Comparative Clinical Effectiveness of Elagolix for Endometriosis

Research Protocol

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Institute for Clinical and Economic Review

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Background, Objectives, and Research Questions

Background

Endometriosis is a chronic gynecological condition characterized by the attachment and proliferation of endometrial cells outside of the uterus.[1] It affects 6-10% of women of reproductive age, with peak prevalence between 25 to 35 years of age.[2,3] Common symptoms of endometriosis include painful menstrual periods, non-menstrual pelvic pain, pain during intercourse (dyspareunia) and infertility.[1] Pain associated with endometriosis can decrease a patient's quality of life by increasing depressive symptoms, reducing sexual satisfaction, and disrupting personal relations.[4,5] It can also affect ability to work,[6] and results in estimated health care costs of over $10,000 per patient per year in the United States and over $15,000 per patient per year in lost work productivity.[7,8]

Endometriosis is a cause of pelvic pain identified during diagnostic evaluation in up to 60% of teenage girls and women, and 50% of women with infertility.[3] A number of other conditions of the reproductive tract can cause pelvic pain as well as other non-gynecological disorders. Physical examination findings, blood tests and non-invasive imaging can help exclude other causes of pelvic pain, but are not accurate enough to establish a definitive diagnosis of endometriosis in most cases.[9] As such, the diagnosis of endometriosis is often delayed in women and contributes to the burden of pain, infertility, and quality of life.[4] Direct visualization at surgery is the definitive way to diagnose and stage endometriosis, but the extent of disease observed often does not correlate with the intensity or character of reported pain.[10] Nevertheless, empirical therapy is often initiated without surgery after other conditions are excluded, but without a definitive diagnosis of endometriosis. In addition to direct visualization at the time of surgery, removal of implants (endometrial lesions found in the ovaries, Fallopian tubes, or the peritoneum) provides pathological confirmation and symptom relief.

Treatment recommendations have been developed by the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine.[11,12] A range of pharmacologic and surgical treatments are available and have been shown to decrease patient symptoms. Initial treatment includes a trial of nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapy, typically combination oral contraceptives (OCPs).[13] Combined estrogen-progestin OCPs given on a continuous basis are favored because they are well-tolerated, provide birth control, and can be used long-term. In addition to OCPs, progestins alone are used and can be administered orally, or via depot injections, implants or levonorgestrel-releasing intrauterine devices (IUDs). Gonadotropin-releasing hormone [GnRH] agonists work as hormonal therapy by reversibly suppressing ovarian estrogen productive to levels seen in women whose ovaries are removed.

All hormonal therapies studied (OCPs, progestins and GnRH agonists) have shown similar benefits, but have major differences in side effects and costs, and only some are FDA-approved specifically for endometriosis.[14,15] In addition, GnRH agonists are not considered first-line therapy and are not recommended for adolescents because of concerns about long-term bone loss. If a GnRH agonist is used, estrogen and/or progestin add-back therapy is commonly recommended.[16] In addition to GnRH agonists and certain progestins, danazol is also FDA-approved for treatment of endometriosis but is rarely used in clinical practice for this indication. Finally, aromatase inhibitors, which are approved for breast cancer in women and gynecomastia in men, have been used off-label to treat endometriosis.[17]

Surgery can be a first-line therapy, often at the time of a diagnostic laparoscopy, or initiated after an insufficient response to medical therapy.[18,19] Hormonal therapy after surgery may prolong treatment benefit in some patients, especially those with more severe symptoms and findings. Though women with endometriosis have higher rates of infertility, pregnancy often results in decreased symptoms, and symptoms typically disappear permanently with the onset of menopause.[20] For those with moderate or severe symptoms, pain management may require repeated courses of hormonal or surgical treatments until menopause,[21] and chronic pain due to endometriosis is a cause of chronic opioid use with its attendant risks.[22] Definitive therapy with removal of the uterus and both ovaries (hysterectomy and bilateral salpingo-oophorectomy) is reserved for women with symptoms that are not controlled with other treatments and who have completed childbearing.

There are currently three GnRH agonists approved by the FDA for the treatment of pelvic pain caused by endometriosis: leuprolide (Eligard®, Tolmar Pharmaceuticals; Lupron Depot®, AbbVie), nafarelin (Synarel®, Pfizer), and goserelin (Zoladex®, TerSera Therapeutics/AstraZeneca). These agents have been in clinical use for over 25 years and have well described limitations. First, during the first 10-14 days of treatment with these agents, binding to the GnRH receptor stimulates the pituitary gland to release hormones (luteinizing hormone [LH] and follicle stimulating hormone [FSH]) that will increase symptoms. This necessitates the use of a OCP or a progestin, commonly norethindrone, at the same time to prevent worsening symptoms. With prolonged, continuous exposure to these agents, pituitary secretion of hormones is decreased due to down-regulation of the GnRH receptor and pituitary desensitization. The decrease in these hormone levels lead to suppression of production of estradiol and progesterone by the ovaries. The low estrogen state induced by GnRH agonists lead to the main side effects including hot flashes, vaginal dryness, decreased libido, mood swing and headache. In addition, prolonged use of GnRH agonists can lead to decreased bone density (osteoporosis). Therefore, these medicines are approved for only up to six months of continuous use. The use of add-back hormonal therapy is commonly given to decrease symptoms and can permit longer-term use.

A new agent, elagolix (investigational, AbbVie), is under FDA review for patients with endometriosis. It is a GnRH antagonist, and unlike GnRH agonists, it does not cause an initial surge in LH and FSH, suppresses ovarian hormone levels immediately rather than taking 7-14 days, and the degree of ovarian suppression is dose dependent. Moreover, it is an oral medication, unlike GnRH agonists that are given by injection or intranasally.

Objectives

The scope of this project was previously available for public comment and was revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of elagolix for patients with endometriosis. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence (including a network meta-analysis if sufficient data are available) and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan for details on the proposed methodology and model structure that will be used for the economic evaluation.

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients, and patient groups:

- In women with endometriosis, what is the comparative clinical efficacy, safety, and effectiveness of elagolix versus placebo and other medical therapies (GnRH agonists, hormonal therapies, aromatase inhibitors) on outcomes such as dysmenorrhea, non-menstrual pelvic pain, dyspareunia, pain medication usage, and quality of life?

Study Eligibility Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design) elements.

Populations

The population of focus for this review is adult premenopausal women with symptomatic endometriosis.

Interventions

The intervention of interest for this review is the GnRH antagonist elagolix. Intervention(s) of interest were developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include.

Comparators

Data permitting, we intend to compare elagolix to GnRH agonists (with or without estrogen and/or progestin add-back therapy), hormonal contraceptives, aromatase inhibitors, and placebo.

Outcomes

This review will examine key clinical outcomes associated with endometriosis. The anticipated outcomes of interest and key harms are described in the table below. We will seek evidence on patient reported outcomes to enrich the available clinical data. Initial discussion with patients, patient groups, and clinicians indicate that clinical trials may lack robust information on the broader impact that endometriosis can have on the lives of women and their families.

Outcomes and key harms of interest from clinical trials will include:

Table 1. Key Outcomes and Harms

Outcomes	Key Harms
Dysmenorrhea	Amenorrhea
Dyspareunia	Arthralgia
Healthcare utilization	Decreased libido
Non-menstrual pelvic pain	Headache
Productivity	Hot flashes
Quality of life	Insomnia
Surgery after medical treatment	Lipid profile changes
Use of opioids and other analgesic medicines	Mental health outcomes
	Night sweats
	Pregnancy outcomes (e.g. congenital malformation)
	Reduced bone mineral density
	Vaginal dryness

Evidence tables will be developed for each selected study and results will be summarized in a qualitative fashion; if feasible, random- or fixed-effects meta-analysis will be used to quantitatively summarize outcomes for the therapies of interest. In addition, we will consider network meta-analysis to combine direct and indirect evidence of effectiveness if available data permit.

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least three months duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Study Eligibility Criteria

All eligible randomized controlled trials (RCTs) will be included regardless of sample size. Relevant existing systematic reviews will be evaluated for pertinence to our research questions (and PICOTS) and methodological quality. We will primarily use the existing systematic reviews for their reference lists, but we will also compare them to our study- and review-level findings as a check for consistency.

Single-group and non-randomized comparative studies will be included based on criteria that will be finalized after the eligible RCTs have been assessed and the gaps in the evidence base are known. A limited number of single-group studies will be included to address outcomes in populations not adequately covered by the randomized studies. We will also include all observational, open-label extensions of included RCTs, regardless of sample size or follow-up duration.

