NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Comparative Clinical Effectiveness of Treatment Options for Moderate-to-Severe Plaque Psoriasis

Research Protocol (Update)

February 20, 2018

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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Background, Objectives, and Research Questions

Background

Psoriasis is a common disease that causes itchy, red, scaly, raised lesions on the skin, most commonly on the elbows, knees, scalp, and back.[1] Psoriasis affects about 2% of the population and significantly decreases health-related quality of life, particularly if lesions are in areas that can affect daily functioning (e.g., the hands or soles of the feet) or social functioning (e.g., the face).[2-4] Psoriasis is a chronic inflammatory condition that is associated with systemic diseases including psoriatic arthritis, other autoimmune diseases, metabolic syndrome, and cardiovascular disease.[5]

Cutaneous psoriasis types include plaque psoriasis, guttate psoriasis, pustular psoriasis, inverse psoriasis, nail psoriasis, and erythrodermic psoriasis. Chronic plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis. Up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis.[6]

Plaque psoriasis is caused by dysregulation of innate and adaptive immunity in genetically susceptible people.[5] This dysregulation produces an overabundance of inflammatory mediators such as tumor necrosis factor (TNF)-α and interleukins (IL)-12, 23, and 17A. Activated immune cells and inflammatory mediators lead to overgrowth, scaling, redness, and other changes in psoriatic skin.

Roughly 70% to 80% of patients with plaque psoriasis have mild disease that can be adequately managed with topical therapy. Definitions of "moderate-to-severe" plaque psoriasis vary, but generally consist of psoriasis that affects at least 3% of a patient's body surface; produces lesions that have significant redness, thickness, and scale; or significantly reduces quality of life.[7,8]

Treatments for psoriasis can be grouped within four broad categories: 1) topical therapies such as steroids, vitamin D analogues, retinoids, and calcineurin inhibitors; 2) older systemic therapies, such as cyclosporine and methotrexate; 3) phototherapy such as psoralen and ultraviolet A radiation (PUVA); and 4) biologics or "targeted immunomodulators." Clinical interest in this last category is high, as many patients with chronic plaque psoriasis do not see adequate or durable benefit from older systemic therapies or phototherapy. Additionally, targeted immunomodulators are associated with a high financial cost, some of which is passed on to patients. Targeted immunomodulators approved, or nearing approval, for the treatment of moderate-to-severe plaque psoriasis in the United States consist of medications with activity against the following targets:

- **Anti-TNF-α agents**: adalimumab (Humira®, AbbVie Inc.), etanercept (Enbrel®, Amgen Inc.), infliximab (Remicade®, Janssen Biotech Inc., approved only for severe plaque psoriasis),

certolizumab pegol (Cimzia®, UCB Inc., approved for rheumatoid arthritis, under FDA review for psoriasis)

- **Anti-IL-17A agents**: secukinumab (Cosentyx®, Novartis AG), ixekizumab (Taltz®, Eli Lilly and Co.), brodalumab (Siliq™, Ortho Dermatologics)
- **Anti-IL-12/23 agent**: ustekinumab (Stelara®, Janssen Biotech Inc.)
- **Anti-IL-23 agents**: guselkumab (Tremfya™, Janssen Biotech Inc., approved in July 2017), tildrakizumab (Sun Pharma / Merck and Co., under FDA review)
- **Phosphodiesterase (PDE-)4 agent**: apremilast (Otezla®, Celgene Corp.) Although not technically a biologic, apremilast is a novel, targeted, oral agent also approved for treatment of patients with moderate-to-severe plaque psoriasis.

Treatment of plaque psoriasis can be challenging for patients. It can be difficult to apply topical therapies, especially when the affected area involves the scalp or covers a large part of the body. Therapies can be inconvenient to use; some require multiple injections on a daily or weekly basis. Insurance plans generally mandate "step therapy," which requires patients and clinicians to first try a list of preferred medications and, only after repeated treatment failures, progress to non-preferred treatments.

Studies have found that up to half of patients are dissatisfied with psoriasis treatment.[2,9] Dissatisfaction may be due to the unpredictable effectiveness of agents, poor tolerability, lack of durable response, and lack of access to medications because of coverage restrictions or costs.[2] The newer targeted immunomodulators are generally more expensive than older medications and there are questions regarding how these costs align with the clinical value brought to patients. ICER conducted a review in 2016 to assess the comparative clinical effectiveness and value of targeted immunomodulators (biologics plus apremilast) for adults with moderate-to-severe plaque psoriasis.

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 is an update on a previous report we published in 2016 (Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value (2016)) that assessed the comparative clinical effectiveness and economic impacts of eight targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis. The current project aims to systematically evaluate and update evidence on the eight drugs in the 2016 review and include evidence on three new drugs (certolizumab pegol, guselkumab, and tildrakizumab). 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 Question

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

- In patients with moderate-to-severe plaque psoriasis, what is the comparative efficacy, safety, and effectiveness of targeted immunomodulators versus placebo or other active treatments in terms of 50%, 75%, 90% or 100% reduction in Psoriasis Area and Severity Index (PASI 50, 75, 90, 100), Dermatology Life Quality Index (DLQI), adverse events, and other key outcomes?

PICOTS Criteria

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

Population

The population of focus for this review is adults with moderate-to-severe chronic plaque psoriasis. We will also seek evidence on key subpopulations and/or data stratifications of interest including those defined by: (a) presence of psoriatic arthritis or other concomitant psoriasis types; (b) previous treatment with a targeted immunomodulator; and (c) demographics (e.g. age, race)

Interventions

The interventions of interest are the targeted immunomodulators (biologics and apremilast) approved or expected to be approved, by July 2018 for the treatment of moderate-to-severe plaque psoriasis:

- **Anti-TNF-α agents**: adalimumab, etanercept, infliximab, certolizumab pegol (not yet approved for psoriasis)
- **Anti-IL-17A agents**: secukinumab, ixekizumab, brodalumab
- **Anti-IL-12/23 agent**: ustekinumab
- **Anti-IL-23 agents**: guselkumab (approved in 2017), tildrakizumab (not yet approved)
- **Anti-PDE-4 agent**: apremilast

Comparators

Wherever possible, we will evaluate head-to-head trials of these interventions. Other comparators may include placebo or other active treatments not listed above (e.g., methotrexate).

Outcomes

We will be evaluating the same outcomes as the 2016 review. These outcomes include:

Clinical Trial and Study Outcomes

- Psoriasis Area and Severity Index (PASI): 50, 75, 90. PASI 100 was not assessed in the 2016 review. For this review, we will look for data on PASI 100, and present it where it is reported.
- Physician Global Assessment (PGA)
- Investigator Global Assessment (IGA)
- Treatment-related adverse events

Patient-Reported Outcomes

- Dermatology Life Quality Index (DLQI)
- Other measures of health-related quality of life
- Psoriasis Symptom Inventory (PSI)
- Symptom control
- Treatment tolerability

Timing

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies of any duration. Because psoriasis is a chronic condition with no cure, we are particularly interested in evidence of durability of response to medications, as well as long-term safety.

Setting

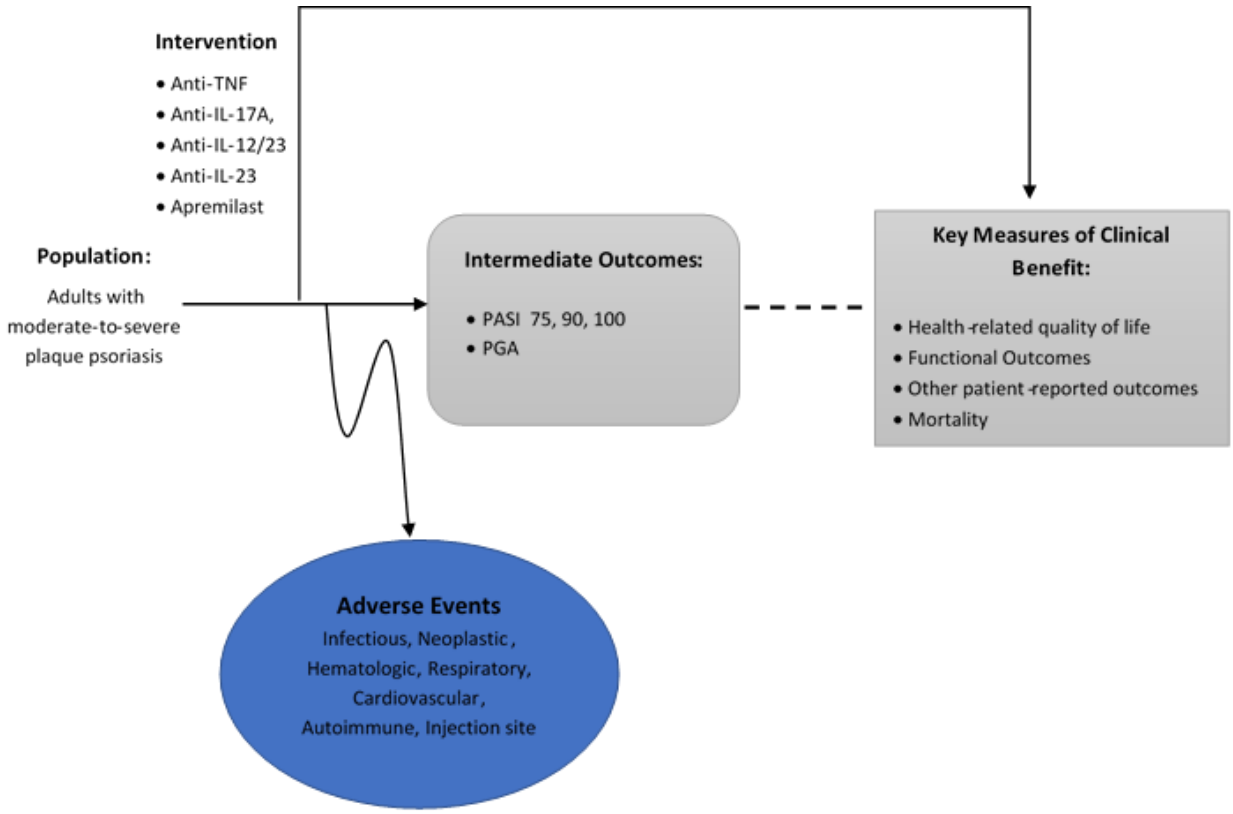
Plaque psoriasis is generally treated in outpatient and/or clinic settings, which will be the focus of our review.

Study design

Randomized controlled trials with any sample size will be included. Higher quality comparative observational studies (sample size > 500) will also be evaluated as necessary.

Analytic Framework

The proposed analytic framework for this project is depicted below:



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in blood pressure), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on targeted immunomodulators for moderate-to-severe plaque psoriasis will follow established best methods.[10,11] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials 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, and are presented in Tables 1-2 below.

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 1: Updated search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials on 2016 review

1	Psoriasis/	18421
2	psoria$.ti,ab.	28290
3	(secukinumab or cosentyx).ti,ab.	518
4	(ustekinumab or stelara).ti,ab.	979
5	(ixekizumab or taltz).ti,ab.	234
6	brodalumab.ti,ab.	138
7	(apremilast or otezla).ti,ab.	334
8	1 or 2	30099
9	3 or 4 or 5 or 6 or 7	1953
10	8 and 9	1541
11	limit 10 to english language	1468
12	limit 11 to humans	1467
13	(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.conference or congresses).pt.	3057911
14	12 not 13	1059
15	remove duplicates from 14	884
16	limit 15 to ed=20160628-20171208	632
Date of Search: January 2, 2018		

Table 2: Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials on new drugs

1	Psoriasis/	18421
2	psoria$.ti,ab.	28290
3	(certolizumab pegol or cimzia).ti,ab.	647
4	(guselkumab or tremfya).ti,ab.	42
5	tildrakizumab.ti,ab.	28
6	1 or 2	30099
7	3 or 4 or 5	705
8	6 and 7	154
9	limit 8 to english language	152
10	limit 9 to humans	152
11	(guideline or practice guideline or letter or editorial or news or case reports or clinical conferences or congresses).pt	2049847
12	10 not 11	149
13	remove duplicates from 12	129
Date of Search: January 2, 2018		

Table 3. Update on the 2016 search strategy in EMBASE

#21	#20 AND [28-6-2016]/sd	712
#20	#19 AND [humans]/lim	1568
#19	#18 NOT 'case report' NOT 'case study'	1679
#18	#15 NOT #16 NOT #17	1184
#17	#15 AND [humans]/lim AND [animals]/lim	32
#16	#15 AND [animals]/lim	40
#15	#13 NOT #14	1224
#14	#12 AND [medline]/lim	413
#13	#12 AND [english]/lim	1622
#12	#10 NOT #11	1683
#11	#3 AND #9 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR	122
#10	#3 AND #9	1805
#9	#4 OR #5 OR #6 OR #7 OR #8	2235
#8	'brodalumab':ab,ti	127
#7	'apremilast':ab,ti OR 'otezla':ab,ti	331
#6	'ixekizumab':ab,ti OR 'taltz':ab,ti	156
#5	'ustekinumab':ab,ti OR 'stelara':ab,ti	1454
#4	'secukinumab':ab,ti OR 'cosentyx':ab,ti	399
#3	#1 OR #2	58457
#2	psorias*:ab,ti OR psoriat*:ab,ti	57572
#1	'psoriasis vulgaris'	8040

Table 4. search strategy in EMBASE

#18	#17 AND [humans]/lim	211
#17	#16 NOT 'case report' NOT 'case study'	1679
#16	#13 NOT #16 NOT #17	1184
#15	#13 AND [humans]/lim AND [animals]/lim	32
#14	#13 AND [animals]/lim	40
#13	#11 NOT #12	1224
#12	#10 AND [medline]/lim	413
#11	#10 AND [english]/lim	1622
#10	#8 NOT #7	1683
#9	#3 AND #7 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR	122
#8	#3 AND #7	1805
#7	#4 OR #5 OR #6	1546
#6	'certolizumab pegol':ab,ti OR 'cimzia':ab,ti	1463
#5	'tildrakizumab':ab,ti	40
#4	'guselkumab':ab,ti OR 'tremfya':ab,ti	61
#3	#1 OR #2	58457
#2	psorias*:ab,ti OR psoriat*:ab,ti	57572
#1	'psoriasis vulgaris'	8040

Eligibility Criteria

Studies that do not meet the PICOTS criteria defined above will be excluded. We will include information on biosimilar agents that are FDA-approved for the treatment of plaque psoriasis, if clinical studies have been conducted in the target population that focus on the outcomes of interest. Studies focused only on bioequivalence (e.g., pharmacokinetics, pharmacodynamics) of biosimilar and originator products will be excluded. Additional excludion criteria include: (a) studies in which comparator arm is a class of drugs (e.g., anti-TNFs) that do not report drug specific outcomes; (b) studies that describe only outcomes that are specific to other concomitant psoriasis types (e.g., American College of Rheumatology (ACR) in psoriatic arthritis).

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 DistillerSR (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.

Data Extraction Strategy

Data will be extracted into Excel spreadsheet. 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.

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."[13]

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 these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include [the name of each drug in our review] AND [psoriasis]. 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.

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 and (2) a synthesis of outcome results.

Summary of Evidence Base

All studies selected from the systematic review will be summarized in the text and in evidence tables of the Evidence Report. An example of the evidence table shell is presented in Appendix B. This summary is key to understanding the existing evidence base pertaining to the topic. 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.

All studies deemed sufficiently similar in terms of the key population, intervention, and outcome measures will be included in a quantitative synthesis. For this report, a network meta-analysis (NMA) under a Bayesian framework will be conducted on PASI 50, 75 and 90 responses. PASI 100 will be included, if data permits. A NMA simultaneously combines both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)). [14,15] PASI responses will be evaluated at 12-16 weeks. If a

study reports results at more than one time point between 12 and 16 weeks (inclusive), the results at the later time point will be used.

PASI 50, 75, and 90 responses will be analyzed jointly in an ordered multinomial model with probit link.[16] The model assumes the presence of an unobserved underlying continuous variable (e.g., PASI) that has been categorized at different thresholds (e.g., 50%, 75%, 90% response). This model allows for the inclusion of data from trials that use different thresholds or a different number of thresholds. We will make the following additional assumptions for this model: the thresholds will be fixed across trials, trial-specific treatment effects will be drawn from a common distribution (i.e., random treatment effects model), and the amount of between-study variance (i.e., heterogeneity) will be constant across all treatment comparisons. The base case model will also include a covariate for placebo response, which will be assumed to be common across all treatments, and will provide a control for known and unknown differences between study populations.[17]

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[18] If there is evidence of inconsistency, the results will be presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

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 patients with psoriatic arthritis, patients that have been previously treated with a targeted immunomodulator. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist. As noted above, the base case model will include a covariate for placebo response; we will also conduct a separate analysis without the covariate for comparison.

All NMAs will be conducted using JAGS software (version 4.3.0) via R using the R2jags package.[19] For all analyses we will use noninformative prior distributions for all model parameters. We will initially discard the first 40,000 iterations as "burn-in" and base inferences on an additional 40,000 iterations using three chains. Convergence of chains will be assessed with the Gelman-Rubin statistic and visually using trace plots. If the chains do not converge, an additional 10,000 iterations will be run, sequentially, until convergence. Data included in each analysis along with the corresponding code will be included in an appendix of the report. Results for all pairwise comparisons will be presented in tabular fashion in terms of a point estimate and 95% credible intervals.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[12] Additional explanation of each item can be found in Liberati et al. 2009.[20]

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.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shell

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