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Cost-effectiveness of emicizumab prophylaxis for haemophilia A with inhibitors: an adaptive health technology assessment for the Indian setting

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Abstract

Objective To assess the cost-effectiveness of emicizumab prophylaxis for patients having haemophilia A with inhibitors in the Indian context using an adaptive health technology assessment (aHTA) methodology.

Design Economic evaluation using multiple approaches aimed at adjusting previously generated cost-effectiveness results based on (1) price differences only ('simple') and (2) differences in cost and expected treatment duration ('moderate') and differences in cost, inflation and life expectancy ('complex').

Setting Typical haemophilia care in India.

Participants Patients with haemophilia A and inhibitors.

Intervention Emicizumab prophylaxis using two vial strengths (30 or 150 mg/mL) in comparison to no prophylaxis.

Main outcome measures Adjusted incremental cost-effectiveness ratio (ICERa), incremental costs and incremental quality-adjusted life years associated with emicizumab prophylaxis from both the health system and societal perspectives.

Results Using the simple ICER adjustment method, emicizumab prophylaxis resulted in potential cost savings from the payers' perspective for both vial strengths in patients aged ≥12 and <12 years. However, from a societal perspective, emicizumab prophylaxis was not cost-effective. Using the moderate adjustment method, emicizumab prophylaxis showed potential cost saving from the health system perspective. The complex adjustment method also revealed cost savings for emicizumab prophylaxis from the health system and societal perspectives across different age groups.

Conclusion We found that implementing emicizumab prophylaxis for patients with haemophilia A and inhibitors in India has the potential to result in cost savings. This study highlights the feasibility of using the expanded aHTA methodology for rapid evidence generation in the Indian context. However, it is crucial to address certain research gaps, including data limitations, challenges in translating international evidence to Indian context and associated uncertainties. Additionally, conducting a comprehensive budget impact analysis is necessary. These findings hold significant implications for decision-making regarding the potential provision of emicizumab prophylaxis through federal or/and state government-funded programmes and institutions in India.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Limited understanding exists regarding the cost-effectiveness of emicizumab prophylaxis for patients with haemophilia A and inhibitors in India. Our study fills this gap by employing an expanded adaptive health technology assessment (aHTA) methodology.

WHAT THIS STUDY ADDS

⇒ We found that implementing emicizumab prophylaxis in India has the potential to result in cost savings. Additionally, we demonstrated the feasibility of using the expanded aHTA methodology for rapid evidence generation in the Indian context.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings have significant implications for practice and policy decisions regarding the provision of emicizumab prophylaxis through federal or/and state government-funded programmes and institutions in India. The study contributes to the research and body of evidence on the application of pragmatic or aHTA methods and highlights limitations encountered due to research gaps, data constraints and challenges in adapting international evidence to the country context.

Introduction

Haemophilia affects a significant number of individuals worldwide, particularly the developing countries. In India, the expected number of affected individuals is 1 lakh, with only about

15 218 patients registered.[1 2] Treatment for haemophilia involves lifelong therapy to replace the missing clotting factor, either as prophylactic treatment or as needed for bleeding episodes. The costs associated with clotting factor usage form a substantial portion of haemophilia drug expenses. Additionally, direct costs include expenses related to haemarthroses, infections, hospitalisations and surgical procedures to replace damaged joints while productivity losses contribute to significant indirect costs.[1 3]

A major complication for patients with haemophilia A is the development of inhibitors, which greatly impact their quality of life.[4] The global prevalence of inhibitors among patients with severe haemophilia A ranges from 20% to 40%[5 6] and in India, the estimated prevalence is 19.5%.[7] Bypassing agents (BPAs) are administered to manage bleeding episodes and are also employed as a prophylactic measure to safeguard against potential bleeding complications associated with invasive procedures.[4]

Currently, in India, the treatment approach for patients having haemophilia A with inhibitors primarily involves on-demand treatment using BPAs. The administration of BPA prophylaxis incurs significant costs as it requires frequent intravenous injections, typically three times a week. This regimen presents challenges for patients and their families, including the need for repeated painful injections, difficulty in accessing intravenous sites in small children and the inconvenience of travelling to distant hospitals for treatment.

In the recent years, the emergence of emicizumab, a novel monoclonal antibody that mimics factor VIII, has shown promising results in reducing bleed frequency and improving the quality of life for individuals with haemophilia A. Clinical trials, such as HAVEN 1, 2, 4 and 5, have demonstrated a significant reduction in bleeding episodes among patients with inhibitors receiving emicizumab prophylaxis compared with those without prophylaxis and those on BPA prophylaxis.[8–11]

Further, emicizumab, being a subcutaneous injection, offers a more convenient and patient-friendly treatment option. Emicizumab can be administered weekly, every 2 weeks or every 4 weeks, and parents can administer it at home. For patients with inhibitors, it is usually administered weekly. Studies have proved that emicizumab demonstrates better haemostatic efficacy and safety profiles in comparison to BPA prophylaxis.[12] Therefore, introducing emicizumab in India could address the existing limitations associated with treatment using BPAs, resulting in potential improvements in patients' quality of life, productivity and reduction in healthcare costs. Various economic evaluations conducted in other countries and health technology assessment (HTA) reports have also recognised emicizumab as cost-effective option for patients with inhibitors.[13–17] But, the evidence on this regard is currently lacking in India.

Given the limited accessibility of emicizumab prophylaxis in India, we aimed to assess its cost-effectiveness for patients with haemophilia A and inhibitors. Given the level of urgent interest in this treatment and limitations on capacity to conduct formal economic evaluation using local data, we used a novel adaptive HTA (aHTA) methodology. For evidence synthesis step of this aHTA work, we adopted key methodological aspects of rapid evidence synthesis (RES) approach aiming to rapidly synthesise the evidence required for undertaking the aHTA.

The study also aimed to provide insights into the feasibility of implementing this aHTA methodology in the Indian context. The findings of this exploratory research will inform decision-making regarding the use of emicizumab in the Indian healthcare system, particularly as governments like the state of Punjab and Union Territory of Jammu and Kashmir are considering its delivery at public hospitals. This study also offers valuable information for other states and centrally funded health systems in the country to consider emicizumab prophylaxis as a standard care option.

Methodology

Study approach

Traditional HTA is a process of evaluating health technologies to identify the most cost-effective interventions, maximising health outcomes per investment. It is a resource-intensive, data-driven process that employs systematic methodologies and explicit procedures to optimise the allocation of limited healthcare resources in support of informed policy decisions. While developed countries typically conduct traditional HTAs to inform healthcare system inclusion decisions, low and middle-income countries with nascent HTA systems face challenges in conducting traditional HTAs due to time constraints, shortage of expertise, data and sufficient resources.[18–20]

In circumstances where a full HTA is not practical, such as a stated urgent timeline to address an important health policy need or lack of trained personnel and general resources for traditional HTA, aHTA approaches have emerged as a means to expedite evidence-informed policy decisions. aHTA is a structured 'fit for purpose' approach to conducting the optimal HTA analysis. They produce efficient HTA results by adjusting for analytical time, data, capacity and source of conduct, leveraging information from other settings where possible. These approaches modify or use international data, traditional economic evaluations, models and conclusions from existing HTA agencies while considering its transferability to the local context and uncertainty related to any transfer.[21]

Globally, developed countries like the UK, Canada and the European Union, and developing countries including Romania, Argentina and India have already developed and employed aHTA methodologies.[21 22] In this study, we have expanded on these aHTA methodologies and developed a four-step aHTA process to assess the cost-effectiveness of emicizumab prophylaxis in India, considering the imbalance between volume of policy decisions and capacity for de novo modelling that currently exists in the country. This approach holds potential for informing decisions related to healthcare provisioning in India and also expediting policy decisions regarding cost-effective health technologies, as evaluated through traditional HTAs conducted elsewhere.

The genesis for developing this aHTA methodology, and the initial steps taken for deciding on the topic are detailed in the online supplemental file 1 under the subheading 'Topic selection'. Following this, we developed the PICO components for the study:

- Population—patients with haemophilia A with inhibitors.
- Intervention—emicizumab prophylaxis.
- Comparator—no prophylaxis (ie, on-demand treatment using BPAs).
- Outcomes—reduction in annualised bleeding rates (online supplemental table 1).

The four steps employed for conducting the study are described below.

Step 1: topic prioritisation

The first step in the aHTA process is ensuring that the topic is of sufficiently high priority in the local setting. To determine this, we considered various criteria, including expert consultations to assess the topics' relevance, the magnitude of the health problem, clinical and economic impact, feasibility, availability and relevance of evidence, urgency for a health policy need and social

value judgements. The specific aspects of these criteria that led to ascertaining the high priority of this topic are described in the online supplemental file.

Step 2: conducting RES

Following the topic prioritisation, we initiated the RES process to conduct an initial rapid assessment of available evidence for undertaking the aHTA on the topic. We adopted key methodological aspects of RES approach which is designed to conduct rapid assessment of existing evidence to inform a time-bound (short time span) healthcare decision-making.[23] 24 We initiated the RES process by providing a comprehensive description of the decision problem, namely the clinical benefits, risks and cost-effectiveness of emicizumab prophylaxis when compared with no prophylaxis in India. This involved contextualising the decision problem within the Indian healthcare setting and defining the relevant parameters, such as population, intervention, comparisons and outcomes, that would guide the assessment.

We revisited and expanded on the PICO framework by reassessing the parameters of the study to align with existing evidence on the 'emicizumab' and 'no' prophylaxis groups. Once the PICO framework and the information required for conducting this aHTA were determined, we initiated the rapid literature search to identify the evidence. The protocol developed for the RES approach is included in the online supplemental file 1.

Step 3: acquiring evidence

We adopted a pragmatic and iterative process for acquiring evidence. Initially, our search query was tailored to conduct a narrow search to maximise relevance, before broadening the search approach. We conducted rapid searches across three key data sources to gather evidence on the clinical impact and cost-effectiveness of emicizumab prophylaxis: (1) HTA agency reports, (2) published systematic reviews and cost-effectiveness analyses (CEA) and (3) newly published clinical evidence (figure 1). We also conducted reference checking to identify any additional evidence. The search query used in this stage is presented in the online supplemental file 1.

We also consulted clinical experts treating patients with haemophilia A to gather any additional evidence on the topic. We continued the step 3 until sufficient intervention-specific evidence was identified. Full text of the identified literature was reviewed for data extraction. To ensure consistency and facilitate comparisons across the selected documents, a data extraction template was used. This template served as a standardised tool for aggregating information and reporting the collected data uniformly. It included background information on the type of evidence and extracted critical findings related to the effectiveness, safety, cost-effectiveness and other pertinent aspects of the intervention (online supplemental tables 2–4).

Step 4: evidence appraisal and cost-effectiveness synthesis

On completion of data collection of available evidence on the topic in step 3, we proceeded to appraise the full evidence package. The aim was to provide a comprehensive assessment of the accumulated information, including the effectiveness, cost-effectiveness, safety, level of confidence in the evidence and any remaining uncertainties that should be taken into account. By employing the RES approach, we appraised a range of seminal work from reputable sources in a short time frame, at the same time we ended up collecting necessary information required for the 'cost effectiveness synthesis'. We concluded the RES process by producing a narrative summary to report the intervention and cost-effectiveness effect estimates along with their appraisal of certainty and relevance. Further details regarding information sources, search strategy, search queries, data extraction, data charting process, risk of bias assessment and the strategy to data synthesis are presented in the online supplemental file.

For the cost-effectiveness synthesis, since the collected information on costs, health benefits and incremental cost-effectiveness ratios (ICERs) originated from diverse settings, adjustments were made to increase their potential applicability to the Indian context. Three adjustment methods were employed, each of which is intended to reflect the fact that an aHTA approach will not have the luxury of access to an operating and modifiable economic model, only published model findings. For ease of interpretation, they are known as 'simple', 'moderate' and 'complex' adjustments based on the number of data steps and assumptions required. As noted below, each of the three adjustments requires assumptions and has limitations; for this reason, all approaches were implemented to evaluate the consistency of findings, taking the available data into consideration. Detailed description of the methods

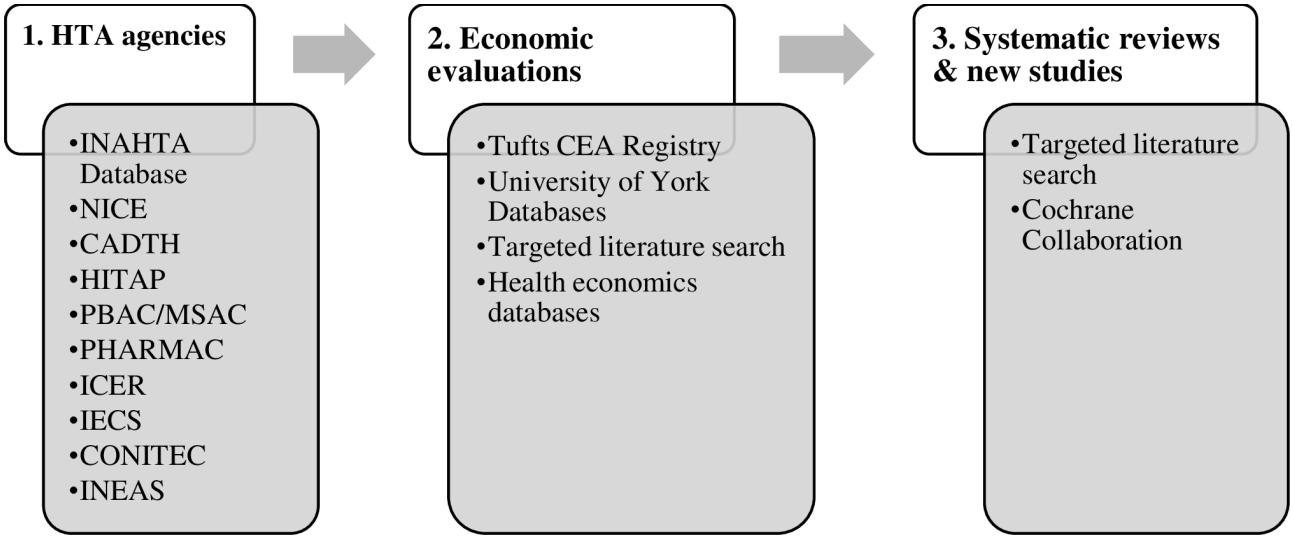

Figure 1 Hierarchical selection of potential sources of evidence. HTA, health technology assessment.

can be found in the online supplemental file 1, and the input parameters used for the adjustments are provided in table 1.

ICER adjustment methods

Simple adjustment

To perform a simple adjustment, the study-reported ICER was multiplied by the ratio of the price of emicizumab in India (P_A) to the price in the original study country (Po), as noted below:

$$ICER_A = ICER_O \times (P_A/P_O)$$

The simple adjustment requires accurate estimates of the intervention price in both settings, assumes that intervention price is the dominant driver of cost-effectiveness findings and may be of lower utility when the distribution of costs is more complex or when other parameters are significant drivers of findings.

Moderate adjustment

The moderate adjustment method estimated the monthly treatment cost (Ci) and the duration of therapy (in months) for both the intervention and its comparator (Mi and Mc, respectively) based on data from the original clinical study or CEA. The formula for the moderate adjustment was as follows:

$$ICERi = (Ci \times Mi) - (Cc \times Mc)/((MiMc)/12)$$

where Ci and Cc represent the monthly cost, and Mi and Mc represent the number of months of treatment for the intervention and comparator, respectively. The moderate adjustment requires detailed estimation of monthly cost for both intervention and comparator and assumes the availability of data to estimate typical duration of therapy. If this is not directly available from a clinical trial, expert opinion may be required, which may limit the applicability and generalisability of the estimates.

Complex adjustment

In situations where multiple expenses, beyond the intervention cost, or variations in disease characteristics between countries needed to be considered, a more sophisticated formula was employed. This involved separate adjustments for costs and quality-adjusted life years (QALYs). The detailed formula is included in the online supplemental file 1; in brief, costs are adjusted for both purchasing power parity (PPP) and inflation, and QALYs are adjusted for differences in life expectancy across settings. PPP and inflation indices are typically accessible via public sources, but the underlying assumption that these factors largely explain cost differences may be challenging, as differences in infrastructure and settings of care may also differ substantially between countries. In addition, life expectancy adjustment should ideally be made from the time of diagnosis of a given disease, but these data may only be available from birth.

We conducted a comprehensive evidence appraisal and employed all three adjustment methods to enhance the robustness of the CEA and assess comparability of adjusted ICERs (ICERa) in the Indian context after accounting for factors such as price differentials, duration of therapy, cost variations, inflation and epidemiological differences between countries. In the analysis, India's per capita gross domestic product ($2256.59; ₹185 605) was considered as the cost-effectiveness threshold.

After a careful appraisal of the evidence in step 4, the key parameters necessary for the ICER adjustment methods, including ICERs, costs and QALYs for both the intervention and comparator relevant to this study, were obtained from the cost-effectiveness report published by the Institute for Clinical and Economic Review.[16] Data required on the total number of bleeds per year among ≥12 and <12 years age group patients in the moderate adjustment method, certain patient-related parameters such as mean weight of different age group patients, mean treatment duration, drug costs, life expectancy and number of bleeding episodes were obtained from expert opinion. Various data used for the analysis are presented in table 1.

Results

In this study, a team of six researchers, comprising three junior and three senior-level researchers, conducted the project alongside their other responsibilities. The project lasted 4 months from March to June 2023. The junior researchers dedicated approximately 60 hours each from conceptualisation to manuscript writing, while the senior researchers contributed around 20 hours each. Additionally, two expert clinicians were involved for consultations who were specialised in the treatment of patients with haemophilia in India.

As per the RES methodology, a narrative summary of the evidence used for the aHTA is presented in the online supplemental file 1. The narrative summary included the information synthesis on intervention effects, and the cost-effectiveness along with their critical appraisal as reported in the report published by the Institute for Clinical and Economic Review, USA, from which the data required for this aHTA were obtained. Other HTA studies sourced from the literature search either did not align with the study's PICO or did not report the parameters relevant to this study.

Data collected at the end of RES process are presented in online supplemental tables 2–4. We did not conduct evidence appraisal of each study/report identified at the end of RES process as they were not used as input parameters in the aHTA and did not aim to present a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram that are mainly recommended for traditional systematic reviews.

We used the economic evaluation conducted by the Institute for Clinical and Economic Review, USA, to inform the ICERa in the Indian context. The Institute for Clinical and Economic Review's report conducted comparisons of the cost-effectiveness of emicizumab prophylaxis with no prophylaxis in patients aged ≥12 and <12 years, considering both the health system and societal perspectives. The report revealed that emicizumab resulted in greater QALYs while also being cost saving in terms of total costs, when compared with no prophylaxis, from both health system and societal perspectives.

Simple adjustment

We found that providing emicizumab prophylaxis using the vial strength of 30 mg/mL resulted in cost savings from the payers' perspective for both age groups (<12 and ≥12) of patients in India. Costs were lowered by −$8 913 222 (−₹733 112 509) with an incremental QALY of 0.91 for patients ≥12 years old, and −$10 329 148 (−₹849 572 423) with an incremental QALY of 2.39 for patients <12 years old. However, from the societal perspective, giving emicizumab prophylaxis using this vial strength was not cost-effective. Similar results were observed for the vial strength of 150 mg/mL, where cost savings were seen from the payers' perspective for both the age groups, but it was not cost-effective from the societal perspective for both age groups of patients in India (table 2).

Moderate adjustment

The total cost of treatment for patients on no prophylaxis was higher ($163 777 751; ₹13 470 720 019) when compared with the

Table 1 Input parameters used for the ICER adjustment methods

Parameters	₹	$	Reference
Simple adjustment (payer's perspective)			
ICERo (<12 years old)	−344 673 971	−4 190 565	ICER report
ICERo (≥12 years old)	−806 100 255	−9 800 611	ICER report
Simple adjustment parameters (societal perspective)			
ICERo (<12 years old)	360 754 763	4 386 076	ICER report
ICERo (≥12 years old)	838 631 936	10 196 133	ICER report
Cost parameters			
PA (drug price in India) for 30 mg/mL (as of 19 April 2023)	58 900		Manufacturer (Roche Medical Information)
Po (drug price in USA) for 30 mg/mL (as of 19 April 2023)	282 499	3435	www.drugs.com/price-guide/hemlibra
PA (drug price in India) for 150 mg/mL (as of 19 April 2023)	294 392		Manufacturer (Roche Medical Information)
Po (drug price in USA) for 150 mg/mL (as of 19 April 23)	1 409 369	17 135.18	www.drugs.com/price-guide/hemlibra
Cost parameters for moderate adjustment			
Cost of EMI per vial (30 mg/mL)	58 900		Manufacturer (Roche Medical Information)
Mean dose per kilogram body weight (mg/kg) per month	6		Expert opinion
Mean weight of patients on prophylaxis (kg), 2–5 years	12		Expert opinion
Mean weight of patients on prophylaxis (kg), 6–10 years	25		Expert opinion
Mean weight of patients on prophylaxis (kg), 6–10 years	44		Expert opinion
Mean duration of treatment (in months) (Mi)	420		Expert opinion
Cost of BPA per vial (500 IU)	80 000		Expert opinion
Mean duration of patients on FEIBA (Factor eight inhibitor bypass activity) regimen (in months) (Mc)	300		Expert opinion
Dose per kilogram body weight (IU)	500		Expert opinion
Frequency of administration (per day)	2		Expert opinion
Approximate number of bleeding episodes per month	2		Expert opinion
Complex adjustment			
PPP GDP for study country (USA)		59 915	World Bank data
PPP GDP for study country (India)		6112.0	World Bank data
Consumer Price Index (CPI) for health in India for current year (2023)		183.4	MOSPI, Government of India
CPI for health in India for publication year (2018)		135.2	MOSPI, Government of India
Life expectancy from birth in study country (USA)		78.54	World Bank data
Life expectancy from birth in India		70.47	World Bank data
Reduction in life expectancy (in years)		10	Expert opinion
Life expectancy from disease in study country (2017)		68.54	Calculated
Life expectancy from disease in India (2017)		60.47	Calculated
Health system perspective			
Emicizumab prophylaxis (≥12 years old)		19 221 932	ICER report
No prophylaxis (≥12 years old)		28 135 154	ICER report
Emicizumab prophylaxis (<12 years old)		20 683 787	ICER report
No prophylaxis (<12 years old)		31 012 935	ICER report
Societal perspective			
Emicizumab prophylaxis (≥12 years old)		19 623 275	ICER report
No prophylaxis (≥12 years old)		28 901 756	ICER report
Emicizumab prophylaxis (<12 years old)		21 212 892	ICER report
No prophylaxis (<12 years old)		31 695 614	ICER report
Study-reported QALYs (2017)			
Emicizumab prophylaxis (≥12 years old)	15.41		ICER report
No prophylaxis (≥12 years old)	14.5		ICER report
Emicizumab prophylaxis (<12 years old)	22.79		ICER report
No prophylaxis (<12 years old)	20.4		ICER report

BPA, bypassing agent; EMI, emicizumab; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; PPP, purchasing power parity; QALY, quality-adjusted life year.

Table 2 Adjusted incremental cost-effectiveness ratios (ICERa) for different vial strengths of emicizumab among patients with haemophilia A and inhibitors compared with those without prophylaxis using the simple adjustment method for payers and societal perspectives in India

		Emicizumab (30 mg/mL)		Emicizumab (150 mg/mL)	
Perspective	Age group	ICERa* (₹)	ICERa* ($)	ICERa* (₹)	ICERa* ($)
Payers	<12	Cost saving	Cost saving	Cost saving	Cost saving
Payers	≥12	Cost saving	Cost saving	Cost saving	Cost saving
Societal	<12	75 216 001	914 480	75 355 248	916 173
Societal	≥12	174 851 580	2 125 855	175 175 281	2 129 791

*The exchange rate used was ₹82.25 for US$1, as of 15 May 2023.

total cost of treatment for patients on emicizumab prophylaxis ($2 525 965; ₹207 760 621). The mean duration of treatment among patients on emicizumab prophylaxis (Mi) is estimated to be 10 years longer when compared with patients on 'no prophylaxis' (Mc). The ICERa indicated that implementing emicizumab prophylaxis could be cost saving from the health system perspective in India (table 3).

Complex adjustment

From the health system perspective, implementing emicizumab prophylaxis resulted in cost savings. For patients aged <12 years, the costs were lowered by –$1 429 359 (–₹117 564 777), with an incremental adjusted QALY of 2.11. Similarly, for patients aged ≥12 years, the costs were lowered by –$1 233 421 (–₹101 448 877), with an incremental adjusted QALY of 0.8. These findings highlight the cost-saving potential of emicizumab prophylaxis from the health system perspective.

From the societal perspective, emicizumab prophylaxis also demonstrated cost savings. For patients aged <12 years, costs were lowered by –$1 450 611 (–₹119 312 754), with an incremental adjusted QALY of 2.11 compared with no prophylaxis. Likewise, for patients aged ≥12 years, costs were lowered by –$1 283 966 (–₹105 606 203), with an incremental adjusted QALY of 0.8. These results indicate that implementing emicizumab prophylaxis can be a cost-saving approach across different perspectives and age groups in India compared with the current no prophylaxis scenario (table 4).

Table 3 Adjusted ICERs for emicizumab prophylaxis among patients with haemophilia A and inhibitors compared with those without prophylaxis in India using the moderate adjustment method

Parameters	Values
Monthly cost ($) of emicizumab (EMI) intervention (Ci)	1918
Mean duration of treatment (in months) for different patient age groups (Mi)	
2–5 years	48
6–10 years	60
>10 years	312
Total	420
Total cost ($) of treatment using EMI (Ci*Mi)	
2–5 years	92 063
6–10 years	239 746
>10 years	2 194 156
Total	2 525 965
Monthly cost ($) of comparator (Cc) using FEIBA	186 748
Mean duration (in months) for different patient age groups on FEIBA regimen (Mc)	
2–5 years	48
6–10 years	60
>10 years	192
Total	300
Total cost ($) of treatment using FEIBA (Cc*Mc)	
2–5 years	8 963 891
6–10 years	23 343 465
>10 years	131 470 395
Total	163 777 751
(Mi–Mc)/12 (in years)	10
Adjusted ICER ($) for India (ICERi)	Cost saving
Adjusted ICER (₹) for India (ICERi)*	Cost saving

*The exchange rate used was ₹82.25 for US$1, as of 15 May 2023.

FEIBA, factor eight inhibitor bypass activity; ICER, incremental cost-effectiveness ratio.

