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REVIEW ARTICLE

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Systematic review of cost-effectiveness modelling studies for haemophilia

Niklaus Meier[a], Daniel Ammann[b], Mark Pletscher[b], Jano Probst[b], and Matthias Schwenkglenks[a,c]

[a]Institute of Pharmaceutical Medicine (ECPM), University of Basel, Basel, Switzerland; [b]Institute of Health Economics and Health Policy, Bern University of Applied Sciences, Bern, Switzerland; [c]Health Economics Facility, Department of Public Health, University of Basel, Basel, Switzerland

ABSTRACT

Aims: Haemophilia is a rare genetic disease that hinders blood clotting. We aimed to review model-based cost-effectiveness analyses (CEAs) of haemophilia treatments, describe the sources of clinical evidence used by these CEAs, summarize the reported cost-effectiveness of different treatment strategies, and assess the quality and risk of bias.

Methods: We conducted a systematic literature review of model-based CEAs of haemophilia treatments by searching databases, the Tufts Medical Center CEA registry, and grey literature. We summarized and qualitatively synthesized the approaches and results of the included CEAs, without a meta-analysis due the diversity of the studies.

Results: 32 eligible studies were performed in 12 countries and reported 53 pairwise comparisons. Most studies analysed patients with haemophilia A rather than haemophilia B. Comparisons of prophylactic versus on-demand treatment indicated that prophylaxis may not be cost-effective, but there was no clear consensus. Emicizumab was generally cost-effective compared with clotting factor treatments and was always dominant for patients with inhibitors. Immune tolerance induction following a Malmö protocol was found to be cost-effective compared to bypassing agents, while there was no consensus for the other protocols. Gene therapies as well as treatment with extended half-life coagulation factors were always cost-effective over their comparators. Studies were highly heterogenous regarding their time horizons, model structures, the inclusion of bleeding-related mortality and quality-of-life impacts. This heterogeneity limited the comparability of the studies. 19 of the 32 included studies received industry funding, which may have biased their results.

Limitations: It was not possible to perform a quantitative synthesis of the results due to the heterogeneity of the underlying studies.

Conclusion: Differences in results between previous CEAs may have been driven by heterogeneity in modelling approaches, clinical input data, and potential funding biases. A more consistent evidence base and modelling approach would enhance the comparability between CEAs.

PLAIN LANGUAGE SUMMARY

Haemophilia is a rare genetic disease that hinders blood clotting. Patients with haemophilia lack crucial clotting factors in their blood. This study analyzed the cost-effectiveness of various treatments for haemophilia. Cost-effectiveness measures whether it is efficient to use a particular treatment in a health care system. We systematically reviewed cost-effectiveness studies based on mathematical models, in order to judge which treatments for haemophilia were cost-effective or not. We found that preventative (prophylactic) treatments with clotting factor were sometimes cost-effective compared to treating bleeds as they occurred (on-demand), though there was no clear consensus. Longer-lasting clotting factors were always cost-effective compared to traditional clotting factors. Emicizumab, a newer treatment option, was generally cost-effective compared with clotting factor treatments, and was always more effective and less costly for patients with inhibitors. Immune tolerance induction is used to treat patients who develop inhibitors to clotting factors, but only some forms of immune tolerance induction were consistently found to be cost-effective. Gene therapies were always cost-effective compared with other forms of treatment. The reviewed studies used different methods, timeframes, and were conducted in many different countries. The cost-effectiveness of the treatments depended heavily on the assumptions and methods of the studies. Nearly 60% of studies were funded by pharmaceutical companies, which may have introduced some bias into their findings. More consistent evidence and modelling approaches would enhance the comparability between CEAs.

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CONTACT Niklaus Meier niklaus.meier@unibas.ch Institute of Pharmaceutical Medicine (ECPM), University of Basel, Klingelbergstrasse 61, Basel, CH-4056, Switzerland

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1. Introduction

Haemophilia is a rare genetic disease that hinders blood clotting. Untreated haemophilia has severe consequences for patients. Haemophilia A results from a congenital deficit of coagulation factor VIII, while haemophilia B results from a deficit of coagulation factor IX. Medical improvements in recent decades have significantly changed the treatment of haemophilia[1]. In addition to "on-demand" therapy, wherein patients are treated with coagulation factors upon the occurrence of bleeding, many patients are now treated prophylactically[2]. Plasma-derived coagulation factors have generally been replaced by recombinant factors, including varieties with extended half-lives, thus enabling longer intervals between infusions[3]. Some patients develop high-titre inhibitors of coagulation factors and must be treated with bypassing agents (FVIIa or activated prothrombin complex concentrates), immune tolerance induction agents, or emicizumab[4]. The most recent innovation in the treatment of haemophilia is the use of gene therapies, some of which have already received marketing approval and may even have the potential to simultaneously cure patients and reduce the financial burden on healthcare systems[5].

Cost-effectiveness analyses (CEAs) of new treatments for haemophilia are challenging due to the heterogeneity of the patient population and the constantly evolving standard of care. Modelling the clinical course of haemophilia for different treatments is complex, as haemophilia can be characterized by both acute and chronic sequelae. Acute bleeds lead to reduced quality of life[6] and increased mortality[7]. The most important chronic consequence of haemophilia is arthropathy, caused by internal joint bleeding. Haemophilic arthropathy can best be prevented by keeping the bleeding rates of patients consistently low over time[8]. When the arthropathy progresses to a more severe stage, surgery (including synovectomy, joint debridement, arthrodesis, and arthroplasty) becomes necessary[9].

Most clinical trials have not been able to observe patients for a sufficiently long period to directly collect satisfactory evidence regarding the long-term chronic symptoms of haemophilia[10] and therefore, trial-based CEAs have not been able to cover a sufficient time period[11]. It is necessary to design decision-analytic models that enable the consideration of short-term and long-term effects by drawing on generalizable clinical data that can fit into the model structure.

The most recent systematic literature reviews of CEAs for interventions targeting haemophilia were published in 2018 and covered CEAs published from 2000 to 2017[2,12]. Since then, additional CEAs for interventions, including emicizumab and gene therapies, targeting haemophilia have been published. Herein, we conducted a systematic review of model-based CEAs for haemophilia treatments to provide an overview of the literature on this topic, summarize the results of these studies, assess their quality and risks of bias, and describe the most important clinical evidence and model characteristics of these analyses. As CEAs need to extrapolate the long-term consequences of treatment based on short-term data, we have focused on model-based CEAs in our review. By model-based, we specifically refer to decision-analytic models which do not purely rely on individual patient data from clinical studies but synthesize information from multiple sources and apply mathematical techniques to establish the effectiveness and costs of two or more treatments.

2. Methods

We performed a systematic review of model-based haemophilia-related CEAs published between 1 January 2000 and 2 October 2023. Due to the advancements in the treatment of haemophilia[7], we considered that studies published before 2000 were no longer informative or relevant for current medical practice; therefore, we excluded such studies. Our protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 11 November 2022 (registration ID CRD42022374600). This protocol was developed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines[13]. The initial search was conducted on 16 November 2022. The results of the initial search were updated with an additional search on 2 October 2023. The inclusion and exclusion criteria were established based on the population, intervention, comparator, outcomes (PICO) framework as well as the study design, publication date, publication type, and language. These criteria are detailed in Table 1.

2.1. Objectives

The first objective of this systematic review was to provide an overview of model-based CEAs for haemophilia treatments, in terms of the properties of eligible studies, their decision-analytical modelling approaches, quality and risk of bias, and cost-effectiveness results. The second objective was to summarize the clinical effectiveness literature used by the included CEAs to inform key model inputs, including those relating to quality of life (QoL), haemophilic bleeding rates, and mortality. An overview of types of evidence used, related inconsistencies between studies, and where there may be gaps in the evidence, may support future modellers in their decision-making on choosing their sources of evidence.

2.2. Search strategy

We searched the Embase and MEDLINE databases using the Ovid search interface. We adapted search strategies that were designed and validated by the Canadian Agency for Drugs and Technologies in Health (CADTH)[14] and were more recently updated for both Embase[15] and MEDLINE[16] to identify economic evaluations in the medical and health economic literature. The Embase and MEDLINE searches were combined and restricted to only include studies with the search term "h*emophilia" in the title or as a keyword. We searched titles and abstracts for terms that identify treatments for haemophilia, including generic terms and the names of specific products. Before finalizing the protocol, we

Table 1. Eligibility criteria.

Criteria	Description
Population	Patients diagnosed with haemophilia A or B of any severity.
Intervention	On-demand or prophylactic infusion of coagulation factors VIII (for haemophilia A) or IX (for haemophilia B), emicizumab, bypassing agents, immune tolerance induction, or gene therapies.
Comparator	Same as intervention.
Outcomes	Costs per treatment strategy, QALYs per treatment strategy, and incremental cost-effectiveness information must be reported in the study.
Study design	Any CEA that uses a modelling approach such as a decision tree, Markov model, or a microsimulation. We excluded purely trial-based cost-effectiveness analyses, but we included CEAs that combined trials with modelling.
Publication date	Studies published between January 1, 2000, and October 2, 2023.
Publication type	Full-length studies published in peer-reviewed journals, or grey literature from governmental agencies or nongovernmental organizations.
Language	English

Abbreviations. APCC, activated prothrombin complex concentrate; CEA, cost-effectiveness analysis; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

pilot tested these search strategies and compared the results to the previously identified literature of interest to ensure that relevant articles were not missed. The search process was repeated for the initial and updated searches, restricted to the relevant time periods, and then combined. Details of the search strategy with full Ovid syntax can be found in the full protocol on PROSPERO as well as in the electronic supplementary appendix (ESM).

To identify grey literature, we searched for "hemophilia" and "haemophilia" on the websites of the Tufts Medical Center CEA registry (www.cearegistry.org), the National Institute for Health and Care Excellence, the Canadian Agency for Drugs and Technologies in Health, and the Institute for Clinical and Economic Review. The identified studies were added to our body of literature after removing any duplicates. For CEAs that had been submitted by manufacturers to an agency and subsequently revised, we selected only the revised CEAs.

2.3. Study selection

The search results were exported from Ovid to Rayyan[17], which was used to manage the inclusion and exclusion of studies during the abstract and full-text screening processes. For both the initial and the updated searches, two reviewers independently screened the studies. Any differences between the reviewers were resolved *via* discussion.

2.4. Data extraction

The data extracted from the included studies were entered into an Excel table. The extracted data encompassed country of interest, cost year, study funder, perspective, model type, time horizon, discount rate, cost-effectiveness threshold, health states, cycle length, patient population characteristics, interventions, comparator, approach to sensitivity analysis, life years, quality-adjusted life years (QALYs), costs, incremental cost-effectiveness ratios (ICERs), net monetary benefit information, and the evidence used to inform model inputs.

The data extraction sheets were independently pilot tested by two reviewers to ensure their suitability for the data and to ensure consistency between the reviewers. Pilot testing of the data extraction sheets was performed for the properties of the studies and the results extracted from the studies. Any further differences in extraction methodology were resolved *via* discussion.

2.5. Sources of evidence

We examined the clinical sources of evidence used to inform model parameters in the reviewed studies. We extracted information on the sources of evidence of mortality, bleeding rates, and quality of life. For mortality, we extracted evidence on background mortality and haemophilia-related mortality. We extracted annualized bleeding rates if they were reported; otherwise, we extracted the transition probabilities or relative risks. For quality of life, we extracted utilities or disutilities based on five categories of symptoms and treatment: bleeding, arthropathy, infusions, surgery, or treatment arm/other. We chose these five categories as they were generalizable across all included studies, which used a variety of model structures and many different health states.

All relevant citations were extracted and entered into the evidence extraction sheet. A brief description of how this evidence was used in a given model was written alongside this reference in the sheet. Sources of evidence were categorized as either clinical trials, real-world data, meta-analyses, models (decision-analytic or pharmacodynamic–pharmacokinetic), or unclear regarding the underlying data source. Sources of evidence which were cited by at least four of the included CEAs were described in greater detail, in order to illustrate what types of studies were frequently used to source a given category of model inputs.

2.6. Risk of bias and quality assessment

The quality of the studies was assessed using the Consensus Health Economic Criteria (CHEC) list[18]. This quality assessment was performed according to the CHEC-Extended interpretation of the individual criteria on the list[19] and our own interpretations of how to apply these criteria to our own review. Each included study was scored on the basis of 20 criteria, while each individual criterion was scored as either fulfilled or not fulfilled. We extracted data regarding whether the study received some form of industry funding.

2.7. Data synthesis

A meta-analysis was considered in the original protocol, but not performed, as the included studies were too diverse for an average of their results to be considered meaningful. As per Cochrane guidelines[20], we performed a systematic review without meta-analysis, and describe our qualitative synthesis methods explicitly in this section.

We organized the most relevant extracted data into tables and described their contents in a qualitative manner to answer our research questions. Regarding the properties of the studies, we summarized the frequencies of countries for which the studies were performed, haemophilia subtypes, treatments, and types of models. Our summaries of the models included any health states, which we categorized to facilitate comparisons of different model structures.

For the cost-effectiveness results, we grouped the most frequent types of comparisons, and within each comparison, described the frequency of cost-effective or dominant results for a given treatment type. For the sake of more tractable data extraction and analysis, we focused exclusively on pairwise comparisons. For the pairwise comparisons, we categorized all treatments into 8 categories: prophylaxis with standard half-life factor, prophylaxis with extended half-life factor, On-demand with standard half-life factor, on-demand with extended half-life factor, prophylaxis with emicizumab, gene therapy, immune tolerance induction, and bypassing agents. This categorization required some simplification.[i]

When necessary, we calculated the relevant incremental outcomes and ICERs based on the provided costs and QALYs of the treatments. For the quality assessment, we summarized how frequently the individual CHEC criteria were fulfilled across the included studies. We described how frequently the products related to a study's funder were cost-effective or dominant for the subset of industry-funded CEAs. For the sources of evidence, we summarized how often types of evidence within our defined categories were used in the included CEAs. All data measured in currency were converted to 2023 United States dollars and adjusted for inflation and purchasing power parity[21].

3. Results

3.1. Study identification

We initially retrieved 1,712 studies from the Embase and MEDLINE databases (Figure 1). A total of 365 duplicates were excluded. We screened 1,347 abstracts and subsequently excluded 1,282 studies because they did not fulfil our inclusion criteria. The full texts of the remaining 65 studies were screened, and subsequently excluded 36 studies. The reasons for exclusion are described in Figure 1. Our search of the grey literature yielded 35 additional studies. We screened their abstracts and subsequently excluded 31 duplicate studies. The remaining 4 studies were subjected to full-text screening; one study was excluded because it did not report all the outcomes of interest described in the inclusion criteria. Ultimately, 32 studies were included from Ovid and the grey literature.

3.2. Description of included studies

Table 2 provides an overview of the 32 included studies. For studies that did not clearly designate a single base case[ii], we

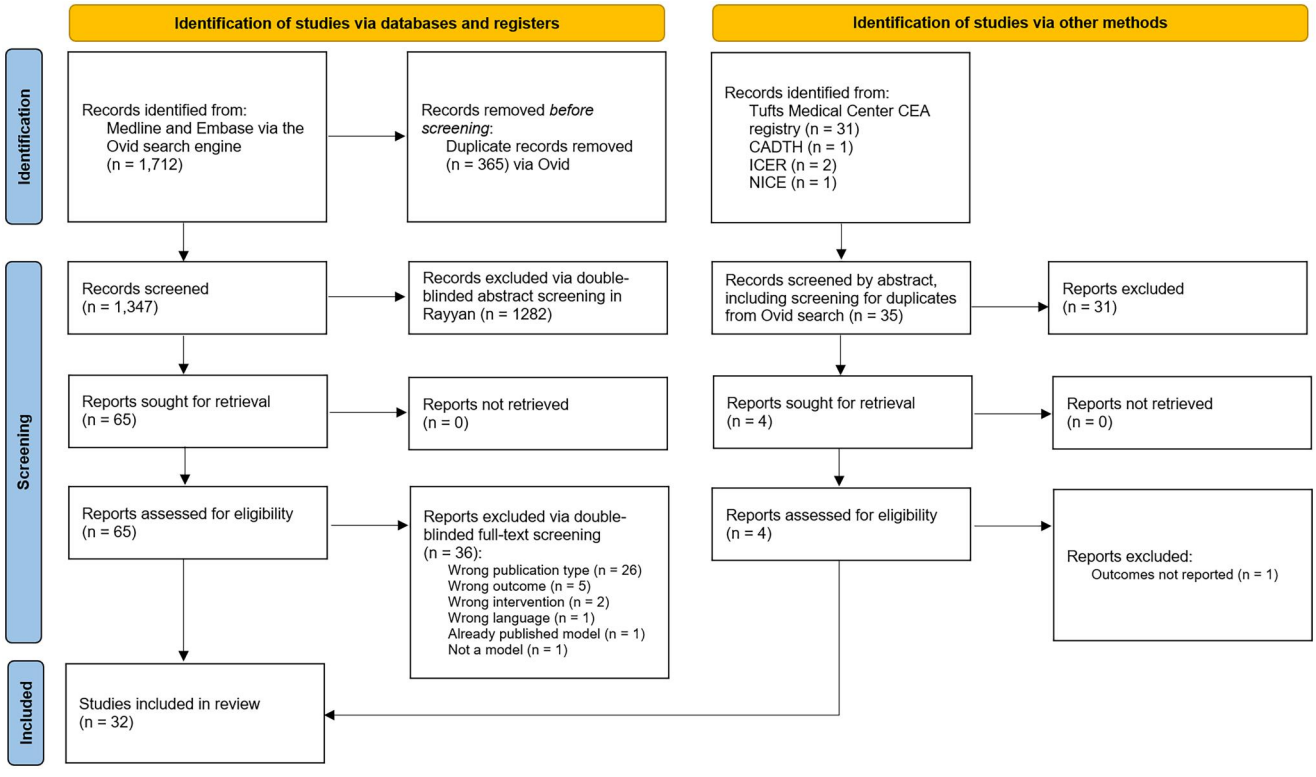

Figure 1. PRISMA diagram[62] of the review, pooling results from both initial and updated searches.

Table 2. Overview of the included studies.

Study	Country	Industry funding	Population	Interventions	Model type and health states	Time horizon/cycle length
Haemophilia A						
Benson et al. (2021)[60]	United Kingdom	Yes	Severe haemophilia A Age at model entry: 12	Prophylactic extended half-life FVIII: Turoctocog alfa pegol Rurioctocog alfa pegol Efmoroctocog alfa Damoctocog alfa pegol	Pharmacodynamic–pharmacokinetic decision model Health states based on factor levels, and death	70 years/28 days
Bitran et al. (2022)[25]	Peru	Yes	Severe haemophilia A Age at model entry: 18	Prophylactic emicizumab Prophylactic anti-inhibitor coagulant complex	Markov model Health states based on bleeding frequency, and death	52 years/1 week
Bullement et al. (2021)[58]	United States	Yes	Severe haemophilia A without inhibitors Age at model entry: 1	Prophylactic extended half-life rFVIII (Elocta) Prophylactic extended half-life rFVIII (Adynovate) Prophylactic standard half-life rFVIII (Advate)	Markov model Health states based on joint damage, and death	Lifetime/1 year
Bullement et al. (2020)[57]	Italy	Yes	Severe haemophilia A without inhibitors Age at model entry: 1	Prophylactic extended half-life rFVIII (Elocta) Prophylactic standard half-life rFVIII (Advate)	Markov model Health states based on joint damage, and death	Lifetime/1 year
CADTH (2021)[36]	Canada	Yes	Severe haemophilia A without inhibitors Age at model entry: 2	Prophylactic emicizumab Prophylactic rFVIII On-demand rFVIII	Markov model Health states based on death	Lifetime/1 year
Colombo et al. (2021)[41]	Italy	Yes	Severe haemophilia A Age at model entry: 0	Primary prophylactic rFVIII (ReFacto) On-demand rFVIII (ReFacto)	Markov model Health states based on surgery, and death	70 years/1 year
Cook et al. (2020)[30]	United States	Yes	Severe haemophilia A without inhibitors Age at model entry: 30	Valoctocogene roxaparvovec Prophylactic rFVIII	Microsimulation Markov model Health states based on combination of bleeding and joint damage, and death	Lifetime/1 week
Coppola et al. (2017)[42]	Italy	Yes	Severe haemophilia A without inhibitors Age at model entry: 12	Late prophylactic rFVIII (Kogenate) On-demand rFVIII (Kogenate)	Markov model Health states based on joint damage, and death	70 years/1 year
Cortesi et al. (2020)[31]	Italy	Yes	Mix of moderate and severe haemophilia A with inhibitors Age at model entry: 4	Prophylactic emicizumab Prophylactic activated prothrombin complex concentrates Prophylactic rFVIIa	Markov model Health states based on treatment, and death	Lifetime/1 year
Farrugia et al. (2013)[32]	United States	NR	Severe haemophilia A with and without inhibitors Age at model entry: 1	Prophylactic rFVIII On-demand rFVIII	Markov model Health states based on inhibitor status, and death	Lifetime/1 year
Gu et al. (2022)[61]	China	Yes	Severe haemophilia A Mean age at model entry: 29.3	Prophylactic pharmacokinetic-guided FVIII (myPKFit) Prophylactic rFVIII	Discrete event simulation Health states based on bleeding	1 year/NA
Henry et al. (2018)[59]	Sweden	Yes	Severe haemophilia A Age at model entry: 1	Prophylactic extended half-life rFVIII (Elocta) Prophylactic standard half-life rFVIII	Markov model Health states based on death	70 years/1 year
ICER (2020)[49]	United States	No	Severe haemophilia A without inhibitors Age at model entry: 18	Valoctocogene roxaparvovec Prophylactic rFVIII Prophylactic emicizumab	Markov model Health states based on joint damage, surgery, and death	Lifetime/6 months
Jaramillo (2016)[26]	Columbia	No	Severe haemophilia A without inhibitors Age at model entry: 2	Prophylactic FVIII/rFVIII On-demand FVIII/rFVIII	Markov model Health states based on joint damage, and death	70 years/1 year
Kim (2020)[27]	United States	No	Acquired haemophilia A Age at model entry: Adult (year not specified)	rpFVIII rFVIIa Activated prothrombin complex concentrates	Markov model Health states based on bleeding, and death	6 days/1 day
Knight et al. (2003)[33]	United Kingdom	No	Severe haemophilia A with inhibitors Age at model entry: 2	Immune tolerance induction, Bonn protocol/Malmö protocol/low dose On-demand bypassing agents	Markov model Health states based on inhibitor status	Lifetime/3 months

(*continued*)

Table 2. Continued.

Study	Country	Industry funding	Population	Interventions	Model type and health states	Time horizon/cycle length
Kragh et al. (2023)[50]	United Kingdom	Yes	Severe haemophilia A without inhibitors Age at model entry: 29	Prophylactic extended half-life factor VIII (efmoroctocog alfa) Prophylactic emicizumab	Markov model Health states based on bleeding, and death	Lifetime/6 months
Lee et al. (2021)[34]	Korea	Yes	Any severity haemophilia A with inhibitors Age at model entry: 12	Prophylactic emicizumab On-demand bypassing agents	Markov model Health states based on bleeding, and death	Lifetime/1 year
Machin et al. (2018)[28]	United States	No	Severe haemophilia A Age at model entry: 30	Gene therapy Prophylactic rFVIII	Markov model Health states based on treatment, joint damage, bleeding, and death	10 years/1 month
Miners et al. (2002)[43]	United Kingdom	NR	Severe haemophilia A or von Willebrand disease Age at model entry: Not reported	Prophylactic FVIII On-demand FVIII	Markov model Health states based on surgery, and death	70 years/1 year
Miners (2009)[44]	United Kingdom	Yes	Severe haemophilia A Age at model entry: 0	Prophylactic FVIII On-demand FVIII	Markov model Health states based on surgery, and death	70 years/1 year
Polack et al. (2021)[51]	France	Yes	Haemophilia A with inhibitors Age at model entry: Variable based on real cohort	Prophylactic emicizumab Mix of prophylactic and on-demand bypassing agents	Markov model Health states based on inhibitor status, and death	5 years/1 year
Rasekh et al. (2011)[53]	Iran	No	Haemophilia A with inhibitors Age at model entry: 2	Immune tolerance induction, Bonn protocol/Malmö protocol/low dose On-demand bypassing agents	Markov model Health states based on inhibitor status	10 years/3 months
Risebrough et al. (2008)[46]	Canada	Yes	Severe haemophilia A Age at model entry: 1	Standard dose prophylactic rFVIII Escalating dose prophylactic rFVIII On-demand rFVIII	Markov model Health states based on joint damage	5 years/3 months
Saiyarsarai et al. (2021)[35]	Iran	Yes	Severe haemophilia A with inhibitors Age at model entry: 2	Prophylactic emicizumab On-demand bypassing agents	Markov model Health states based on treatment, bleeding, and death	Lifetime/1 year
Ten Ham et al. (2022)[56]	Netherlands	None	Severe haemophilia A without inhibitors Age at model entry: 31	Valoctocogene roxaparvovec Prophylactic FVIII Prophylactic emicizumab	Markov model Health states based on treatment, bleeding, joint damage, and death	10 years/1 week
Yu et al. (2023)[52]	Canada	None	Severe haemophilia A without inhibitors Age at model entry: 2	Prophylactic emicizumab Prophylactic standard half-life rFVIII Prophylactic extended half-life rFVIII	Markov model Health states based on inhibitor status, joint damage, and death	Lifetime/1 month
Zahedi et al. (2021)[47]	Iran	None	Severe haemophilia A Age at model entry: <12	Prophylactic plasma derived FVIII On-demand plasma-derived FVIII	Markov model Health states based on joint damage, and death	70 years/1 year
Haemophilia B						
Bolous et al. (2021)[54]	United States	No	Severe haemophilia B Age at model entry: 18	Gene therapy + standard half-life FIX Gene therapy + extended half-life FIX On-demand standard half-life FIX On-demand extended half-life FIX Prophylactic standard half-life FIX Prophylactic extended half-life FIX	Microsimulation Markov model Health states based on treatment, joint damage, bleeding frequency, and death	Lifetime/1 week
Liu et al. (2021)[45]	China	Yes	Mix of moderate and severe haemophilia B Age at model entry: 2	Prophylactic FIX (BeneFIX) On-demand FIX (BeneFIX)	Markov model Health states based on bleeding, and joint damage	17 years/1 year

(*continued*)

Table 2. Continued.

Study	Country	Industry funding	Population	Interventions	Model type and health states	Time horizon/cycle length
Zhou et al. (2023)[29]	China	Yes	Mix of moderate and severe haemophilia B Age at model entry: 2	Prophylactic extended half-life FIX (eftrenonacog alfa), low dose and high dose Prophylactic standard half-life FIX, low dose, and high dose	Markov model Health states based on surgery, and death	75 years/1 year
Haemophilia A and B						
ICER (2022)[55]	United States	No	Severe haemophilia A and B without inhibitors Age at model entry: 18	Etranacogene dezaparvovec Valoctocogene roxaparvovec Prophylactic rFIX Prophylactic emicizumab	Markov model Health states based on joint damage, surgery, and death	Lifetime/6 months

Nonproduct-specific terms were used to designate interventions unless specific products were the focus of the analysis, in which case the product names are included in parentheses. An effort was made to adhere closely to the details of the study while also making the terminology for interventions as consistent as possible across studies for easier comparison. For instance, whether the coagulation factor is recombinant or plasma-derived is mentioned if this was specified in the study, and else is kept broad.
Abbreviations. rFIX, Recombinant factor IX; rFVIIa, Recombinant FVII A; rFVIII, Recombinant factor VIII; rpFVIII, Recombinant porcine-sequence factor FVIII.

selected a main analysis from the paper based on the order and the context of the paper's contents to present herein as a base case. Further data were also extracted and are included in the ESM.

The studies were performed in 12 different countries; the most common countries were the United States ($n = 8$), United Kingdom ($n = 5$), and Italy ($n = 4$). Most studies analysed patients with haemophilia A ($n = 28$) rather than patients with haemophilia B ($n = 4$). 11 studies analysed populations without coagulation factor inhibitors, 6 studies analysed populations with inhibitors, and 15 studies analysed populations with mixed or unspecified inhibitor status. Studies focusing on populations treated with inhibitors assessed immune tolerance induction therapy, bypassing agents or emicizumab. The most commonly studied intervention was prophylactic factor VIII ($n = 21$), followed by prophylactic emicizumab ($n = 11$) and on-demand factor VIII ($n = 9$). Gene therapies were analysed in 5 studies, despite their relatively recent emergence as a potential treatment strategy. More than half ($n = 18$) of the models analysed a paediatric population aged 0–12 years at the start of the model.

Almost all ($n = 30$) of the models were Markov models that used transitions across discrete health states to reflect changes over time. Of those Markov models, 26 models examined health states for death, 14 models examined health states for accruing joint damage, 6 models examined health states for patients receiving surgery, 5 models examined health states for treatment assignment, and 5 models examined health states for changes in inhibitor status. Fewer than half of the studies used a lifetime horizon ($n = 14$), despite the long-term mortality and QoL impacts that haemophilia treatments can have on patients.

3.3. Evidence informing the CEA models

Table 3 provides an overview of the types of evidence used by the included studies in their analysis. More details, including the exact values and citations of all extracted parameters, are included in the supplementary files.

Bleeding rates: of the 32 included studies, almost all studies used evidence on bleeding rates ($n = 30$), as most models included the annualized bleeding rate, which is usually reported as a key intermediary outcome in clinical trials. 19 included studies used at least one clinical trial as their related source of evidence. 15 studies used multiple sources of evidence to determine bleeding rates, including real-world data and other models, as the bleeding rates of the compared interventions came from multiple sources rather than from direct comparisons. 3 studies used meta-analyses of the effect on annualized bleeding rates associated with factor VIII or emicizumab. The most frequently used sources for bleeding rates were Mahlangu et al. (2014)[30] and Mahlangu et al. (2018)[31]. Mahlangu et al. (2014)[30] analyzed a phase 3 clinical trial of the efficacy of a recombinant extended half-life factor VIII coagulation factor, efraloctocog alfa. Three study arms compared individualized prophylaxis, weekly prophylaxis, and on-demand. This article was used by four included studies as a source for the annualized bleed rate of patients when receiving extended half-life factor VIII. Mahlangu et al. (2018)[31] analyzed a phase 3 clinical trial of the efficacy of emicizumab, a monoclonal antibody which replaces the function of missing activated factor VIII. Three study arms compared emicizumab once weekly, emicizumab every 2 weeks, and no prophylaxis. This article was used by four included studies as a source for the annualized bleed rate of patients when receiving emicizumab.

Mortality: 28 included studies used evidence on mortality. Mortality effects were not available from clinical trials, and the majority of included studies ($n = 26$) used various types of real-world data for mortality parameters in their model, such as national statistics for background mortality or data from haemophilia registries. Despite the well-documented link between haemophilia and mortality[24], only 11 studies considered bleeding-related mortality, either *via* specific transition probabilities[25–29], or by using standardized mortality ratios relative to background mortality[30–36]. The most frequently used source for bleeding-related mortality was Darby et al.[7]. This retrospective analysis of a UK haemophilia registry analyzed the mortality of life expectancy of patients with

Table 3. Overview of the types of evidence used by included studies. After each evidence type, the number of cited sources of evidence used by the study is stated.

Study	Quality of life					Mortality	Bleeding rates
	Treatment arm/other	Bleeding	Arthropathy	Infusion	Surgery		
Benson et al. (2021)[60]	RWD: 2	RWD: 1				RWD: 1	CT: 1
Bitran et al. (2022)[25]		Model: 1				Model: 1 RWD: 1	RWD: 1
Bolous et al. (2021)[54]	Model: 1 RWD: 3	RWD: 1	RWD: 1	Model: 1	RWD: 1	RWD: 2	CT: 7 RWD: 4
Bullement et al. (2021)[58]	CT: 1 Model: 1	RWD: 1	RWD: 1			RWD: 1	CT: 5
Bullement et al. (2020)[57]		RWD: 2	RWD: 1			RWD: 1	CT: 4 MA: 1
CADTH (2021)[36]	RWD: 1	RWD: 1		RWD: 1		RWD: 1	CT: 1 RWD: 1
Colombo et al. (2021)[41]	Model: 1 RWD: 1				CT: 1	Model: 1	RWD: 1
Cook et al. (2020)[30]		RWD: 3	RWD: 1	RWD: 1	Model: 1	RWD: 2	CT: 3 RWD: 2
Coppola et al. (2017)[42]	CT: 1		Unclear: 1		CT: 1	RWD: 2	CT: 1
Cortesi et al. (2020)[31]	CT: 2					RWD: 1	CT: 2
Farrugia et al. (2013)[32]	Model: 1 RWD: 3					RWD: 1	RWD: 1
Gu et al. (2022)[61]		RWD: 1					Model: 1
Henry et al. (2018)[59]		RWD: 2		Unclear: 1		RWD: 1	CT: 5 MA: 1
ICER (2020)[49]		RWD: 2	RWD: 1		CT: 1	RWD: 1	CT: 1 RWD: 1
ICER (2022)[55]		RWD: 2	RWD: 1		CT: 1	RWD: 1	CT: 2 RWD: 1
Jaramillo (2016)[26]	RWD: 1		RWD: 1			RWD: 1	CT: 4 RWD: 1 Unclear: 2
Kim (2020)[27]		RWD: 2				CT: 1 RWD: 1	
Knight et al. (2003)[33]	RWD: 1					RWD: 2	Model: 3
Kragh et al. (2023)[50]	CT: 2	CT: 2					CT: 3
Lee et al. (2021)[34]	CT: 1 RWD: 1		Model: 1	CT: 1		RWD: 3	CT: 1
Liu et al. (2021)[45]		Model: 2	Model: 2				CT: 1 Model: 1
Machin et al. (2018)[28]	Model: 2	Model: 1	RWD: 1			RWD: 1	CT: 1
Miners et al. (2002)[43]	RWD: 2				CT: 1	RWD: 1	RWD: 1
Miners (2009)[44]	RWD: 1				CT: 1	RWD: 1	RWD: 1
Polack et al. (2021)[51]	CT: 1					RWD: 1	CT: 1
Rasekh et al. (2011)[53]	Model: 1					Model: 1	Mixed: 1
Risebrough et al. (2008)[46]	RWD: 1		RWD: 1				RWD: 1
Saiyarsarai et al. (2021)[35]	Model: 2					RWD: 1 Unclear: 1	RWD: 2
Ten Ham et al. (2022)[56]		RWD: 2	RWD: 1		Model: 1	RWD: 1	CT: 1
Yu et al. (2023)[52]	RWD: 1	Model: 1	RWD: 1		Model: 1	RWD: 1	MA: 1 RWD: 1
Zahedi et al. (2021)[47]	RWD: 1					RWD: 1 Unclear: 1	
Zhou et al. (2023)[29]		RWD: 1	RWD: 1	RWD: 1	RWD: 1	RWD: 1 Unclear: 1	CT: 5

Coloured fields indicate that evidence regarding quality of life, mortality, or bleeding rates was used in an included study. Within each coloured field the specific evidence types and the number of cited sources of evidence are stated. For instance, Cook et al.[30] cited 3 clinical trials and 2 sources of real-world evidence to inform the bleeding rates in their model.

Abbreviations. CT, Clinical trial; MA, Meta-analysis; RWD, Real-world data.

Table 4. Cost-effectiveness results of the included studies.

Study	Original currency and cost year	Cost-effectiveness threshold [2023 USD]	Comparisons	Incremental QALYs	Incremental costs [2023 USD]	Deterministic ICER [2023 USD]
Benson et al. (2021)[60]	GBP 2020	NR	Turoctocog Alfa Pegol vs. Rurioctocog Alfa Pegol (Both prophylactic extended half-life FIX)	1.05	−49,688	Dominant
			Turoctocog Alfa Pegol vs. Efmoroctocog Alfa (Both prophylactic extended half-life FIX)	0.90	−39,086	Dominant
			Turoctocog Alfa Pegol vs. Damoctocog Alfa Pegol (Both prophylactic extended half-life FIX)	0.35	−131,302	Dominant
Bitran et al. (2022)[25]	USD 2019	NR	Prophylactic emicizumab vs. Prophylactic anti-inhibitor coagulant complex	0.56	−13,854,156	Dominant
Bullement et al. (2021)[58]	EUR 2020	NR	Prophylactic extended half-life rFVIII (Elocta) vs. Prophylactic extended half-life rFVIII (Adynovate)	0.47	−2,275,571	Dominant
			Prophylactic extended half-life rFVIII (Elocta) vs. Prophylactic standard half-life rFVIII (Advate)	0.85	−57,962	Dominant
Bullement et al. (2020)[57]	EUR 2019	NR	Prophylactic extended half-life rFVIII (Elocta) vs. Prophylactic standard half-life rFVIII (Advate)	0.36	−2,067,990	Dominant
CADTH (2021)[36]	CAD 2017	50,258	Prophylactic emicizumab vs. Prophylactic rFVIII	1.57	8,736,272	5,559,308
			Prophylactic emicizumab vs. On-demand rFVIII	8.48	24,706,798	2,071,963
Colombo et al. (2021)[41]	EUR 2010	68,913	Primary prophylactic rFVIII (ReFacto) vs. On-demand rFVIII (ReFacto)	19.57	1,356,590	69,320
Cook et al. (2020)[30]	USD 2019	NR	Valoctocogene roxaparvovec vs. Prophylactic rFVIII	0.75	−7,997,844	Dominant
Coppola et al. (2017)[42]	EUR 2016	96,155	Late prophylactic rFVIII (Kogenate) vs. On-demand rFVIII (Kogenate)	4.26	368,103	86,504
Cortesi et al. (2020)[31]	EUR 2019	155,957	Prophylactic emicizumab vs. Prophylactic activated prothrombin complex concentrates	0.94	−31,167,171	Dominant
			Prophylactic emicizumab vs. Prophylactic rFVIIa	0.94	−39,413,748	Dominant
Farrugia et al. (2013)[32]	USD 2012	65,951	Prophylactic rFVIII vs. On-demand rFVIII	6.06	544,754	89,837
Gu et al. (2022)[61]	USD 2020	37,486	Prophylactic pharmacokinetic-guided FVIII (myPKFit) vs. Prophylactic rFVIII	0.0001	−12,728	Dominant
Henry et al. (2018)[59]	SEK 2018	68,488	Prophylactic extended half-life rFVIII (Elocta) vs. Prophylactic standard half-life rFVIII	0.59	−1,230,397	Dominant
ICER (2020)[49]	USD 2019	117,436	Valoctocogene roxaparvovec vs. Prophylactic rFVIII	0.004	−5,857,718	Dominant
			Prophylactic emicizumab vs. Prophylactic rFVIII	0.00	−1,768,589	Dominant
ICER (2022)[55]	USD 2021	110,940	Valoctocogene roxaparvovec vs. Prophylactic emicizumab	0.10	−4,445,362	Dominant
Jaramillo (2016)[26]	COP 2013	59,776	Prophylactic FVIII On-demand FVIII	4.62	598,684	129,622
			Prophylactic rFVIII vs. On-demand rFVIII	4.62	993,402	214,833
Kim (2020)[27]	USD 2018	59,771	rpFVIII vs. Activated prothrombin complex concentrates	−0.0000547	6'217	−368,335
			rFVIIa vs. Activated prothrombin complex concentrates	−0.0000273	14'547	−1,724,354

(*continued*)

Table 4. Continued.

Study	Original currency and cost year	Cost-effectiveness threshold [2023 USD]	Comparisons	Incremental QALYs	Incremental costs [2023 USD]	Deterministic ICER [2023 USD]
Knight et al. (2003)[33]	GBP 2000	75,435	Immune tolerance induction, Bonn protocol vs. On-demand bypassing agents	7.90	2,959,932	371,606
			Immune tolerance induction, low dose vs. On-demand bypassing agents	4.00	563,120	140,616
			Immune tolerance induction, Malmö protocol vs. On-demand bypassing agents	3.00	−346,267	Dominant
Kragh et al. (2023)[50]	GBP 2022	45,701	Prophylactic extended half-life factor VIII (efmoroctocog alfa) vs. Prophylactic emicizumab	0.014	−7,030,143	Dominant
Lee et al. (2021)[34]	USD 2018	35,863	Prophylactic emicizumab vs. On-demand bypassing agents	3.04	−3,123,509	Dominant
Machin et al. (2018)[28]	USD 2018	NR	Gene therapy vs. Prophylactic rFVIII	1.71	−802,586	Dominant
Miners et al. (2002)[43]	GBP 2000	NR	Prophylactic FVIII vs. On-demand FVIII	11.79	1,745,241	116,924
Miners (2009)[44]	GBP 2007	84'573	Prophylactic FVIII vs. On-demand FVIII	5.63	452,467	80,345
Polack et al. (2021)[51]	EUR 2017	NR	Prophylactic emicizumab vs. Mix of prophylactic and on-demand bypassing agents	0.8812	−347,731	Dominant
Rasekh et al. (2011)[53]	USD 2011	NR	Immune tolerance induction, Malmö protocol vs. On-demand bypassing agents	3.00	−2,551,155	Dominant
			Immune tolerance induction, low dose vs. On-demand bypassing agents	4.00	−5,323,160	Dominant
			Immune tolerance induction, Bonn protocol vs. On-demand bypassing agents	7.90	−909,139	Dominant
Risebrough et al. (2008)[46]	CAD 2003	NR	Standard dose prophylactic rFVIII vs. Escalating dose prophylactic rFVIII	0.01	166,557	>1,315,098
			Escalating dose prophylactic rFVIII vs. On-demand rFVIII	0.30	218,275	714,017
Saiyarsarai et al. (2021)[35]	USD 2020	19,197	Prophylactic emicizumab vs. On-demand bypassing agents	8.62	−159,973,947	Dominant
Ten Ham et al. (2022)[56]	EUR 2019	117,095	Valoctocogene roxaparvovec vs. Prophylactic FVIII	0.65	−525,418	Dominant
			Valoctocogene roxaparvovec vs. Prophylactic emicizumab	0.13	−2,068,119	Dominant
Yu et al. (2023)[52]	CAD 2022	41,746	Prophylactic emicizumab vs. Prophylactic standard half-life rFVIII	0.49	−864,386	Dominant
			Prophylactic emicizumab vs. Prophylactic extended half-life rFVIII	0.22	−12,961,181	Dominant
Zahedi et al. (2021)[47]	USD 2017	25,646	Prophylactic plasma derived FVIII vs. On-demand plasma-derived FVIII	0.98	−52,436	Dominant
Haemophilia B						
Bolous et al. (2021)[54]	USD 2020	173,885	Gene therapy + standard half-life FIX vs. Gene therapy + extended half-life FIX	−0.04	−1,185,212	29,630,305
			Gene therapy + standard half-life FIX	11.19	−6,147,538	Dominant

(*continued*)

Table 4. Continued.

Study	Original currency and cost year	Cost-effectiveness threshold [2023 USD]	Comparisons	Incremental QALYs	Incremental costs [2023 USD]	Deterministic ICER [2023 USD]
			vs. On-demand standard half-life FIX			
			Gene therapy + standard half-life FIX	10.80	−1,882,846	Dominant
			vs. On-demand extended half-life FIX			
			Gene therapy + standard half-life FIX	2.05	−10,219,270	Dominant
			vs. Prophylactic standard half-life FIX			
			Gene therapy + standard half-life FIX	1.43	−16,264,942	Dominant
			vs. Prophylactic extended half-life FIX			
ICER (2022)[55]	USD 2021	110,940	Etranacogene Dezaparvovec vs. Prophylactic rFIX	0.64	−6,482,218	Dominant
Liu et al. (2021)[45]	RMB 2015	64,202	Prophylactic FIX (BeneFIX) vs. On-demand FIX (BeneFIX)	1.23	63,589	51,548
Zhou et al. (2023)[29]	USD 2021	41,772	Prophylactic extended half-life FIX (eftrenonacog alfa), high dose	0.58	−2,631,611	Dominant
			vs. Prophylactic standard half-life FIX, high dose			
			Prophylactic extended half-life FIX (eftrenonacog alfa), low dose	0.06	−591,762	Dominant
			vs. Prophylactic standard half-life FIX, low dose			

Abbreviations. CAD, Canadian dollar; EUR, Euro; GBP, British pound sterling; NR, Not reported; rFIX, Recombinant factor IX; rFVIIa, recombinant FVIIA; rFVIII, recombinant factor VIII; rpFVIII, Recombinant porcine-sequence factor FVIII; RMB, Renminbi; SEK, Swedish krona; USD, United States dollars.

haemophilia in the United Kingdom from 1977 to 1998, and was used by seven included studies to inform the mortality of patients with haemophilia while excluding the impact of HIV on their life expectancy. This is important as HIV had a strong impact on mortality rates in the 80s and 90s, until the emergence of recombinant coagulation factors diminished this mortality risk[37]. Studies therefore tried to exclude this HIV-specific mortality risk.

QoL impact of treatment: 21 studies used evidence on the QoL impacts of treatments and other causes based on utilities observed in treated populations, meaning that QoL was modelled as an inherent property of the treatments themselves, thus implicitly including the QoL effects of bleeding *via* the differences between the treatments. Of these 21 studies, 13 used real-world data, 7 used other models, and 6 used clinical trials, in some cases combining multiple sources. The most frequently used source on the QoL impact of treatments was Miners et al.[38]. This survey study analyzed the QoL of patients with differing severities of haemophilia registered at a haemophilia centre in the UK. It was used by four included studies to assume different QoL utilities based on whether patients were treated prophylactically or on-demand. The utilities of patients with untreated mild or moderate haemophilia in Miners et al. were used for patients being treated prophylactically in the models, while the utilities of patients with severe haemophilia in Miners et al. were used for patients being treated on-demand in the models.

QoL impact of bleeding: 18 included studies used evidence for the direct impact of bleeding on QoL. 13 studies used real-world data, 4 used other models, and only 1 drew on data from a clinical trial. The most frequently used source for the QoL impact of bleeding was Neufeld et al.[6]. This phase IV diary study analyzed the QoL of patients with haemophilia based on regular EQ-5D diary assessments, and was used by nine included studies to inform the QoL impact of haemophilic bleeds on a daily basis, or due to individual bleeds. This allowed modelers to combine the QoL impact of bleeding with the observed bleeding rates of patients, which is an outcome of their treatment. A more effective treatment would thereby improve the QoL of patients by lowering the bleeding rate, which is a plausible assumption.

Other modifiers of QoL: Evidence on the QoL impacts of haemophilic arthropathy ($n = 15$), joint surgery ($n = 11$), or coagulation factor infusions ($n = 6$) were used less frequently. The evidence for these QoL parameters also came mostly from real-world data, followed by models and, rarely, clinical trials. The most frequently used source on the QoL impact of arthropathy was O'Hara et al.[39]. This paper analyzed data from a socioeconomic survey of haemophilia patients in 5 European countries. It was used by five included studies to inform the QoL disutilities from arthropathy and joint bleeds. The most frequently used source on the QoL impact of surgery was Laupacis et al.[40]. This paper used the results of a clinical trial to inform the effect of total hip replacements on health related QoL. It was used by six studies to reflect the impact of surgery for haemophilic joint damage on QoL, generally for one month after the surgery.

3.4. Cost-effectiveness results

The 32 included studies contained 53 pairwise comparisons between treatments (Table 4). Of the 53 comparisons, the results of 35 comparisons indicated that one intervention was dominant. In most cases, this was due to a small increase in incremental

Table 5. An overview of all 53 treatment comparisons in the included studies, simplified into 8 categories of treatments.

Treatment		Comparator (Com)							
		Prophylaxis SHL	Prophylaxis EHL	On-demand SHL	On-demand EHL	Emicizumab	Gene therapy	ITI	Bypassing agent
Intervention (Int)	Prophylaxis SHL	2	0	10 [2 Int, 4 Com, 4 Unclear]	0	0	0	0	0
	Prophylaxis EHL	6	4	0	0	0	0	0	0
	On-demand SHL	0	0	0	0	0	0	0	0
	On-demand EHL	0	0	0	0	0	0	0	0
	Emicizumab	3 [2 Int, 1 Com]	2	2 [1 Int, 1 Com]	0	0	0	0	5
	Gene therapy	5	2	1	1	2	0	0	0
	ITI	0	0	0	0	0	0	0	6 [4 Int, 2 Com]
	Bypassing agent	0	0	0	0	0	0	0	2

The numbers in each field indicate how many comparisons between the two treatment categories were identified in the included studies. If a field is coloured blue, it means that the intervention was cost-effective vs. the comparator. If a field is coloured yellow, it means that comparisons reached different conclusions regarding the cost-effectiveness of treatments. In the yellow fields, the numbers in brackets indicate how many comparisons favour the intervention (Int), how many comparisons favour the comparator (Com), and how many comparisons were unclear. Green fields on the diagonal indicate a comparison within a treatment category. For prophylaxis SHL, these comparisons examined escalating dose prophylaxis or pharmacokinetic-guided prophylaxis vs. standard prophylaxis. For prophylaxis EHL, different types of EHL factors were compared against each other. For bypassing agents, recombinant porcine-sequence factor VIII was compared with activated prothrombin complex concentrate and recombinant activated factor VII.
Abbreviations. Com, comparator; EHL, extended half-life; Int, intervention; ITI, immune tolerance induction; SHL, standard half-life.

QALYs and considerable cost savings over a comparator with high total costs. Table 5 provides a simplified overview of the 53 comparisons. In the following paragraphs, we describe the most common types of comparisons.

Prophylactic and on-demand coagulation factor (VIII or IX) treatments were compared in 9 studies[26,32,41–47] across 10 different comparisons. In 3 studies[26,44,46], prophylaxis was clearly not cost-effective compared to on-demand treatment in the base case. These 3 studies were conducted in Canada in 2008, in the United Kingdom in 2009, and in Colombia in 2016. In 4 studies[32,41,–43], the conclusions were unclear due to the lack of a clear cost-effectiveness threshold or because the base case was not clearly defined. The ICERs ranged from USD 69,320–116,924 per QALY gained and the authors concluded that prophylaxis may be cost-effective compared to on-demand treatment, if a sufficiently high threshold within a range the authors deemed plausible is selected.

The costs of prophylaxis treatment may have been underestimated by some studies: real-world evidence suggested average annual costs of EUR 189,285 for treating severe haemophilia in five European countries (France, Germany, Italy, Spain, UK) in 2015, which may imply that the total costs reported in Colombo et al.[41] and Coppola et al.[42] for prophylaxis were implausibly low. This in turn may mean that the incremental costs between on-demand and prophylaxis were also too low, skewing the results in favour of prophylaxis. In the 2 remaining studies, prophylaxis was found to be cost-effective versus on-demand treatment. Among these two studies, Liu et al.[45] analysed patients with haemophilia B. The annual costs of prophylactic treatment described in Liu et al.[45] were extremely low (RMB 24,000/USD 3,627) in comparison to other studies, which may reflect low costs of FIX coagulation factor in China, though unit costs were not cited. It may also be partially due to the patient population consisting of children, who due to their weight require lower dosages of coagulation factor than adults, and thus incur lower costs. Zahedi et al.[47] was the only study that found prophylactic treatment to be less expensive than on-demand treatment. In Zahedi et al. prophylaxis led to lower FVIII coagulation factor costs than on-demand treatment did, implying that patients being treated prophylactically consumed less FVIII overall than they would with on-demand treatment. This is in contrast to every other included study as well as real-world evidence[48].

All 9 studies indicated that prophylactic coagulation factors provided an incremental QALY benefit over on-demand treatment, ranging from 0.30–19.57 additional QALYs. The 19.57 incremental QALYs found by Colombo et al.[41] are an outlier. Given that bleed-related mortality was not modelled in this study, all incremental QALYs must have emerged from quality of life differences. The model had a cycle length of 1 year and the structure included only the health states "Alive", "Require major surgery", "Surgery, and "Dead". The high incremental QALYs may have resulted from applying low utilities for individuals in the surgery-related health states for the period of an entire year. No other studies, including those considering the disutility of surgery, found such a large QALY difference between treatments. This large difference was impactful, as it led to the conclusion that prophylaxis may be cost-effective.

Emicizumab was compared with a current standard-of care (prophylactic/on-demand treatment with coagulation factor VIII or a bypassing agent for patients treated with inhibitors) in 9 studies[25,31,34–36,49,–52] across 12 comparisons. In 7 studies, emicizumab was cost-effective in comparison with other treatments, primarily due to cost savings. Bypassing agents were always dominated. Emicizumab was not found to be cost.-effective in comparison with prophylactic FVIII in the study by CADTH[36] or in the study by Kragh et al.[50], both of which only included patients without inhibitors in their models. The study by Kragh et al.[50] was also the only CEA in which emicizumab led to fewer QALYs than its comparator, as it was assumed that emicizumab would lead to a slightly higher bleed rate than extended half-life factor VIII (efmoroctocog alfa), based on a matching-adjusted indirect comparison. In the other 8 comparisons, the increase in QALYs ranged from 0–8.62 in favour of emicizumab. In CADTH[36], emicizumab led to much higher total costs than rFVIII (both on-demand and prophylactic), such that prophylactic emicizumab was found to have an ICER of 5'559'308 USD per QALY when compared with prophylactic rFVIII and 2'071'963 USD per QALY when compared with on-demand rFVIII.

Treatment with immune tolerance induction agents was compared with bypassing agents in 2 studies[33,53] across 6 comparisons, for haemophilia A with high-titre inhibitors. In both studies, immune tolerance induction following a Malmö protocol was found to be cost-effective compared to bypassing agents. Rasekh et al.[53] found that immune tolerance induction treatments following low-dose and Bonn protocols were also cost-effective, while Knight et al.[33] found they were not cost-effective. The model of Rasekh et al.[53] was adapted from the model of Knight et al.[33], but with some differences: implemented for Iran instead of the UK, it only used a time horizon of 10 years instead of lifetime, and it only included medication costs without any additional treatment costs.

Gene therapy was compared with a current standard of care in 5 studies[30,49,54–56] across 11 comparisons, for both haemophilia A and haemophilia B. In all studies, the analysed gene therapy was found to be dominant over all potential comparators due to cost savings and incremental QALY gains.

Treatment with extended half-life coagulation factor was compared with standard half-life coagulation factor in 4 studies[29,57,–59] across 6 comparisons, for both haemophilia A and haemophilia B. An extended half-life coagulation factor was found to be the dominant treatment option in all 4 studies due to cost savings and due to being more effective than the standard half-life coagulation factor.

3.5. Risk of bias and quality assessment

The studies fulfilled between 7 and 18 (35–90%) of the 20 CHEC points, with a mean of 13.53 (67.66%), thus indicating heterogeneity of the included studies in terms of methodological and reporting quality. The full CHEC assessments are included in the ESM.

The fulfilment of the individual CHEC points ranged from 6–100%. For 9 criteria (#1, #2, #3, #4, #5, #14, #15, #17, and #19), more than 80% of the studies fulfilled the requirements. These 9 criteria pertained to minimal reporting and writing standards for health economic evaluations. The criterion that was fulfilled by the lowest proportion of studies was #11, as only 6% of studies included all relevant clinical outcomes in their model, such as haemophilia-related mortality, disutilities from bleeding, and chronic progression of symptoms due to haemophilic arthropathy. Other clinical outcome-based criteria (#12 and #13) were fulfilled by 38% and 50% of the studies, respectively. Ethical and distributional issues were discussed by 9% of the studies, as this is not a focus of most cost-effectiveness studies. The appropriate lifetime horizon was modelled by 47% of the studies, and 50% of the studies either chose a societal perspective or justified another perspective in the context of their local health care system. A total of 69–78% of the studies fulfilled the cost-related criteria (#8, #9, #10).

19 of the 32 included studies (59%) received industry funding, meaning that the study was either directly sponsored or commissioned by a pharmaceutical company or that there was a disclosed financial link between the study's first author and a pharmaceutical company that manufactured one of the treatments being compared in the study. Of these 19 studies, 15 studies[25,29–31,34,35,41,44,50,51,57–61] found that the company's product was cost-effective. On average, studies with industry funding fulfilled 64% of the CHEC criteria, whereas studies without industry funding fulfilled 74% of the CHEC criteria, leading to a difference of almost 10% in favour of studies without industry funding.

The CEAs of emicizumab were industry funded in 7 out of 9 cases, and in 6 of the 7 of cases where emicizumab was found to be cost-effective, the study was industry sponsored. In Kragh et al.[50], it was instead rFVIII (efmoroctocog alfa), the product of the study's funder, which was found to be cost-effective when compared with emicizumab.

4. Discussion

Within the included set of studies and their models, we observed many different comparisons of treatments and summarized the most frequent comparisons. We found for comparisons of prophylaxis vs. on-demand coagulation factor treatment that prophylaxis was usually far more expensive than on-demand treatment. Studies came to different conclusions, and there was no clear consensus regarding the cost-effectiveness of prophylaxis, but several studies may have underestimated the costs of prophylaxis[45,47], while another study may have overestimated the incremental benefit of prophylaxis when compared to other CEAs[41], skewing

the results in favour of prophylaxis. Emicizumab dominated the standard of care in 7 of 9 comparisons, and was always dominant for patients with inhibitors. Immune tolerance induction following a Malmö protocol always dominated bypassing agents, while there was no consensus for immune tolerance induction following low-dose or Bonn protocols. Gene therapies always dominated the standard of care, though these results were subject to uncertainty due to the high prices of the gene therapies and the lack of long-term evidence on the effectiveness of the gene therapies. Extended half-life coagulation factors always dominated standard half-life coagulation factors. We found that 19 of the 32 included studies had received industry funding and that 15 of these studies found that the company's product was cost-effective. On average, studies without industry funding fulfilled more CHEC criteria than did those with industry funding. Especially in the case of Emicizumab, industry funding was prevalent, and may have biased the results. Our CHEC quality assessment showed that the inclusion of relevant haemophilia-related clinical outcomes as model input parameters was of inconsistent quality across studies.

Our findings are broadly consistent with the previous reviews by Thorat et al.[2] and Cortesi et al.[12]. All reviews found that the heterogeneity of treatments, countries, time horizons, discount rates, and the implementation of QoL in the included CEAs was too large to provide a quantitative summary of the results, even though the number of included studies increased to 32 in our up-to-date review. Thorat et al.[2] revealed that approximately 60% of CEAs received industry funding, while in Cortesi et al.[12] 73% of CEAs received industry funding, similar to the 59% we found in our set of included studies. Our study adds to these findings by including CEAs of emicizumab and gene therapies, which were not included in the previous reviews.

The primary limitation of this study was the inability to quantitatively summarize the results of the included CEAs due to their substantial heterogeneity. The analysis of the included studies was therefore primarily of a qualitative nature, potentially introducing some subjectivity.

Future modellers should consider carefully which model inputs they use to inform their model. Our review provides an overview of the common types of clinical parameters required and of the types of evidence and specific sources that have most commonly been used in the past. These frequently cited studies could be taken as a starting point for future analyses of clinical haemophilia outcomes for use in economic evaluations, as they clearly provided useful inputs to modellers. In order to make CEAs comprehensive but also comparable, we suggest that all of the described QoL effects, as well as the effect of haemophilic bleeds on mortality, should be included in the model. When observed treatment-dependent long-term utilities are not available, the QoL effects of treatments, bleeding, arthropathy, surgery, and infusions should all be reported and modelled separately. As haemophilic bleeding and surgery are events with acute consequences, cycle lengths should be sufficiently short to avoid overestimating the QoL impacts of individual bleeds or surgeries. Given the chronic nature of haemophilia, time horizons should extend over the entire lifetime of patients unless there is a strong and explicit justification for a shorter time horizon. We believe that adhering to these standards for the modelling of haemophilia would help to avoid such large inconsistencies in terms of incremental QALYs as we found for the comparison of on-demand with prophylactic coagulation factor as well as comparisons of emicizumab with the standard of care.

The CEAs comparing on-demand with prophylactic coagulation factor showed the importance of accurate cost modelling. Dosages and patient weight must be carefully considered and clearly described. The costs of coagulation factors will remain important in the evaluation of novel gene therapies compared to on-demand and prophylactic coagulation factor therapy. As the prices of both gene therapies and coagulation factors are constantly changing, researchers will need to revisit this topic thoroughly in future evaluations.

Further analyses of patient registries, as well as meta-analyses of the existing evidence with the explicit goal of informing the relevant model parameters, could help to provide a more stable set of parameters that modellers could share, even when assessing cost-effectiveness in different countries or subpopulations. Gathering more data on QoL within the clinical trials themselves also would also help to inform CEAs with more robust evidence.

5. Conclusions

It remains unclear whether prophylactic treatment is cost-effective compared to treatment with on-demand coagulation factors. However, treatments with emicizumab, gene therapies, and extended half-life coagulation factors were found cost-effective over their comparators. The quality of the included studies was heterogeneous, and the results may have been driven by the modelling approaches, clinical input data, and funding sources. Including a standard set of haemophilia-related inputs based on the clinical outcomes of the best available evidence in all models would help to provide more consistent analyses and aid in establishing more uniform model structures.

Notes

i. Haemophilia A and haemophilia B were combined for the categorization. Different prophylaxis regimens (such as "late prophylaxis" or "primary prophylaxis") were simplified as "prophylaxis". Different types of coagulation factor were categorized as "standard half-life" or "extended half-life", and not further differentiated by brand or by production method of the factor. All gene therapies were simplified into one category. All protocols for immune tolerance induction were simplified into one category. All types of bypassing agents were simplified into one category. When a treatment strategy included multiple treatments within the intervention or comparator, only the most relevant treatment for that specific comparison was included.

ii. Some studies compared more than two treatments in a head-to-head comparison, leading to more than one comparison. Other studies compared their treatments in varying scenarios, without clearly designating a base case.

Transparency

Declaration of funding

This study received no additional funding.

Declaration of financial/other relationships

MP is an employee of Novartis Pharma AG and holds stock of Novartis Pharma AG. During the time of his main contribution to this study, MP

was an employee of the Bern University of Applied Sciences, Institute of Health Economics and Health Policy. The other authors report no conflicts of interest. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors' contributions

NM is the guarantor of this review. NM drafted the study protocol. MP and MS reviewed and approved the protocol. NM and MP developed the search strategy. NM, DA, and JP screened the abstracts and full texts, extracted the data, and assessed the quality of the included articles based on checklists. MP and MS served as arbitrators to resolve disagreements that arose during screening and data extraction. MP and MS provided expertise on cost-effectiveness and statistical methodology. All the authors contributed to the manuscript and reviewed it for important intellectual content.

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Data availability statement

The study protocol and search strategy, as well as all extracted data, evidence, and our CHEC evaluations, are included in the electronic supplementary material.

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ORCID

Niklaus Meier http://orcid.org/0009-0008-4099-355X
Daniel Ammann http://orcid.org/0009-0006-9117-6942
Mark Pletscher http://orcid.org/0000-0003-2134-4542
Matthias Schwenkglenks http://orcid.org/0000-0001-7217-1173

References

[1] Knobe K, Berntorp E. New treatments in hemophilia: insights for the clinician. Ther Adv Hematol. 2012;3(3):165–175. doi: 10.1177/2040620712440007.
[2] Thorat T, Neumann PJ, Chambers JD. Hemophilia burden of disease: a systematic review of the cost-utility literature for hemophilia. J Manag Care Spec Pharm. 2018;24(7):632–642. doi: 10.18553/jmcp.2018.24.7.632.
[3] Ar MC, Balkan C, Kavaklı K. Extended half-life coagulation factors: a new era in the management of hemophilia patients. Turk J Haematol. 2019;36(3):141–154. doi: 10.4274/tjh.galenos.2019.2018.0393.
[4] Meeks SL, Batsuli G. Hemophilia and inhibitors: current treatment options and potential new therapeutic approaches. Hematology Am Soc Hematol Educ Program. 2016;2016(1):657–662. doi: 10.1182/asheducation-2016.1.657.
[5] Shima M. Current progress and future direction in the treatment for hemophilia. Int J Hematol. 2020;111(1):16–19. doi: 10.1007/s12185-019-02786-9.
[6] Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. Value Health. 2012;15(6):916–925. doi: 10.1016/j.jval.2012.05.005.
[7] Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. Blood. 2007;110(3):815–825. doi: 10.1182/blood-2006-10-050435.
[8] Gualtierotti R, Solimeno LP, Peyvandi F. Hemophilic arthropathy: current knowledge and future perspectives. J Thromb Haemost. 2021;19(9):2112–2121. doi: 10.1111/jth.15444.
[9] Chin B, Wee I, Syn NLX, et al. Surgery for chronic arthropathy in people with haemophilia. Cochrane Database Syst Rev. 2020;11(11):CD013634. doi: 10.1002/14651858.CD013634.
[10] Dolan G, Iorio A, Jokela V, et al. Haemophilia in a real-world setting: the value of clinical experience in data collection. Eur J Haematol. 2016;96 Suppl 82(S82):3–9. doi: 10.1111/ejh.12715.
[11] Lippert B, Berger K, Berntorp E, et al. Cost effectiveness of haemophilia treatment: a cross-national assessment. Blood Coagul Fibrinolysis. 2005;16(7):477–485. doi: 10.1097/01.mbc.0000178830.39526.ff.
[12] Cortesi PA, D'Angiolella LS, Lafranconi A, et al. Modern treatments of haemophilia: review of cost-effectiveness analyses and future directions. Pharmacoeconomics. 2018;36(3):263–284. doi: 10.1007/s40273-017-0588-z.
[13] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647. doi: 10.1136/bmj.g7647.
[14] Glanville J, Fleetwood K, Yellowlees A, et al. Development and testing of search filters to identify economic evaluations in MEDLINE and EMBASE. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
[15] CADTH. Economic evaluations & models – Embase; 2022. Available from: https://searchfilters.cadth.ca/link/15.
[16] CADTH. Economic evaluations & models – MEDLINE; 2022. Available from: https://searchfilters.cadth.ca/link/16.
[17] Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. doi: 10.1186/s13643-016-0384-4.
[18] Evers S, Goossens M, Vet H D, et al. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. Int J Technol Assess Health Care. 2005;21(2):240–245. doi: 10.1017/S0266462305050324.
[19] Odnoletkova I. Cost-effectiveness of therapeutic education to prevent the development and progression of type 2 diabetes: systematic review: appendix. J Diabetes Metab. 2014;05(09):1–7. doi: 10.4172/2155-6156.1000438.
[20] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Hoboken, NJ: Wiley; 2008.
[21] Shemilt I, James T, Marcello M. A web-based tool for adjusting costs to a specific target currency and price year. Evidence & Policy. 2010;6(1):51–59. doi: 10.1332/174426410X482999.
[22] Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014;123(3):317–325. doi: 10.1182/blood-2013-10-529974.
[23] Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379(9):811–822. doi: 10.1056/NEJMoa1803550.
[24] Hay CRM, Nissen F, Pipe SW. Mortality in congenital hemophilia A – a systematic literature review. J Thromb Haemost. 2021;19(Suppl 1):6–20. doi: 10.1111/jth.15189.
[25] Bitrán R, Peña C, Arpón P, et al. Cost-effectiveness study of prophylaxis with emicizumab versus bypassing agents in patients with severe hemophilia A in Peru. Medwave. 2022;22(2):e8703–e002118. doi: 10.5867/medwave.2022.02.002118.
[26] Jaramillo HEC, Viscaya MM, Mejia AE. Cost-utility analysis of primary prophylaxis, compared with on-demand treatment, for patients with severe hemophilia type a in Colombia. Int J Technol Assess Health Care. 2016;32(5):337–347. doi: 10.1017/S0266462316000544.
[27] Kim CH, Simmons SC, Wang D, et al. An economic analysis of different treatments for bleeding in patients with acquired haemophilia. Vox Sang. 2020;115(3):192–199. doi: 10.1111/vox.12877.

[28] Machin N, Ragni MV, Smith KJAO, et al. Gene therapy in hemophilia A: a cost-effectiveness analysis. Blood Adv. 2018;2(14):1792–1798. doi: 10.1182/bloodadvances.2018021345.

[29] Zhou T, Wang S, Zhang Y, et al. Cost-effectiveness analysis of recombinant factor IX Fc fusion protein compared with recombinant factor IX for the treatment of moderate-severe to severe hemophilia B in China. Pediatr Blood Cancer. 2023;70(6):e30264. doi: 10.1002/pbc.30264.

[30] Cook K, Forbes SP, Adamski K, et al. Assessing the potential cost-effectiveness of a gene therapy for the treatment of hemophilia A. J Med Econ. 2020;23(5):501–512. doi: 10.1080/13696998.2020.1721508.

[31] Cortesi PA, Castaman G, Trifirò G, et al. Cost-effectiveness and budget impact of emicizumab prophylaxis in haemophilia A patients with inhibitors. Thromb Haemost. 2020;120(2):216–228. doi: 10.1055/s-0039-3401822.

[32] Farrugia A, Bansal M, Cassar J, et al. Treatment for life for severe haemophilia A. A costutility model for prophylaxis vs. on-demand treatment. J Thromb Haemost. 2013;11:353–354.

[33] Knight C, Paisley S, Wight J, et al. Economic modelling of different treatment strategies for haemophilia A with high-responding inhibitors. Haemophilia. 2003;9(4):521–540. doi: 10.1046/j.1365-2516.2003.00783.x.

[34] Lee H, Cho H, Han JW, et al. Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitors in Korea. Haemophilia. 2021;27(1):e12–e21. doi: 10.1111/hae.14143.

[35] Saiyarsarai P, Robabpour Derakhshan A, Khedmati J, et al. A comparison between on-demand usage of rFVIIa vs prophylaxis use of emicizumab in high titer inhibitory hemophilia A patients in Iran: a cost-utility analysis. Medicine (Baltimore). 2021;100(40):e27303. doi: 10.1097/MD.0000000000027303.

[36] Canadian Agency for Drugs and Technologies in Health. Pharmacoeconomic Report: emicizumab (HEMLIBRA); 2021.

[37] Lee CA. The natural history of HIV disease in haemophilia. Blood Rev. 1998;12(3):135–144. doi: 10.1016/S0268-960X(98)90011-X.

[38] Miners AH, Sabin CA, Tolley KH, et al. Assessing health-related quality-of-life in individuals with haemophilia. Haemophilia. 1999;5(6):378–385. doi: 10.1046/j.1365-2516.1999.00347.x.

[39] O'Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. Health Qual Life Outcomes. 2018;16(1):84. doi: 10.1186/s12955-018-0908-9.

[40] Laupacis A, Bourne R, Rorabeck C, et al. The effect of elective total hip replacement on health-related quality of life. J Bone Joint Surg Am. 1993;75(11):1619–1626. doi: 10.2106/00004623-199311000-00006.

[41] Colombo GL, di Matteo S, Elisa Mancuso M, et al. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. Clinicoecon Outcomes Res. 2011;3:55–61. doi: 10.2147/CEOR.S16670.

[42] Coppola A, D'Ausilio A, Aiello A, et al. Cost-effectiveness analysis of late prophylaxis vs. on-demand treatment for severe haemophilia A in Italy. Haemophilia. 2017;23(3):422–429. doi: 10.1111/hae.13185.

[43] Miners AH, Sabin CA, Tolley KH, et al. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. Pharmacoeconomics. 2002;20(11):759–774. doi: 10.2165/00019053-200220110-00005.

[44] Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A. Haemophilia. 2009;15(4):881–887. doi: 10.1111/j.1365-2516.2009.02019.x.

[45] Liu G, Xin Q, Chen Z, et al. Cost-effectiveness analysis of prophylaxis versus on-demand treatment for children with hemophilia B without inhibitors in China. Clin Ther. 2021;43(9):1536–1546. doi: 10.1016/j.clinthera.2021.07.004.

[46] Risebrough N, Oh P, Blanchette V, et al. Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia A. Haemophilia. 2008;14(4):743–752. doi: 10.1111/j.1365-2516.2008.01664.x.

[47] Zahedi Z, Karimi M, Keshavarz K, et al. A cost-effectiveness analysis of the prophylaxis versus on-demand regimens in severe hemophilia A patients under 12 years old in southern Iran. Hematology. 2021;26(1):240–248. doi: 10.1080/16078454.2021.1885123.

[48] Jamal M, Sathar J, Jamari J, et al. A comparison of the incidence rate for joint bleeding and FVIII consumption between on-demand versus prophylaxis factor VIII replacement therapy and the direct cost of prophylaxis treatment in severe haemophilia A patients. Malays J Med Sci. 2023;30(1):129–136. doi: 10.21315/mjms2023.30.1.11.

[49] Institute for Clinical and Economic Review. Valoctocogene roxaparvovec and emicizumab for hemophilia A without inhibitors: effectiveness and value: final report; 2020.

[50] Kragh N, Tytula A, Pochopien M, et al. Cost-effectiveness of recombinant factor VIII Fc versus emicizumab for prophylaxis in adults and adolescents with haemophilia A without inhibitors in the UK. Eur J Haematol. 2023;110(3):262–270. doi: 10.1111/ejh.13901.

[51] Polack B, Trossaert M, Cousin M, et al. Cost-effectiveness of emicizumab vs bypassing agents in the prevention of bleeding episodes in haemophilia A patients with anti-FVIII inhibitors in France. Haemophilia. 2021;27(1):e1–e11. doi: 10.1111/hae.14129.

[52] Yu JK, Wong WWL, Keepanasseril A, et al. Cost-utility analysis of emicizumab for the treatment of severe hemophilia A patients in Canada. Haemophilia. 2023;29(2):488–497. doi: 10.1111/hae.14723.

[53] Rasekh HR, Imani A, Karimi M, et al. Cost-utility analysis of immune tolerance induction therapy versus on-demand treatment with recombinant factor VII for hemophilia A with high titer inhibitors in Iran. Clinicoecon Outcomes Res. 2011;3:207–212. doi: 10.2147/ceor.s25909.

[54] Bolous NS, Chen Y, Wang H, et al. The cost-effectiveness of gene therapy for severe hemophilia B: a microsimulation study from the United States perspective. Blood. 2021;138(18):1677–1690. doi: 10.1182/blood.2021010864.

[55] Institute for Clinical and Economic Review. Gene therapy for hemophilia B and an update on gene therapy for hemophilia A: effectiveness and value: evidence report; 2022.

[56] Ten Ham RMT, Walker SM, Soares MO, et al. Modeling benefits, costs, and affordability of a novel gene therapy in hemophilia A. Hemasphere. 2022;6(2):E679. doi: 10.1097/HS9.0000000000000679.

[57] Bullement A, McMordie ST, Hatswell AJ, et al. Cost-effectiveness analysis of recombinant factor VIII Fc-fusion protein (rFVIIIFc) for the treatment of severe hemophilia A in Italy incorporating real-world dosing and joint health data. Pharmacoecon Open. 2020;4(1):133–142. doi: 10.1007/s41669-019-0158-8.

[58] Bullement A, Knowles ES, DasMahapatra P, et al. Cost-effectiveness analysis of rFVIIIFc versus contemporary rFVIII treatments for patients with severe hemophilia A without inhibitors in the United States. Pharmacoecon Open. 2021;5(4):625–633. doi: 10.1007/s41669-021-00283-6.

[59] Henry N, Jovanović J, Schlueter M, et al. Cost-utility analysis of lifelong prophylaxis with recombinant factor VIIIFc vs recombinant factor VIII for the management of severe hemophilia A in Sweden. J Med Econ. 2018;21(4):318–325. doi: 10.1080/13696998.2017.1405816.

[60] Benson G, Morton T, Thomas H, et al. Long-term outcomes of previously treated adult and adolescent patients with severe hemophilia a receiving prophylaxis with extended half-life fviii treatments: an economic analysis from a united kingdom perspective. Clinicoecon Outcomes Res. 2021;13:39–51. doi: 10.2147/CEOR.S280574.

[61] Gu C, Huang H, Han Y, et al. Cost-effectiveness analysis of pharmacokinetic-guided prophylaxis versus standard prophylaxis in adults with severe hemophilia A in China. Adv Ther. 2022;39(8):3777–3788. doi: 10.1007/s12325-022-02220-3.

[62] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.