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COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A:

Effectiveness and Value

Research Protocol

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Table of Contents

Background, Objectives, and Research Questions 2
Background 2
Objectives 4
Research Questions 5
PICOTS Criteria 5
Evidence Review Methods 7
Search Methods and Data Sources 7
Selection of Eligible Studies 10
Data Extraction Strategy 11
Quality Assessment Criteria 11
Publication Bias Assessment 12
Evidence Synthesis 12
References 13
Appendix A. PRISMA Checklist 1
Appendix B. Data Extraction Summary Table Shell 2

Background, Objectives, and Research Questions

Background

ICER reviewed emicizumab for hemophilia A in patients with factor inhibitors in 2018 (Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value). Much of the background information in this research protocol document is reproduced from that report.

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, which disrupts the clotting cascade (Figure 1). Hemophilia A has X-linked recessive inheritance, and so predominately affects males. It is the most common of the hemophilias with an incidence of one in 5,000 male births.[1] The exact prevalence of hemophilia in the United States (US) is not known, but is estimated to be around 20,000.[2] Approximately 77% of all hemophilia patients in the US have hemophilia A.[3]

Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into a joint (hemarthrosis) or muscle is more common and can lead to substantial disability.[4] Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint.

Severity of hemophilia A has generally been defined by factor levels (the percentage of normal factor that a patient has).[5] However, severity based on factor levels does not perfectly correlate with actual clinical severity.[6] Despite this, other severity classifications are not yet widely accepted, and factor levels define severity in most clinical trials. Using factor level classifications, severe disease is defined by factor VIII levels below 1% of normal.[5] Patients with severe disease who are not receiving prophylactic treatment experience an average of 20 to 30 episodes of spontaneous bleeding or excessive bleeding after minor trauma per year.[1] Patients with moderate disease (factor VIII levels of 1% to 5% of normal) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous bleeding.[7] Individuals with mild disease (factor VIII levels between 5% to 40% of normal) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries.

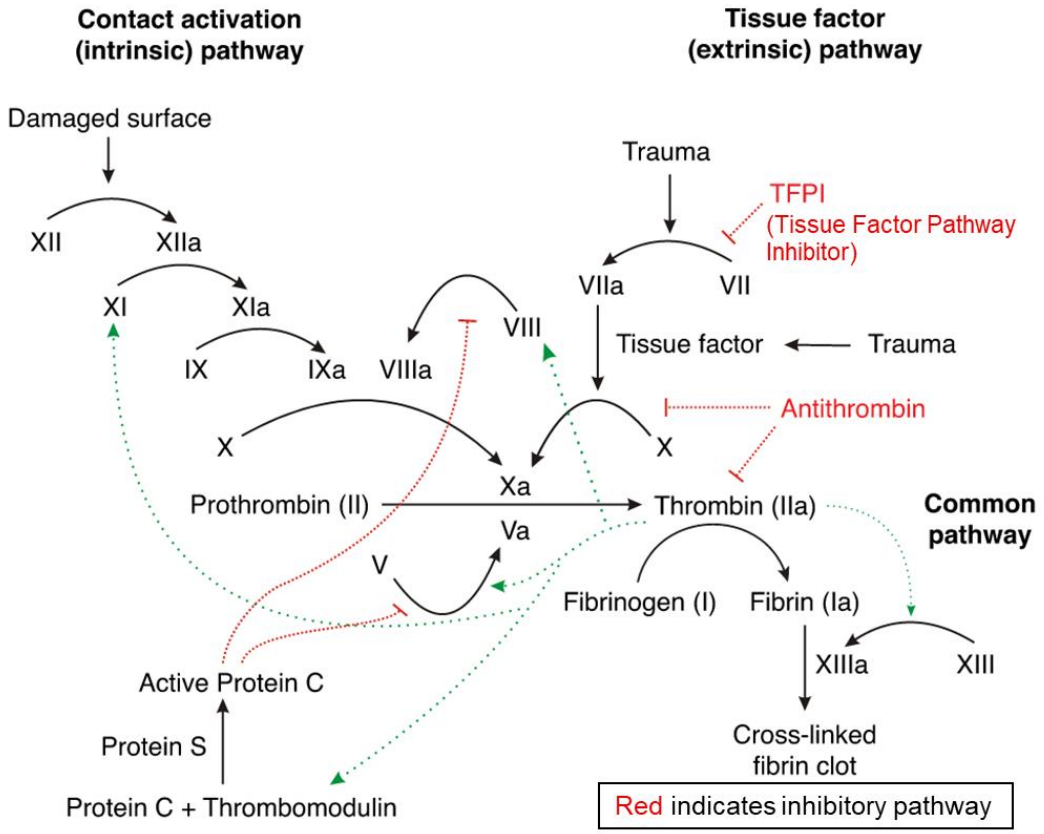
To reduce the risk of bleeding, patients with severe hemophilia A have typically administered factor VIII concentrate intravenously multiple times per week.[7,8] The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A. However, prophylaxis with factor replacement is burdensome and does not maintain patients at normal levels of factor VIII. A number of factor VIII preparations are available for prophylaxis, some with modifications to extend the half-life of the therapy, some prepared from human plasma, and some prepared using recombinant technology.

Emicizumab-kxwh (Hemlibra®, Genentech, referred to as "emicizumab" in this draft scope) is a monoclonal antibody with dual targets ("bispecific") that allow it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade (Figure 1).[9] Emicizumab was approved by the US Food and Drug Administration (FDA) as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII in 2017 and in those without inhibitors in 2018.[10] Emicizumab is administered subcutaneously and may be dosed weekly, every two weeks, or every four weeks based on provider and patient preference.

ICER found in 2018 that in patients with factor inhibitors, prophylaxis with emicizumab was cost saving (Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value), even though the wholesale acquisition cost (WAC) of emicizumab was approximately $482,000 for the first year of treatment and $448,000 for subsequent years at the time.

Valoctocogene roxaparvovec is an adeno-associated virus serotype 5 (AAV5) mediated gene therapy for hemophilia A.[11] It delivers a B-domain-deleted gene to cells in the liver, resulting in production of an active variant of factor VIII. Published information is available on a limited number of patients who received therapy with valoctocogene roxaparvovec, with up to three years of follow-up. BioMarin submitted a biologics license application for valoctocogene roxaparvovec to the FDA in December 2019.

Figure 1. Illustration of Activated Factor VIII in the Clotting Cascade



Source: Joe Dunckley, own work. Adapted with permission under the conditions of CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=1983833.

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 valoctocogene roxaparvovec and emicizumab for the treatment of hemophilia A. 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 hemophilia A without inhibitors to factor VIII, what is the comparative efficacy, safety, and effectiveness of valoctocogene roxaparvovec versus emicizumab in terms of bleeding events, pain, quality of life, mental health status, mortality, burdens of treatment, adverse events and other key outcomes?
- In patients with hemophilia A without inhibitors to factor VIII, what is the comparative efficacy, safety, and effectiveness of valoctocogene roxaparvovec versus prophylaxis with factor VIII preparations in terms of bleeding events, factor activity level, pain, quality of life, mental health status, mortality, burdens of treatment, adverse events and other key outcomes?
- In patients with hemophilia A without inhibitors to factor VIII, what is the comparative efficacy, safety, and effectiveness of emicizumab versus prophylaxis with factor VIII preparations in terms of bleeding events, pain, quality of life, mental health status, mortality, burdens of treatment, adverse events and other key outcomes?

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 focus for this review will be people with hemophilia A without inhibitors to factor VIII who would be appropriate for routine prophylaxis with factor VIII. For valoctocogene roxaparvovec, we will limit the review to an adult population.

Interventions

The interventions of interest for this review are listed below:

- Valoctocogene roxaparvovec
- Emicizumab

Comparators

Data permitting, we intend to compare the interventions to each other and to prophylaxis with factor VIII preparations.

Outcomes

For this review, we will look for evidence on the following outcomes of interest:

- Patient Important Outcomes:
    - Patient-reported quality of life
    - Rates of bleeding events
    - Rates of treated bleeding events
    - Rates of treated joint bleeding and treated target joint bleeding
    - Pain (chronic and acute)
    - Mental health status
    - Burdens of therapy
    - Mortality
    - Adverse events including:
        - Thrombosis
        - Liver toxicity

- Other outcomes:
    - Factor level (factor activity level)
    - Duration of expression of the clotting factor gene
    - Utilization of healthcare system
    - Adverse events including:
        - Immune response to FVIII (Inhibitor development)
        - Immune response to gene therapy

We will also look for evidence on additional patient-reported outcomes, such as employment, disability status, social engagement, overall well-being, mobility (activity), anxiety, and depression, as available, as well as outcomes for family and caregivers, particularly for younger children with hemophilia A.

Timing

Evidence on intervention effectiveness will be derived from studies of any duration, as long as they meet the study design criteria set forth above and measure the outcomes of interest.

Setting

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Study design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. Comparative observational studies will also be included.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on valoctocogene roxaparvovec and emicizumab for hemophilia A will follow established best methods.[12,13] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] 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 https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/).

Table 1: Search Strategy for Interventions: Medline 1996 to Present with Daily Update, and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations

1	(emicizumab or ace910 or ace 910 or ace-910 or rg6013 or rg 6013 or rg-6013 or emicizumab-kxwh or emicizumab kxwh or hbs910).ti,ab

2	(valoctocogene roxaparvovec or valrox or bmn 270 or bmn270 or bmn-270 or aav5-hfviii or aav5-hfviii-sq or aav5 hfviii or aav5 hfviii sq).ti,ab
3	1 or 2
4	animals.sh.
5	3 not 4
6	limit 5 to english language
7	remove duplicates from 6

Table 2. Search strategy for Interventions: EMBASE SEARCH

1	emicizumab':ti,ab OR 'ace910':ti,ab OR 'ace 910':ti,ab OR 'ace-910':ti,ab OR 'rg6013':ti,ab OR 'rg 6013':ti,ab OR 'rg-6013':ti,ab OR 'emicizumab-kxwh':ti,ab OR 'emicizumab kxwh':ti,ab OR 'hbs910':ti,ab
2	valoctocogene roxaparvovec':ti,ab OR 'valrox':ti,ab OR 'bmn 270':ti,ab OR 'bmn270':ti,ab OR 'bmn-270':ti,ab
3	#1 OR #2
4	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
5	#3 NOT #4
6	#5 AND [english]/lim

Table 3: Search Strategy for Comparators: Medline 1996 to Present with Daily Update, and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations

1	h?emophilia a/
2	(hemophilia a or haemophilia a or hemophilia type a or haemophilia type a).ti,ab
3	(classical hemophilia or classical haemophilia or classic hemophilia or classic haemophilia).ti,ab
4	(factor viii adj2 deficienc* or factor 8 adj2 deficienc* or factor viii' adj1 deficienc* or factor 8' adj1 deficienc*).ti,ab
5	1 or 2 or 3 or 4
6	(factor viii product or fviii product or factor 8 product or recombinant factor viii or recombinant fviii or recombinant factor 8 or rfviii or r-fviii or rhfviii or antihemophilic adj1 factor* OR antihaemophilic adj1 factor* OR anti adj1 hemophilic adj1 factor* OR anti adj1 haemophilic adj1 factor*).ti,ab
7	('factor viii' OR 'fviii' OR 'factor 8').ti,ab AND (treatment OR therapy OR treated OR regimen* OR concentrate* OR recombinant OR dose*: OR dosing OR prophylaxis OR prophylactic OR agent* OR medication* OR infusion* OR 'plasma-derived').ti,ab
8	(advate or antihemophilic factor or recombinant or recombin* or rahf-pfm or rahf pfm or octocog alfa).ti,ab
9	(adynovate* or adynovi* or recombinate* or BAX 855 OR BAX-855 OR BAX855 OR SHP660).ti,ab
10	(afstyla or rviii-sc or rfviii sc).ti,ab
11	(eloctate or biib031 or rfviiifc or elocta* or elocta or efmoroctocog alfa).ti,ab
12	(humate-p or humate p or haemate-p or haemate p).ti,ab
13	(jivi or bay94-9027 or bay94 9027 or BAY 94 -9027 or BAY 94 9027).ti,ab
14	(kogenate fs or kogenate bayer or bay14-2222 or bay 14 2222 or bay14 2222 or octocog alfa or helixate nexgen).ti,ab

15	(kovaltry or iblias or bay818973 or bay 81 8973 or bay 81-8973).ti,ab
16	(novoeight or n8 or nove eight or nn7008 or nn 7008 or nn-7008 or turoctocog alfa).ti,ab
17	(nuwiq or simoctocog alfa).ti,ab
18	(refacto or xyntha or refacto af).ti,ab
19	(alphanate or fahndi).ti,ab
20	(hemofil m or haemofil m or monarc m).ti,ab
21	(koate or koate dvi or koate-dvi).ti,ab and infusion.ti,ab
22	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	5 and 22
24	animals.sh
25	23 not 24
26	25 not (case report OR human tissue OR nonhuman OR practice guideline OR questionnaire OR chapter OR conference review OR editorial OR letter OR note OR review OR short survey).pt.
27	26 and (clinical trial or randomized controlled trial or placebo or open label or crossover or cross-over or prospective study or clinical trial or clinical trial, phase i 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 or (random?ed adj6 (study or trial* or (clinical adj2 trial*)))).ti,ab
28	Limit 27 to English Language
29	Remove duplicates from 28

Table 4. Search strategy for Comparators: EMBASE SEARCH

1	'hemophilia a'/exp OR 'haemophilia a'/exp
2	'hemophilia a':ti,ab OR 'haemophilia a':ab,ti OR 'hemophilia type a':ti,ab OR 'haemophilia type a':ti,ab
3	'classical hemophilia':ti,ab OR 'classical haemophilia':ti,ab OR 'classic hemophilia':ti,ab OR 'classic haemophilia':ti,ab
4	(('factor viii' NEAR/4 deficienc*):ti,ab) OR (('factor 8' NEAR/4 deficienc*):ti,ab) OR (('factor viii' NEXT/1 deficienc*):ti,ab) OR (('factor 8' NEXT/1 deficienc*):ti,ab)
5	#1 OR #2 OR #3 OR #4
6	'factor viii product':ti,ab OR 'fviii product':ti,ab OR 'factor 8 product' OR 'recombinant factor viii':ti,ab OR 'recombinant fviii':ti,ab OR 'recombinant factor 8' OR rfviii:ti,ab OR 'r-fviii':ti,ab OR rhfviii:ti,ab OR (antihemophilic NEXT/1 factor*):ti,ab OR (antihaemophilic NEXT/1 factor*):ti,ab OR (anti NEXT/1 hemophilic NEXT/1 factor*):ti,ab OR (anti NEXT/1 haemophilic NEXT/1 factor*):ti,ab
7	'factor viii':ti,ab OR fviii:ti,ab OR 'factor 8':ti,ab AND (treatment:ti,ab OR therapy:ti,ab OR treated:ti,ab OR regimen*:ti,ab OR concentrate*:ti,ab OR recombinant:ti,ab OR dose*:ti,ab OR dosing:ti,ab OR prophylaxis:ti,ab OR prophylactic:ti,ab OR agent*:ti,ab OR medication*:ti,ab OR infusion*:ti,ab OR 'plasma-derived':ti,ab)
8	(advate OR antihemophilic factor OR recombinant OR recombin* OR rahf-pfm OR rahf pfm OR octocog alfa):ti,ab
9	(adynovate* OR adynovi* OR recombinate* OR BAX 855 OR BAX-855 OR BAX855 OR SHP660):ti,ab
10	(afstyla OR rviii-sc OR rfviii sc):ti,ab

11	(eloctate OR biib031 OR rfviiifc OR elocta* OR elocta OR efmoroctocog alfa):ti,ab
12	(humate-p OR humate p OR haemate-p OR haemate p):ti,ab
13	(jivi OR bay94-9027 OR bay94 9027 OR BAY 94 -9027 OR BAY 94 9027):ti,ab
14	(kogenate fs OR kogenate bayer OR bay14-2222 OR bay 14 2222 OR bay14 2222 OR octocog alfa OR helixate nexgen):ti,ab
15	(kovaltry OR iblias OR bay818973 OR bay 81 8973 OR bay 81-8973):ti,ab
16	(novoeight OR n8 OR nove eight OR nn7008 OR nn 7008 OR nn-7008 OR turoctocog alfa):ti,ab
17	(nuwiq OR simoctocog alfa):ti,ab
18	(refacto OR xyntha OR refacto af):ti,ab
19	(alphanate OR fahndi):ti,ab
20	(hemofil m OR haemofil m OR monarc m):ti,ab
21	(koate OR koate dvi OR koate-dvi):ti,ab AND infusion:ti,ab
22	#6 or #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23	#5 AND #22
24	(‘animal’/exp or ‘nonhuman’/exp or ‘animal experiment’/exp) NOT ‘human’/exp
25	#23 NOT #24
26	#25 NOT ('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)
27	#26 AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'placebo'/de OR 'open label' OR 'crossover' OR 'cross-over' OR 'prospective study'/de)
28	#27 AND [english]/lim
29	#28 AND [medline]/lim
30	#28 NOT #29

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; 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. 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."[15]

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 "valoctocogene roxaparvovec", and "emicizumab". 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

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 intervention on each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base. Key considerations for interpreting the results will be specified and described in the Evidence Report.

For each outcome of interest, we will assess the feasibility of conducting a pairwise meta-analyses and/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. [16] A network meta-analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)).[17,18] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[14] Additional explanation of each item can be found in Liberati et al. 2009.[19]

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

Table Footnote