

BMJ Open Risks and benefits of antioxidant dietary supplement use during cancer treatment: protocol for a scoping review

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To cite: Wieland LS, Moffet I, Shade S, *et al.* Risks and benefits of antioxidant dietary supplement use during cancer treatment: protocol for a scoping review. *BMJ Open* 2021;**11**:e047200. doi:10.1136/bmjopen-2020-047200

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-047200>).

Received 21 November 2020

Revised 15 February 2021

Accepted 24 March 2021



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ABSTRACT

Introduction Antioxidant dietary supplements are used by many patients with cancer to reduce the side effects of chemotherapy and improve prognosis. While some research indicates oral antioxidant supplementation reduces side effects and improves patient survival, other studies suggest the use of antioxidant dietary supplements may interfere with chemotherapy and reduce its curative effects. There is a need to clarify the evidence base on the impact of dietary antioxidant supplementation during chemotherapy on both side effect and treatment efficacy outcomes. We will use a scoping review approach to identify what systematic review evidence exists regarding beneficial and harmful effects of dietary antioxidant supplements when used during cancer treatment.

Methods and analysis We will use Arksey & O'Malley and Joanna Briggs Institute methods for scoping reviews. We will systematically search PubMed, Embase, CINAHL, Scopus, Dissertations & Theses Global and the Cochrane Library from inception to October 2020. Systematic reviews of randomised controlled trials of oral dietary antioxidant supplements used by participants receiving curative chemotherapy, radiotherapy or other biological therapy for cancer will be eligible. Two reviewers will screen citations and full texts for inclusion and chart data on research questions from included reviews. Two reviewers will assess the overall confidence in systematic review results using A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2), and summarised evidence will focus on reviews rated at high or moderate overall confidence. Tables will be used to map existing evidence and identify evidence gaps for safety and effectiveness outcomes.

Ethics and dissemination This scoping review does not require ethical approval as it is a secondary assessment of available literature. The results will be presented at conferences and submitted for publication in a peer-reviewed journal. We will also disseminate results to community and clinical stakeholders and involve them in developing subsequent research to address critical existing gaps in the evidence as identified by the scoping review.

INTRODUCTION

Cancer is the second-leading cause of death in the USA,¹ having a significant deleterious impact on individual patients and society at

Strengths and limitations of this study

- This will be the first scoping review to provide an up-to-date overview of the available systematic review literature on the potential benefits and harms of antioxidant dietary supplement use during curative treatment for cancer.
- The review will focus on understanding whether existing systematic reviews have examined the relationship between the use of antioxidant dietary supplements and the therapeutic efficacy of chemotherapy.
- The review will use the A Measurement Tool to Assess Systematic Reviews-2 tool to distinguish between systematic reviews providing different levels of certainty for results and emphasise reviews at overall high or moderate certainty.
- Results from this scoping review will be used to further the understanding of the breadth of antioxidant dietary supplement interventions and their effects during chemotherapy and to identify current gaps in knowledge.

large. Approximately one in two men and one in three women will develop cancer in their lifetime.² Cancer treatment is a broad area of research, as cancer is a complex, dynamic set of diseases, requiring newer technologies and innovative treatments with fewer adverse effects. Conventional medical therapies for those with cancer include but are not limited to chemotherapy and radiotherapy, both of which are associated with potentially debilitating side effects and reduced quality of life.³

Chemotherapy is a treatment approach designed to stop cancer growth either by preventing the reproduction of new cancer cells or killing cancer cells directly. Most chemotherapy drugs target the cell cycle, by altering or damaging DNA in the cell.⁴ One of the most significant causes of oxidative stress and inflammation is related to DNA damage.⁵ Additionally, anticancer drugs cannot distinguish between cancer cells and healthy cells, which is thought to be a reason

for chemotherapy's negative side effects.^{4 6} A majority of patients receiving chemotherapy report at least one side effect from the drug, most notably fatigue, nausea, vomiting, diarrhoea, pain, rash, constipation and shortness of breath.⁶ For this reason, patients receiving cancer treatment often seek complementary and alternative adjuvant therapies to reduce side effects and improve quality of life.

