MIDWEST CEPAC
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COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

Inclisiran and Bempedoic Acid for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value

Research Protocol

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Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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1. Background, Objectives, and Research Questions

1.1 Background

Atherosclerotic cardiovascular disease (ASCVD) encompasses a set of common, complex, and burdensome conditions. Three prevalent types of ASCVD are coronary artery disease, peripheral artery disease, and cerebrovascular disease, all of which result from atherosclerosis, a chronic degenerative process involving fat and cholesterol build-up in the arteries that is commonly known as "hardening of the arteries." Over the life course, ASCVD can result in angina, claudication, myocardial infarction, or stroke, among other problems. Risk factors for ASCVD include diabetes mellitus, hypertension, obesity, smoking, and elevated levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-C).

Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disorder of cholesterol metabolism which results in very elevated plasma concentrations of LDL-C and premature ASCVD.[1] Heterozygous FH (HeFH) is the most common form of FH, affecting approximately 1 in 250 people in the US, with men and women equally affected.

Overall in the US, over one-half of adults are estimated to have some form of ASCVD[2] and ASCVD remains the leading cause of death.[3] The financial burden of ASCVD is also substantial, with total costs of the disease expected to reach $1.1 trillion by 2035.[2] Between 2007 and 2013, death rates from ASCVD decreased for all race/ethnic groups in the United States but disparities in the overall burden of ASCVD continue to exist according to race/ethnicity and sex. The overall rates of death attributable to ASCVD in 2013 were 356.7 per 100,000 for non-Hispanic black men, 270.6 per 100,000 for non-Hispanic white men, 197.4 per 100,000 for Hispanic men, 246.6 per 100,000 for non-Hispanic black women, 183.8 per 100,000 for non-Hispanic white women, and 136.4 per 100,000 for Hispanic women.[4]

Treatment of patients with HeFH and those with established ASCVD includes lifestyle and behavior modification (i.e., diet, weight reduction, physical activity, smoking cessation) for all patients to slow or potentially reverse the atherosclerotic process. Risk factor management is also a staple of care, including blood pressure control, treatment with statins and other cholesterol-lowering agents, and antiplatelet therapy with aspirin or other agents. When necessary, surgical or percutaneous revascularization is also used to treat the condition.

Even with the aforementioned treatment options, patients with HeFH and established ASCVD remain at high residual risk for further major atherosclerotic cardiovascular events, particularly if LDL-C levels remain elevated. Thus, there is an important public health need for additional

treatment options to improve outcomes for patients at risk for major atherosclerotic cardiovascular events.

Two new treatments, bempedoic acid with or without ezetimibe (Nexlizet™ and Nexletol™, Esperion Therapeutics, Inc.) and inclisiran (Novartis), are proposed as the focus for this review. Bempedoic acid is an orally administered inhibitor of adenosine triphosphate citrate lyase. It received FDA approval in February 2020 as an adjuvant oral therapy for adults with HeFH on maximal statin therapy or with established ASCVD requiring additional LDL-C lowering. Inclisiran is a small interfering RNA agent targeting hepatic PCSK9 synthesis. It is delivered as a subcutaneously administered injection given twice yearly. A new drug application was submitted to the FDA in December 2019 for inclisiran for use in secondary prevention of ASCVD and patients with FH, with a regulatory decision expected in the latter half of 2020.

1.2 Objectives

The scope of this project was previously available for public comment and has been 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 inclisiran and bempedoic acid with or without ezetimibe in patients with HeFH and for secondary prevention of ASCVD. 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, and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). The modeling analysis plan will include details on the proposed methodology and model structure that will be used for the economic evaluation (expected publication date: September 22, 2020)

1.3 Research Questions

To inform our review of the clinical evidence, we have developed the following research questions:

- For patients in the population(s) described below with elevated LDL-C levels despite treatment with maximally tolerated lipid-lowering therapy, what is the net health benefit of adding inclisiran to their treatment?
- For patients in the population(s) described below with elevated LDL-C levels despite treatment with maximally tolerated lipid-lowering therapy, what is the net health benefit of adding bempedoic acid with or without ezetimibe to their treatment?
- For patients in the population(s) described below with elevated LDL-C levels despite treatment with maximally tolerated lipid-lowering therapy, what is the comparative clinical effectiveness of inclisiran, bempedoic acid with or without ezetimibe, and PCSK9 inhibitors?

1.4 PICOTS 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.

Population

The population of interest for this review is adults (≥ 18 years old) with elevated LDL-C levels despite treatment with maximally tolerated lipid-lowering therapy. We will consider evidence across relevant populations including patients with HeFH (primary and secondary prevention) and established ASCVD (secondary prevention). As noted in the description of the scope for the comparative value analysis, not all patient subpopulations will be evaluated in the economic model.

We will evaluate the evidence, where available, on the following subpopulations:

- Patients with HeFH with and without established ASCVD (primary and secondary prevention)
- Patients with established ASCVD at relatively higher risk (e.g., patients with a recent myocardial infarction)
- Patients with statin intolerance

Interventions

The interventions of interest for this review will be inclisiran (Novartis) and bempedoic acid with or without ezetimibe (Nexlizet™ and Nexletol™, Esperion Therapeutics, Inc.) added to maximally tolerated lipid-lowering therapy.

Comparators

We will compare the use of each of the interventions in conjunction with maximally tolerated background lipid-lowering therapy versus ongoing maximally tolerated lipid-lowering therapy (i.e., intervention vs. placebo arms of clinical trials). We will explore comparing the interventions to each other and to PCSK9 inhibitors via network meta-analysis.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - All-cause mortality
    - CV mortality

    - Myocardial infarction
    - Stroke
    - Unstable angina
    - Revascularization
    - Health-related quality of life
- Other Outcomes
    - LDL-C
    - High-density lipoprotein cholesterol (HDL-C)
    - Total cholesterol
    - Non-HDL-C
    - Triglycerides
    - Apolipoprotein B
    - Lipoprotein(a)
    - High-sensitivity C-reactive protein (hsCRP)
    - PCSK9 level (for inclisiran and PCSK9 inhibitors)
- Safety
    - Treatment-emergent AEs, including:
        - Muscle-related AEs
        - Increase in liver function tests
        - Tendon rupture
        - Uric acid level
        - Injection-site reactions
        - Discontinuation due to AEs
        - Serious AEs, including:
            - Death

Timing

We will consider evidence from studies with at least four weeks of follow-up.

Setting

We will consider all relevant settings.

Study design

We will include randomized controlled trials (RCTs), non-randomized controlled trials, and observational studies of inclisiran and bempedoic acid with or without ezetimibe with any sample size. In addition, we will include RCTs of PCSK9 inhibitors with any sample size.

2. Evidence Review Methods

2.1 Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on inclisiran and bempedoic acid with or without ezetimibe for HeFH and secondary prevention of ASCVD will follow established best methods.[5,6] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE and EMBASE for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. 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. We will conduct a de novo search for inclisiran and bempedoic acid with or without ezetimibe with no time restriction (Tables 2.1 and 2.2). We will also conduct a search for new RCT evidence on the benefits and harms of PCSK9 inhibitors that has become available since our last systematic literature review of both agents (Tables 2.2 and 2.3).[8]

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://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 2.1. Search Strategy of MEDLINE via Ovid* for Inclisiran and Bempedoic Acid

1	Hypercholesterolemia/ or Hyperlipoproteinemia Type II/ or Cardiovascular Diseases/
2	(((high or elevated) adj (cholesterol or LDL* or low-density lipoprotein)) or hypercholesterolemia or hypercholesterolemia or HeFH or heterozygous familial hypercholesterolemia or familial hypercholesterolemia or FH).ti,ab
3	(((cardiovascular or heart or coronary or atherosclero*) adj2 (disease* or disorder* or syndrome*)) or ASCVD or CVD).ti,ab.
4	1 or 2 or 3
5	(inclisiran or ALN-PCSsc or ALNPCSsc or ALN PCSsc or ALN-60212 or ALN60212 or ALN 60212).ti,ab
6	(bempedoic acid or Nexletol or Nexlizet or ezetimibe or ETC1002 or ETC 1002 or ETC-1002).ti,ab.
7	5 or 6
8	4 and 7
9	(addresses or autobiography or bibliography or biography or clinical trial, phase I 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.
10	8 not 9
11	(exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.)
12	10 not 11
13	limit 12 to English language

*Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

Table 2.2. Search Strategy of EMBASE for Inclisiran and Bempedoic Acid

#1	'Hypercholesterolemia'/exp OR 'Cardiovascular Disease'/mj
#2	(((high OR elevated) NEAR/1 (cholesterol OR ldl* OR 'low-density lipoprotein')):ti,ab) OR hypercholesterolemia:ti,ab OR hypercholesterolaemia:ti,ab OR hefh:ti,ab OR 'heterozygous familial hypercholesterolemia':ti,ab OR 'familial hypercholesterolemia':ti,ab OR fh:ti,ab
#3	(((cardiovascular OR heart OR coronary OR atherosclero*) NEAR/2 (disease* OR disorder* OR syndrome*)):ti,ab) OR ascvd:ti,ab OR cvd:ti,ab
#4	#1 OR #2 or #3
#5	inclisiran:ti,ab OR 'aln-pcssc':ti,ab OR alnpcssc:ti,ab OR 'aln pcssc':ti,ab OR 'aln-60212':ti,ab OR aln60212:ti,ab OR 'aln 60212':ti,ab
#6	'bempedoic acid':ti,ab OR nexletol:ti,ab OR nexlizet:ti,ab OR ezetimibe:ti,ab OR 'etc1002':ti,ab OR 'etc 1002':ti,ab OR 'etc-1002':ti,ab
#7	#5 OR #6
#8	#4 AND #7
#9	'case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
#10	#8 NOT #9
#11	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#12	#10 NOT #11
#13	#12 AND [English]/lim
#14	#13 AND [medline]/lim
#15	#13 NOT #14

Table 2.3. Search Strategy of MEDLINE via Ovid* for PCSK9 Inhibitors

1	Hypercholesterolemia/ or Hyperlipoproteinemia Type II/ or Cardiovascular Diseases/
2	(((high or elevated) adj (cholesterol or LDL* or low-density lipoprotein)) or hypercholesterolemia or hypercholesterolaemia or HeFH or heterozygous familial hypercholesterolemia or familial hypercholesterolemia or FH).ti,ab
3	(((cardiovascular or heart or coronary or atherosclero*) adj2 (diseas* or disorder* or syndrome*)) or ASCVD or CVD).ti,ab.
4	1 or 2 or 3
5	(PCSK9 inhibitor* or PCSK9 antibod* or alirocumab or evolocumab or amg 145 or regn727 or sar236553 or praluent or repatha).ti,ab
6	4 and 5
7	(addresses or autobiography or bibliography or biography or clinical trial, phase I 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.
8	6 not 7
9	(exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.)
10	8 not 9
11	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 (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
12	10 and 11
12	limit 12 english language
13	limit 13 to yr=”2015-Current”

Table 2.4. Search Strategy of EMBASE for PCSK9 Inhibitors

#1	'Hypercholesterolemia'/exp OR 'cardiovascular disease'/mj
#2	(((high OR elevated) NEAR/1 (cholesterol OR ldl* OR 'low-density lipoprotein')):ti,ab) OR hypercholesterolemia:ti,ab OR hypercholesterolaemia:ti,ab OR hefh:ti,ab OR 'heterozygous familial hypercholesterolemia':ti,ab OR 'familial hypercholesterolemia':ti,ab OR fh:ti,ab
#3	(((cardiovascular OR heart OR coronary OR atherosclero*) NEAR/2 (diseas* OR disorder* OR syndrome*)):ti,ab) OR ascvd:ti,ab OR cvd:ti,ab
#4	#1 OR #2 OR #3
#5	'pcsk9 inhibitor*':ti,ab OR 'pcsk9 antibod*':ti,ab OR 'alirocumab':ti,ab OR 'evolocumab':ti,ab OR 'amg 145':ti,ab OR 'regn727':ti,ab OR sar236553:ti,ab OR praluent:ti,ab OR repatha:ti,ab
#6	#4 AND #5
#7	'case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
#8	#6 NOT #7
#9	('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab or control*:ti,ab OR 'control group'/exp OR 'drug therapy':lnk
#10	#8 AND #9
#11	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#12	#10 NOT #11
#13	#12 AND [english]/lim
#14	#13 AND [2015-2020]/PY
#15	#14 AND [medline]/lim
#16	#14 NOT #15

2.2 Eligibility Criteria

We will exclude studies that do not meet the PICOTS criteria defined above. As noted above, adult patients are the population of interest, so we will exclude studies that focus on children or adolescent patients.

2.3 Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using Distiller (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

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

2.4 Data Extraction Strategy

Data will be extracted into Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, 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.

2.5 Quality Assessment Criteria

We will use criteria published 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."[9]

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.*

2.6 Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include inclisiran, ALN-PCSsc, ALN-60212, bempedoic acid, and ETC-1002. We will select studies which would have met our inclusion criteria, and for which no findings have 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.

2.7 Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base, (2) synthesis of outcome results, and (3) heterogeneity and subgroups.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between 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.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

For key outcomes of interest, we will assess the feasibility of conducting pairwise meta-analyses or network meta-analyses by exploring the differences in study populations, study design, analytic methods, and outcome assessments. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[10] An NMA 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)).[11,12] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report.

Heterogeneity and Subgroups

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include baseline LDL-C, study follow-up, and background lipid-lowering therapy. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

References

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[13] Additional explanation of each item can be found in Liberati et al. 2009.[14]

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 B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion & Exclusion Criteria	Patient Characteristics	Outcomes