MIDWEST CEPAC
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Comparative Clinical Effectiveness of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

Research Protocol

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Institute for Clinical and Economic Review

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Background, Objectives, and Research Questions

Background

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the *CFTR* gene. Children born with CF inherit two pathogenic mutations, one from each parent. It is a relatively rare condition, occurring in approximately 1 in 2,500 to 3,000 live births, but it is the most common lethal genetic disease in Caucasian populations.[1-4] CF is a progressive disease that affects many organ systems, but most of its morbidity and mortality are associated with its impact on the respiratory system.[5]

The life expectancy of patients with CF has increased substantially over the past 10-20 years, due in part to successes in the coordinated delivery of care and advances in CF management.[6] Prior treatment for CF focused on reducing symptoms and managing complications. This review focuses on novel agents that directly modulate the pathophysiology of the disease; namely, ivacaftor, lumacaftor, and tezacaftor.

In epithelial cells, the *CFTR* gene is transcribed and translated to produce the CFTR protein, which is then transported to the apical membrane, the part of the cell wall that faces towards the lumen of an organ. In the cell membrane the CFTR protein acts as a gate that regulates the flow of chloride ions, bicarbonate ions, and, indirectly, sodium ions and other substances in and out of the cell. Mutations to the *CFTR* gene can reduce the amount of CFTR protein that is produced or transferred to the apical membrane or the CFTR protein's ability to regulate ion and water flow.[6] This reduction leads to thickened secretions that can block passages in organs, including the lungs, pancreas, and reproductive organs, which may result in frequent lung infections, reduced respiratory capacity, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems in those affected.[7] More than 1,700 different *CFTR* mutations have been identified, with varying effects on the quantity and function of the CFTR protein.[8]

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 CFTR modulators for patients with cystic fibrosis. 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). 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 patients with cystic fibrosis and a genetic mutation for which ivacaftor (Kalydeco®, Vertex Pharmaceuticals) has been approved, what are the comparative efficacy, safety, and effectiveness of ivacaftor plus best supportive care versus best supportive care alone on outcomes such as forced expiratory volume in one second (FEV_1), body mass index (BMI), pulmonary exacerbations, hospitalizations, and quality of life?
- In patients with cystic fibrosis who are homozygous for the *F508del* mutation, what are the comparative efficacy, safety and effectiveness of lumacaftor/ivacaftor (Orkambi®, Vertex Pharmaceuticals) plus best supportive care versus tezacaftor/ivacaftor (investigational, Vertex Pharmaceuticals) plus best supportive care versus best supportive care alone on outcomes such as FEV_1, BMI, pulmonary exacerbations, hospitalizations, and quality of life?
- In patients with cystic fibrosis who are heterozygous for the *F508del* mutation and have a residual function mutation that is potentially responsive to tezacaftor/ivacaftor, what are the comparative efficacy, safety and effectiveness of tezacaftor/ivacaftor plus best supportive care versus ivacaftor plus best supportive care versus best supportive care on outcomes such as FEV_1, BMI, pulmonary exacerbations, hospitalizations, 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.

Population

We will review evidence in three populations of humans with CF dependent on which drug is being investigated, as follows:

The first population includes individuals with CF and mutations consistent with the FDA-approved indications for ivacaftor. In this population, we will review evidence on ivacaftor monotherapy. We will include studies of individuals with either gating or non-gating (e.g., *R117H*) mutations (although external commenters suggested that most of the clinical evidence for ivacaftor will be in patients with gating mutations).

The second population includes individuals with CF who are homozygous for the *F508del* mutation. In this population we will review evidence on both lumacaftor/ivacaftor and tezacaftor/ivacaftor combination therapy.

The third population includes individuals with CF who are heterozygous for the *F508del* mutation and a residual function mutation that is potentially responsive to tezacaftor/ivacaftor. In this population we will review evidence on tezacaftor/ivacaftor combination and ivacaftor monotherapy.

Within these populations, subgroups of interest are defined according to presence of advanced nonreversible lung disease (e.g., patients with or without bronchiectasis; who have predicted FEV_1 below 40%, between 40-90%, or above 90%) and age (groups as defined in each study). Predicted FEV_1 is a measure of lung function defined as the forced expiratory volume during the first second of expiration, adjusted for age, height, sex, and race.[9,10] Other subgroups of interest are people with advanced non-pulmonary disease, such as recurrent pancreatitis, diabetes, liver transplantation, poor growth, and infertility.

We will include studies of individuals of any age, regardless of their past medical history, comorbidities, or the severity of their CF; however, we will exclude studies conducted in individuals after lung transplantation (for whom CFTR modulation therapy would not affect lung function). We will impose no other restrictions regarding population eligibility.

Interventions and Comparators

Data permitting, we plan to examine the following comparisons in the appropriate populations:

1. For individuals who are candidates for ivacaftor monotherapy, we will compare adding ivacaftor to best supportive care versus best supportive care alone.
2. For individuals who are homozygous for the *F508del* mutation, we will compare adding lumacaftor/ivacaftor or tezacaftor/ivacaftor to best supportive care versus best supportive care alone. We will also compare lumacaftor/ivacaftor to tezacaftor/ivacaftor.
3. For individuals who are candidates for tezacaftor/ivacaftor combination therapy because they carry one *F508del* mutation and residual function mutation that is potentially responsive to tezacaftor/ivacaftor, we will compare adding tezacaftor/ivacaftor to best supportive care versus adding ivacaftor monotherapy to best supportive care versus best supportive care alone.

We will exclude studies of lumacaftor and tezacaftor monotherapy, because, based on stakeholder feedback, neither is intended to be used as monotherapy. We will exclude studies of ivacaftor monotherapy, lumacaftor/ivacaftor, or tezacaftor/ivacaftor conducted in populations for whom the drugs are not approved or are not anticipating approval based on their genetic mutations. We will also exclude studies of composite treatment strategies that, for example, start with ivacaftor

monotherapy and shift to a combination regimen after a period of time, if they are conducted in populations in which at least one of the regimens is not approved.

Outcomes

Outcomes of interest include patient-centered outcomes, other clinical outcomes, important physiologic measurements, adverse events, and costs.

Clinical outcomes pertain to measures of health status or events. Examples of clinical outcomes of interest include:

- Mortality
- Pulmonary exacerbations (acute and severe worsening of pulmonary symptoms)
- Hospitalizations
- Acute pancreatitis
- Fertility

Physiologic measurements are surrogate or intermediate measures for symptom severity, disease progression, or patient-centered outcomes. Examples of physiologic measurements of interest include:

- FEV_1 (predicted), including rate of FEV_1 decline
- Vital capacity (maximum amount of air a person can expel from the lungs after a maximum inhalation)
- Lung clearance index (LCI)
- Weight, body mass index (BMI), and growth (surrogate measures of nutrition status)
- Fasting glucose and related measures of glucose control or diabetes

Patient-centered outcomes include many outcomes that are also classified as clinical or cost outcomes listed separately below, but also include specific outcomes that directly relate to the lived experiences of patients and their families. Examples of patient-centered outcomes of interest include:

- Disease-specific quality of life (specifically, as measured with the Cystic Fibrosis Questionnaire-Revised [CFQ-R] and the EuroQol-5D [EQ-5D].[11])
- Mental health and affect, including depression, worry, and anxiety (as measured with validated instruments)
- Functional status, including work, social/family, emotional, physical, etc. (as measured with validated instruments)
- Time lost from school or work
- Worry, stress, and anxiety about the disease or its financial impact
- Ability to participate in athletic activities and social functions
- Financial insecurity
- Caregiver burden

Adverse events pertain to complications, harms, or other such events caused by or attributed to the intervention, not the disease process. Examples of adverse events of interest include:

- Liver dysfunction
- Upper respiratory infections
- Gastrointestinal complaints (e.g., nausea, diarrhea, abdominal pain)
- Headache
- Rash
- Chest discomfort
- Dyspnea
- Cataracts
- Adverse events leading to treatment discontinuation

Other outcomes will be considered and reviewed depending on relevance to patients and availability of data.

Evidence on drug-drug interactions from the eligible studies will also be included.