A popular group of complementary therapies used by patients with cancer is antioxidants, which can be administered through dietary interventions, intravenous infusion or most commonly, dietary supplementation.⁷ Antioxidants are substances that act to prevent or delay cellular damage, notably by stabilising free radicals and reducing oxidative stress. The observation in laboratory studies that antioxidants decrease oxidative stress has made the use of antioxidants common, although somewhat controversial, in the attempt to prevent or treat chronic disease.⁸ Commonly used antioxidants include vitamins, minerals, phytochemicals and other related substances, and amino acids.⁹

While antioxidant supplements are popular among the general public, the evidence on antioxidant supplementation to prevent chronic disease or improve health outcomes is equivocal.^{10–12} Although there is an increased willingness of medical professionals to use complementary therapies, the belief persists among many providers that alternative therapies could harm patients.^{13–15} When patients use over the counter dietary supplements without informing their physician, this may increase risk of interactions with prescription medications and undermine the patient–provider relationship.^{16 17}

A 2016 overview concluded that antioxidant supplementation reduces adverse effects and chemotoxicities from chemotherapy, though the authors noted inconsistencies in the literature.⁹ The most studied oral antioxidant supplement may be melatonin, shown in vitro to have antitumour activity when used with irradiation.¹⁸ However, while some research suggests that oral antioxidant supplementation during chemotherapy may increase patient survival, other research suggests that it may diminish the efficacy of the chemotherapeutic treatment.^{19 20} There is concern that antioxidant therapies may interact with the cytotoxic effects of chemotherapy, lessening adverse side effects and improving quality of life, but also rendering the cancer treatment less effective.²¹ For example, a recently published secondary data analysis from a clinical trial comparing chemotherapy schedules in breast cancer identified an increased hazard of recurrence in women using antioxidant supplements both before and during chemotherapy.²²

We are aware of many studies over the past 20 years that discuss dietary supplements during cancer treatment; several of these are systematic reviews.^{9 23–29} However, most systematic reviews focus on the potential reduction in chemotherapy side effects with supplements. We are not aware of a review systematically collecting evidence on the relationship between antioxidant supplements

and therapeutic response to chemotherapy, with the exception of one systematic review conducted more than 10 years ago.¹⁹ Since publication of that review, there have been changes in chemotherapy regimens and antioxidant use patterns, and more current systematic reviews may have captured but not highlighted relevant information on response to chemotherapy. There is, therefore, a need to systematically identify the best currently available evidence on this topic. Currently, there is no comprehensive overview of the literature outlining the benefits and harms of antioxidant supplements for patients receiving conventional cancer therapies, and evidence appears particularly scant on the question of whether antioxidant supplementation may negatively interact or interfere with chemotherapeutic treatment. This apparent paucity of evidence precludes the ability to make evidence-based recommendations on use of antioxidant supplements by patients with cancer.

Although we have not identified recent systematic reviews on the topic of antioxidant supplementation and effectiveness of cancer therapies, we think it is possible that for some antioxidants the question of a relationship between supplementation and efficacy of treatment may have already been asked and possibly even answered by systematic reviews of randomised controlled trials (RCTs), perhaps as one component of reviews on the effects of antioxidant supplements on treatment side effects. We do not wish to undertake a large systematic review on the topic if some areas have already been addressed, and it is unclear if the area is ready for an overview of systematic review findings, given that the topic itself may be underexplored. Our goal is to evaluate the status of systematic review research questions on antioxidant oral supplementation during cancer treatment, with a particular focus on whether and how antioxidant effects on chemotherapy have been addressed. This information will provide direction, in conjunction with guidance from patient and clinician stakeholders, on the next steps in addressing this critical topic.

We will use scoping review methodology to identify and compile the data from previous systematic reviews of RCTs regarding not only the reduction of chemotherapy side effects but also the efficacy of chemotherapy when oral antioxidant supplements are used in conjunction by persons with cancer. A scoping review is a form of knowledge synthesis that 'aims to map key concepts, types of evidence and gaps in a defined area or field by systematically searching, selecting and charting available evidence.'³⁰ Extracting information from systematic reviews will allow us to identify what is known and where there remain knowledge gaps on the topic. Specifically, this paper is focused on identifying (1) to what extent previous systematic reviews of RCTs have assessed the efficacy of chemotherapy in the presence of adjuvant antioxidant supplementation, and (2) what is known from systematic reviews of RCTs on the potential benefits and harms of adjuvant antioxidant supplementation during chemotherapy for cancer, including relationships

between supplementation and the efficacy of chemotherapy. The results will inform future cancer research activities in this area.

METHODS

This protocol follows the Joanna Briggs Institute (JBI) guidance on protocols for scoping reviews and has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols checklist.^{31 32} The completed scoping review will be reported in accordance with the PRISMA extension for scoping reviews (PRISMA-ScR).³¹

We will follow the Arksey and O'Malley scoping review framework, modified by Levac *et al* and JBI (2017 and 2020),^{33–37} consisting of the following steps:

1. Identifying the research question.
2. Identifying relevant studies.
3. Selecting studies for inclusion.
4. Charting data from included studies.
5. Collating, summarising and reporting the results.
6. Consultation (optional, included).

Step 1: identifying the research question

The areas of uncertainty concerning the use of antioxidant supplements during chemotherapy for cancer have been described above. We will answer the following research questions:

1. Among systematic reviews of RCTs on antioxidant supplements during chemotherapy, to what extent have research questions been posed regarding the effects of antioxidant supplementation on the therapeutic efficacy of chemotherapy?
2. What systematic review evidence exists regarding the use of antioxidant dietary supplements during chemotherapy with respect to:
 - (a) Whether supplementation with specific antioxidants promotes or attenuates the efficacy of chemotherapeutic treatment?
 - (b) Improvement of chemotherapy-related side effects and quality of life?
 - (c) Adverse clinical effects potentially associated with antioxidant supplementation?

Step 2: identifying relevant studies

Types of evidence sources

The types of evidence of interest for this scoping review will be systematic reviews of RCTs. This is the most efficient way to identify comprehensive evaluations of available high-quality evidence. For the purposes of this scoping review, we will define systematic reviews of RCTs as reviews that: (1) have a clear research question; (2) specify eligibility criteria for including studies; (3) seek to comprehensively identify RCTs relevant to the research question; (4) report the critical appraisal (eg, risk of bias) of the included RCTs and (5) present a synthesis, either quantitative or qualitative, of the characteristics and findings of the RCTs.³⁸ We will include systematic

reviews focused on efficacy, effectiveness, or safety. We will include both published and unpublished systematic reviews but will exclude those reported solely as conference abstracts because they generally contain limited information. We will not exclude systematic reviews on the basis of language or date of publication.

While the current approach focuses on evidence from systematic reviews of RCTs, we will not exclude reviews that also seek to identify additional sources of evidence (eg, observational studies). Furthermore, narrative (non-systematic) reviews addressing our outcomes of interest will be excluded initially but may be given secondary consideration dependent on the quantity of systematic reviews identified. Depending on when the last search was run for the systematic reviews we identify and if time permits, we may also search for RCTs published since that date to ensure we have captured the most recently published evidence. While we believe that scoping systematic reviews of RCTs is the most practical first step in characterising the body of evidence on this topic, the flexibility of the scoping approach permits us to extend our investigation beyond systematic reviews, if the results of our initial scoping suggests that this could be useful, and time and resources permit.

Data sources and search for studies

The initial search strategy was developed by an experienced medical information specialist (EFG) in collaboration with the remainder of the review team. The search strategy will be finalised after peer-review by another experienced medical information specialist using the PRESS Peer Review of Electronic Search Strategies.³⁹ Databases searched from inception will include PubMed (Pubmed.gov), Embase (Embase.com), CINAHL (EBSCOhost), Scopus (Scopus.com), Dissertations & Theses Global (ProQuest), and the Cochrane Library (WileyOnline). A combination of keywords and subject headings will be adapted for use according to the specifications of each database. All records retrieved will include at least one antioxidant-related term and a term related to cancer therapies. Examples of antioxidant terms include but are not limited to vitamin C, lycopene and melatonin. Cancer therapy terms include but are not limited to chemotherapy, radiotherapy, antineoplastic and anticancer. The initial search strategy for Embase, which resulted in retrieval of more than 7000 records, is reported in online supplemental appendix 1. In addition to screening records retrieved from searching bibliographic databases, we will search the PROSPERO database of registered systematic reviews, scan the reference lists of included reviews and contact experts in the field to identify additional relevant systematic reviews.

Step 3: selecting studies for inclusion

We will use the Population, Concepts and Context framework to implement eligibility criteria for included studies.³⁷

Population

Participants with cancer who are receiving chemotherapy, radiotherapy or other biological therapy for treatment of cancer will be sought. There will be no restrictions by population characteristics (eg, sex, age, comorbidities, geographic location), or type or stage of cancer.

Concepts

The core intervention of interest is antioxidant dietary supplements concomitant with chemotherapy, radiotherapy or other biological therapy for cancer. We are defining antioxidant dietary supplements as orally consumed products with known ability to prevent cellular damage by reacting with oxidising free radicals.⁴⁰ Antioxidant dietary supplements cover a wide range of substances, including vitamins (eg, vitamin C), minerals (eg, selenium), amino acids (eg, n-acetylcysteine), carotenoids (eg, lycopene), botanicals (eg, polyphenols), and hormones (eg, melatonin). Studies involving intravenous administration of antioxidants in a medical setting (eg, intravenous vitamin C) will be excluded from this scoping review. Oral and intravenous antioxidants are not only processed differently by the body but oral supplements may be taken by patients without direct assistance of medical professionals, and thus, have different clinical and public health implications. Studies involving mushrooms and mushroom products will be excluded because their mechanism is primarily through immunomodulation.⁴¹ Studies involving compound herbal formulas will also be excluded due to the potential for multiple mechanisms of activity that confound the research question. Finally, although many foods such as fruits and vegetables are good sources of antioxidants, whole food dietary interventions (eg, changes in food habits) will also be excluded from this scoping review due to the potential for confounding by non-antioxidant dietary components with known activity against cancer (eg, histone deacetylase-inhibition, DNA methylation).^{42 43}

The core outcomes of interest will consist of (1) therapeutic response to treatment with chemotherapy, radiotherapy or other biological therapy, (2) improvements in chemotherapy-related side effects and quality of life and (3) increases in adverse effects potentially related to antioxidant supplementation. Response to treatment may be measured as mortality or with indicators of morbidity (eg, cancer progression, recurrence). Because it may not be possible to establish whether side effects and other adverse events are more likely related to the cancer treatment or to the supplement use, we will document when adverse events are presented within the reviews as side effects due to either cancer treatment or supplement use, but we will discuss the findings both separately and jointly. We will include outcomes measured at any time point.

Context

The context is cancer treatment with curative intent. The palliative use of chemotherapy, radiotherapy, or other biological therapies will be excluded because a core aspect

of this scoping review is the evaluation of the evidence on antioxidant supplements with regard to possible interference with the curative objectives of treatment. We will not restrict context by date, healthcare setting or country.

Data management

Citations for retrieved records will be downloaded into EndNote X8 and deduplicated. Citations will then be uploaded to Covidence and screened for inclusion in two stages.⁴⁴ At the first stage, two team members will independently screen all records for relevance on the basis of record title and abstract. Prior to title and abstract screening, the team members will carry out a pilot screening of randomly selected records, to ensure that they understand and agree on the initial inclusion criteria. During the title and abstract screening, discrepancies between screeners will regularly be resolved, to prevent development and continuation of differing interpretations of the inclusion criteria.⁴⁵ All records that are deemed to be potentially relevant to the scoping review will progress to full-text screening. Once records are ready for full-text screening, a calibration exercise will be performed in which all team members screen a set of the same randomly selected 25 records against the inclusion and exclusion criteria for the review. The results of this screening will be compared between team members, and any necessary clarifications to the inclusion and exclusion criteria, or modifications of those criteria, will be made and documented in the completed scoping review. After any clarification or modification of the selection criteria, and agreement among the team on the results of the calibration exercise, two team members will independently screen each full text record for inclusion. Discrepancies between screeners will be resolved by discussion or involvement of a third team member. The study citation and brief reason for exclusion will be provided for each excluded record and a flow chart of the screening process will be provided in accordance with PRISMA-ScR.

Step 4: charting data from included studies

Data will be extracted from each included systematic review. These data will include bibliographic information (eg, authors, date of publication, journal of publication), information on the methods (eg, the research question, study enrolment criteria and design), information on results, and the key findings for each included review. See online supplemental appendix 2 for a draft of the data charting form displaying the elements to be extracted from each review. To ensure that the data charting form is comprehensive and clear, we will pilot test the form prior to embarking on the full data extraction. Three members of the author team will use the form to chart data from the same three reviews and compare the extracted information across authors. Anything that is unclear or missing from the data charting form will be discussed and clarifications and modifications will be addressed in collaboration with the full author team until all authors are satisfied that the data charting form is suitable for

extraction of all relevant results. Data extraction will then be carried out for each study by one author and verified by a second author.

Quality assessment

Although critical assessment of the evidence is optional for scoping reviews, previous research has estimated that almost one-quarter of scoping reviews do include a critical appraisal step.⁴⁶ Methodological shortcomings in the conduct of systematic reviews may lead to incomplete and biased findings and reduce our confidence in review conclusions. Because we wish to concentrate on available systematic review evidence in which we can have confidence, we will carry out a critical assessment of the systematic reviews we find.

In addition to extracting key data from all systematic reviews, we will carry out and report an assessment of the conduct of each of the included systematic reviews, using the updated version of A Measurement Tool to Assess Systematic Reviews (AMSTAR-2).⁴⁷ AMSTAR-2 is a critical appraisal tool for systematic review conduct that is based on 16 yes/no questions about the conduct of the review. Four of these questions are considered to be of critical importance. Based on the total number of apparent flaws in review conduct, and whether any of these flaws are of critical importance, the overall confidence in the results of the systematic review is rated at one of four levels: high, moderate, low and critically low. The interpretation of an overall high level of confidence is that 'the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest,' while the interpretation of an overall low level of confidence is that 'the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.'⁴⁷ See online supplemental appendix 3 for the detailed AMSTAR-2 rating criteria, rubric and interpretation for overall assessment of confidence in review results. AMSTAR-2 assessment will be carried out for each study by one author and verified by a second author.

We will highlight the charted data extracted from the reviews judged at moderate or high level of confidence, and we may also extract additional data, using the methods described above to develop and pilot an additional data charting form, to capture further details on the findings of these reviews.

Step 5: collating, summarising and reporting the results

As scoping reviews do not formally synthesise the evidence, this review will provide a descriptive summary of the evidence and map this summary against the objectives of the review. For example, we will identify evidence on individual antioxidants with regard to the questions of interest from each review, indicating the underlying populations (types and stages of cancer, chemotherapeutic regimens) the evidence is sourced from, and the AMSTAR-2 rating of the reviews providing this information. Results will be presented in tables and charts, with

frequencies calculated for data elements when appropriate (eg, the number of reviews on a particular antioxidant). We will conclude by discussing whether we believe there is reliable systematic review evidence on the potential benefits and risks of antioxidant supplements during chemotherapy and suggesting potential avenues for further research.

Step 6: consultation

As described under the data sources and search for studies, we will consult experts in the field to identify additional systematic reviews not found through database searching. We will also consult with stakeholders in cancer treatment (eg, clinicians, patients) to inform the elements to be included in the data charting. Through consultation with these stakeholders we will ensure that relevant characteristics of the populations, interventions and outcomes are captured and important gaps in the evidence may be identified. In keeping with best practices in community-engaged research, we will disseminate the findings of the review to community stakeholders and patients. Community engagement will also be used to inform recommendations for future research based on the review.

Ethics and dissemination

This scoping review does not require ethics approval as it is a secondary review of the literature. Based on the results of this review, we will disseminate our findings of both reliable evidence (where it exists) or a gap in reliable evidence and a need for additional research. This dissemination will be carried out through presentations at relevant conferences and publication in a peer-reviewed open-access journal. As mentioned above, we will also disseminate the findings to community and patient stakeholders. We will ask these stakeholders to join with clinical and research stakeholders to identify the best ways to address any critical existing gaps in the evidence (eg, a focused systematic review, further randomised trials) and prioritise the next steps.

Patient and public involvement

As described above, we will consult with patients to inform the development of data charting. We will also engage with patients, clinicians and other stakeholders to disseminate summaries of the review findings in appropriate formats and venues. Finally, we will involve patients and the public in developing and prioritising future research activities based on the findings of this project.

DISCUSSION

The impact of oral antioxidant supplementation on the effectiveness of curative therapies for cancer is of critical importance for patients who use these supplements to reduce treatment side effects and improve quality of life. Because oral antioxidant supplements are used to mitigate the side effects of cancer therapies, it is expected that

antioxidant supplementation will lead to better tolerance for therapy, and thus to improved outcomes for patients. However, if antioxidant supplements interfere with the cytotoxic effects of chemotherapy, the cancer treatment may become less effective and lead to worse rather than better patient outcomes. Recent observational data has suggested that antioxidant supplements during and after cancer treatment are associated with an increased risk of cancer recurrence, raising concern about the place of antioxidant supplements during treatment for cancer.²²

Because we are unsure to what extent the relationship between antioxidant supplements and the effectiveness of cancer therapies has been assessed in the research literature, we are conducting a scoping review to explore this. We are focusing our exploration on systematic reviews of randomised trials because they are summaries of the highest level of evidence on the effects of interventions. We believe that most systematic reviews in this area have focused on the effectiveness of supplements in ameliorating side effects and improving quality of life, but that these reviews may incorporate research questions on the effectiveness of chemotherapy in the presence of antioxidant supplementation. Identifying where these research questions have been asked, and with what results, will be a first step in identifying gaps in the evidence base and developing a plan of research to ensure that the relationship between antioxidant supplements and the effectiveness of cancer therapies is understood.

Implications

We will use the findings from this review to develop to develop future research priorities and initiatives to help fill remaining critical gaps in the current literature and contribute to key next steps. We will then work with patients and clinicians to prioritise evidence needs, and consult with clinical, research and patient stakeholders on the most appropriate methods (eg, new or updated systematic reviews vs additional primary studies) for addressing these gaps. Near the end of the scoping review process, when we are able to characterise the extent of available reliable evidence, we will begin to formalise partners and processes for these next steps. Our target date for completion of this scoping review is the second half of 2021.

Potential limitations and mitigation strategies

Though scoping the entirety of observational and clinical evidence on this topic is beyond the scope of the current initiative, we believe that focusing on systematic reviews is the most efficient first step in characterising the weight of the current research evidence. We are also uncertain about the volume of review evidence, which makes it difficult to plan ahead for either superficial or very detailed data extraction. The iterative nature of scoping reviews allows us to be flexible in response to the quantity and quality of the evidence and prioritise summarising evidence according to characteristics such as review quality or recency. Regular engagement with clinical

and research partners during the conduct of the scoping review will allow us to modify our methods in such a way as to develop summaries of review evidence that are maximally relevant and useful to inform practice. We plan to ensure the transparency of our methods by devoting a section of the final publication to changes from and refinements to this protocol, together with the rationale for any revisions. At the conclusion of this project, we will develop a plan, including potential future funding applications, for the next steps in a research agenda to inform decisions by patients and providers on the potential benefits or harms of dietary antioxidant supplementation during chemotherapy.

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Acknowledgements We thank Becky Skidmore, MLS (Senior Information Specialist consultant, Ottawa, ON) for her peer review of the Embase search strategy. We would also like to acknowledge Drs. Brian Hutton and Chantelle Garritty (Knowledge Synthesis Group, Ottawa Hospital Research Institute) for their methodological input and guidance in developing this protocol.

Contributors AE, CK and CD jointly conceived the study and developed the research questions. LSW proposed the scoping review methodology and developed the protocol with IM and SS. EFG developed the search strategy. LSW drafted the manuscript. All authors revised the manuscript and approved the final text. LSW is guarantor of the review.

Funding LSW is supported by the National Center for Complementary and Integrative Health of the National Institutes of Health (R24 AT001293). AE and CK are supported by the University of Maryland Greenebaum Comprehensive Cancer Center Support Grant (P30CA134274) and the State of Maryland's Cigarette Restitution Funds (N/A).

Disclaimer The funders had no role in developing the protocol.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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