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SYSTEMATIC REVIEW

A Systematic Review of Modelling Approaches in Economic Evaluations of Treatments for Inherited Bleeding Disorders

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Abstract

Objective The aim of this review is to identify and assess modelling approaches in published model-based economic evaluations of treatments for individuals with inherited bleeding disorders.

Methods A literature search was performed on seven electronic databases, from database inception until 30 May, 2024. Inclusion criteria were cost-effectiveness or cost-utility analyses using decision-analytic models. The approaches from included models were identified and assessed, and these approaches were compared across bleeding disorders and treatments.

Results This review included a total of 47 decision-analytic models. The identified models primarily evaluated treatments for severe haemophilia A and B. For haemophilia without inhibitors, factor concentrates were the most evaluated intervention ($n = 21$, 68%), followed by gene therapies ($n = 6$, 19%) and emicizumab ($n = 4$, 13%). For haemophilia with inhibitors, assessed interventions included emicizumab ($n = 8$, 50%), immune tolerance induction with factor concentrates ($n = 5$, 31%) and bypassing agents ($n = 3$, 19%). Markov models were often used as a model type ($n = 27$, 57%), followed by decision trees ($n = 9$, 19%), Markov decision trees and decision process ($n = 5$, 11%) and individual-level models ($n = 5$, 11%). Regardless of the model type, most authors used a lifetime horizon, a 1-year cycle length, and bleeding events—particularly joint bleeds—as key health states of the models.

Conclusions As the reviewed decision-analytic models mainly assessed treatments for severe haemophilia, the identified common approaches may only be generalisable to evaluating these treatments. Further research is required to evaluate their relevance for evaluating treatments of milder forms of haemophilia or other inherited bleeding disorders.

Systematic Review Protocol Registration PROSPERO registration number CRD42023416560.

1 Introduction

Inherited bleeding disorders (iBDs) are a heterogeneous group of coagulation disorders characterised by atypical bleeding due to quantitative or qualitative defects of coagulation proteins [1]. Haemophilia A and B are the most recognised type, but other iBDs exist such as Von

Key Points for Decision Makers

This review identified and assessed 47 published model-based economic evaluations of treatments for inherited bleeding disorders.

Despite the variations, most studies used a lifetime Markov model with a 1-year cycle length and included bleeding events, particularly joint bleeds, as health states.

Using the common approaches identified in this review may enhance treatment comparisons and expedite the health technology assessment process.

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Willebrand disease (VWD) and Glanzmann thrombasthenia [2–4]. Von Willebrand disease is the most common iBD, with prevalence estimates that ranged from 109 to 2200 per 100,000 general population [5]. The second most common type is haemophilia, with prevalence rates of 17.1 per 100,000 male individuals for haemophilia A and 3.8 per 100,000 male individuals for haemophilia B [6]. The hallmark of iBD treatment is still replacement therapy, in which the deficient or defective factor is replaced by factor concentrate, plasma, platelets or a specific drug [1]. Currently, non-factor replacement therapies, including emicizumab and gene therapies, are being increasingly adopted as alternative treatments in several countries [7, 8]. In the near future, more innovative treatments are anticipated to enter the market, such as increased extended half-life factor products, factor mimetics, agents targeting natural anticoagulants, and gene- and RNA-based therapies [9–11]. These emerging treatments are expected to undergo comprehensive health technology assessment (HTA) processes to determine their cost effectiveness.

Several studies have reported the costs associated with iBD treatments [12, 13]. In the EU5 countries (France, Germany, Italy, Spain and the UK), the average annual per-individual treatment costs for severe haemophilia range from €116,963 (UK) to €313,068 (Germany) [12]. For VWD, the average annual per-individual treatment costs range from €29,669 (France) to €84,448 (Italy) across all VWD types [13]. The cost ratios of severe haemophilia compared to VWD were approximately 6:1 (France), 5:1 (Germany), 2.5:1 (Italy), 2:1 (Spain) and 3:1 (UK) [12, 13]. Notably, treatment costs for type 1 VWD are substantially lower than for types 2 and 3, with costs rising from €23,287 (type 1) to €83,663 (type 2) and €133,518 (type 3) [13]. Treatment costs for other iBDs are unreported. Given limited healthcare budgets and the expected influx of novel therapies for iBDs, concerns raise amongst HTA bodies and payers [14]. Therefore, economic evaluations (EEs) supporting reimbursement decisions for novel treatments, including treatment for iBDs, are necessary and are increasingly required by the healthcare authorities [15].

Economic evaluations can be conducted alongside clinical trials, referred to as trial-based evaluations, or designed as model-based evaluations using data from multiple sources [16]. In the context of chronic diseases such as iBDs, clinical trials may end before all benefits and costs of assessed treatments have been fully observed and considered [17]. Hence, model-based EEs are used as they allow for the extrapolation of benefits and costs beyond the clinical trial horizon [18]. Several model-based EEs have been published to evaluate the cost effectiveness of iBD treatments [19, 20]. However, variations in modelling approaches were apparent. For example, while the review by Cortesi et al. did not specifically focus on the assessment of approaches in model-based EEs but aimed to identify potential issues associated with EEs of new haemophilia treatments, the EEs included in their analysis indicate different model types and time horizons were applied in the evaluation of treatments for haemophilia [21]. These varying approaches limit the comparability of treatment outcomes across different countries and over time. Therefore, the aim of this research is to conduct a systematic review to identify and assess modelling approaches in published model-based EEs evaluating treatments for iBDs.

2 Methods

2.1 Study Design

A systematic review was conducted to identify and assess modelling approaches in published EEs of treatments for iBDs. Modelling approaches were defined as the structural design of a model, characterised by elements such as the model type, time horizon, cycle length, health states and clinical outcomes. Here, treatments refer to pharmaceutical interventions, specifically medications aimed at improving health outcomes. The cost-effectiveness outcomes of the identified models were not assessed, as this review primarily focused on the model structure. The protocol for this systematic review was registered in PROSPERO (registration number CRD42023416560) prior to conducting the study. The study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework [22].

2.2 Search Strategy and Study Selection

The search was performed in seven electronic databases, including MEDLINE, Embase, Web of Science, Cochrane, Google Scholar, EconLit and NHS Economic Evaluation Database. In each database, we included the following general search terms: "blood coagulation disorder*", "economic evaluation*" and "cost*". See Table 1 in the Electronic Supplementary Material (ESM) for the comprehensive search query per database. The search was performed in the databases from inception until 30 May, 2024, with the exception of the NHS Economic Evaluation Database as this database has not been updated since January 2015 [23]. An additional snowball search was conducted to identify individual studies from systematic reviews, meta-analyses and references from included studies.

The inclusion criteria for this review were: (i) the use of a decision-analytic model; (ii) cost-effectiveness or cost-utility analyses evaluating treatments for iBDs; (iii) original models (i.e. the first published version of a specific

modelling approach); (iv) articles written in English; and (v) availability of the full-text article. Accordingly, studies were excluded if they: (i) conducted trial-based EEs; (ii) reported other forms of EEs, such as costing studies, cost-outcome analyses, cost-benefit analyses or cost-minimisation analyses; (iii) evaluated non-pharmaceutical interventions (e.g. diagnostics, surgery, medical devices, lifestyle interventions); (iv) used adapted versions of previously published models; or (v) non-English articles. Additionally, conference abstracts, systematic reviews and meta-analyses were excluded from the analysis, although systematic reviews and meta-analyses were used for snowball searching. Health technology assessment reports were included if they met the predefined inclusion and exclusion criteria and were retrieved through our search strategy.

Following the initial search, duplicates were removed using EndNote 20 (Clarivate, St. Helier, Jersey). Two independent reviewers (DMP and RMTtH) assessed studies for eligibility using Rayyan (Rayyan Systems Inc., Cambridge, MA, USA) in two phases. During phase 1, eligibility criteria were applied to the title and abstract. Both reviewers assessed 100% of identified studies in phase 1. In phase 2, the full-text articles of included studies from phase 1 were retrieved and reviewed, in which the reasons for exclusions were documented. In phase 2, DMP assessed all the full-text articles, while RMTtH reviewed 75% of them. In both phases, any discrepancies between the two reviewers were resolved through discussion.

2.3 Data Extraction and Analysis

Data of included studies were extracted by the first reviewer (DMP) using a predefined data extraction form developed in Microsoft Excel (Microsoft, Redmond, WA, USA). The following details were extracted: authorship, year, funding source (industry or non-industry), EE type (cost-effectiveness analysis [CEA] or cost-utility analysis [CUA]), type and severity of iBDs, assessed treatments (intervention and comparator), country, perspective, clinical outcomes, quality-adjusted life-year (QALY)-related information (data source and utility instrument), cycle length and time horizon, health states/disease pathways, model type and rationale. A descriptive analysis was conducted to assess the extent of commonalities and differences in modelling approaches. Additionally, the model type was compared across iBDs, treatments and countries. No quality assessment of the models was conducted, as the objective of this review is not to synthesise quantitative evidence through a meta-analysis, but rather to qualitatively assess the modelling approaches used in evaluating iBD treatments.

3 Results

3.1 Identified Studies

A total of 3554 studies were identified, of which 1806 were identified through a database search and 1748 through snowball search (Fig. 1). After removing 910 duplicates, 2644 unique articles remained for initial screening (phase 1), where we applied eligibility criteria to titles and abstracts. In this phase, 2508 articles were excluded, although specific reasons for exclusion were not recorded. The remaining 136 articles were selected for a full-text review. Two articles could not be retrieved, as their abstracts appeared in Rayyan but the corresponding full-text articles could not be located. As a result, 134 articles were available for full-text screening in phase 2. During this phase, 80 articles were excluded based on the following reasons: 37 articles did not have full text available; 10 were systematic reviews or meta-analyses; 3 were not published in English; 22 were not CEA/CUAs; 4 were not model-based EEs; 2 focused on non-pharmaceutical interventions; and 2 were not iBDs. Ultimately, 54 studies fulfilled the eligibility criteria. However, only original models were included in the analysis and thus seven studies using adaptation models were further excluded [24–30]. These adaptations were mainly country adapted, with modifications in aspects such as intervention arm [24, 28], perspective [26–29], cycle length [28] and time horizon [26] (see Table 2 in the ESM).

The analysis encompassed 47 decision-analytic models. The publication years range from May 1996 to April 2024. The majority of EEs ($n = 40$, 85%) were published from 2011 onwards. Nineteen studies were published between January 2021 and May 2024, representing 40% of the total publications. More than half of the included studies ($n = 26$, 55%) were funded by industry. Fourteen studies were funded by non-industry sources, and seven did not disclose their funding information. The included studies consist of 12 CEAs (25%), 13 CUAs (28%), and 22 analyses combined CEA and CUA (47%) [Table 3 of the ESM]. These EEs mainly assessed treatments for haemophilia, with 38 studies (81%) focusing on haemophilia A (Table 1) and 6 studies (13%) on haemophilia B (Table 2). Among studies in haemophilia A, 15 studies (39%) were dedicated to haemophilia A with inhibitors (Table 3). Additionally, three EEs (6%) were conducted in the mixed populations of haemophilia A and B (Table 4) [31–33]. One of these studies simulated hypothetical cohorts of 100 individuals with severe haemophilia A, severe haemophilia B or severe VWD, but utilised the same data inputs for severe haemophilia A and VWD [31]. With regard to the severity level, most studies ($n = 39$, 83%) included individuals with severe haemophilia, of which only

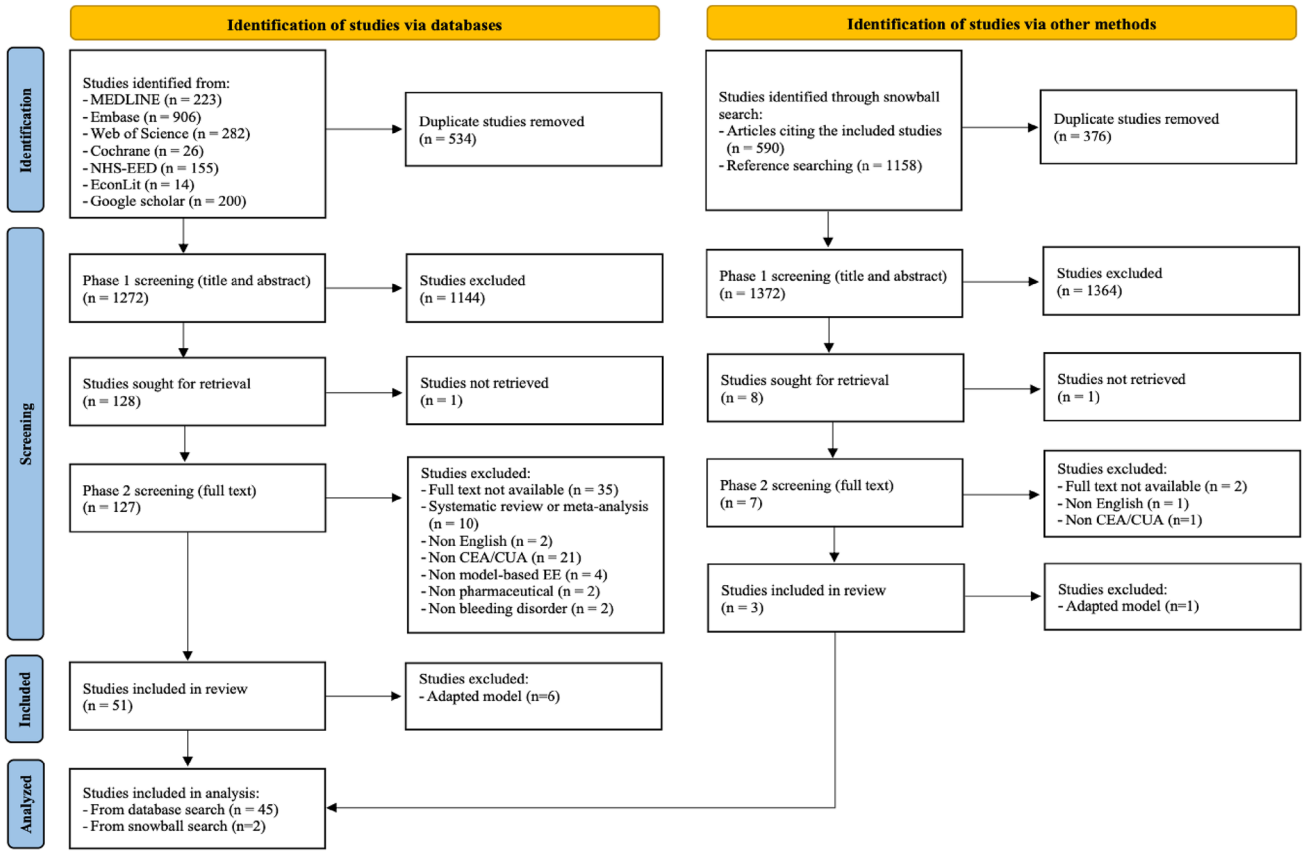

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flowchart. *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *EE* economic evaluation, *NHS-EED* National Health Service Economic Evaluation Database

three studies ($n = 3$, 6%) incorporated individuals with all levels of severity (mild, moderate and severe) [34–36].

A healthcare-related perspective was adopted in the majority of studies ($n = 20$, 43%). Among these, ten studies explicitly specified the healthcare system as the adopted perspective, six referred to the healthcare service, one to the healthcare sector and one to the Ministry of Health. Two studies included only direct costs and described their perspective as either "healthcare" or "collective", without further clarification [37, 38]. Other perspectives reported included societal ($n = 10$, 21%), payer ($n = 9$, 19%) and multiple perspectives used within each study ($n = 5$, 11%). Of the studies using multiple perspectives, three used payer and societal perspectives [39–41], one used healthcare and societal perspectives [37], and one included payer, patient and societal perspectives [42]. Additionally, two studies conducted multinational cost-effectiveness analyses, with one applying different perspectives (healthcare service or payer) by country and the other using payer perspective across all countries [32, 43]. One study did not explicitly report its perspective but included only direct treatment costs in the analysis [44].

The EEs were conducted in the continents of America, Europe and Asia. Studies conducted in high-income countries evaluated a broader range of treatment options compared with those from low- and middle-income countries. For example, gene therapies were evaluated in studies from the USA, the Netherlands and Germany. In low- and middle-income countries, the evaluations primarily focused on factor concentrates and emicizumab. No pattern was found suggesting that on-demand treatments were only assessed in low- and middle-income countries, as most studies evaluated prophylactic treatments irrespective of geographic location.

A variety of intervention and comparator combinations were evaluated. For haemophilia A and B without inhibitors, factor concentrates were the most evaluated intervention ($n = 21$, 68%), with 15 studies assessing short half-life (SHL) factors and 6 studies focusing on extended half-life (EHL) factors. SHL therapies included recombinant or plasma-derived factor concentrates, while EHL therapies consisted of recombinant factor Fc fusion proteins. Studies on SHL therapies primarily compared their prophylactic use to on-demand use of the same product or compared two different SHL therapies. Studies on EHL therapies compared their prophylactic use with SHL therapies or emicizumab.

Table 1 Details of included studies for haemophilia A without inhibitors

Author	Funding source	EE type	Severity	Intervention	Comparator	Country, perspective	Clinical outcomes	Cycle length, time horizon	Health states/disease pathways
Decision tree									
Patel et al. (2019) [50]	Industry	CEA	Severe	PRO emicizumab	PRO FVIII	USA, payer	Breakthrough bleeds, time to inhibitor development	NA, 20 years	No inhibitors, low-titre inhibitors, high-titre inhibitors
Lofti et al. 2020 [53]	Non-industry	CUA	Not stated	rFVIII	pd-FVIII	Southern Iran, societal	QALYs	NA, 1 year	Abnormal bleeding, no abnormal bleeding
Markov									
Salinas-Escudero et al. (2013) [54]	Not stated	CEA	Severe	PRO rFVIII	OD pd-FVIII	Mexico, health care system	Joint bleeds	2 weeks, 16 years	Without bleeding, bleeding, dead
Jaramillo et al. (2016) [55]	Non-industry	CUA	Severe	PRO pd-FVIII	OD pd-FVIII	Colombia, healthcare system	QALYs	1 year, lifetime	Alive (no arthropathy), alive (with arthropathy), dead
Coppola et al. (2017) [37]	Industry	CEA + CUA	Severe	PRO rFVIII	OD rFVIII	Italy, healthcare and societal	Joint bleed events, total bleeds, QALYs	1 year, lifetime	79 health states (level of the PS S0-S78), dead
Zahedi et al. (2021) [56]	Non-industry	CEA + CUA	Severe	PRO pd- FVIII	OD pd- FVIII	Southern Iran, societal	Joint health score, QALYs	1 year, 70 years	Alive, TJ, dead
Seth et al. (2023) [57]	Industry	CEA + CUA	Moderate and severe	PRO FVIII intermediate dose	OD FVIII	India, societal	LYs, QALYs	1 year, lifetime	Base state, bleeding incident without joint involvement, bleeding incident with joint involvement, joint disease state, dead
Henry et al. (2018) [58]	Industry	CEA + CUA	Severe	PRO EHL rFVII-IFc	PRO SHL rFVIII	Sweden, healthcare system	QALYs, ABR	1 year, lifetime	Alive, dead
Bullement et al. (2019) [59]	Industry	CEA + CUA	Severe	PRO EHL rFVIIIFc	PRO SHL rFVIII	Italy, healthcare service	QALYs, ABR, annual probability of developing or resolving TJs	1 year, lifetime	No TJs, TJs, dead
CADTH (2021) [51]	Industry	CUA	Severe	PRO emicizumab	PRO rFVIII OD rFVIII	Canada, payer	QALYs	1 year, lifetime	Alive with HA, dead

Table 1 (continued)

Author	Funding source	EE type	Severity	Intervention	Comparator	Country, perspective	Clinical outcomes	Cycle length, time horizon	Health states/disease pathways
Yu et al. (2023) [49]	Not stated	CEA + CUA	Severe	PRO emicizumab	PRO EHL FVIII PRO SHL FVIII	Canada, payer	QALYs, bleeding events	1 month, lifetime	FVIII prophylactic, inhibitor development, emicizumab prophylaxis, dead
Seth et al. (2024) [42]	Not stated	CUA	Severe	PRO emicizumab	OD FVIII PRO FVIII low dose PRO FVIII intermediate dose PRO FVIII high dose	India, payer, patient, and society	QALYs	1 year, lifetime	HA without complications, major bleed, joint bleed, soft-tissue bleed, orthopaedic complications/disability, dead
Machin et al. (2018) [45]	Non-industry	CUA	Severe	Gene therapy	PRO FVIII	USA, healthcare system	QALYs	1 month, 10 years	Prophylaxis, gene therapy, joint damage, bleeding event with joint damage, bleeding event, dead
ICER (2020) [46]	Non-industry	CEA + CUA	Severe	Valrox PRO emicizumab	PRO FVIII	USA, healthcare sector	Joint bleeds, treated non-TJ bleeds, treated TJ bleeds, infusions, LYs, QALYs	6 months, lifetime	No arthropathy, arthropathy, joint replacement surgery, dead
Ten Ham et al. (2022) [19]	Non-industry	CEA + CUA	Severe	Valrox	PRO emicizumab PRO rFVIII	Netherlands, societal	LYs, QALYs, PS, (joint) bleeds	1 week, 10 years	No bleed, untreated bleed, treated bleed not into TJ, treated TJ bleed, dead
Chen et al. (2022) [60]	Industry	CEA + CUA	Severe	PK-driven PRO rFVIII	PK-driven PRO rAHF-PFM	China, healthcare system	Bleeding events, hospitalisation days, orthopaedic surgeries, PS, QALYs	1 year, lifetime	Alive, dead
Kragh et al. (2023) [44]	Industry	CEA + CUA	Not stated	Individualised PRO rFVIIIFc	PRO emicizumab	UK, not stated	QALYs, LYs, bleeds	6 months, lifetime	No bleeds, any bleeds, dead
Markov decision tree									

Table 1 (continued)

Author	Funding source	EE type	Severity	Intervention	Comparator	Country, perspective	Clinical outcomes	Cycle length, time horizon	Health states/disease pathways
Farrugia et al. (2013) [43]	Not stated	CUA	Severe	PRO FVIII	OD FVIII	UK, NHS USA, third-party payer Sweden, not stated	QALYs	1 year, lifetime	Alive (no inhibitors), alive (with inhibitors), dead
Risebrough et al. (2008) [61]	Industry	CEA + CUA	Severe	Tailored PRO FVIII	PRO FVIII OD FVIII	Canada, societal	Joint bleed avoided, QALYs	3 months, 5 years	0 TJ, 1 TJ, 2 TJ, 3 TJ
Microsimulation									
Iannazzo et al. (2017) [62]	Industry	CEA	Severe	PK-driven PRO rFVIII	PRO rFVIII	Italy, NHS	AJBR	1 week, 1 year	Not stated
Cook et al. (2020) [20]	Industry	CEA + CUA	Severe	Valrox	PRO FVIII	USA, healthcare system	ABR, change in PS, LYs, QALYs, bleed events, FVIII infusions	1 week, lifetime	No bleed, joint bleed, non-joint bleed, dead
Gu et al. (2022) [63]	Industry	CEA + CUA	Severe	PK-driven PRO rFVIII	PRO rFVIII	China, healthcare system	AJBR, QALYs	Not stated, 1 year	Bleeding, non-bleeding
Smith et al. (1996) [64]	Not stated	CEA	Severe	PRO FVIII	OD FVIII	USA, societal	Bleeding event averted	Not stated, lifetime	Not stated

Studies are grouped by model type. Within each group, studies are ordered chronologically according to the type of intervention evaluated

ABR annualised bleeding rate, *AJBR* annualised joint bleeding rate, *CADTH* Canada's Drug and Health Technology Agency, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *EE* economic evaluation, *EHL* extended half-life, *FVIII* factor VIII, *HA* haemophilia A, *ICER* incremental cost-effectiveness ratio, *LY* life-year, *NA* not applicable, *NHS* national health service, *OD* on-demand, *pd-FVIII* plasma-derived FVIII, *PK* pharmacokinetic, *PRO* prophylaxis, *PS* Pettersson score, *QALY* quality-adjusted life-year, *rAHF-PFM* anti-haemophilic factor (recombinant) plasma/albumin-free method, *rFVIII* recombinant FVIII, *rFVIIIFc* rFVIII Fc fusion protein, *SHL* standard half-life, *TJ* target joint, *Valrox* valoctocogene roxaparvovex

Table 2 Details of included studies for haemophilia B without inhibitors

Author	Funding source	EE type	Severity	Intervention	Comparator	Country, perspective	Clinical outcomes	Cycle length, time horizon	Health states/disease pathways
Markov									
Liu et al. (2021) [34]	Industry	CUA	Mild, moderate and severe	PRO PCC	OD FIX OD pd-PCC + FIX OD pd-PCC	China, healthcare system	QALYs	1 year, 17 years	Non-articular bleeding, articular bleeding, joint damage, joint deformity
Li et al. (2021) [39]	Industry	CEA	Moderate and severe	PRO SHL FIX PRO EHL FIX	OD SHL FIX OD EHL FIX	USA, third-party payer and societal	Total bleeding events, joint bleeds	1 week, lifetime	No bleed, bleed (not joint), bleed (joint), dead
Zhou et al. (2023) [65]	Industry	CUA	Moderate and severe	PRO and OD rFIXFc	PRO and OD rFIX	China, healthcare system	QALYs	1 year, lifetime	Alive, requiring surgery, dead
Pochopien et al. (2024) [66]	Industry	CEA + CUA	Moderate and severe	PRO rFIXFc	OD rFIX	Italy, NHS	LYs, QALYs, bleeds, joint surgeries	6 months, lifetime	No bleeds, any bleeds, dead
Microsimulation									
Bolous et al. (2021) [47]	Non-industry	CEA + CUA	Severe	AAV-FIX-Padua gene therapy	PRO and OD FIX	USA, third-party payer	QALYs, number of bleeds, joint surgeries, life expectancy, QoL	1 week, lifetime	Alive, alive with joint damage, dead
Meier et al. (2024) [48]	Non-industry	CEA + CUA	Moderate and severe	Etranadez	PRO EHL FIX	Germany, healthcare payer	LYs, QALYs	3 months, lifetime	Not stated

Studies are grouped by model type. Within each group, studies are ordered chronologically according to the type of intervention evaluated

AAV adeno-associated virus, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *EE* economic evaluation, *EHL* extended half-life, *Entranadez* entranacogene dezaparvovec, *FIX* factor IX, *HB* haemophilia B, *LY* life-year, *NHS* national health service, *OD* on-demand, *PCC* prothrombin complex concentrate, *pd-PCC* plasma-derived PCC, *PRO* prophylaxis, *QALY* quality-adjusted life-year, *QoL* quality of life, *rFIX* recombinant FIX, *rFIXFc* rFIX Fc fusion protein, *SHL* standard half-life

Table 3 Details of included studies for haemophilia A with inhibitors

Author	Funding source	EE type	Severity	Intervention	Comparator	Country, perspective	Clinical outcomes	Cycle length, time horizon	Health states/disease pathways
Decision tree									
Jimenez-Yuste et al. (2013) [67]	Industry	CEA	Severe	OD rFVIIa	OD pd-aPCC	Spain, NHS	Treated joint bleeds	NA, 7 days	Bleed stops, bleed continues
Golestani et al. (2016) [68]	Industry	CEA	Not stated	OD biogeneric rFVIIa	OD aPCC	Iran, healthcare system	Scoring system based on pain and movement limitation	NA, not stated	Not stated
Earnshaw et al. (2015) [52]	Industry	CEA + CUA	Severe	ITI FVIII	PRO aPCC OD rFVIIa	USA, third-party payer	Bleeding events, LYs, QALYs	NA, lifetime	Bethesda unit <10, Bethesda unit ≥10
Kenet et al. (2017) [69]	Industry	CEA	Not stated	ITI PRO BPA (aPCC or rFVIIa) high dose	ITI PRO BPA (aPCC or rFVIIa) low dose	USA, third-party payer	Expected bleeds	NA, not stated	Low dose (3×/week), high dose (daily), OD
Camelo et al. (2023) [70]	Non-industry	CEA	Severe	PRO emicizumab	PRO BPA (aPCC or rFVIIa)	Brazil, Ministry of Health	Treated bleeding events	NA, 1.8 and 3.1 years	ITI success, ITI failure
Markov									
Berger et al. (2013) [71]	Industry	CEA	Severe	ITI FVIII high dose ITI FVIII low dose ITI FVIII risk assessment	OD BPA (pd-aPCC or rFVIIa)	Germany, statutory health insurance	Total bleeds, minor bleeds, joint bleeds, severe bleeds, hospital days	Not stated, 18 years	Pre-ITI, ITI, ITI success, low inhibitors titre, ITI failure
ICER (2018) [40]	Non-industry	CEA + CUA	Not stated	PRO emicizumab	PRO BPA (aPCC or rFVIIa) OD BPA (aPCC or rFVIIa)	USA, health system payer and societal	Bleed events, LYs, QALYs	1 week, lifetime	No bleed, untreated bleed, treated bleed not into TJ, treated TJ bleed, dead
Cortesi et al. (2019)[36]	Industry	CUA	Mild, moderate, severe	PRO emicizumab	PRO aPCC PRO rFVIIa	Italy, NHS	QALYs	1 year, lifetime	HA with inhibitors, dead
Polack et al. (2020)[38]	Not stated	CEA + CUA	Not stated	PRO emicizumab	PRO BPA	France, collective perspective	LYs, QALYs, treated bleeds	1 year, 5 years	HA with inhibitors, dead
Lee et al. (2020) [35]	Industry	CEA + CUA	Mild, moderate, severe	PRO emicizumab	OD BPA (rFVIIa or aPCC)	South Korea, societal	Prevented bleeding, LYs, QALYs	Not stated, lifetime	Alive with bleeds, dead
Saiyarsarai et al. (2021) [41]	Industry	CUA	Not stated	PRO emicizumab	OD rFVIIa	Iran, societal and payer	QALYs	1 year, lifetime	PRO emicizumab, OD rFVIIa, dead
Bitran et al. (2022) [72]	Industry	CUA	Severe	PRO emicizumab	PRO aPCC	Peru, payer	QALYs	1 week, 16 and 52 years	No bleeding, mild bleeding, severe bleeding, dead

Table 3 (continued)

Author	Funding source	EE type	Severity	Intervention	Comparator	Country, perspective	Clinical outcomes	Cycle length, time horizon	Health states/disease pathways
Markov decision tree									
Krishnamoorthy et al. (2024) [73]	Non-industry	CEA + CUA	Severe	PRO emicizumab	OD BPA (rFVIIa and aPCC)	India, healthcare system	Bleeding events averted, QALYs	1 year, 10 years	No bleeding, mild bleeding, severe bleeding, dead
Markov decision process									
Colowick et al. (2000) [74]	Non-industry	CEA	Severe	ITI FVIII	OD aPCC or pd-FVIII	USA, societal	Life expectancy	1 year, lifetime	Short-term morbidity only, short-term morbidity superimposed on irreversible arthropathy, dead
Knight et al. (2003) [75]	Non-industry	CUA	Severe	ITI rFVIII Bonn protocol ITI rFVIII Malmo protocol ITI rFVIII Dutch protocol	OD BPA strategy 1 OD BPA strategy 2 OD BPA strategy 3	UK, societal	QALYs	3 months, lifetime	Individuals with haemophilia without inhibitors, individuals with haemophilia with inhibitors low responders, individuals with haemophilia with inhibitors high responders

Studies are grouped by model type. Within each group, studies are ordered chronologically according to the type of intervention evaluated

aPCC activated prothrombin complex concentrate, *BPA* bypassing agent, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *EE* economic evaluation, *FVIII* factor VIII, *HA* haemophilia A, *ICER* incremental cost-effectiveness ratio, *ITI* immune tolerance induction, *LY* life-year, *NA* not applicable, *NHS* national health service, *OD* on-demand, *pd-aPCC* plasma-derived aPCC, *PRO* prophylaxis, *QALY* quality-adjusted life-year, *rFVIII* recombinant FVIII, *rFVIIa* recombinant activated factor VII, *TJ* target joint

Table 4 Details of included studies for a mixed population of inherited bleeding disorders

Author	Funding source	EE type	Bleeding disorder	Severity	Intervention	Comparator	Country, perspective	Clinical outcomes	Cycle length, time horizon	Health states/disease pathways
Decision tree										
Odeyemi et al. (2002) [33]	Industry	CEA	HA and HB with inhibitors	Not stated	OD rFVIIa	OD aPCC	UK, NHS	Time to bleed resolution	NA, not stated	Bleed stops, bleed continues
Lippert et al. (2005) [32]	Non-industry	CEA + CUA	HA and HB	Severe	PRO FVIII or FIX	OD FVIII or FIX	Germany, Sweden, UK, Netherlands (third-party payer)	QALYs, avoided joint bleeds	NA, 1 year	Not stated
Markov										
Miners et al. (2002) [31]	Not stated	CUA	HA, HB and VWD	Severe	PRO FVIII or FIX	OD FVIII or FIX	UK, societal	QALYs	1 year, lifetime	Alive, require major surgery, surgery, dead

Studies are grouped by model type. Within each group, studies are ordered chronologically according to the type of intervention evaluated

aPCC activated prothrombin complex concentrate, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *EE* economic evaluation, *FVIII* factor VIII, *FIX* factor IX, *HA* haemophilia A, *HB* haemophilia B, *NA* not applicable, *NHS* national health service, *OD* on-demand, *PRO* prophylaxis, *QALY* quality-adjusted life-year, *rFVIIa* recombinant activated factor VII, *VWD* Von Willebrand disease

Other interventions assessed for haemophilia without inhibitors included gene therapies for haemophilia A and B ($n = 6$, 19%) and emicizumab for haemophilia A ($n = 4$, 13%). For gene therapies targeting haemophilia A, the comparators were prophylaxis factor (F) VIII and prophylaxis emicizumab [19, 20, 45, 46]. For gene therapies targeting haemophilia B, the comparators included prophylaxis and on-demand FIX [47, 48]. The comparators for emicizumab were prophylaxis and on-demand FVIII [42, 49–51].

For haemophilia A with inhibitors, assessed interventions included prophylaxis emicizumab ($n = 8$, 50%), immune tolerance induction with FVIII ($n = 5$, 33%) and on-demand bypassing agents (BPAs) ($n = 2$, 13%). Comparators for these interventions were on-demand BPAs [40, 52]. One study included a mixed population of individuals with haemophilia A and B with inhibitors and compared the on-demand use of two different BPAs [33].

3.2 Modelling Approaches

3.2.1 Model Type and Rationale

Cohort-based models were predominantly used in the EEs, with the most adopted models being Markov models ($n = 27$, 57%) and decision trees ($n = 9$, 19%). Additionally, five studies (11%) combined decision tree and Markov structures. Of these, three used a Markov decision tree [43, 61, 73], while two applied a Markov decision process [74, 75]. Only a few studies used individual-level models ($n = 5$, 11%), such as microsimulation [20, 47, 48, 62] and discrete-event simulation (DES) [63]. Additionally, only 11 studies (23%) provided a justification for their choice of model. Justifications were provided for seven Markov models, three microsimulations and one DES model. Regardless of the model type, the common rationale for model selection was indication or treatment-specific advantages offered by the chosen structure, such as using Markov models to account for recurrent bleeds in individuals with haemophilia [73].

Over time, clear patterns emerged in model selection. Before 2000, only two studies used cohort-based models—one Markov decision process and one unspecified [64, 74]. Between 2001 and 2010, studies tripled, primarily using decision trees, Markov models and Markov decision trees. From 2011, study numbers grew significantly with increased use of individual-level models, especially microsimulation. Since 2021, individual-level modelling expanded further, including a 2022 study using DES model [63]. Despite this, Markov models remained the most common approach from 2011 to 2024, applied in 26 studies. Regarding the relationship between model type and funding source, no significant differences were observed between industry- and non-industry-funded studies. Nearly all model types appeared across both funding categories. Notably, the only DES model

identified was an industry-funded study [63], whereas the only two studies using Markov decision process were funded by non-industry sources [74, 75].

3.2.2 Time Horizon and Cycle Length

The majority of studies (n = 43, 91%) reported the time horizon of the models. Irrespective of model type, a lifetime horizon was often used (n = 27, 63%). No consistent pattern was observed in the choice of time horizon across different interventions, conditions and model types. For example, among the Markov models, 20 studies (74%) adopted a lifetime horizon, with other horizons that ranged from five [38] to 52 years [72].

For the decision trees, one study used a lifetime horizon [52], while others used horizons of 1 year or 20 years [32, 50, 53]. For models with combined structures, both Markov decision processes used a lifetime horizon, while the Markov decision trees used horizons of 5 years, 10 years or lifetime [43, 61, 73–75]. Individual-level models used either 1-year [62, 63] or lifetime horizons [20, 47, 48].

Cycle length was reported in most models (n = 34, 92%). One year (n = 18, 53%) was the most frequently chosen cycle length. There was no consistent pattern observed in the use of cycle length across different interventions and conditions. For evaluating the cost effectiveness of gene therapies for haemophilia A and B, included models used cycle lengths that ranged from 1 week [19, 20, 47] to 6 months [46]. For evaluating emicizumab for haemophilia A, cycle lengths were 1 week [40, 72], 1 month [49] or 1 year [36, 38, 41, 42, 51]. For evaluating factor concentrates for haemophilia A and B, cycle lengths varied from 1 week [39, 62] to 1 year [37, 43].

3.2.3 Health States

Most models (n = 35, 92%) used health states to represent the progression of disease. Variations were observed in the quantity of health states used. The number of states ranged from 2 to 80, in which the standard choices were three (n = 11, 31%) or four states (n = 9, 26%) [37]. The two-state models were mainly Markov models that applied simplistic structures using only alive and dead states [35, 36, 38, 51, 58, 60]. Meanwhile, the 80-state model comprised 79 states representing Pettersson scores (PSs) from 0 to 78, along with one state representing death [37]. For decision trees, most models featured two nodes for the initial decision [33, 52, 53, 67, 69, 70], whereas one used three nodes [50], and two lacked an explanation of the decision pathways [32, 68].

Various types of bleeding events were selected as health states in the models, such as bleed, joint bleed and treated bleed. Of these, joint bleeds were most often used (n = 14, 40%). Notably, the definition of bleeds provided by the authors varied. For example, joint bleed could refer to any joint or specifically to a target joint [54, 59, 61, 62]. Another commonly used health state was related to joint issues (n = 10, 29%). This included joint disease or damage, PS (i.e. a scoring system to assess the severity of joint damage) and joint surgery [31, 38, 49, 64]. Only three models combined bleeding and joint states in their structure, while others uses various health state combinations [34, 45, 57]. The most common combination included no bleeding, bleeding and dead states, with some studies further divided bleeding states as non-joint and joint, or as mild and severe bleeding [20, 39, 72, 73]. The selection of health states varied across treatments and conditions, with no specific pattern observed.

3.2.4 Clinical Outcomes

The majority of studies (n = 34, 72%) reported QALYs gained as the clinical outcome of EEs. Additionally, bleeding events were also reported, either in conjunction with QALYs (n = 19, 40%) or separately (n = 9, 19%). Among these bleeding outcomes, joint bleeds were reported in 12 studies (43%). The remaining studies mainly reported total bleeds, encompassing joint and non-joint bleeds [20, 34, 40, 48]. Some studies also included bleeding as the annualised bleeding rate [20, 58, 59] and the annualised joint bleeding rate [62, 63]. Other clinical outcomes included were the scoring system based on pain and movement limitation [68], hospitalisation duration [60, 71], factor infusion [20, 46], PS [19, 20, 60], time to bleed resolution [33], time to inhibitor development [50], life expectancy [47, 74] and life-years gained [35].

QALYs and bleeding events were the only outcomes consistently included across all model types. Different model types tended to select and measure different outcomes. For instance, joint surgery was assessed exclusively in Markov and individual-level models [47, 60, 66]. Short-duration outcomes, such as time to bleed resolution and time to inhibitor development, were predominantly evaluated using decision tree models [33, 50]. In general, Markov and individual-level models used a broader range of outcomes compared with other model types, including measures such as factor infusions, annualised bleeding rate and PS [19, 20, 46, 58–60]. No pattern was observed indicating that specific outcomes were consistently selected for particular treatments or conditions.

Among the studies that reported outcomes in terms of QALYs, only six (13%) employed a primary data collection to assess health-related quality of life (Tables 4–7 of the ESM). The remaining 41 studies (87%) derived utility values from secondary sources, predominantly the previously published literature. Of the studies that collected primary health-related quality-of-life data, three used the EQ-5D instrument [53, 55, 56], one used the SF-6D [32] and

two did not specify the measurement instrument used [42, 51]. Among those relying on secondary data, most studies assigned utility values to define health states. However, nine studies applied utility estimates directly to treatment strategies rather than to discrete health states.

The most frequently cited source for utility values related to bleeding versus non-bleeding health states was Neufeld et al. [76], referenced in nine studies. Other sources varied depending on the health state of interest. For target joint-related health states, utility values were commonly obtained from O'Hara et al. [77] and Mazza et al. [78]. For arthropathy or health states linked to the PS, Fischer et al. [79] was the primary source in six studies. Surgical health states were most often informed by Ballal et al. [80], although some studies utilised values from Laupacis et al. [81] or Miners et al. [31].

In studies where utility values were assigned to treatment regimes, a variation in data sources was observed. Four studies cited Noone et al. [82] for utility estimates related to prophylactic and on-demand FVIII therapy. Ara and Brazier [83] was also frequently referenced and appeared in three studies. For emicizumab prophylaxis, utility values were commonly derived from the HAVEN 1 clinical trial [84], as reported in three studies. Two studies used utility values for severe and mild/moderate haemophilia from Miners et al. [85] and applied these estimates to on-demand and prophylaxis treatment strategies, respectively.

3.2.5 Models Used Across Populations and Treatments

This study also compared models used across populations and treatments. For individuals with haemophilia A without inhibitors, a diverse array of model types was used, including Markov, decision tree, Markov decision tree, microsimulation and DES. In comparison, a more limited range of model types was used for other haemophilia populations. For haemophilia A with inhibitors, the selected models included decision tree, Markov, Markov decision tree and Markov decision process. In the evaluation of treatments for haemophilia B, only Markov and microsimulation models were used. No study exclusively focused on individuals with haemophilia B with inhibitors. One study included both haemophilia A and B with inhibitors in a decision tree model. Studies involving mixed populations of individuals with haemophilia A and B used either Markov models or decision trees.

With regard to assessed treatments, several trends were observed in the types of models used. Of the four studies evaluating gene therapies for haemophilia A, three used Markov model [19, 45, 46] and one used microsimulation [20]. In contrast, both studies assessing gene therapies for haemophilia B used microsimulation exclusively [47, 48]. No significant differences were observed in the models used to evaluate emicizumab in haemophilia A populations with or without inhibitors. Most studies in both populations used Markov models, with one study from each population used a decision tree [50, 70]. Irrespective of the comparator approaches (prophylaxis or on-demand), prophylaxis factor concentrates were mainly assessed using Markov models ($n = 14$, 66%). No patterns were found in the model types used for the individualised dosing strategy and ITI with factor concentrates, as different model types were applied. For studies in which both intervention and comparator used on-demand BPAs, they only used decision trees [33, 67, 68].

4 Discussion

This review identified common modelling practices in EEs of treatments for severe haemophilia A and B. Markov models were the most commonly used and were applied to different types of haemophilia and treatments. Common model features included a lifetime time horizon, a 1-year cycle length and the use of bleeding events — especially joint bleeds — as key health states. Additionally, bleeding events and QALYs were commonly selected as clinical outcomes. Among studies reporting QALYs as outcomes, the majority derived utility values from secondary sources, primarily the previously published literature. Of the 47 models reviewed, all focused on haemophilia, with one study including a mixed cohort of individuals with severe haemophilia A, haemophilia B and VWD. In this study, treatment effects between severe haemophilia A and severe VWD were assumed equivalent, consequently, the authors applied the same inputs of transition probabilities, utilities and resource use for both conditions in the model [31]. Therefore, no studies were found that specifically evaluated treatments for iBDs other than haemophilia. Although Markov models were commonly used to evaluate a range of treatments, decision trees and microsimulation tended to be used for specific treatment strategies. No consistent pattern was identified between the type of model used and the source of funding.

Previous reviews of EEs for haemophilia treatments have consistently reported variability in the modelling approaches used to assess cost effectiveness [21, 86]. They further indicate that these variations create challenges in comparing interventions across studies. Our current review builds upon these studies by specifically focusing on modelling approaches and examining how these choices have evolved over time. For example, compared with the review by Cortesi et al. [36], our study included more recent publications, including those evaluating newer haemophilia treatments such as emicizumab and gene therapies. Despite the introduction of these novel therapies, our findings confirm that the Markov model remains the most commonly used

model. Its dominance has persisted over time, particularly from 2001 onward when most studies used Markov models. While the use of individual-level models such as microsimulation and DES has increased in recent years, these remain less common than Markov models. The current review also explored whether authors justified their choice of model type; however, only 11 studies provided an explicit rationale for model selection. Nearly all individual-level models included a justification for model choice, whereas none of the decision trees did. While the absence of justification does not imply inappropriate model selection, the reasons for this omission remain unclear. This lack of reporting limits the ability to assess whether model selection was guided by methodological appropriateness, practical considerations or a trade-off between the two. Therefore, providing a clear justification is essential to ensure transparency in model selection.

The selection of appropriate modelling approaches has been discussed by several authors, including Barton et al. who propose a straightforward framework for model selection [18, 87, 88]. Following this framework, the Markov model is deemed sufficient for evaluating haemophilia treatments owing to its ability to account for recurrent bleeding events over an individual's lifetime. Therefore, the frequent use of Markov models among identified studies may indicate an implicit consensus among researchers regarding their suitability for this indication. Given the identified commonalities among Markov models regarding time horizon, cycle length and health states, there may be potential to apply these common approaches to evaluate haemophilia treatments in general.

However, the complexity of Markov models included in this review varied. While most models feature three or four health states, some authors used as few as two or as many as 80 states [35–38, 51, 58, 60]. In their appraisal of a two-state Markov model for emicizumab, the Canadian Agency for Drugs and Technologies in Health stated that this model structure inadequately represents the disease pathway and treatment effects [51]. Conversely, one could question what the added value was of a model comprising 80 health states [37]. As indicated by Briggs et al., an insufficient number of health states may result in an overly simplistic model, whereas an excessive number may have no additional value [89].

The selection of health states in the model is an equally important factor to consider. Bleeding events were frequently chosen as health states in the included studies. Given the prevalence of bleeding events in the progression of haemophilia, it therefore seems appropriate to use them as health states of the model [90]. However, individuals with haemophilia can also develop long-term complications, including arthropathy that may require surgery [91]. Only a few models in this review included these complications as health states in the model [31, 46, 65]. It is important to note that the bleeding tendency and the development of arthropathy can differ depending on the severity of haemophilia. Van den Berg et al. found large heterogeneity in bleeding patterns and arthropathy among individuals with severe haemophilia, which suggests that such clinical phenotypes can vary even within the same severity level [92]. Given that the tendency to bleed and develop arthropathy may be influenced by individual specific characteristics, individual-level modelling may be more appropriate in this context.

However, the types of assessed treatments and the combination of the intervention and comparator arms may affect the model choice [87]. For example, models evaluating on-demand BPAs represented the mechanism to resolve bleeding, which lasts for 1–5 days [33, 67, 68]. Here, a decision tree may be adequate because of the short time horizon [88]. Another example is a model designed to account for individual variations in dosage and treatment frequency. In this scenario, individual-level modelling may be more appropriate as this variability can influence both the benefits and costs of treatment [93]. For instance, Gu et al. emphasise that a DES model could incorporate individualised dose adjustments as part of a pharmacokinetic-guided approach for prophylactic FVIII therapy [63]. Similarly, Cook et al. assert that microsimulation allows for the variation of specific parameters for gene therapy [20]. In their discussion, ten Ham et al. also criticised their use of a Markov model for evaluating gene therapy and recommended adopting an individual-level simulation instead [19].

Although individual-level models may be more suitable in the presence of heterogeneity, the availability of data will inevitably influence the structuring of model [94]. Trade-offs must be made between model simplicity, data availability and their potential impact on result validity [95]. However, Barton et al. challenge the assumption that complex models necessarily require more data than simpler models and emphasise the importance of a sensitivity analysis when data are limited [18]. In this context, simplicity refers to the size of the model rather than the specific modelling technique used. They underline that sensitivity analyses should examine all scenarios that align with existing data in order to identify key uncertainties and guide further data collection [18]. The ISPOR-SMDM Joint Modeling Good Research Practices Task Force also recommends conducting sensitivity analyses when data are limited and ensuring the initial problem discussion covers all aspects of the disease and its outcomes [95].

Variations in the modelling approaches used among the included studies may complicate the comparative assessment of haemophilia treatments [21, 96]. Therefore, adopting common modelling approaches may enhance the comparability of treatment evaluations both within and across countries. This review shows that commonly

cited approaches were frequently used across a range of comparisons, including prophylaxis versus on-demand therapies, extended half-life versus standard half-life therapies, different prophylaxis therapies and even various dosing strategies. However, the frequent use of common approaches identified in this review should not be interpreted as an indicator of better model quality or that these models represent the best choice for all research contexts. As outlined by Briggs et al., model structure should be determined, among other factors, by the nature of the disease, the stability of event risks over time and the anticipated duration of intervention effectiveness [89]. The use of common modelling approaches identified in this review should be considered together with this recommendation. Another important consideration is that the common modelling approaches identified were predominantly applied to severe haemophilia. Individuals with milder forms of haemophilia may only require on-demand treatments, similar to the treatments for many other iBDs [97]. Further research is warranted to assess the applicability of common approaches and to explore potential modifications that could better accommodate evaluations for mild haemophilia and the broader iBD population.

4.1 Study Limitations

This review has several limitations, three of which stem from decisions made during the study design. First, the inclusion criterion requiring availability of the full text may have led to the exclusion of studies reported solely as abstracts. Among these abstract-only studies, a few evaluated the cost effectiveness of VWD, and their omission may have influenced our findings. Second, this review only included articles written in English language. However, it is anticipated that most articles are in English because haemophilia is a widely recognised disease on an international scale. Third, excluding the grey literature from our search may have resulted in overlooking unpublished or non-peer-reviewed studies, thereby potentially introducing publication bias. Beyond these procedural limitations, the generalisability of the review findings warrants consideration. Despite efforts to include all types of iBDs, the studies identified predominantly focused on treatments for severe haemophilia A and B. Consequently, the findings of this review may only be generalisable to severe haemophilia and caution is required in generalisation to the broader field of iBDs.

4.2 Recommendations for Future Studies

The common modelling approaches identified in this review provide a solid foundation for future researchers aiming to evaluate treatments for severe haemophilia. Future studies should consider adopting these common approaches, particularly when evaluating prophylaxis factor concentrates and emicizumab as they are most frequently applied to these treatments. Using common approaches can increase outcome comparisons across different countries and over time. In addition, future studies using common approaches should consider making their models open source. Such efforts could enhance efficiency, reproducibility and transparency, thereby facilitating adaptation by other researchers. However, it is important to recognise that the widespread use of a common approach does not equate to it being the optimal choice. Ultimately, the selection of a modelling approach should be guided by the specific study objectives, the complexity of the clinical decision, and the availability and quality of relevant data, rather than by convention alone.

For evaluating on-demand treatments such as BPAs, this review indicates that decision trees were exclusively used in the included studies. Thus, decision trees are recommended when the focus is mainly on evaluating the benefits and costs of resolving short-term bleeding episodes. A simple decision tree is generally suitable when the time frame is short and individual mortality does not vary across strategies [18]. In the case of gene therapies, this review reveals an equal number of studies using either Markov or microsimulation models. Although Markov model remains a feasible option, future studies should consider the underlying characteristics of a population. When population heterogeneity is present, individual-level models may be more appropriate [89]. Adapting previously published decision trees for BPAs and individual-level models for gene therapies may enhance the comparability of outcomes. Future research can utilise the review's findings to select the most appropriate model for their specific decision-making needs.

As the identified EEs were primarily for severe haemophilia, the common approaches found may not be generalisable to milder forms of haemophilia or other iBDs. However, with advanced clinical development of new treatments for VWD and Glanzmann thrombasthenia [98], EEs for these conditions will likely become available in the near future. Health technology assessment bodies are expected to mandate such evaluations for decision-making purposes because of the substantial costs involved. Furthermore, given the anticipated arrival of numerous new treatments for haemophilia, the range of available treatment options will expand, and EEs are needed to guide decision making. Therefore, a periodic systematic reassessment of modelling approaches in both published studies and the grey literature is recommended to continue advancing toward a standardised evaluation for haemophilia. This practice could potentially be extended to encompass all iBDs in the future as more EEs become available.

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Declarations

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References

1. Sharathkumar A, Pipe S. Bleeding disorders. Pediatr Rev. 2008;29(4):121–30.
2. Leebeek FW, Eikenboom JC. Von Willebrand's disease. N Engl J Med. 2016;375(21):2067–80.
3. Nurden AT. Glanzmann thrombasthenia. Orphanet J Rare Dis. 2006;1:10.
4. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. Blood. 2015;125(13):2052–61.
5. Du P, Bergamasco A, Moride Y, et al. Von Willebrand disease epidemiology, burden of illness and management: a systematic review. J Blood Med. 2023;14:189–208.
6. Quintana Paris L. Foundations of hemophilia and epidemiology. Blood Coagul Fibrinolysis. 2023;34(S1):S35–6.
7. Mahlangu J, Iorio A, Kenet G. Emicizumab state-of-the-art update. Haemophilia. 2022;28(Suppl. 4):103–10.
8. Nathwani AC. Gene therapy for hemophilia. Hematol Am Soc Hematol Educ Program. 2022;2022(1):569–78.
9. Mannucci PM. Hemophilia treatment innovation: 50 years of progress and more to come. J Thromb Haemost. 2023;21(3):403–12.
10. Gogia P, Tarantino M, Schramm W, et al. New directions to develop therapies for people with hemophilia. Expert Rev Hematol. 2023;16(6):417–33.
11. Abdelgawad HAH, Foster R, Otto M. Nothing short of a revolution: novel extended half-life factor VIII replacement products and non-replacement agents reshape the treatment landscape in hemophilia A. Blood Rev. 2024;64: 101164.
12. O'Hara J, HughesD, Camp C, et al. The cost of severe haemophilia in Europe: the CHESS study. Orphanet J Rare Dis. 2017;12(1):106.
13. Morgan G, Brighton S, Laffan M, et al. The cost of Von Willebrand disease in Europe: the CVESS study. Clin Appl Thromb Hemost. 2022;28:10760296221120584.
14. Ozelo MC, Yamaguti-Hayakawa GG. Impact of novel hemophilia therapies around the world. Res Pract Thromb Haemost. 2022;6(3): e12695.

15. Brousselle A, Lessard C. Economic evaluation to inform health care decision-making: promise, pitfalls and a proposal for an alternative path. Soc Sci Med. 2011;72(6):832–9.
16. Abbott JH, Wilson, Pryymachenko Y, et al. Economic evaluation: a reader's guide to studies of cost-effectiveness. Arch Physiother. 2022;12(1):28.
17. Xie F. Model-based economic evaluation for medical decision making: learn from the past and prepare for the future. J Thorac Dis. 2013;5(3):209–10.
18. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care. J Health Serv Res Policy. 2004;9(2):110–8.
19. 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.
20. 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):501–12.
21. 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):263–84.
22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
23. Wijnen B, Van Mastrigt GAPG, Redekop WK, et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (Part 3/3). Expert Rev Pharmacoecon Outcomes Res. 2016;16(6):723–32.
24. 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):625–33.
25. Rodriguez-Zepeda MDC, Gonzalez L, Bravo A, et al. Cost-effectiveness of rFVIIa versus pd-aPCC in the management of mild to moderate bleeds in pediatric patients with hemophilia A with inhibitors in Mexico. Value Health Reg Issues. 2018;17:164–73.
26. 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;3:207–12.
27. Colombo GL, Matteo SD, Mancuso ME, et al. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. Clinicoecon Outcomes Res. 2011;3:55–61.
28. Zhou Z-Y, Raimundo K, Patel AM, et al. Model of short- and long-term outcomes of emicizumab prophylaxis treatment for persons with Hemophilia A. J Manag Care Spec Pharm. 2020;26(9):1109–20.
29. Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A. Haemophilia. 2009;15(4):881–7.
30. Odeyemi I, Guest J. Modelling the economic impact of recombinant activated factor VII and activated prothrombin complex concentrate in the treatment of a mild to moderate bleed in adults with inhibitors to clotting factors VIII and IX at a comprehensive care center in the UK. J Med Econ. 2008;5:51–64.
31. Miners A, Sabin CA, Tolley KH, et al. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. Phamacoeconomics. 2002;20(11):759–74.
32. Lippert B, Berger K, Berntorp E, et al. Cost effectiveness of haemophilia treatment a cross-national assessment. Blood Coagul Fibrinolysis. 2005;16(7):477–85.
33. Odeyemi I, Guest J. Modelling the economic impact of recombinant activated factor VII compared to activated prothrombin complex concentrate in the home treatment of a mild to moderate bleed in adults with inhibitors to clotting factors VIII and IX in the UK. J Med Econ. 2008;5:119–33.
34. 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):1536–46.
35. 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):e12-21.
36. Cortesi PA, Castaman G, Trifiro G, et al. Cost-effectiveness and budget impact of emicizumab prophylaxis in haemophilia A patients with inhibitors. Thromb Haemost. 2020;120(2):216–28.
37. 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):422–9.
38. 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):e1-11.
39. Li N, Sawyer EK, Maruszczyk K, et al. Adult lifetime cost of hemophilia B management in the US: payer and societal perspectives from a decision analytic model. J Med Econ. 2021;24(1):363–72.
40. Rind D, Agboola F, Kumar V, et al. Emicizumab for hemophilia A: effectiveness and value final evidence report. 2018;1-162.
41. Saiyarsarai P, Derakhshan AR, 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.
42. Seth T, John MJ, Chakrabarti P, et al. Cost-effectiveness analysis of emicizumab prophylaxis in patients with haemophilia A in India. Haemophilia. 2024;30(2):426–36.
43. Farrugia A, Cassar J, Kimber MC, et al. Treatment for life for severe haemophilia A: a cost-utility model for prophylaxis vs. on-demand treatment. Haemophilia. 2013;19(4):e228–38.
44. 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):262–70.
45. Machin N, Ragni MV, Smith KJ. Gene therapy in hemophilia A: a cost-effectiveness analysis. Blood Adv. 2018;2(14):1792–8.
46. Rind DM, Agboola F, Herron-Smith S, et al. Valoctocogene roxaparvovec and emicizumab for hemophilia A: effectiveness and value. 2020;1-188.
47. Bolous N, 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):1677–90.
48. Meier N, Fuchs H, Galactionova K, et al. Cost-effectiveness analysis of etranacogene dezaparvovec versus extended half-life prophylaxis for moderate-to-severe haemophilia B in Germany. Pharmacoeconomics. 2024;8(3):373–87.
49. 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):488–97.

50. Patel AM, Corman SL, Chaplin S, et al. Economic impact model of delayed inhibitor development in patients with hemophilia A receiving emicizumab for the prevention of bleeding events. J Med Econ. 2019;22(12):1328–37.
51. CADTH. Drug reimbursement review pharmacoeconomic report emicizumab (hemlibra). 2021;1-39.
52. Earnshaw SR, Graham CN, McDade CL, et al. Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. Haemophilia. 2015;21(3):310–9.
53. Lotfi F, Talebianpour H, Keshavarz K, et al. Cost-utility analysis of factor VIII diet therapies prepared using blood plasma vs. recombinant technique for patients with hemophilia A. Daru. 2020;28(1):287–93.
54. Salinas-Escudero G, Galindo-Suarez RM, Rely K. Cost-effectiveness analysis of prophylaxis vs. on demand approach in the management in children with hemophilia A in Mexico. Bol Med Hosp Infant Mex. 2013;70(4):290–7.
55. 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):337–47.
56. 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):240–8.
57. Seth T, Garg K, Mandal PK, et al. Cost-effectiveness analysis of low-dose prophylaxis versus on-demand treatment for moderate-to-severe hemophilia A in India. Hematology. 2023;28(1):2277497.
58. Henry N, Jovanovic J, Schlueter M, et al. Cost-utility analysis of life-long prophylaxis with recombinant factor VIIIFc vs recombinant factor VIII for the management of severe hemophilia A in Sweden. J Med Econ. 2018;21(4):318–25.
59. 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. Pharmacoecon Open. 2020;4(1):133–42.
60. Chen R, Gultyaev D, Lister J, et al. Pharmacokinetic parameter driven outcomes model predicts a reduction in bleeding events associated with BAY 81–8973 versus antihemophilic factor (recombinant) plasma/albumin-free method in a Chinese healthcare setting. BMC Med Res Methodol. 2022;22(1):215.
61. 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):743–52.
62. Iannazzo S, Cortesi PA, Crea R, et al. Cost-effectiveness analysis of pharmacokinetic-driven prophylaxis vs. standard prophylaxis in patients with severe haemophilia A. Blood Coagul Fibrinolysis. 2017;28(6):425–30.
63. Gu C, Huang H, Han y. Cost-effectiveness analysis of pharmacokinetic-guided prophylaxis versus standard prophylaxis in adults with severe hemophilia A in China. Adv Ther. 2022;39(8):3777–88.
64. Smith P, Teutsch SM, Shaffer PA, et al. Episodic versus prophylactic infusions for hemophilia A a cost-effectiveness analysis. J Pediatr. 1996;129:424–31.
65. 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.
66. Pochopien M, Tytula A, Toumi M, et al. Cost-effectiveness of recombinant factor IX Fc prophylaxis and recombinant factor IX on-demand treatment in patients with haemophilia B without inhibitors. Adv Ther. 2024;41(6):2307–23.
67. Jimenez-Yuste V, Nunez R, Romero JA, et al. Cost-effectiveness of recombinant activated factor VII vs. plasma-derived activated prothrombin complex concentrate in the treatment of mild-to-moderate bleeding episodes in patients with severe haemophilia A and inhibitors in Spain. Haemophilia. 2013;19(6):841–6.
68. Golestani M, Eshghi P, Rasekh HR, et al. Cost-effectiveness analysis of biogeneric recombinant activated factor VII (Aryo-Seven TM) and activated prothrombin complex concentrates (FEIBA TM) to treat hemophilia A patients with inhibitors in Iran. Iran J Pharm Res. 2016;15(2):669–77.
69. Kenet G, Oladapo A, Epstein JD, et al. Estimating the potential cost of a high dose immune tolerance induction (ITI) therapy relative to the cost of a combined therapy of a low dose ITI therapy with bypassing agent prophylaxis. Haemophilia. 2017;23(5):e394–402.
70. Camelo RM, Barbosa MM, Araujo MS, et al. Economic evaluation of immune tolerance induction in children with severe hemophilia A and high-responding inhibitors: a cost-effectiveness analysis of prophylaxis with emicizumab. Value Health Reg Issues. 2023;34:31–9.
71. Berger K, Schopohl D, Eheberg D, et al. Treatment of children with severe haemophilia A and inhibitors: a health economic evaluation for Germany. Klin Padiatr. 2013;225(3):152–8.
72. Bitran R, Pena C, Arpon 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.
73. Krishnamoorthy Y, Govindan D, Kannan N, et al. Budget impact and cost-utility analysis of prophylactic emicizumab versus on-demand bypassing agents for adolescent severe haemophilia A patients with inhibitors in India. Heliyon. 2024;10(5):e27089.
74. Colowick AB, Avorn RJ, Ewenstein B. Immune tolerance induction in hemophilia patients with inhibitors costly can be cheaper. Blood. 2000;96(5):1698–702.
75. Knight C, Paisley S, Wight J, et al. Economic modelling of different treatment strategies for haemophilia A with high-responding inhibitors. Haemophilia. 2003;9:521–40.
76. 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;15:916–25.
77. 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.
78. Mazza G, O'Hara J, Carroll L, et al. The impact of haemophilia complications on health-related quality of life for adults with severe haemophilia. Value Health. 2016.
79. Fischer K, Lewandowski D, Janssen MP. Modelling lifelong effects of different prophylactic treatment strategies for severe haemophilia A. Haemophilia. 2016;22(5):e375–82.
80. Ballal RD, Botteman MF, Foley I, et al. Economic evaluation of major knee surgery with recombinant activated factor VII in hemophilia patients with high titer inhibitors and advanced knee arthropathy: exploratory results via literature-based modeling. Curr Med Res Opin. 2008;24(3):753–68.
81. Laupacis A, Bourne R, Rorabeck C, et al. The effect of elective total hip replacement on health-related quality of life. J Bone Jt Surg. 1993;75(11):1619–26.
82. Noone D, O'Mahony B, Van Dijk JP, et al. A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18–35-year old men with severe haemophilia in six countries. Haemophilia. 2013;19(1):44–50.

83. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509–18.
84. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377(9):809–18.
85. Miners AH, Sabin A, Tolley KH, et al. Assessing health-related quality-of-life in individuals with haemophilia. Haemophilia. 1999;5(6):378–85.
86. 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;24:632–42.
87. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Econ. 2006;15(12):1295–310.
88. Schulper M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. Phamacoeconomics. 2000;17(5):461–77.
89. Briggs A, Scupher M, Claxton K, et al. Decision modelling for health economic evaluation. Oxford University Press; 2006:236.
90. Shapiro AD, Hardesty BM, Peyvandi F, et al. Prevalence of selected bleeding and thrombotic events in persons with hemophilia versus the general population: a scoping review. Res Pract Thromb Haemost. 2023;7(1):100007.
91. Chin B, Wee I, Syn NLX, et al. Surgery for chronic arthropathy in people with haemophilia. Cochrane Database Syst Rev. 2022;11(11):CD013634.
92. van den Berg HM, De Groot PH, Fischer K. Phenotypic heterogeneity in severe hemophilia. J Thromb Haemost. 2007;5(Suppl. 1):151–6.
93. Iorio A, Edginton AN, Blanchette V, et al. Performing and interpreting individual pharmacokinetic profiles in patients with hemophilia A or B: rationale and general considerations. Res Pract Thromb Haemost. 2018;2(3):535–48.
94. Philips Z, Ginnelly L, Schulper M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004;8(36): 1–158.
95. Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force-2. Med Decis Mak. 2012;32(5):678–89.
96. Miners AH. Economic evaluations of prophylaxis with clotting factor for people with severe haemophilia: why do the results vary so much? Haemophilia. 2013;19(2):174–80.
97. Benson G, Auerswald G, Dolan G, et al. Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management. Blood Transfus. 2018;16(6):535–44.
98. EHC. Novel treatments in haemophilia and other bleeding disorders: a periodic EHC Review. European Hemophilia Consortium. 2024;1–52.