We will exclude measures of cellular (as opposed to organ) function and other blood, serum, or urine laboratory measures (other than glucose), such as sweat chloride, fecal elastase, sputum inflammatory measures, and nasal potential difference. We will also exclude novel or "candidate" measures, such as metrics based on high resolution computerized tomography.

Timing

Randomized controlled and non-randomized comparative studies of all follow-up durations are eligible. Observational studies must report outcomes at least one month following treatment. However, we may lengthen the follow-up time point based on the number of short-term observational studies and completeness of short-term evidence from comparative studies. Single-dose studies of any type will be excluded. Our focus will be on studies in which patients are prescribed a course of treatment.

Setting

All settings will be considered. Studies conducted in any country will be considered.

Study design

All eligible randomized controlled trials (RCTs) and non-randomized comparative studies will be included regardless of sample size or follow-up duration. 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 accuracy.

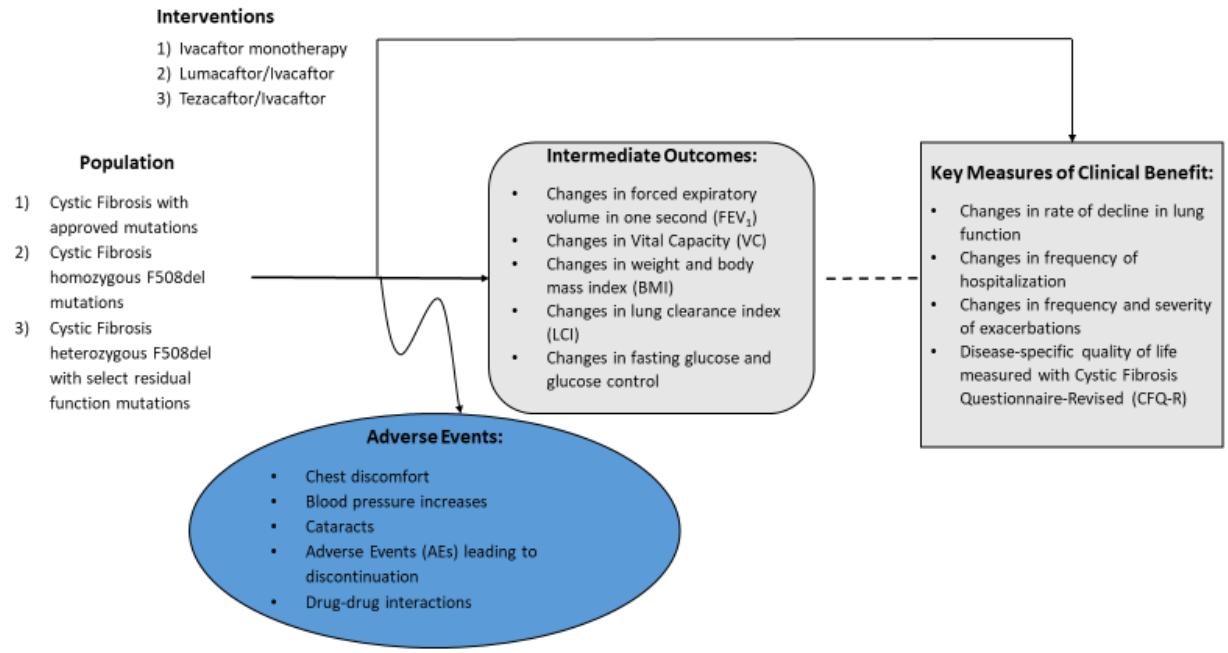
Single-group (noncomparative) studies of eligible CFTR modulators will be included based on criteria that will be finalized after the eligible comparative studies have been assessed and the gaps in the comparative study evidence base are known. A limited number of single-group studies will be included to address outcomes in populations not adequately covered by the comparative studies (e.g., age <6 years, history of recurrent pancreatitis) and to address longer-term outcomes (particularly changes in FEV_1 and adverse events). 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 ClinicalTrials.gov).

In vitro, in silico, animal, and modeling studies will be excluded.

Analytic Framework

The analytic framework for this project is depicted below:



Evidence Review Methods

Procedures for the systematic literature review assessing the evidence on CFTR modulators for cystic fibrosis will follow established best methods.[12-14] 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.[15]

Search Methods and Data Sources

We will conduct the literature searches in PubMed and EMBASE. No limitations will be placed on the searches regarding language, age, country, type of subject (animal or human), study design, or publication type (e.g., peer-reviewed or conference proceeding). All search strategies will be generated utilizing the Population, Intervention, and Study Design elements described above. The search strategies include a combination of indexing terms (MeSH terms in MEDLINE, searched through PubMed, 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 December 19, 2017.

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 known conference proceedings (within last 5 years), regulatory documents, information submitted by manufacturers, ClinicalTrials.gov, and other grey literature when the evidence meets ICER standards and is not duplicative (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 1: PubMed® search strategy (covers MEDLINE)

#1	Search cystic fibrosis[MeSH Terms]
#2	Search cystic fibrosis transmembrane conductance regulator[MeSH Terms]
#3	#1 or #2
#4	Search cystic fibrosis transmembrane conductance regulator (CFTR) potentiator
#5	Search cystic fibrosis transmembrane conductance regulator (CFTR) corrector
#6	Search cystic fibrosis transmembrane conductance regulator (CFTR) modulator
#7	Search CFTR potentiator
#8	Search CFTR corrector
#9	Search CFTR modulator
#10	Search ivacaftor
#11	Search lumacaftor
#12	Search tezacaftor

#13	Search VX-770
#14	Search VX-809
#15	Search VX-661
#16	Search Kalydeco
#17	Search Orkambi
#18	#4 or #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
#19	#3 and #18

Table 2. EMBASE search strategy

#1	'cystic fibrosis transmembrane conductance regulator (CFTR) potentiator'
#2	'cystic fibrosis transmembrane conductance regulator (CFTR) corrector'
#3	'cystic fibrosis transmembrane conductance regulator (CFTR) modulator'
#4	'CFTR potentiator'
#5	'CFTR corrector'
#6	'CFTR modulator'
#7	'ivacaftor':de OR 'ivacaftor':ab,ti
#8	'lumacaftor':de OR 'lumacaftor':ab,ti
#9	'tezacaftor':de OR 'tezacaftor':ab,ti
#10	'ivacaftor plus lumacaftor':de OR 'ivacaftor plus lumacaftor':ab,ti
#11	'ivacaftor plus tezacaftor':de OR 'ivacaftor plus tezacaftor':ab,ti
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

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; 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, and study design.

Citations accepted during abstract-level screening will be retrieved in full text for review. These will be re-reviewed in duplicate in full text, following the same procedures as the title/abstract screening, except that full-text articles will also be screened based on reported outcomes. 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 SRDR™ (https://srdr.ahrq.gov). Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features (e.g.,

open-label or cross-over periods), interventions (drug, dosage, frequency, schedules), 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 by one reviewer extracting information from the full articles and a second reviewer validating the extracted data.

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."[16]

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 CFTR modulators, we will scan the ClinicalTrials.gov site to identify completed studies. Search terms include "ivacaftor", "Kalydeco", "lumacaftor", "Orkambi" and "tezacaftor". 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 interventions 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.

All relevant evidence will be synthesized qualitatively. Data permitting, we will conduct quantitative analyses. Wherever feasible and appropriate, we will meta-analyze head-to-head studies of these interventions. If feasible and appropriate given the available evidence, we will also conduct network meta-analyses to add indirect comparisons (comparisons of interventions that have not been directly compared in head-to-head studies).

Summary of Evidence Base

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 individuals in the U.S. with CF for whom CFTR modulators are indicated.

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.

For this review, analyses are expected to be only descriptive in nature for many genetic subtypes of CF, 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 CFTR modulators and optimal medical therapy. Nevertheless, if studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random-effects model pairwise meta-analyses, and estimate indirect effects, where feasible.[17] Specifically, we anticipate estimating the indirect effect of tezacaftor/ivacaftor versus

lumacaftor/ivacaftor among homozygotes for the 508del mutation, based on the comparisons of each regimen versus placebo, using the Bucher method for adjusted indirect comparison.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[15] Additional explanations of each item can be found in Liberati et al. 2009.[18]

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 B. 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