Living Evidence Synthesis Protocol
A Unidade de Asesoramento Científico-técnico (AVALIA-T)

TITLE: Effectiveness and safety of deep brain stimulation in severe and treatment-resistant obsessive-compulsive disorder

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ABSTRACT

Objective To provide a rigorous and updated synthesis of the evidence available on the role of Deep Brain Stimulation for the treatment of patients with severe and treatment-resistant obsessive-compulsive disorder.

Methods

Design

This is a Living Evidence synthesis, which will start with a baseline synthesis report of the effects of the Deep Brain Stimulation on the severity of symptoms, psychological, social, and professional functioning, quality of life, cognitive functioning, and adverse events in patients with severe and treatment-resistant obsessive-compulsive disorder. Based on its conclusions, we will set up the living evidence approach, and the evidence monitoring will begin.

Evidence identification

The evidence identification, screening, and selection will be supported by technological enablers developed by the Epistemonikos Foundation and included in its "Living Overview of Evidence (L.OVE) platform. The team maintaining the L·OVE platform will devise the literature search aimed to identify systematic reviews, randomized clinical trials, and non-randomized studies (e.g. cohort and case-control studies). An automated living search will be performed in all databases following high-standard procedures. The results of the literature searches will be automatically incorporated into the L·OVE platform where two reviewers will then screen the titles and abstracts of classified references against selection criteria. We will continuously monitor the evidence by performing daily searches and a monthly screening of the retrieved references. To support the screening and monitoring, we will use an automatic classifier based on artificial intelligence (AI) algorithm and other technologies, that excludes references with a low probability of being relevant when appropriate. Additionally, every three months we will manually search for ongoing studies in the International Clinical Trials Registry Platform trial registries.

Study selection and data extraction

Two reviewers will independently screen each study for eligibility, extract data, and assess its methodological quality using appropriate tools.

For the baseline synthesis report, we will include systematic reviews, randomized and non-randomized studies evaluating the effect of Deep Brain Stimulation in comparison to sham stimulation, treatment as usual, or ablative surgery in patients with severe and refractory obsessive-compulsive disorder.

We will perform meta-analyses of the study's results when pertinent. We will assess the certainty of the evidence for each outcome by applying the GRADE approach. These findings will be used to refine the parameters for setting up the living evidence approach.

Living evidence approach

We will continuously monitor the evidence for 12 months. If a new study is identified as eligible, we will follow the same procedures described above prior to updating the metanalysis of the outcomes reported. We will follow a systematic and reproducible process for taking decisions related to incorporating or postponing the incorporation of new studies, updating of conclusions or recommendations this synthesis informs and for periodically reviewing the question to define its

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continuation, changes, or withdrawal of the living mode. The question will withdraw according to predefined specific criteria.

Results

For the baseline synthesis and the subsequent synthesis updates, the estimates for all outcomes evaluated will be presented in the GRADE summary of findings tables. Regular updates will include key messages on changes in the evidence synthesis conclusions. We will resubmit new complete updates every time the conclusions change or whenever there are substantial updates for the main outcomes of interest.

Keywords: deep brain stimulation (DBS), neuromodulation, obsessive-compulsive disorder.

LIVING EVIDENCE TO INFORM HEALTH DECISIONS

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Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by unwanted obsessions and/or compulsions. OCD affects 1–3% of the general population making it a common mental health disorder (1). It is a disease with a significant impact on quality of life, can lead to disability and a significant burden on family and caregivers (1-3).

Serotonin reuptake inhibitors (SRI: selective serotonin reuptake inhibitors, SSRIs; clomipramine) or/and cognitive behavioral therapy (CBT) involving exposure and response prevention (ERP), represent the first-line treatment for OCD. Next-step treatment strategies may include continuing with the chosen SRI for an extended period of time, switching to another SRI, augmenting the SRI with a second-generation antipsychotic agent or raising the dose of SRI to the highest tolerated level (4-8).

A relevant number of patients (10–40%) do not respond to any available therapy and suffer from severe, persistent symptoms and dysfunction (5). For this severe and refractory patient group, ablative neurosurgery and deep brain stimulation (DBS) remain modalities to be considered. These procedures are usually delivered as an adjunct to existing pharmacological treatments, and CBT is frequently also administered, either during the acute treatment phase or follow-up. DBS is considered an experimental treatment but has an FDA 'humanitarian device exemption' for severe refractory OCD. However, there is as yet insufficient evidence to determine which technique to choose at an individual patient level (5).

The aim of this review is to synthesize the evidence available to inform decision-making on the use of deep brain stimulation in patients with obsessive-compulsive disorder attending the Galician Health Service. Because it is considered an emerging technology, it is expected new evidence will arise within the following months, this justifies setting up a living evidence synthesis approach. Therefore, this systematic review has been included as part of the Living Evidence to Inform Health Decisions Program that provides training, support and tools for the living evidence process (9).

Methods

Design

This is a Living Evidence synthesis, which will start with a baseline synthesis report of the effects of the Deep Brain Stimulation on the severity of symptoms, psychological, social, and professional functioning, quality of life, cognitive functioning, and adverse events in patients with severe and treatment-resistant obsessive-compulsive disorder. Based on its conclusions, we will set up the living evidence approach, and the evidence monitoring will begin.

This LES design and planning comply with the Methods for Planning and Reporting Living Evidence Synthesis checklist proposed by *Bendersky et al*. (10). This manuscript complies with the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guidelines (11) (see Appendix 1).

Evidence Identification

The evidence identification, screening, and selection will be supported by the technological enablers developed by the Epistemonikos Foundation and included in its "Living Overview of Evidence (L.OVE)

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platform (12). The team maintaining the L·OVE platform devised the literature Boolean search aimed to identify systematic reviews, randomized clinical trials, and non-randomized studies (i.e cohort and case-control studies) (see table 1).

An automated living search will be performed in the multiple information sources and databases maintaining the Epistemonikos database and following its procedures (13) (see Appendix 2. for a detailed description of sources and procedures used by the Epistemonikos database).

The results of the literature searches will be automatically incorporated (automated retrieval) into the L·OVE platform, specifically deployed in this question *[Deep brain stimulation for treatment-resistant obsessive-compulsive disorder*] where automated classifiers will exclude references with a low probability of being relevant for this question. The results of the literature will be de-duplicated by an algorithm comparing unique identifiers (database ID, DOI, trial registry ID), and citation details (i.e. author names, journal, year of publication, volume, number, pages, article title, and article abstract) before incorporated into the L·OVE platform.

Search strategies

Table 1 presents the searches defined by the type of sources. No date, language, study design, publication status, or language restriction will be applied to the searches.

Table 1. Boolean Searches by source

Source	Epistemonikos Database
Boolean Strategy	((obsess* OR compulsi* OR OCD*) AND ((("deep brain" OR "deep-brain") AND (stimulat* OR neurostimulation*)) OR DBS) AND ("critical review" OR "electronic search" OR "evidence-based analysis" OR "evidence-based review" OR "literature search" OR "meta analysis" OR "meta synthesis" OR "meta-analyse" OR "meta-analytic review" OR "meta-study" OR "meta-synthesis" OR "metaanalysis" OR "metasynthesis" OR "meta-analysis" OR "pooled effect" OR "random-effects model" OR "systematic quantitative review" OR "systematically searched" OR "systemic review" OR (review AND randomized) OR (systematic AND review) OR MEDLINE OR "literature review" OR PubMed))
Type of studies	Systematic reviews
Date of coverage	From inception to 27/04/2023

Source	Epistemonikos Database, Pubmed
Boolean Strategy	((obsess* OR compulsi* OR OCD*) AND ((("deep brain" OR "deep-brain") AND (stimulat* OR neurostimulation*)) OR DBS) AND (randomi* OR RCT OR placebo* OR trial OR "controlled-trial" OR randomly*))
Type of studies	Randomized controlled trials

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Date of coverage	From inception to 10/10/2023

