MIDWEST CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Project: Clinical Effectiveness of Dupilumab and Crisaborole for Atopic Dermatitis

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BACKGROUND, OBJECTIVES, AND RESEARCH QUESTIONS

Background

Atopic dermatitis (eczema) is a chronic/chronically-relapsing skin condition characterized by itching and dry skin. Lesions can be acute, subacute, or chronic, and these can involve papules, vesicles, erythema, crusting and exudate, swelling, scaling, and thickening/lichenification.

Atopic dermatitis is common. It affects 5-20% of children worldwide,[1] and approximately 11% of children in the US.[2] It is also estimated to affect around 3-7% of adults in the US.[3,4] Management of atopic dermatitis can create burdens for the family,[5] and the disorder can decrease quality of life.[6] Itching, in particular, can disrupt sleep and lead to daytime sleepiness,[7] irritability, and psychological stress, and cosmetically important lesions can lead to social stress and isolation.[6]

Atopic dermatitis has a strong genetic component,[8] and a family history of atopic disease is an important risk factor.[9] Approximately 67-82% of children with atopic dermatitis have mild disease, 12-26% have moderate disease, and 4-7% have severe disease.[10,11] There is less evidence on severity of disease in adults or on the frequency with which adults are refractory to topical therapies, but severe disease appears to make up a greater percentage of disease in adults than in children. The majority of children experience improvement or resolution of atopic dermatitis by late childhood, although the exact percentage in whom disease persists into adulthood is uncertain.[12]

The mainstays of therapy for atopic dermatitis include emollients to improve the epidermal barrier, avoidance of triggers, and topical treatment with corticosteroids or calcineurin inhibitors, aimed at decreasing inflammation.[12] Patients with severe disease can be treated with phototherapy or systemic immunomodulators such as cyclosporine, azathioprine, or, for short periods, oral corticosteroids.[13,14] While phototherapy is generally available to patients in the US, all of the systemic treatments other than oral corticosteroids lack approval by the FDA for atopic dermatitis and few patients in the US receive them. Cyclosporine appears to be the most commonly used of these non-steroid systemic agents and to have the best evidence of efficacy.[14]

Prolonged use of topical corticosteroids can result in telangiectasia, increased hair, and thinning/atrophic changes, which can be permanent,[15,16] and higher potency topical corticosteroids can produce systemic effects including adrenal suppression,[17] particularly when used for long periods on large surface areas or more permeable areas of the skin. However, many patients can use these preparations without developing atrophy or other side effects,[18] and concerns about the use of topical steroids are referred to as “steroid phobia” or “topical corticosteroid phobia”, both in the literature[19] and by a number of clinicians and patient groups with whom we spoke. Topical calcineurin inhibitors can sting when they are first used, and the US FDA label includes a warning regarding a theoretical risk for skin cancers and lymphoma. Phototherapy may increase the risk of skin cancer,[20] and systemic immunomodulators can have potentially serious side effects.[14]

Crisaborole is a topical phosphodiesterase 4 (PDE 4) inhibitor that has been evaluated as a new therapy for mild-to-moderate atopic dermatitis in adults and children, and is a potential alternative to topical corticosteroids and calcineurin inhibitors. Dupilumab is a monoclonal antibody against interleukin-4 receptor alpha that has been evaluated as a novel systemic therapy for moderate-to-severe atopic dermatitis in adults. Crisaborole was approved by the FDA in December, 2016, and dupilumab is undergoing review at the FDA with a projected approval date in the first quarter of 2017.

Overview

This project will evaluate the comparative clinical effectiveness of crisaborole for its indication in the treatment of mild-to-moderate atopic dermatitis in children and adults. Separately, the report will also evaluate the comparative clinical effectiveness and value of dupilumab for its expected indication in the treatment of moderate-to-severe atopic dermatitis in adults. The report will not compare the clinical effectiveness of crisaborole and dupilumab.

We will limit our review to those studies that capture the outcomes of interest however, when assessing adverse events and harms, we will also look for randomized trials of dupilumab therapy for conditions other than atopic dermatitis. We will not restrict studies according to study setting. In evaluating phototherapy and cyclosporine as comparators, we will look for systematic reviews that compare these therapies with dupilumab, with placebo/no treatment, or with topical therapy to potentially inform a network meta-analysis. We will 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/).

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.”[21]

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.

PICOTS Inclusion Criteria

All search algorithms for the systematic literature review will be generated utilizing PICOTS-related elements: Patient, Interventions, Comparisons, Outcomes, Timing, and Setting.

Population

The populations of focus for the review will be:

- For crisaborole: adults and children with mild-to-moderate atopic dermatitis
- For dupilumab: adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable

Interventions

- Crisaborole for mild-to-moderate atopic dermatitis
- Dupilumab for moderate-to-severe atopic dermatitis

Comparators

- For crisaborole: emollient therapy alone for mild-to-moderate atopic dermatitis; if possible, we will also compare to topical corticosteroids and calcineurin inhibitors
- For dupilumab: topical therapy for moderate-to-severe atopic dermatitis (emollients with or without a topical corticosteroid or calcineurin inhibitor), phototherapy, or cyclosporine

Outcomes

This review will examine key clinical outcomes that occur in patients being treated for atopic dermatitis.

Discussions with patient groups and clinicians indicated that atopic dermatitis creates symptoms for patients and burdens for patients and families that may not be well-captured by standard trial outcomes. We heard that while itch and the effects of atopic dermatitis on sleep are central to quality of life, the latter is not always adequately captured in clinical trials. Burden and symptom outcomes that are typically not well captured include psychological issues (depression, anxiety, suicidal ideation, stress on relationships, effects on developmental milestones, effects on self-esteem, and bullying), pain (distinct from itch), burden of treatment (time spent on treatment, caregiver burdens, difficulty of adherence by children at school [such as reapplying moisturizers], perceived burdens of injections versus oral medications, cost, travel to seek medical care), and interference with life activities (missed days of school; missed days of work for parents; missed days of work for patients; disability for the patient's chosen profession; presentism effects on work and school; restrictions on diet, exercise, and recreation; effects on intimacy).

We recognize that many of these outcomes will not be adequately addressed within randomized trials, but will look for such evidence where available.

Outcomes from clinical trials:

- Investigator's Static Global Assessment (ISGA)
- Investigator's Global Assessment (IGA)
- Eczema Area and Severity Index (EASI): 50, 75, 90
- Scoring Atopic Dermatitis (SCORAD) score
- Pruritus (by any scale)
- Dermatology Life Quality Index (DLQI)
- Patient-Oriented Eczema Measure (POEM)
- Hospital Anxiety and Depression Scale (HADS)
- EuroQol five dimensions questionnaire (EQ-5D) if available
- Treatment-related adverse events

We will also look for evidence on additional patient-reported outcomes, including other measures of health-related quality of life and measures of sleep. Additionally, we will look for evidence regarding effects of therapy on the long-term course of atopic dermatitis through disease modification. Since dupilumab may have effects on other atopic disease, we will try to assess whether there are differential effects on broader health outcomes. To do this, we will seek evidence on quality of life measures (such as EQ-5D) in subgroups with and without asthma or nasal polyposis and/or compare such broader measures with measures more narrowly focused on dermatologic quality of life (such as DLQI).
We will develop evidence tables for each selected study, and results will be summarized in a qualitative fashion; meta-analysis will be considered to quantitatively summarize outcomes for the therapies of interest. If data permit, we may perform a network meta-analysis of indirect evidence to compare crisaborole with topical therapies (corticosteroids and calcineurin inhibitors) and to compare dupilumab with phototherapy and cyclosporine.

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least four week's duration.

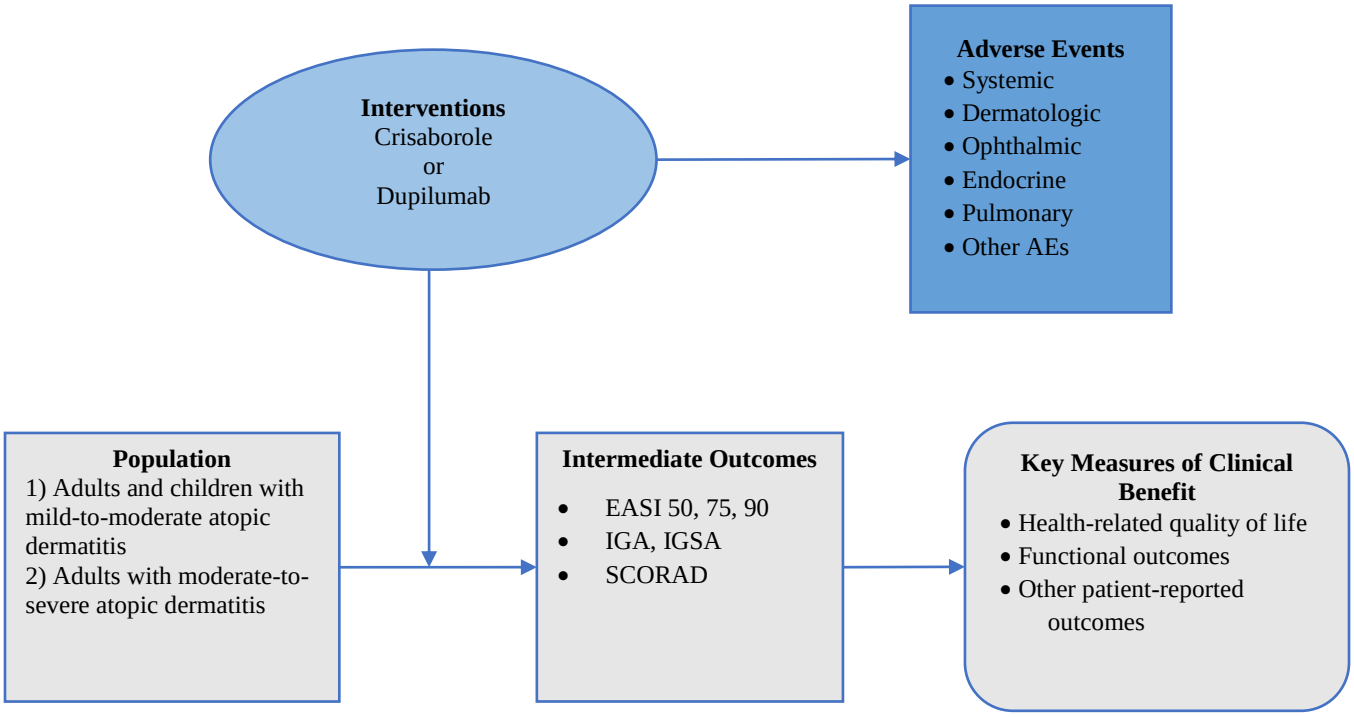
Setting

We will examine results in patients treated in clinic and outpatient settings.

Analytic Framework

The proposed analytic framework for this project is depicted below.

Figure 1. Analytic Framework: Atopic Dermatitis



EVIDENCE REVIEW METHODS

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on treatment concerning dupilumab and crisaborole for atopic dermatitis will follow established best methods.[22,23] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. We will focus on previous systematic reviews and only the most recent trials of calcineurin inhibitors and phototherapy as the evidence base for these comparator treatments. Each search will be limited to English-language studies of human subjects and will focus on trials of at least 16 weeks' duration; articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items will be excluded.

The 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 1-4 on the following pages. In order to supplement the above searches and ensure optimal and complete literature retrieval, we will perform a manual check of the references of recent relevant reviews and meta-analyses.

Table 1: Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Ovid)

1	observational study.pt.	26306
2	exp case-control studies/	714934
3	exp cohort studies/	1363044
4	exp cross-over studies/	66861
5	exp matched-pair analysis/	4386
6	multicenter study.pt.	257316
7	1 or 2 or 3 or 4 or 5 or 6	1737237
8	randomized controlled trial.pt.	735147
9	controlled clinical trial.pt.	134161
10	randomized.ab.	556472
11	placebo.ab.	270751
12	drug therapy.fs.	1244365
13	randomly.ab.	326478
14	trial.ab.	484151
15	groups.ab.	1351782
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	3215161
17	comparative study.pt. or compare.ab,ti. or compares.ab,ti. or compared.ab,ti. or comparing.ab,ti. or comparison.ab,ti. or comparison.ab,ti. or comparative.ab,ti. or effective.ab,ti. or effectiveness.ab,ti. or versus.ab,ti. or vs.ab,ti.	4463550
18	7 and 17	990175
19	16 or 18	3663976
20	exp animals/	11666631
21	humans.sh.	9607372
22	20 not 21	2059259
23	19 not 22	3299754
24	limit 23 to english language	2943956
25	(case reports or comment or congresses or editorial or letter or review).pt.	3404522
26	24 not 25	2391448
27	exp Eczema/ or eczema.mp.	10057
28	exp Dermatitis, Atopic/	11850
29	neurodermatitis.mp. or exp Neurodermatitis/	361
30	exp Dermatitis/ or dermatitis.mp.	56920
31	27 or 28 or 29 or 30	59874
32	dupilumab.mp.	73
33	crisaborole.mp.	7

34	phototherapy.mp.	8466
35	uva.mp.	4949
36	uvb.mp.	6797
37	uva1.mp.	279
38	puva.mp.	2409
39	32 or 33	80
40	31 and 39	47
41	34 or 35 or 36 or 37 or 38	18673
42	31 and 41	1273
43	limit 42 to yr="2012 - 2017"	218
44	"nasal polyps".mp.	4657
45	"nasal polyposis".mp.	1877
46	44 or 45	5126
47	exp asthma/ or asthma.mp.	111598
48	46 or 47	115647
49	40 or 43	264
50	26 and 49	80
51	39 and 48	44
52	50 or 51	112

Table 2. Search strategy of Cochrane Database of Systematic Reviews (Ovid)

1	eczema.mp.	155
2	neurodermatitis.mp.	17
3	dermatitis.mp.	211
4	'atopic dermatitis'.mp.	61
5	1 or 2 or 3 or 4	303
6	dupilumab.mp.	1
7	crisaborole.mp.	0
8	phototherapy.mp.	133
9	topical$.mp.	902
10	'calcineurin inhibitor$'.mp.	64
11	"uva".mp.	29
12	"uvb".mp.	26
13	"uva1".mp.	1
14	"puva".mp.	27
15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1031
16	5 and 15	131

Table 3. Search strategy of EMBASE (trials)

1	'eczema'/exp OR eczema	43437
2	'atopic dermatitis'/exp OR 'atopic dermatitis'	37422
3	'neurodermatitis'/exp OR neurodermatitis	3914
4	'dermatitis'/exp OR dermatitis	167368
5	#1 OR #2 OR #3 OR #4	171432
6	dupilumab:ti,ab	83
7	crisaborole:ti,ab	19
8	phototherapy:ti,ab	8572
9	#6 OR #7	102
10	#5 AND #9	70
11	uva:ti,ab	9048
12	uvb:ti,ab	11049
13	uva1:ti,ab	387
14	puva:ti,ab	4051
15	#8 OR #11 OR #12 OR #13 OR #14	26596
16	#5 AND #15 AND [2012-2017]/py	630
17	#10 OR #16	698
18	random*:ab,ti OR placebo*:ab,ti OR 'single blind*':ab,ti OR 'double blind*':ab,ti OR 'triple blind*':ab,ti	1,274,898
19	'cohort analysis'/de OR 'cohort analysis'	267025
20	'longitudinal study'/de OR 'longitudinal study'	111437
21	'prospective study'/de OR 'prospective study'	408068
22	'follow-up'/de OR 'follow-up'	1469464
23	'case control study'/de OR 'case control study'	146162
24	'matched-pair analysis'/de OR 'matched-pair analysis'	232273
25	'cross-over study'/de OR 'cross-over study'	52778
26	'cohort*':ti,ab	607980
27	'case* and control*':ti,ab	21736
28	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	2631363
29	'compar*':ti,ab	5632213
30	'effective*':ti,ab	1962911
31	'versus':ti,ab	673974
32	'vs.':ti,ab	948187
33	#29 OR #30 OR #31 OR #32	7619900
34	#28 AND #33	1256865
35	#28 AND #33	2,315,603
36	#17 AND #35	121