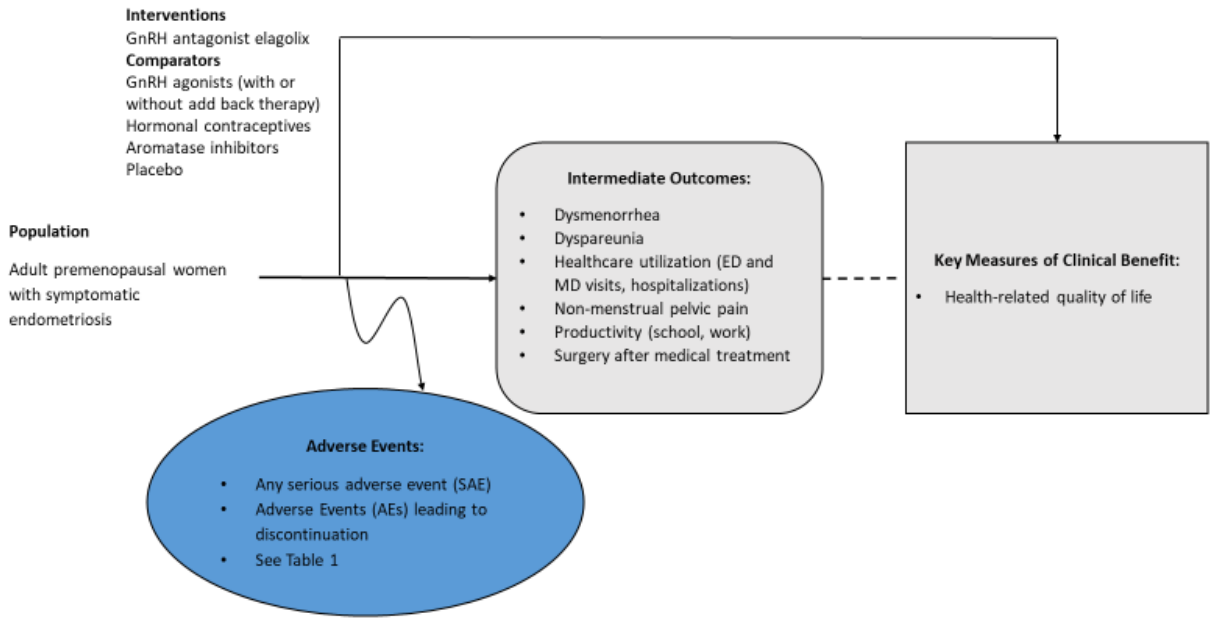
All eligible studies will be included regardless of publication type or status, including peer-reviewed articles, conference abstracts or presentations, and registry entries (e.g., completed study data from https://clinicaltrials.gov/).

In vitro, in silico, animal, and non-English language studies will be excluded.

Analytic Framework

The analytic framework for this project is depicted below:

Figure 1. Analytic Framework



Evidence Review Methods

Procedures for the systematic literature review will follow established best methods.[23-25] We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) when reporting our approach and findings. The PRISMA checklist includes 27 items, which are described further in Appendix A. The completed PRISMA table will be included in the review.[26]

Search Methods and Data Sources

We will search MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials via the Ovid platform, and EMBASE directly via the EMBASE website. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below. The date of the most recent search is February 16, 2018.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of

this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icerreview.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 2: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Central Register of Controlled trials

1	exp endometriosis/
2	(adenomyo$ or endometriosis$).tw.
3	(adenomyo$ or endometrio$).tw.
4	chocolate cyst$.tw.
5	or/1-4
6	contraceptives, oral/
7	contraceptives, oral, synthetic/
8	contraceptives, oral, combined/
9	(combin$ adj3 (oral$ or hormon$) adj3 (pill$ or contracept$)).tw.
10	contraceptives, oral, hormonal/
11	contraceptive ring/
12	contraceptive ring.tw.
13	vaginal ring/
14	vaginal ring.tw.
15	contraceptive patch/
16	contraceptive patch$.tw.
17	progesterone/
18	progesterone congeners/
19	progesterone$.tw.
20	progestins/
21	(progestin$ or progestogen$ or gestagen$).tw.
22	dydrogesterone/
23	dydrogesterone$.tw.
24	norethindrone/
25	(norethindrone$ or norethisterone$).tw.
26	levonorgestrel/
27	levonorgestrel$.tw.
28	medroxyprogesterone 17-acetate/
29	medroxyprogesterone$.tw.
30	depo.tw.
31	dmpa.tw.

32	dienogest/
33	dienogest.tw.
34	intrauterine devices, medicated/
35	lng-ius.tw.
36	mirena.tw.
37	((intrauterine$ or intra uterine$) adj3 levonorgestrel$).tw.
38	gonadotropins/
39	gonadotrop?in$.tw.
40	GnRH$.tw.
41	GnRH/
42	goserelin/
43	goserelin$.tw.
44	leuprolide/
45	(leuprolide$ or leuprorelin$).tw.
46	nafarelin/
47	nafarelin$.tw.
48	elagolix/
49	elagolix.tw.
50	degarelix/
51	degarelix.tw.
52	aromatase inhibitors/
53	aromatase inhibitor$.tw.
54	aromatase inhibit$.tw.
55	anastrozole/
56	anastrozole.tw.
57	letrozole/
58	letrozole.tw.
59	exemestane/
60	exemestane.tw.
61	or/6-60
62	5 and 61
63	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase i or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
64	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.
65	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or

	(random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
66	64 or 65
67	62 not 63
68	66 and 67
69	(animals not (humans and animals)).sh.
70	68 not 69
71	limit 70 to english language
72	remove duplicates from 71

* Run February 14, 2018

Table 3. EMBASE search strategy

#1	'endometriosis'/exp OR 'endometriosis'
#2	'adenomyosis'/exp
#3	'chocolate cyst'
#4	#1 OR #2 OR #3
#5	'oral contraceptive agent'
#6	'vagina ring'
#7	'contraceptive ring'
#8	'contraceptive patch'
#9	'progesterone'
#10	'progesterone derivative'
#11	'dydrogesterone'
#12	'norethisterone'
#13	'levonorgestrel'
#14	'medroxyprogesterone acetate'
#15	'medroxyprogesterone'
#16	depo
#17	dmpa:de
#18	depo:de
#19	'dienogest'
#20	'intrauterine contraceptive device'
#21	'levonorgestrel releasing intrauterine system'
#22	mirena:ti,ab
#23	'gonadotropin'
#24	gnrh:de
#25	'gonadorelin'
#26	'gonadorelin agonist'
#27	'goserelin'
#28	'leuprorelin'
#29	'nafarelin'
#30	'elagolix'
#31	'degarelix'
#32	'gonadorelin antagonist'
#33	'aromatase inhibitor'
#34	'anastrozole'

#35	'letrozole'
#36	'exemestane'
#37	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
#38	#4 AND #37
#39	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#40	'human'/exp
#41	#39 AND #40
#42	#39 NOT #41
#43	#38 NOT #42
#44	#43 NOT [english]/lim
#45	#44 AND [medline]/lim
#46	#45 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#47	#45 NOT #46

* Run February 16, 2018

Selection of Eligible Studies

After removal of duplicate citations using both online and local software tools, citations will go through two levels of screening, at the abstract and full-text levels. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. Abstracts will be screened based on population, intervention, relevant outcomes and study design.

Citations accepted during abstract-level screening will be retrieved in full text for review. These will be re-reviewed following the same procedures as the title/abstract screening. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted directly into the Systematic Review Data Repository (SRDR™; https://srdr.ahrq.gov/). From SRDR, data will be transferred into tables. The basic design and elements of the extraction forms will follow those used for other ICER reports (see Appendix B Table Shell). Elements include a description of patient populations, sample size, duration of follow-up, study design features (e.g., open-label or cross-out periods), outcome assessments (e.g., timing, definitions, and methods of assessment), results, and quality assessment for each study. The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.

2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria employed by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[27]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for elagolix, we will scan the ClinicalTrials.gov site to identify completed studies. Search terms include "GnRH antagonist" and "elagolix". We will include and extract studies that meet our eligibility criteria that have not otherwise been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The primary purpose of the evidence synthesis is to estimate the comparative effectiveness of the intervention of interest. The analyses will be based on the data from all relevant studies identified from the systematic review and contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

All relevant evidence will be synthesized qualitatively and all included studies will be summarized in the text and in evidence tables of the Evidence Report. Relevant data include those listed in the data extraction section. Any key differences among the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report. We will assess the applicability (generalizability, relevance) of the included studies to the population of women with endometriosis-related pain.

Synthesis of Results

For each outcome, all studies reporting results will be assessed for similarity in terms of the key characteristics specified in the data extraction section. The reported results from the studies that are sufficiently similar will be then checked to determine if the data are appropriate for analysis (e.g., sample sizes, number of patients experiencing the outcome, and point estimates with uncertainty estimates, are reported as appropriate). When there are no sufficiently-similar studies or inadequate data, analyses in the Evidence Report will be descriptive only. Key considerations for interpreting the results within the context of the evidence base will be specified in the Evidence Report.

Data permitting, we will conduct quantitative analyses. However, for this review, analyses are expected to be only descriptive in nature, as differences in study entry criteria, patient populations, outcome assessments, and other factors are likely to preclude formal quantitative direct or indirect assessments of outcomes with elagolix and comparative treatments. Nevertheless, if studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random effects pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator, for example head-to-head studies of elagolix versus GnRH agonists, hormonal contraceptives, or aromatase inhibitors.[21]

If feasible and appropriate given the available evidence, we will also conduct network meta-analyses. A network meta-analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s).[22,23] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[26] Additional explanations of each item can be found in Liberati et al. 2009.[28]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Appendix A. Data Extraction Summary Table Shell

Table B1. Evidence Tables

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms