struggles with financial, physical, social, psychological/emotional and developmental well-being (perceptions of being ‘on time’ in life circumstances, compared with peers), as well as challenges navigating caring demands and restrictions.10 11 However, it is important to note that there is heterogeneity among definitions of caregiver burden in the literature, along with inconsistencies in which elements of the concept are included across different measurement tools.12 13 The burden experienced by dementia caregivers is most frequently measured using the Zarit Burden Interview14 (ZBI), which a recent factor analysis suggests measures three main dimensions: social consequences for the caregiver, psychological burden and feelings of guilt.10 The common use of the ZBI means that operationalisation of caregiver burden is often capturing emotional and psychological responses to caregiving, and social restrictions associated with this role, although this does not preclude the existence of other types of burden. In fact, it has been argued that assessing burden quantitatively fails to capture all elements of caregivers’ experiences of the phenomenon, and that cultural context is crucial to how caregivers experience and communicate burden.12 15 Despite critiques of the concept of caregiver burden,12 it is a significant concern and thus remains a main focus within many caregiver studies. Although there are also gratifying and positive aspects of caregiving for many caregivers of persons with dementia,16 they are often considered a vulnerable population due to the intensity of caring demands, risk of burden and other negative consequences. This perspective is reflected in the literature on caregiver well-being, which primarily focuses on deficits and how to ameliorate negative caregiver outcomes.17

Many interventions have been developed to support caregivers of persons with dementia, and enhance both caregiver well-being and ability to provide care. A variety of approaches including psychoeducational, cognitive-behavioural therapy, counselling, case management, respite and general support interventions have been implemented with caregivers of persons with dementia, as well as interventions which combine approaches (i.e., multicomponent interventions).17 Previous reviews and meta-analyses have demonstrated the effectiveness of many caregiver interventions on a variety of outcomes, although interventions may have only domain-specific effects (eg, on caregiver depression) and evidence suggests that some types of interventions (eg, multicomponent and psychoeducational) may be the most beneficial.17–19 Moreover, effectiveness of these interventions has been found to vary according to caregiver and care recipient characteristics, such as caregiver sex, relationship to the care recipient and type and severity of dementia.20

Another factor that may be very important when examining caregiver intervention effectiveness is the timing of intervention: whether it begins early or later in the course of the care recipient’s cognitive decline. Few systematic reviews have distinguished between people at different stages of dementia, and Thompson et al25 identified intervention timing as a fundamental question for future research in the area. The effects of some caregiver interventions may be greater depending on their timing; Andrén and Elmståhl25 found that a psychosocial intervention conferred greater benefit to caregivers’ well-being when provided early in the progression of dementia. Dementia is a progressive illness and can begin with cognitive impairment, but no functional impairment; this is conceptualised as mild cognitive impairment (MCI),24 25 although less instrumental caregiving support is required for persons with MCI, their caregivers are still at risk of experiencing burden and depression,26 which indicates the potential utility of interventions at this stage. Moreover, early stage intervention may better position caregivers of cope with dementia progression.27 When the magnitude of cognitive impairment becomes sufficient to impair daily function, dementia can be diagnosed. Although there is no one agreed-upon definition of early stage dementia, the Clinical Dementia Rating scale28 score of 1 or the Global Deterioration Scale29 score of 4 are generally seen as staging tools suggesting early stage dementia. At an early stage of dementia, an individual might continue to live independently with minor assistance. Early stage is, perhaps, best defined as what it is not—it is not functional independence such as is seen in MCI, but it is not consistent with later stages of dementia where an individual would not be able to survive without assistance.

While the utility of early stage intervention for caregivers has been suggested,30 the degree to which interventions of various forms are beneficial to early stage dementia caregivers would benefit from systematic review. This is particularly important due to what Boots and colleagues31 termed the ‘early needs paradox’, wherein caregivers may not fully recognise their needs and find it difficult to accept assistance at earlier stages of dementia, yet retrospectively identify early stage support and guidance as crucial. Understanding the benefits of early stage intervention for caregivers will allow for evidence-informed decision making around the provision and timing of support. Our aim is therefore to assess the potential benefits of intervention for caregivers of persons with
early stage dementia or MCI, via a systematic review. This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P guidelines developed for systematic review and meta-analysis protocols, in order to document and enhance the rigour and transparency of our planned methods, outcomes and analyses. As suggested by Paez, we will also be searching the following sources of grey literature to identify key studies which may not be published: grey literature databases (Proquest Dissertations & Theses Global, OpenGrey); conference abstracts (of included databases) and clinical trial databases (WHO International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, National Institute on Aging Clinical Trials). Due to available resources and feasibility, only English-language studies will be included.

**Research questions**

To achieve our goal of examining the potential benefits of early stage intervention (ie, intervention aimed at caregivers of persons with MCI or early dementia), four research questions are being posed: (1) Do interventions aimed at caregivers of persons with early stage dementia or MCI affect their well-being and ability to provide care? (2) Are particular types of caregiver interventions more effective than others during early stage cognitive decline? (3) To what extent do benefits to caregivers differ when early and later interventions are directly compared? (4) Is there evidence to suggest that benefits of early stage intervention for caregivers vary based on care recipient and caregiver characteristics (eg, relationship, sex, type of dementia, rural vs urban residence, comorbidities, co-residence vs separate residence)?

**METHODS AND ANALYSIS**

A systematic review was chosen to answer our research questions. Systematic reviews aim to identify, evaluate and synthesise the findings of all relevant studies, and can identify what we know about the effects of interventions as well as demonstrate where knowledge is lacking. The guidelines set out by the Centre for Reviews and Dissemination (CRD) are informing our review process, which will consist of the identification of research evidence, study selection, data extraction, quality assessment, data synthesis and evidence grading and conclusions. The planned start date for this review was November 2018, and the estimated date of completion is November 2019.

**Patient and public involvement**

Patients and public were not involved in the development of this systematic review protocol.

**Step 1: the identification of research evidence**

**Information sources**

Published peer-reviewed research will be included in this systematic review. Based on the topic of interest, the electronic databases MEDLINE, EMBASE, PSYCINFO and CINAHL will be searched with no limitations placed on year of publication. This search will be supplemented by scanning the reference lists of included studies, to ensure no relevant studies are missed. If the time from search to data analysis exceeds 6 months, the literature search will be updated within each database. Details of the search process will be documented throughout, for transparency and replication. As suggested by Paez, we will also be searching the following sources of grey literature to identify key studies which may not be published: grey literature databases (Proquest Dissertations & Theses Global, OpenGrey); conference abstracts (of included databases) and clinical trial databases (WHO International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, National Institute on Aging Clinical Trials). Due to available resources and feasibility, only English-language studies will be included.

**Search strategy**

Three main search concepts have been identified as important for this review, namely, dementia/MCI, caregivers and intervention. Search terms were constructed following a search of previous literature to identify specific terms relevant to these concepts. In order to narrow search outcomes to the topic of interest, terms related to caregiver and intervention will be searched together using the adjacency function, so that articles that use these terms within five words of each other will be identified (the adjacency strategy). Terms incorporating medical subject headings (MeSH), text words and ‘exploded’ derivatives related to each concept (the MESH strategy) will also be entered into the included databases using OR. Results from the concepts of dementia/MCI and caregiver interventions (adjacency strategy OR MeSH strategy) will then be searched together using AND. The search strategies for each database are being developed by the review team, in consultation with a Health Science Librarian with expertise in systematic reviews. Draft MEDLINE search terms can be viewed in table 1, and the full strategy in online supplementary file 1. When searching grey literature, we will document the date each database is searched, the search terms used, the number of items retrieved (ie, search results) and the number of items relevant for screening.

**Step 2: study selection**

**Data management**

Studies identified in the literature search will be uploaded to Distiller Systematic Review software, which allows multiple reviewers to screen studies simultaneously. This software will also be used to screen for duplicates when studies are uploaded. Using Distiller SR, the first author will create screening forms based on our eligibility criteria to determine inclusion/exclusion. Separate forms will be created for title/abstract (level 1) and full-text (level 2) review, and each will be pilot-tested by the first author and refined if needed before independent review commences.

**Eligibility criteria**

Studies will be selected according to the inclusion and exclusion criteria outlined below. No restrictions regarding length/timing of follow-up measurement, or intervention setting, will be placed on studies.
Participants

Participants must be caregivers of people with early stage dementia or MCI, who are living in the community. The dementia may be any form, including Alzheimer’s disease, vascular dementia, dementia related to Parkinson’s disease, dementia with Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease and mixed or unspecified dementia; young-onset dementia will also be included. While not all individuals with MCI will progress to dementia, MCI may still be considered a prodromal or ‘pre-dementia’ stage in the context of early stage intervention.27 Caregivers of persons with MCI will therefore be included based on the characterisation of cognitive impairment on a spectrum and the inclusion of MCI in other reviews on early stage dementia interventions.35 36 Stage of dementia will be assessed based on author description of the sample (eg, mild/early stage dementia or MCI), and/ or care recipients’ cognitive testing scores, if reported. Studies will be excluded if caregivers are providing care to individuals who do not have MCI or are not early in the progression of dementia (they are described as having moderate or severe dementia, Clinical Dementia Rating Scale scores >1, Mini-Mental State Examination scores <18 or Global Deterioration scale scores >5), or are a convenience sample of caregivers of individuals across multiple stages of dementia. Studies may compare caregivers of persons with MCI/early stage versus later stage dementia.

Interventions

As identified in previous reviews,17 37 a variety of interventions for caregivers of persons with dementia have been developed and evaluated. All approaches to intervention for caregivers of persons with MCI or early stage dementia will be included in this review, including multicomponent interventions. In order to assess the effects of different types of early stage intervention, interventions will be classified into categories based on their dominant characteristics.17 For example, programmes that focus primarily on formal provision of information and caregiver skills training would be classified as psychoeducational. The intervention must be

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* / indicates MESH terms.
MCI, mild cognitive impairment; MESH, medical subject headings.
primarily focused on caregiver support (interventions primarily for the person with dementia or MCI where the caregiver assists with implementation will not be included).

Comparators
Included studies will include a control or comparison group unless inclusion criteria are relaxed (see Study design section). Comparison groups may include caregivers who did not receive the intervention/received usual care, received it at a different time point (ie, later in the course of the care recipient’s dementia) or received a different type of intervention. Studies may be included if they compare other participant groups who received the intervention (eg, caregivers of people with other conditions) with early stage dementia or MCI groups.

Outcomes
Included studies must include evaluation of the effectiveness of an intervention for caregivers that is intended to enhance caregiver well-being or ability to provide care to the person with dementia or MCI. Although there are many definitions of well-being,\textsuperscript{38} in the current review the term ‘enhanced well-being’ is being used to refer to the positive increases in physical, social, psychological and spiritual domains, and quality of life, which may result from the provision of support and resources to meet caregiver challenges. This inclusive conceptualisation of well-being is in line with the large variety of definitions (both conceptual and operational) in the literature, and with authors who have theorised that decreased well-being occurs when individuals are facing challenges that require additional adaptation and resources to meet.\textsuperscript{39} A recent systematic review of reviews illustrated that within the literature on caregivers of persons with dementia, well-being is most frequently operationalised as burden, depression, stress, quality of life, physical and mental health and the caregiver–recipient relationship.\textsuperscript{16} Based on their review, the authors suggested that quality of life can be considered one part of well-being, along with intrinsic feelings and emotions (positive mental attributes such as self-efficacy, negative mental attributes such as depression, subjective perceptions of one’s own health or well-being) and what they called ‘extrinsic factors’ (interactions with others, mental or physical health). A variety of relevant outcome variables may be measured in the studies included in our review, including (but not limited to) measures of depression, anxiety, stress, quality of life, physical health, emotional well-being, socialisation, leisure time, caregiver burden, time until institutionalisation of the person with dementia, knowledge regarding caregiving/dementia, and perceived ability to provide care or cope with caregiving demands. All outcome variables relevant to caregiver well-being or ability to provide care will be extracted, along with their definition as reported in individual studies.

Study design
Randomised controlled trials (RCTs) are considered the gold standard in assessing intervention outcomes and will be included in this review, including randomised crossover trials and cluster randomised trials. However, implementing randomisation, blinding and control groups may be difficult in psychosocial dementia interventions, and it is therefore important to consider evidence from other types of study designs.\textsuperscript{39} As such, non-randomised studies with a control or comparison group will be included in this review. If few RCT and controlled studies exist, pre-post case series designs (where a group is given an intervention but no comparisons to a control group are made) will also be included due to their frequency of use given the difficulty of conducting randomised and controlled studies in this area. All other designs including qualitative research will be excluded for the purposes of this review.

Selection process
The first author (MB) and another review author will independently screen titles and abstracts of all studies uploaded into Distiller SR, using the level 1 form. This form will be used to screen for articles that report on interventions for caregivers aimed at enhancing caregiver well-being or ability to provide care to recipients with dementia or MCI, and initial screening for study design. As suggested by CRD guidelines,\textsuperscript{33} reviewers will err on the side of inclusion during title and abstract review. Studies that appear to meet inclusion criteria, or those where inclusion is uncertain, will progress to level 2 and full texts will be obtained. The first author and a second reviewer will then screen the full-text reports to determine whether they meet the inclusion criteria. Level 2 screening will include screening for stage of cognitive impairment, as identified by the authors (eg, ‘participants all had early stage dementia’) and/or cognitive testing scores. DistillerAI, which is the software’s language processing technology, may be used to check for accidental exclusions. Disagreements at both stages of review will be resolved through discussion, and a third author (DM) will be consulted in cases where an agreement is not reached. During full-text review, the reason for exclusion will be documented for each study. The reviewers will not be blinded to study titles, authors or institutions, which is considered acceptable during study selection.\textsuperscript{33} A PRISMA flowchart\textsuperscript{40} documenting the number of studies at each stage of the selection process and reasons for full-text exclusion will be created.

Step 3: data extraction
Extraction process
An electronic data extraction form will be created based on the items of interest described below (see sample extraction form in online supplementary file 2). Guidelines for data extraction may also be developed to facilitate standardisation of the process. The extraction form will be piloted on a small sample of included studies, and refined as necessary. Where reported, data will be
extracted into this form for each study by the first author and a second reviewer (JK), in order to reduce errors and missed information. Any disagreements will be discussed and resolved among the review team. As per CRD recommendations, multiple reports of the same study (eg, a preliminary sample followed by the total sample) will be treated as one study for data extraction to reduce biased results. Authors of included studies may be contacted by email to confirm uncertainties or for additional information.

**Data items**
The following information will be extracted about the study, intervention and sample:

1. General information: author/s, year, title of the article, source of funding, geographic location of the study (country).
2. Intervention characteristics: criteria distinguishing the intervention as early stage; intervention name, description, type and theoretical basis (where relevant); length of intervention, setting in which the intervention is delivered.
3. Study characteristics: objectives of the study; study design; recruitment procedures including inclusion and exclusion criteria, comparator group; sample size for each group.
4. Participant characteristics (total sample, intervention group and comparator group/s):
   a. Caregiver characteristics: rural versus urban, sex, relationship of caregiver to care recipient, definition of caregiver, time spent caregiving, primary caregiver status, lives with care recipient.
   b. Care recipient characteristics: rural versus urban, sex, type of dementia, cognitive testing scores, comorbidities.

**Outcomes**
Caregiver well-being and ability to provide care may be operationalised in a number of ways; the main outcome variables we are interested in are caregiver burden and depression (given their importance and prevalence in this population and the literature), self-reported quality of life and perceived ability to provide care. All other variables related to well-being and ability to provide care will be considered secondary outcome variables. When extracting data related to these outcomes, time until intervention follow-up and additional follow-up measurements will be charted. The measurement tool or measurement used for each relevant outcome variable will be recorded, as will the statistical techniques used for analysis. Raw means (with SD), change scores and statistical outcomes will be extracted for each measure pertaining to well-being and ability to provide care. As data are extracted, statistical information from studies will be used to calculate standardised mean differences (or odds ratios if relevant, eg, for risk of institutionalisation). This will allow for comparison between variations in measures of effects across individual studies, and helps to account for differences in sample sizes that affect statistical significance.

Another goal of this review is to assess whether benefits differ between early and later stage interventions; all statistical summary and outcome information will be extracted if studies compare the effects of early to later intervention. Finally, we are interested in assessing whether benefits of early stage intervention vary based on care recipient and caregiver characteristics (eg, sex, type of dementia and rural vs urban residence). All summary data and statistical outcomes pertaining to comparisons of intervention effects between subgroups of caregivers or care recipients will be extracted. These comparisons may be based on the factors noted above which are of particular interest, but may also include other factors (eg, caregiver personality and socioeconomic status). Additional outcomes (those not pertaining to the foci of this review) reported in the article and other information of interest will be recorded narratively without statistical information. We would like to note that while care recipient outcomes of early stage caregiver intervention are also important, they are not included in the current review given our already broad focus and feasibility constraints. The potential impacts of early caregiver interventions on care recipients is a topic that should be addressed in a future review.

**Step 4: quality assessment**
Quality will be assessed to inform conclusions about the effectiveness of early stage intervention with caregivers based on how the study was carried out, not to inform inclusion/exclusion in the review. This means that studies will not be excluded based on poor quality. Potential bias (systematic deviations from the ‘true’ effect due to poor study design or implementation) is important to examine, since it can alter findings of effect and explain different findings between studies assessing the same intervention. To assess the possible risk of bias for each included RCT, we will use the Cochrane risk of bias tool for RCTs (Table 8.5 in the Cochrane Handbook for Systematic Reviews of Interventions). This tool assesses five types of potential bias: selection bias, performance bias, detection bias, attrition bias and reporting bias, as well as additional concerns about bias not addressed by these domains. Based on information in each article, a judgement will be made according to the Cochrane criteria on whether the study is at low risk, high risk or unclear risk of bias. As suggested in the Cochrane Handbook, this tool can also be used for intervention studies that include a control group but are not randomised.

Pre–post case series studies may be included if few RCTs and controlled studies meet inclusion criteria. If these studies are included, the Institute of Health Economics’ Quality Appraisal Checklist for Case Series Studies will be used to assess their quality, including risk of bias. This tool has been initially validated and consists of 20 items covering both risk of bias (eg, pre and post outcome measurement, sufficient follow-up and method...
for recruitment of participants) and quality of reporting (eg, description of patient characteristics, report of any co-interventions and report of any adverse outcomes). Based on previous use, a point will be given for every ‘yes’ answer so that studies of higher quality (including lower risk of bias) will have a higher overall score out of 20, while those of lower quality (and higher risk of bias) will have lower scores. Quality assessment will be carried out for each study included in the review.

**Step 5: data synthesis**

We anticipate that multiple types of early stage intervention will be covered in our systematic review, and that studies will report on various outcomes related to well-being and ability to provide care. Because of this expected heterogeneity, a narrative synthesis is planned. A narrative synthesis relies primarily on textual description to analyse and describe the findings from included studies. Extracted data will be examined for potential relationships between results and key aspects of the studies, and across studies (eg, sample characteristics, outcomes measured and intervention characteristics). Explorations for why early stage interventions are effective are also of interest. Studies will be separated into groups based on type of early stage intervention, in order to better address our second research question (whether effectiveness varies depending on intervention type). Key elements from each study will be presented in summary tables, including results and effect sizes. If studies within intervention subgroups are homogenous enough, statistical pooling of data will be performed through meta-analysis. If relevant evidence exists, differences in effectiveness based on timing of intervention and caregiver or care recipient characteristics will be assessed and presented. Risk of bias assessments will be used to contextualise findings, evaluate the state of the literature and explain potential differences in results across studies.

**Step 6: evidence grading and conclusions**

**Meta-biases**

Unpublished literature is included in this review in an attempt to minimise publication bias. When using the risk of bias tool, selective reporting (another area of meta-bias) will be assessed. This will be facilitated by comparing published studies with their protocols when possible, and assessing the degree to which data are reported for relevant outcomes including findings that are not statistically significant.

Confidence in cumulative evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach will be used to rate the evidence regarding the effectiveness of early stage intervention for caregivers on their well-being and ability to provide care to a person living with MCI or dementia. GRADE involves risk of bias assessment but also assessments of imprecision, inconsistency, indirectness and publication bias. This framework allows informed judgements to be made about the quality of the body of evidence that is being examined: whether we can be confident it accurately represents the true effects of early caregiver interventions. The quality grade (very low, low, moderate and high) helps inform overall conclusions about the state of evidence for each outcome under review.

**ETHICS AND DISSEMINATION**

Findings from this review will be shared via conference proceedings and peer-reviewed publication, and a summary to the Alzheimer’s Society. A full list of relevant studies that do not have data included in the review (eg, in-progress protocols) will be created and available on request. Findings may help inform the use of interventions for caregivers early in the course of the care recipient’s cognitive decline.

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**Contributors** The first author (MB) was the primary developer of the focus and methods of this review, wrote the first draft of the protocol and is the guarantor of the review. DM, JK, AFC and VE constitute the core review team, who provided regular guidance and input into the planning of the review, including focus and methods. They will also be assisting with the acquisition of data and analysis. They reviewed and contributed to drafts of this protocol. AM also provided feedback in the planning stage, is assisting with some of the data acquisition and provided feedback on the initial draft of this proposal. SP and MEO’C provided input on key aspects of the focus and methods, and reviewed/contributed to drafts of this protocol.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

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