Table 4. Search strategy of EMBASE (systematic reviews)

1	'eczema'/exp OR eczema	43437
2	'atopic dermatitis'/exp OR 'atopic dermatitis'	37422
3	'neurodermatitis'/exp OR neurodermatitis	3914
4	'dermatitis'/exp OR dermatitis	167368
5	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis	171432
6	dupilumab:ti,ab	83
7	crisaborole:ti,ab	19
8	phototherapy:ti,ab	8572
9	'calcineurin inhibitor':ti,ab	4975
10	'steroid':ti,ab	162605
11	'topical':ti,ab	108916
12	uva:ti,ab	9048
13	uvb:ti,ab	11049
14	uva1:ti,ab	387
15	puva:ti,ab	4051
16	dupilumab:ti,ab OR crisaborole:ti,ab OR phototherapy:ti,ab OR 'calcineurin inhibitor':ti,ab OR 'steroid':ti,ab OR 'topical':ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab	294432
17	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (dupilumab:ti,ab OR crisaborole:ti,ab OR phototherapy:ti,ab OR 'calcineurin inhibitor':ti,ab OR 'steroid':ti,ab OR 'topical':ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab)	15229
18	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (dupilumab:ti,ab OR crisaborole:ti,ab OR phototherapy:ti,ab OR 'calcineurin inhibitor':ti,ab OR 'steroid':ti,ab OR 'topical':ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	252

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. One reviewer will screen the titles and abstracts of all publications identified through electronic searches according to the inclusion and exclusion criteria defined by the PICOTS elements; a second reviewer will work with the initial reviewer 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.

Data Extraction Strategy

For the systematic literature review, the data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles.
2. Extracted data will be reviewed for logic, and a second reviewer will validate the extracted data.

Information from the accepted studies will be extracted into data extraction forms.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, multiple assessments of publication bias will be performed. We will first scan the ClinicalTrials.gov site to identify studies completed more than two years ago 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, in order to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

Data on relevant outcomes will be summarized in evidence tables, and synthesized qualitatively in the text of the report. Evidence table shells are presented in Appendix B. Data Extraction Summary Table Shells. We will conduct meta-analyses where appropriate to combine results about particular interventions and comparators. To perform indirect comparisons, we will conduct network meta-analyses (NMA) using a mixed treatment comparison approach, where possible.[25] Quantitative analyses will focus attention on the effects of the regimens of interest on treatment response and/or disease activity, and will be conducted using WinBUGS statistical software for Bayesian analysis (MRC Biostatistics Unit, Cambridge, UK). We will fit both fixed and random treatment effect models using non-informative normal priors. A total of 50,000 iterations each will be used for both “burn-in” (for model convergence) and model (for model results) simulations.

Given that dupilumab has not received FDA approval yet, and multiple doses were studied in clinical trials, we will explore whether different doses have differential treatment effects. Dupilumab trials also vary in terms of whether background topical corticosteroids are allowed, which may modify the treatment effects of dupilumab. We will examine these potential effect modifications by conducting subgroup meta-analyses on primary efficacy outcomes to assess the heterogeneity between subgroups. Tests of heterogeneity (I-squared and Q-statistic) will be used to assess the appropriateness of combining trials and arms of trials.

For NMA, review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance to the number of unconstrained data points will be used to assess model fit under multiple alternative assumptions.

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APPENDIX A. PRISMA CHECKLIST

The checklist below is drawn from Moher et al. 2009.[24]Additional explanation of each item can be found in Liberati, A., et al. 2009.[26]

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 SHELLS

Table B1. Study Characteristics

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