NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Comparative Clinical Effectiveness of Emicizumab for Hemophilia A

Research Protocol

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Background, Objectives, and Research Questions

Background

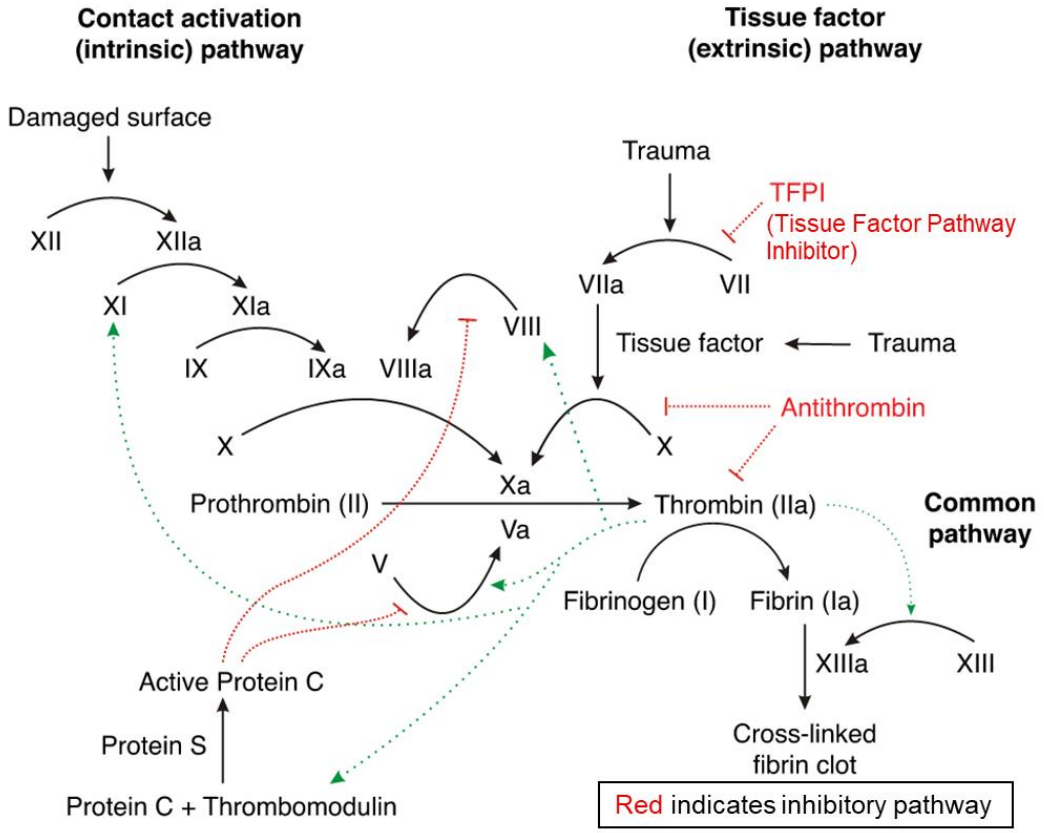
Hemophilia A, due to an inherited deficiency of factor VIII, is the most common type of hemophilia with an incidence of 1 in 5,000 male births.[1] Hemophilia A has X-linked recessive inheritance, and so affects mainly males. The exact prevalence of hemophilia in the United States is not known, but is estimated to be around 20,000.[2] The degree of factor deficiency determines the severity of the condition, with severe disease typically defined by factor levels below 1% of normal.[3] Without prophylactic treatment, patients with severe disease have an average of 20 to 30 episodes per year of spontaneous bleeding or excessive bleeding after minor trauma.[1] Patients with moderate disease (factor VIII levels of 1% to 5%) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous bleeding.[4] Those with mild disease (factor VIII levels of >5% to 40%) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries.

Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into joints (hemarthroses) and muscles is more common and can lead to substantial disability.[5] Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint. To reduce the risk of bleeding, patients with severe hemophilia A are typically administered factor VIII concentrate intravenously multiple times per week.[4,6] The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A.

Approximately 27% of patients with severe disease who receive factor VIII concentrates develop neutralizing antibodies known as "inhibitors."[7] As discussed below, inhibitors can resolve with treatment.[8] The overall prevalence of inhibitors across severity levels appears to be about 5-7%,[9] suggesting a total population of patients with inhibitors in the US of around 1,400; however, the exact prevalence is unknown.[10] Patients with low levels of inhibitors who develop bleeding can often be treated with higher doses of factor VIII, while those with high levels of inhibitors are treated with "bypassing agents" such as activated prothrombin complex concentrate (aPCC) or activated factor VII (FVIIa).[8] Treatment of a single bleeding episode can cost $50,000 or more, and some patients are treated prophylactically with bypassing agents, which can be extremely expensive, with cost estimates for factors in such patients of around $300,000 to $2.5 million per year.[11,12] The presence of inhibitors may increase mortality from hemophilia.[13] In some patients, inhibitors can be eradicated by inducing immune tolerance with high and then continual doses of factor VIII, which is also expensive but allows for prophylactic and episodic therapy with factor VIII alone when successful.[14]

Emicizumab is a monoclonal antibody with dual targets 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).[15] Emicizumab is currently being evaluated by the US Food and Drug Administration (FDA), with orphan and breakthrough designations, as a prophylactic treatment for hemophilia A in patients with factor VIII inhibitors.[15,16] It is administered subcutaneously, and is dosed weekly or less frequently, and is also being studied as a potential alternative for prophylaxis even in patients without inhibitors. For patients with severe hemophilia who have inhibitors, an effective prophylactic therapy could be life changing. Emicizumab is expected to be expensive, but may reduce the need for other costly therapies. The FDA is expected to issue a decision on approval by February 23, 2018.[15]

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 emicizumab for

prophylaxis in patients with hemophilia A and factor VIII inhibitors. 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 and factor VIII inhibitors, what is the comparative efficacy, safety, and effectiveness of prophylaxis with emicizumab versus no prophylaxis in terms of bleeding outcomes, pain, mortality, quality of life, thrombosis, burdens of treatment, and other key outcomes?
- In patients with hemophilia A and factor VIII inhibitors, what is the comparative efficacy, safety, and effectiveness of prophylaxis with emicizumab versus prophylaxis with bypassing agents in terms of bleeding outcomes, pain, mortality, quality of life, thrombosis, burdens of treatment, 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 is hemophilia A patients with inhibitors to factor VIII, who either have failed immune tolerance induction (ITI) or will not be treated with ITI. We plan to evaluate the existing evidence for the following two subgroups, defined by age:

1. Adolescents and adults (ages 12 and older)
2. Children (Younger than 12 years)

We will also seek evidence on other key subpopulations and/or data stratifications of interest, including those defined by: (a) level of hemophilia A severity (i.e., mild, moderate or severe hemophilia); (b) presence of target joint(s); (c) prior ITI attempt; (d) prior prophylaxis with bypassing agent(s); (e) time since diagnosis of inhibitors to factor VIII; and (f) other demographic subpopulations of interest, such as those defined by age (12-18; >18; >65) or race/ethnicity (Asian, Black or African American, Hispanic, white, others).

Interventions

The intervention of interest is subcutaneous injections of emicizumab (Roche, [investigational]) for prophylaxis. Patients may be treated with bypassing agents (recombinant FVIIa [NovoSeven®; Novo Nordisk] or aPCC [FEIBA; Shire]) when they bleed (i.e., on demand).

Comparators

We will compare prophylaxis with emicizumab to two alternatives:

1. No prophylactic therapy.
2. Prophylaxis with bypassing agents (recombinant FVIIa [NovoSeven®; Novo Nordisk] or aPCC [FEIBA; Shire]).

For both comparators, patients may be treated with bypassing agents when they bleed (i.e., on demand).

Outcomes

The following outcomes are of interest for this review.

Intermediate Outcomes

- Rates of bleeding events
- Rates of treated bleeding events
- Rates of treated joint bleeding and treated target joint bleeding
- Burdens of therapy (e.g., frequency of administration, route of administration, pain, etc.)
- Joint damage
- Number of emergency department visits and number of inpatient days
- Hospitalization
- Opioid dependence
- Red cell transfusion requirement
- Adherence
- Patient knowledge
- Additional patient reported outcomes (employment, disability status, social engagement, education attainment, missed days of work or school, anxiety, depression, overall well-being, as well as outcomes for family and caregivers, particularly for younger children with hemophilia A)

Key Measures of Clinical Benefit

- Patient-reported quality of life
- Functional outcomes (including mobility)
- Pain

- Mortality

Harms (e.g. thrombolytic events, thrombotic microangiopathy)

Timing

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies of any duration.

Setting

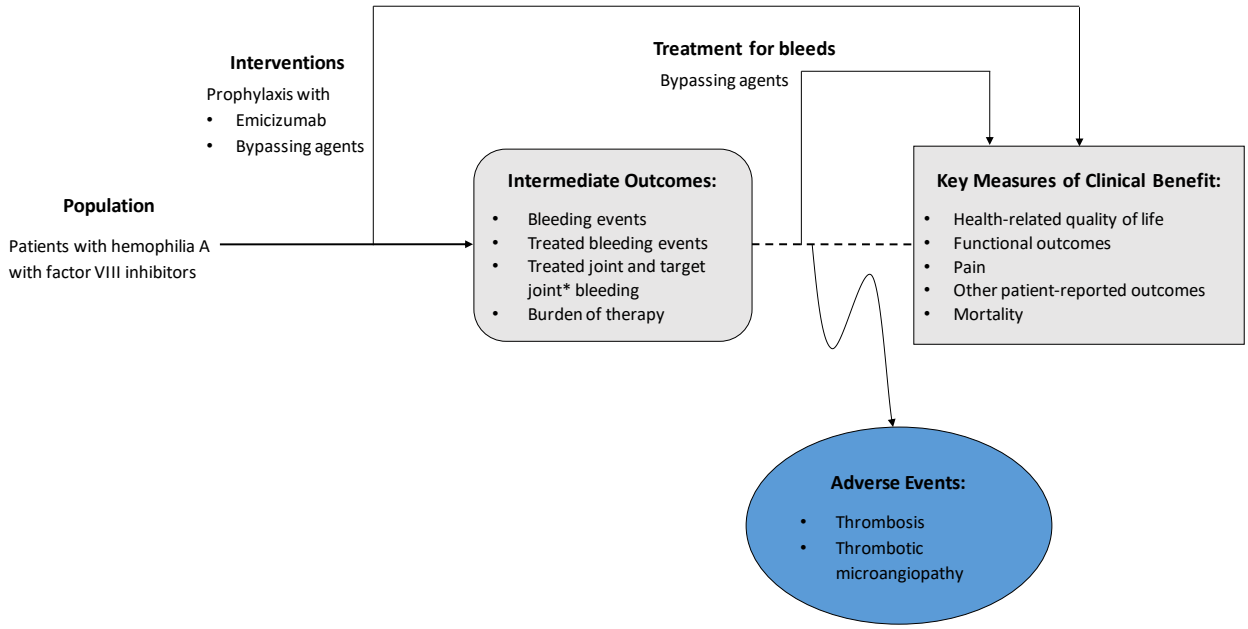
Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Study design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. Comparative observational studies (sample size > 10) will also be included.

Analytic Framework

The proposed analytic framework for this project is depicted below:



The diagram begins with the population of interest on the left (hemophilia A patients). Actions, such as prophylaxis and on-demand 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., bleeding), 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 emicizumab for prophylaxis in patients with hemophilia A and factor VIII inhibitors will follow established best methods.[17,18] The review will be conducted in accordance with the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials via the Ovid platform, and EMBASE directly via the EMBASE website. 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. The date of the most recent search is Oct 20, 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 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: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Central Register of Controlled trials

No.	Search terms	Results
1	h?emophilia A/	20198
2	h?eophilia A.mp.	22139
3	(h?emophilia adj5 factor 8).mp.	24
4	(h?emophilia adj5 factor viii).mp.	4609
5	1 or 2 or 3 or 4	22223
6	h?emophilia/	20198
7	h?emophilia.mp	26528
8	5 or 6 or 7	26528
9	h?emophilia B/	4258
10	h?emophilia B.mp.	5226
11	(h?emophilia adj5 factor 9).mp.	3
12	(h?emophilia adj5 factor ix).mp.	955
13	9 or 10 or 11 or 12	5294
14	13 not (5 and 13)	2240
15	8 not 14	24288
16	Blood Coagulation Factors/	13997
17	aPCC.mp.	241
18	activated PCC.mp.	42
19	activated prothrombin complex concentrate$.mp	385
20	feiba.mp.	397

21	Autoplex.mp.	33
22	anti-inhibitor coagulant complex.mp	44
23	(recombinant adj3 (factor VII$ or fvii$ or f7$ or factor 7$)).mp.	5203
24	rFVII$ or rF7$).mp	2292
25	NovoSeven.mp.	500
26	bypass$ agent$.mp.	360
27	prophylaxis.mp.	117051
28	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	135580
29	15 and 28	4861
30	emicizumab.mp.	23
31	ACE910.mp	29
32	29 or 30 or 31	4877
33	(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.	4659902
34	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.	3284891
35	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.	2301977
36	34 or 35	4859733
37	32 not 33	3321
38	36 and 37	982
39	(animals not (humans and animals)).sh.	4643837
40	38 not 39	969
41	limit 40 to English language	922
42	Remove duplicates from 41	789

Table 2. Search strategy of EMBASE SEARCH

No.	Search terms	Results
#1	'hemophilia a'/exp OR 'haemophilia a'/exp	20,017
#2	'hemophilia a' OR 'haemophilia a'	21,711
#3	(hemophilia OR haemophilia) NEAR/5 ('factor viii' OR 'fviii' OR 'factor 8')	5,458
#4	#1 OR #2 OR #3	22,458
#5	'hemophilia'/exp OR 'haemophilia'/exp	37,322
#6	'hemophilia' OR 'haemophilia'	44,163
#7	#4 OR #5 OR #6	44,163
#8	'hemophilia b'/exp OR 'haemophilia b'/exp	6,918
#9	'hemophilia b' OR 'haemophilia b'	7,586
#10	(hemophilia OR haemophilia) NEAR/5 ('factor ix' OR 'fix' OR 'factor 9')	1,912
#11	#8 OR #9 OR #10	7,819
#12	#11 NOT (#4 AND #11)	3,399
#13	#7 NOT #12	43,924
#14	'apcc' OR 'activated pcc' OR 'activated prothrombin complex concentrate*' OR 'feiba' OR 'autoplex' OR 'anti-inhibitor coagulant complex'	1,947

#15	recombinant NEAR/3 ('factor vii*' OR fvii* OR f7a OR 'factor 7a')	9,657
#16	rfvii* OR rf7* OR novoseven	5,273
#17	'bypass* agent*'	829
#18	'prophylaxis'	203,387
#19	#14 OR #15 OR #16 OR #17 OR #18	213,240
#20	#13 AND #19	9,302
#21	emicizumab	56
#22	ace910	53
#23	#20 OR #21 OR #22	9,349
#24	#23 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	1,771
#25	#23 NOT #24	7,578
#26	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp	25,231,833
#27	'human'/exp	18,673,163
#28	#26 AND #27	18,673,163
#29	#26 NOT #28	6,558,670
#30	#25 NOT #29	7,268
#31	#30 AND [english]/lim	6,993
#32	#31 AND [medline]/lim	2,703
#33	#31 NOT #32	3,999
#34	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR placebo:ti,ab OR 'drug therapy':lnk OR trial:ti,ab OR groups:ti,ab	6,529,548
#35	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compar*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab	12,639,901
#36	#34 OR #35	13,912,700
#37	#33 AND #36	2,529

Eligibility Criteria

Studies that do not meet the PICOTS criteria defined above will be excluded. Studies conducted in patients with acquired hemophilia or in patients taking short-term prophylaxis in preparation for surgery will be excluded. With respect to bypassing agents, studies will be included if they assess one bypassing agent versus another bypassing agent (e.g., recombinant FVIIa versus aPCC) for prophylaxis or for on-demand treatment, or if they assess bypassing agents (individually or in combination) for prophylaxis versus on-demand treatment. In the absence of evidence directly comparing bypassing agents for prophylaxis versus on-demand use, we will consider including single arm studies of bypassing agents, or the bypassing agent arm from other randomized studies (e.g. bypassing agent versus ITI, biosimilars, or analog bypassing agent).

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 directly into predesigned Word tables. 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 (e.g., open-label or cross-out periods), prophylaxis interventions (agent, dosage, frequency, schedules), on-demand therapy allowed and used (agent, 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:

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.”[20]

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 emicizumab, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "emicizumab" and "ACE910". 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 comparative effectiveness of the interventions of interest. The analysis will be based on the data from all relevant studies identified from the systematic review and will have 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 outcome results reported by each study will be presented in tables or text of the report. In addition, 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 then be 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). 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 descriptive in nature only, as differences in entry criteria, patient populations, outcome assessments, and other factors are likely to preclude formal quantitative direct or indirect analyses of prophylaxis with emicizumab versus no prophylactic therapy or prophylaxis with bypassing agents. Nevertheless, if studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random effect pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[21] 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)).[22,23] 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.[19] Additional explanation of each item can be found in Liberati et al. 2009.[24]

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) Quality Rating	Study Design	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms