Systematic literature review for utility data in haemophilia

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BACKGROUND AND OBJECTIVES

Haemophilia A and B are hereditary bleeding disorders resulting in deficiencies of FVIII and FIX clotting factors, respectively. Haemophilia can be severe, moderate, or mild according to the level of deficiency of these clotting factors. The hallmark of haemophilia is recurrent joint bleeding, a primary driver of its morbidity resulting in arthropathy. The Petersson additive score is based on conventional X-rays of joints. It ranges from 0 to 78 and increases with joint bleeds.

Their management includes prevention and treatment of bleeding events. The therapeutic scheme is either episodic, also known as “on demand”, or prophylactic. Episodic treatment is used to stop a patient’s bleeding event while prophylactic is used to prevent bleeding from occurring [1].

Current guidelines (Medical and Scientific Advisory Council and World Federation of Haemophilia) recommend prophylaxis for patients with severe hemophilia and those with moderate hemophilia and a severe bleeding phenotype [2,3]. Current treatments available are factor replacement therapies (FRTs), non-FRTs, and gene therapy.

- FRTs can be either plasma-derived products or produced through recombinant methods [4]. They include standard half-life therapies, extended half-life therapies and bypassing agents
- Non-FRTs include substitution therapy (monoclonal antibody mimicking the action of FVIII) and haemostatic rebalancing agents [2]

While prophylaxis with FRTs has been the mainstay treatment of many years in patients without inhibitors [4-6], treatment can be complicated by inhibitors development due to the patient’s immune response to infused factors. Recombinant or plasma derived by-pass agents are used to treat patients with inhibitors.

This systematic review (SR) was undertaken to identify utilities associated with adolescents and adults with haemophilia A and B, for those with or without inhibitors. The SR focused on the US and the EU5 (France, Germany, Italy, Spain, UK).

METHODS

Nine bibliographic databases and three conference proceedings/websites were searched to identify studies reporting utilities data for adolescents and adults with haemophilia A or B. Targeted searches of three key technology assessment and regulatory agency websites (National Institute for Health and Care Excellence, Canadian Agency for Drugs and Technologies in Health, Institute for Clinical and Economic Review) and two non-database conference searches (European Haematology Association 2022 and World Federation of Haemophilia 2022) were also conducted.

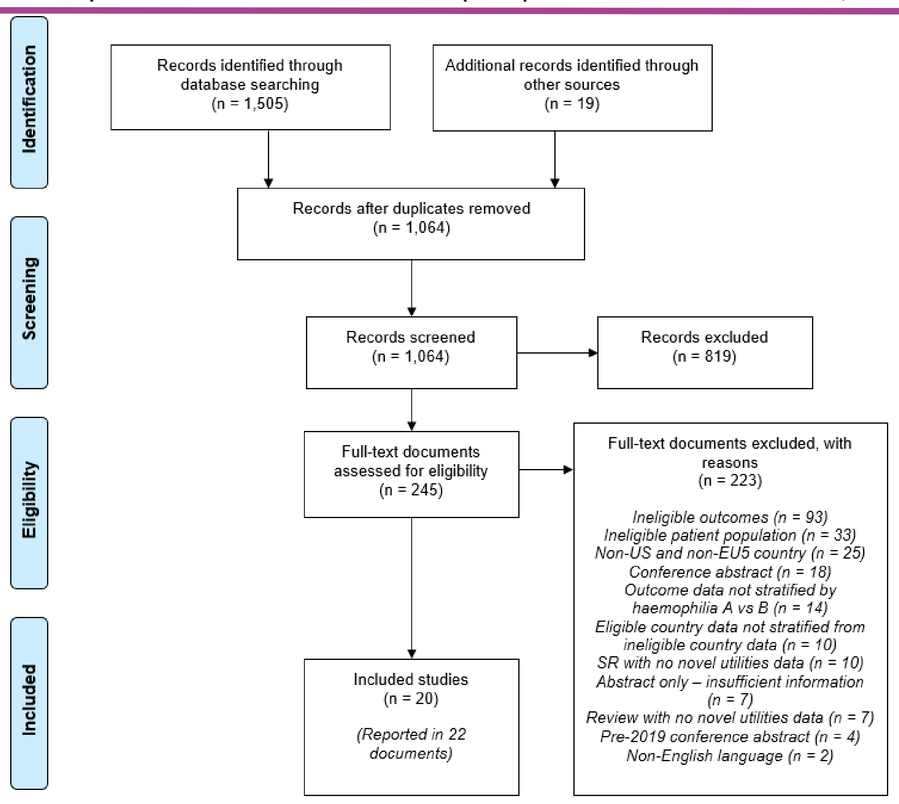
Only studies published between 2011 and June 2022, conducted in US and EU5 and published in the English language were eligible.

Two reviewers independently assessed the records for relevance, with disagreements resolved by discussion. One reviewer extracted data from each study, with a second reviewer checking all the extractions. The study findings were summarised.

RESULTS

The searches identified 1,064 unique records. After title and abstract screening and full-text review, 20 studies (reported in 22 publications) were included for data extraction **(Figure 1)**. Of the 20 studies included, 11 were primary studies and 9 were cost-effectiveness studies.

Figure 1. The simplified PRISMA flow chart (adapted from Moher et al., 2009) [7].



11 studies were in the US, 8 were in the EU5 and 1 was in both. 10 studies were in patients with haemophilia A, 5 studies were in patients with haemophilia B and 5 studies were in patients with haemophilia A or B, where outcome data were stratified by haemophilia type. Four studies were in patients with inhibitors, 10 studies were in patients without inhibitors and 6 studies reported mixed inhibitor status.

Utility data (Table 1) were derived using: EQ-5D-3L (10 studies), EQ-5D-5L (5), SF-6D (2), TTO (1) or were not reported (2).

Table 1: Utility data

Inhibitor status	Country	Study type (publication date)	Haemophilia type	Health states and mean utility data
Patients with inhibitors	US	Primary study (2017)	Haemophilia A	***Continuous prophylaxis*** Current inhibitor: 0.75 Inhibitor positive – age 14 to 20: 0.74 Inhibitor positive – age 21 to 44: 0.75 Inhibitor positive – age 45+: 0.71
		CEA (2018, 2019, 2020)	Haemophilia A	No bleed (n=3 studies): 0.82 Treated bleed (not targeted joint): 0.66 Target joint bleed: 0.54 No bleed with arthropathy, range: 0.72 (Pettersson score: 40 to 78) to 0.82 (Pettersson score: 0 to 4) Continuous bleeding (n=2): 0.66 Bleeding on last day of bleed (n=2) 0.74 Thrombosis (n=2): 0.63
	France	CEA (2020)	Haemophilia A	Prophylactic – emicizumab: 0.7683 Prophylactic – BPA: 0.5697 On demand – BPA: 0.5697
Patients without inhibitors	US	Primary study (2017, 2021)	Haemophilia A	***Continuous prophylaxis*** No current inhibitor: 0.78 Inhibitor negative – age 14 to 20: 0.75 Inhibitor negative – age 21 to 44: 0.74 Inhibitor negative – age 45+: 0.72
			Haemophilia B	Severe haemophilia: 0.74
		CEA (2020, 2020, 2018)	Haemophilia A	No bleed, range: 0.72 to 0.83* Non-joint bleed, range: 0.59 to 0.66* Joint bleed: 0.47 to 0.54* **dependent on Pettersson score* FVIII infusion: -0.0004 Joint replacement surgery: -0.39 *By age: Pettersson score 0; Pettersson score 1 to 27; surgery* Age 0 to 30: 0.94; 0.82; 0.72 Age 31 to 40: 0.84; 0.74; 0.65 Age 41 to 50: 0.86; 0.69; 0.61 Age 51 to 60: 0.83; 0.63; 0.56 Age 61 to 100: 0.73; 0.54; 0.48 rFVIII prophylaxis: 0.93 Hospitalisation: 0.66 Bleed: 0.66 Joint damage: 0.64 Gene therapy: 0.8 (complication) to 1 (no complication)
	EU5	Primary study (2018)	Haemophilia A	0.74 (target joints) to 0.87 (no target joints)
			Haemophilia B	0.67 (severe haemophilia B) to 0.86 (no target joints)
	UK	CEA (2021)	Haemophilia A	Moderate haemophilia A: 0.7 Moderate haemophilia A + spontaneous bleed: 0.68 Moderate haemophilia A + trauma bleed: 0.44 Severe haemophilia A: 0.64 Mild haemophilia: 0.82
	Italy	CEA (2017)	Haemophilia A	Prophylaxis: 0.86 On demand: 0.68
	US and EU5	Primary study (2022)	Haemophilia B	Haemophilia B: 0.77
Mixed population of inhibitors	US	Primary study (2017, 2014)	Haemophilia A	***Continuous prophylaxis*** Age (Age 14-20; 21-44; 45+): 0.85; 0.76; 0.7 Ethnicity (non-Hispanic white; non-Hispanic black; Hispanic; other ethnicity): 0.78; 0.76; 0.77; 0.82 Insurance (commercial insurance; Medicaid; Medicare; other insurance; uninsured): 0.82; 0.75; 0.68; 0.81; 0.74 Student or employed; not a student or employed: 0.82; 0.69 BMI (normal BMI; overweight; obese): 0.78; 0.78; 0.78 Episodic treatments for bleeds: 0.76 Continuous prophylaxis for bleeds: 0.82 HIV; no HIV: 0.72; 0.8 Liver disease; no liver disease: 0.74; 0.85 Joint disease; no joint disease: 0.71; 0.84 Severe bleeding; no severe bleeding: 0.76; 0.81
			Haemophilia B	High physical activity haemophilia B: 0.85 Moderate/low physical activity haemophilia B: 0.76
	EU5	Primary study (2018)	Haemophilia A and B	Severe haemophilia A: 0.78 Severe haemophilia B: 0.76
	France, UK	Primary study (2019)	Haemophilia A and B	Haemophilia A: 0.68-0.75 Haemophilia B: 0.67-0.7

Key: BMI – body mass index; BPA – bypassing agent; CEA – cost effectiveness analysis; FVIII – factor VIII; HIV – human immunodeficiency virus; rFVIII – recombinant factor VIII.

DISCUSSION

The review of utility values published over the last decade suggests prophylactic treatments (0.76 to 0.86) may result in higher utility values when compared to on-demand treatment (0.56 to 0.68), with the exception of BPAs. Furthermore, the data underscores the influence of various factors on utility values, including age, the severity of arthropathy (measured by the Pettersson score), bleeding status, the presence of comorbidities such as liver disease or HIV, and physical activity levels. In the collected evidence, utility values range between 0.72 to 0.78 for those with negative inhibitors status and 0.71 to 0.75 for those with positive inhibitors status. One study estimated a slight utility loss of 0.03 for patients with inhibitors compared to those without inhibitors [8].

Due to the limited availability of data, the published utility values for haemophilia A can be utilised as a common metric for economic modeling in haemophilia B, and vice versa. In fact, one study comparing haemophilia A and B found no significant difference in utility values [9].

These data-driven insights underscore the complex nature of utility values in haemophilia. They provide important inputs for assessing the overall quality of life in economic modeling.

Limitations:

- This SR only included studies in which data were reported separately for haemophilia A and B. However, based on the findings, this distinction may not be critical and future studies of mixed population may be useful.
- There was no assessment of the risk of bias of the included studies.
- Transferability should be considered when using values in an economic model.

RECOMMENDATIONS

For economic modelling of haemophilia, utilities data by Pettersson score are available from the 2020 ICER study (Table 1). The ICER study also provided disutilities for joint bleed (-0.003) and non-joint bleed (-0.002) [10].

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