Source	Epistemonikos Database, Pubmed
Boolean Strategy	((obsess* OR compulsi* OR OCD*) AND (((("deep brain" OR "deep-brain") AND (stimulat* OR neurostimulation*)) OR DBS) AND (((((("follow up" OR "follow-up" OR followup*) OR observation* OR epidemiologic*) AND (stud* OR evaluation*)) OR retrospective* OR prospective* OR longitudinal* OR observational* OR "non-randomized" OR "non-randomised" OR "non randomized" OR "non randomised" OR nonrandomi*) OR ("regression-discontinuity" OR (regression AND discontinuity) OR kink) OR (mendelian AND randomi*) OR (multivaria* OR multinomial* OR logistic* OR regression OR cox OR stepwise* OR adjust* OR independent* OR (receiver* AND operat*) OR AUC OR ROC) OR (focus OR "focus-group" OR qualitative* OR interview* OR "grounded theory" OR "mixed-methods" OR "mixed methods" OR semistructured* OR "semi-structured" OR informant OR ("open-ended" AND question*) OR nvivo OR verbatim) OR ((test-negative OR "test negative") AND (study OR design OR controls OR "case-control")) OR (nested*) OR ((quasiexperiment* OR "quasi experimental" OR "quasi-experimental") OR "pretest-posttest" OR pretest* OR posttest* OR "pre-post" OR "pre-post tests" OR "post test" OR "post tests" OR pretest OR pretests OR "pre test" OR "pre tests" OR (repeated AND measure*) OR "time series" OR "time-series" OR "matched controls" OR beforeafter OR "before-after" OR "before after") OR ("interrupted-time-series" OR (interrupted AND time AND series*) OR ((ITS* OR "time-series" OR "time series") AND (study OR studies OR analys* OR design*)) OR (trend AND (time OR analys*)) OR ((segmented* OR piecewise* OR "broken-stick" OR "broken stick") AND regression*)) OR (extension AND (rct OR randomi* OR trial OR posttrial* OR "post-trial"))))
Type of studies	Primary studies with a design different from a randomized study.
Date of coverage	From inception to *

Selection criteria

Types of participants

We will include studies assessing participants with severe and refractory Obsessive-Compulsive Disorder (OCD) as defined by the authors of the trials. Whenever we find substantial clinical heterogeneity on how the condition was defined, we plan to explore it using a sensitivity analysis.

Type of interventions

The intervention of interest will be deep brain stimulation. We will not restrict our criteria to any anatomical target, electrode design or stimulation parameters.

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The comparisons of interest will be sham stimulation, treatment as usual, waiting list control or ablative surgery.

Type of outcomes

We will not use the outcomes as inclusion criteria during the selection process. Any article meeting all the criteria except for the outcome criterion will be preliminarily included and assessed in full text. The main outcomes of interest are:

- *Severity of symptoms*, assessed with Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) or Clinical Global Impression (CGI);
- *Psychological, social and professional functioning*, assessed with Global Assessment of Functioning (GAF);
- *Quality of life* assessed with a validated tool such as WHOQOL, SF-36, EurQol;
- *Effects on cognitive functioning*, assessed with a validated method such as Cambridge Neuropsychological Test Automated Battery (CANTAB), the Wechsler Adult Intelligence Scale – III (WAIS-III), and The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- *OCD patient reported values and preferences*
- *Adverse events* (related to surgical intervention, related to implantable devices; related to stimulation).

Types of studies

For the baseline synthesis we will include systematic reviews and primary studies not included in the SR (new studies). During the living mode of this question, we will consider non-randomized studies for interventions, randomized controlled trials, non-comparative observational studies that emerged as new primary studies. We will exclude information from studies evaluating the effects on animal models or in vitro conditions.

Selection of studies

For the baseline report, we will screen and select eligible studies identified by searches until July 30th, 2023. From then, we will continuously monitor the evidence and perform monthly screening of the references identified and retrieved (see Living evidence synthesis considerations).

Two researchers (YTP and PGS) will independently screen the titles and abstracts yielded by the search against the inclusion criteria using the L·OVE platform screening tool "Collaboratron" (12). All included studies references will be included in Endnote for reference management. We will obtain the full reports for all titles that meet the inclusion criteria or required further analysis to decide about their inclusion.

We will record the reasons for excluding studies at any stage of the search and outline the study selection process in a PRISMA flow diagram adapted for the purpose of living evidence synthesis by the LE-IHD program (9).

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Extraction and management of data

Two reviewers (YTP and PGS) will independently extract data from each included study using a standardized form. We will collect information on the study design, setting, participant characteristics (including disease severity and age), study eligibility criteria; administered intervention; the outcomes assessed and the time they were measured; the source of funding of the study; the conflicts of interest disclosed by the investigators; and the variables need for the risk of bias assessment.

We will resolve disagreements by discussion, and one arbiter will adjudicate unresolved disagreements.

Risk of bias assessment

We will assess the risk of bias of the whole evidence we identify in searches using appropriate instruments according to the type of study; AMSTAR II tool for SRs, RoB 2 tool for RCTs, ROBINS for NRS, Institute of Health Economic (IHE) - case series checklist (14-16). Two reviewers (JPR and MCMR) will independently assess all the included studies. Discrepancies between review authors will be resolved by discussion to reach a consensus. If necessary, a third review author will be consulted to achieve a decision.

Measures of treatment effect

For dichotomous outcomes, we will express the estimate of treatment effect as risk ratios (RR) or odds ratios (OR) along with 95% confidence intervals (CI). For continuous outcomes, we will use mean difference and standard deviation (SD), and 95% CI to summarize the data. Whenever continuous outcomes are measured using different scales, the treatment effect will be expressed as a standardized mean difference (SMD) with 95% CI. Table 2 presents detailed measures we plan to use in baseline and update reports for submersing each outcome of interest results.

Table 2. Effect measure to be applied for each outcome of interest

Outcome	**Definition/Time frame**	**Effect measure**
Safety variables	Data of adverse events (related to surgical intervention, related to implantable devices; related to stimulation). Time frame not defined a priori.	Risk ratio or Odds ratio
Efficacy variables (Continuous outcomes)	- Severity of symptoms, assessed with Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) or Clinical Global Impression (CGI); - Psychological, social and professional functioning, assessed with Global Assessment of	SMD of the changes from base line using the appropriate rate and score defined by each scale

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	Functioning (GAF); - Quality of life assessed with validated tool such as WHOQOL, SF-36, EurQol; - Effects on cognitive functioning, assessed with a validated method such as Cambridge Neuropsychological Test Automated Battery (CANTAB), the Wechsler Adult Intelligence Scale – III (WAIS-III), and The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS);	
Efficacy variables (qualitative)	Patient values and preferences	Thematic analysis

For RCTs and NRSs, we consider the following factors as baseline potential confounders [e.g. age; comorbidities; co-interventions; and severity].

For outcomes reported by more than one trial, as part of the baseline synthesis, we will conduct a meta-analysis and/or update the existing meta-analysis of studies clinically homogeneous to estimate the intervention effect. We will initially use a fixed-effect model to evaluate the statistical heterogeneity among included studies (I^2 statistics). In the presence of unexplained heterogeneity (I^2> 70%), we will not to meta-analyze them and report the evidence synthesis narratively. If the I^2 is below 90%, we will perform a meta-analysis following a fixed-effects or a random-effects model, whichever was pertinent. All analysis will be run in RevMan 5 (17). If data is insufficient to calculate an effect estimate, we will present a narrative evidence synthesis. Statistical considerations on the meta-analysis updating process during the living mode of this question are discussed in the "Living synthesis considerations" section.

Subgroup and sensitivity analysis

We plan to perform subgroup analysis according to anatomical target and stimulation parameters. In case we identify significant differences between subgroups (test for interaction <0.05), we will report the results of individual subgroups separately.

We will perform sensitivity analysis when substantial differences in the risk of bias of the studies and in the type of intervention (taking into account the stimulation parameters or the therapeutic target) are detected.

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Assessment of certainty of evidence

We will assess the certainty of the evidence for all outcomes using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE Working Group), across the domains of risk of bias, consistency, directness, precision and reporting bias. Certainty will be judged as high, moderate, low or very low. We will present results in a Summary of Findings (SoF) table for the main comparisons and for the planned subgroups resulting from the update (18).

The baseline synthesis results for the main comparisons and outcomes will be presented as a GRADE evidence profile; one profile will be developed for each subgroup of interest if pertinent using GRADEpro-GDT. The updated results during the living mode of this question will be presented in GRADE 'Summary of Findings' tables for the total and for subgroups when apply (19, 20).

Living evidence synthesis considerations

We plan to maintain this question in the "living mode" for 12 months as part of the LE-IHD program. After this period, we will assess the relevance of continuing the living evidence approach for this question taking into account the priority for decision-making, the evidence monitoring results and the availability of resources.

The *LE-IHD framework-based tool* (21) will be used to support the whole monitoring process. This toll allows for the register of the evidence surveillance results as well as guide the decisions to be taken each time new eligible evidence is identified and selected. Results of evidence identification and selection every time the new searches results are screened, will be collected and keep as part of the study records, to be used for updating the Living PRISMA flowchart. We will follow a systematic and reproducible process for taking decisions related to incorporating or postponing the incorporation of new studies, updating of conclusions or recommendations this synthesis informs and for periodically reviewing the question to define its continuation, changes, or withdrawal of the living mode. The question will withdraw according to predefined specific criteria as is presented below.

The evidence identified and retrieved to the L·OVE of this question *[Deep brain stimulation for treatment-resistant obsessive-compulsive disorder*], will be screened in a monthly basis by assessing the title and abstract. To early identify the new arising evidence, we will setting-up weekly alerts in the L·OVE of this question. One reviewer will be in charge of screening evidence identified and retrieved by searches or in the alerts; if a potentially eligible study is found, two reviewers (YTP and PGS) will confirm its eligibility by reading the full text. Any new eligible study will follow the same procedures described above for the data extraction, and quality assessment, prior to updating the metanalysis of the outcomes it is reporting. See appendix 3 for detailed evidence surveillance tasks.

The data synthesis will be updated immediately when the new eligible study is likely to impact the effect estimate of main outcomes taking into account the possible impact on the magnitude of the effect, the direction of the effect, and/or the confidence in the results, otherwise its inclusion on the synthesis will be postpone until a new study arise or to be updated in the fixed term (each 6 months). If new heterogeneity is detected when updating the meta-analysis (i.e., increase the heterogeneity previously identified or new heterogeneity arises where it was previously

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undetected), we will explore its potential sources by reviewing the new studies against previously included studies to identify reasons that may explain inconsistent results. In the presence of unexplained heterogeneity (I^2> 70%) we will follow the same procedures described earlier for the "Measures of treatment effect".

Two authors (YTP and PGS / JPR and MCMR) with expertise in applying the GRADE approach will assess the certainty of evidence every time new studies are incorporated into the metanalysis for the outcomes of interest. Special attention will be paid to changes in the certainty of evidence assessment results which will drive further decisions related to the monitoring parameters and to the update of the recommendations this evidence synthesis informs.

When the new eligible studies do not report on one or more outcomes of interest, the evidence synthesis (i.e. metanalysis) will remain as reported in the baseline synthesis.

Following current guidance for LES, we will re-assess the search strategy, the research question, the PICO components, the outcome measures as well as the living parameters, every six months regardless of whether or not new eligible studies arise (10). We will apply the following criteria for transitioning out the question from the "living mode": a) A reasonable level of certainty has been reached with the existing evidence (i.e., moderate or high certainty evidence - GRADE, therefore new evidence allows the generation of valid conclusions about the outcomes of interest; b) The research question is no longer a priority for decision-making; c) Research that might impact the conclusions of the review is no longer emerging (e.g., based on trials registers); d) Necessary resources are no longer available (e.g., lack of funding) (10).

Results

Each report of this synthesis (baseline and updates) will include the total of studies identified from the initial baseline synthesis up to the given time of the update. The study identification and selection will be summarized by a PRISMA Flowchart specially designed for reporting the living evidence synthesis results and adopted by the LE-IHD program (9). Special attention will be paid to ongoing studies through updates.

For the baseline synthesis and the subsequent synthesis updates, the estimates for all outcomes evaluated will be presented in the GRADE summary of findings tables. Each update will describe the main changes in the effect estimates obtained from the synthesis updates, including forest plots to present meta-analysis results for each outcome when pertinent. Regular updates will include key messages on changes in the evidence synthesis conclusions and in the certainty of evidence assessment. We will resubmit new complete updates every time the conclusions change or whenever there are substantial updates for the main outcomes of interest.

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We would also like to acknowledge the contribution of the Epistemonikos Foundation team, contracted to design and conduct the searches, and provide technological support for the evidence identification and classification in the L.OVE platform.

Roles and contributions

YTP, PGS, JPR and MCMR drafted the protocol. María Ximena Rojas provided methodological advice for the definition of the living evidence approach to be followed in this project. Maria Soledad Isern, Patricia Gavín and María Ximena Rojas, reviewed the final version of the manuscript for approval and made important contributions. The corresponding author is the guarantor and declares that all authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

Competing interests

All authors declare no financial relationships with any organization that might have a real or perceived interest in this work. There are no other relationships or activities that might have influenced the submitted work.

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The funding institution had no role in designing the study, in drafting, reviewing, and approving the protocol, or in the decision to submit it for publication.

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Appendix 1: PRISMA checklist [1]

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6-7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the	Page 9-10

[1] *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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		methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 9-10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 11-12
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 11-12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 11-12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 11-12
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 10-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 11
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	N/A
	16b	Cite studies that might appear to meet the inclusion	N/A

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		criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	N/A
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	N/A
	23b	Discuss any limitations of the evidence included in the review.	N/A
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	N/A
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A

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	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 2
Competing interests	26	Declare any competing interests of review authors.	Page 2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

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Appendix 2: Epistemonikos database procedures and the L.OVE platform

Epistemonikos is a database of health evidence. It is the largest source of systematic reviews and a large source of trials and other types of scientific evidence.

Epistemonikos is maintained by searches in multiple information sources and databases, including Cochrane Database of Systematic Reviews, MEDLINE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library [2].

Additionally, Epistemonikos include systematic reviews identified in overviews of reviews, guidelines, scoping reviews, or other types of broad syntheses and primary studies identified in systematic reviews using a linker function.

- Run cross-citation searches in Google Scholar.
- Evaluate potentially eligible reviews and trials sent by users. Epistemnikos do not restrict searches by language, publication status, or publication date (i.e. databases have been searched from inception).

The Epistemonikos Foundation has developed the Living OVerview of Evidence (L.OVE), a platform system that maps and organizes the scientific evidence to different research questions. To retrieve the relevant evidence, the L.OVE platform automatically search in Epistemonikos database using a pre-developed boolean search strategy for each PICO component. Searches are supported by automatic classifiers based on artificial intelligence (AI) algorithms and other technologies [3].

For each question in PICO format in the L.OVE platform, the literature search is devised by the team maintaining the L·OVE platform using the following approach:

- Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology to the corpus of documents available in Epistemonikos Database.
- Discussion of terms with content and methods experts to identify relevant, irrelevant, and missing terms.
- Creation of a sensitive boolean strategy encompassing all the relevant terms
- Iterative analysis of articles missed by the boolean strategy, and refinement of the strategy accordingly.
- Application of validated filters to identify clinical trials and non-randomized studies in the MEDLINE database.

The information matching the search strategy and/or is detected by the automatic classifiers, is sent in real-time to the screening tool “Collaboratron”, of the L·OVE platform where researchers can

[2] Rada G, Pérez D, Araya-Quintanilla F, et al. Epistemonikos: a comprehensive database of systematic reviews for health decision-making. BMC Med Res Methodol. 2020;20(1):286. Published 2020 Nov 30. doi:10.1186/s12874-020-01157-x

[3] Andres Carvallo, Denis Parra, Gabriel Rada, Daniel Perez, Juan Ignacio Vasquez, Camilo Vergara (2020). Neural language models for text classification in evidence-based medicine. arXiv preprint . https://doi.org/10.48550/arXiv.2012.00584

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screen and select the evidence for its question. From the Collaboratron tool, screeners can access the full text article in Epistemonikos to confirm its eligibility.

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Appendix 3. Evidence surveillance tasks

	Who in the organization will be in charge	Frequency	This task will be supported by technological tools (enablers) and/or artificial intelligence
Searching in bibliographic databases	Epistemonikos team	Living search	Yes
Searching in trial registries	Organization team supported by the Living Evidence team	Every three months	No
De-duplication of references resulting from the search	Epistemonikos team	Continuosly	Yes
Generic classification of papers retrieved	Epistemonikos team	Every month	Yes
Screening titles and abstracts for eligibility	YTP; PGS; JPR; MCMR	Every month	No
Read the full text articles to confirm eligibility	YTP; PGS; JPR; MCMR	Once it is selected for inclusion	No

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