Discussion

Using different ICER adjustment methods, we found that emicizumab resulted in cost savings from the payers' perspective for both the vial strengths (30 and 150 mg/mL), but it did not appear to be cost-effective from the societal perspective. Using moderate adjustment method, implementing emicizumab prophylaxis demonstrated cost-saving potential from the health system perspective. Furthermore, emicizumab prophylaxis appeared to be cost saving using the complex adjustment method across different age groups from both the health system and societal perspectives. These findings highlight the potential value of emicizumab as a cost-saving approach for patients with haemophilia A in India and have implications for decision-making regarding its inclusion in the national health benefits package.

In addition to our source HTA report, it is important to note that multiple economic evaluation studies conducted in France, Korea and Italy consistently demonstrated the cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A and inhibitors. For instance, a study conducted in France reported emicizumab as a dominant treatment option, saving €234 191 with a gain of 0.88 QALYs.[14] In Korea, the cost-utility analysis revealed that lifetime emicizumab prophylaxis prevented 807 bleeding episodes, extended 3.04 QALYs and reduced costs by $2.6 million.[17] Similarly, the Italian study found that emicizumab prophylaxis was more effective (0.94 QALYs) and cost saving (€19.4/€24.4 million per patient lifetime) compared with BPA prophylaxis.[13]

The above findings provide consistent evidence on emicizumab's potential for cost-effective prophylaxis in improving patient outcomes and reducing healthcare costs. It is essential to acknowledge that comparing the ICER estimates between these studies and the current study is challenging due to variations in study population, modelling techniques, assumptions and data sources. Nevertheless, the results of economic evaluations conducted in other settings support the potential cost-effectiveness of implementing

Table 4 Adjusted ICERs for emicizumab prophylaxis among patients with haemophilia A and inhibitors compared with those without prophylaxis in India using the complex adjustment method

Perspective and age group	Parameter	Emicizumab prophylaxis	No prophylaxis
Health system and <12 years	Adjusted cost ($)	2 862 245	4 291 604
	Adjusted QALYs	20.11	18
	Incremental adjusted cost ($)	−1 429 359	–
	Incremental adjusted QALYs	2.11	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–
Health system and ≥12 years	Adjusted cost ($)	2 659 952	3 893 373
	Adjusted QALYs	13.6	12.79
	Incremental adjusted cost ($)	−1 233 421	–
	Incremental adjusted QALYs	0.8	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–
Societal and <12 years	Adjusted cost ($)	2 935 463	4 386 074
	Adjusted QALYs	20.11	18
	Incremental adjusted cost ($)	-1 450 611	–
	Incremental adjusted QALYs	2.11	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–
Societal and ≥12 years	Adjusted cost ($)	2 715 490	3 999 457
	Adjusted QALYs	13.6	12.79
	Incremental adjusted cost ($)	−1 283 966	–
	Incremental adjusted QALYs	0.8	–
	ICER ($)	Cost saving	–
	ICER (₹)*	Cost saving	–

*The exchange rate used was ₹82.25 for US$1, as of 15 May 2023.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

emicizumab in the Indian context, as also signalled by the findings of the current study. However, it is crucial to estimate the budget impact of implementing emicizumab prophylaxis in India which will further inform policy decisions and determining its inclusion in the state or national benefits package.

In the study, various key parameters required for the ICER adjustment methods were obtained from the cost-effectiveness report published by the Institute for Clinical and Economic Review. This report served as a valuable data source for the majority of the essential parameters required in this study as the report used the same PICO framework as the one developed for the aHTA. This further supported the relevance and applicability of the obtained data. It is also important to note that the parameters reported in the Institute for Clinical and Economic Review's report were predominantly derived from the clinical evidence presented in the HAVEN trials, which ensured the inclusion of robust clinical effectiveness data for the ICER adjustments.

Certain patient-related parameters were collected from two expert haematologists specialising in the treatment of patients with haemophilia A and inhibitors at a tertiary care centre in India. This approach allowed for the inclusion of valuable insights from a clinician with direct experience in the Indian context. By incorporating parameters from the Institute for Clinical and Economic Review's report, and expert opinion, this study encompassed a comprehensive and reliable data for the analysis.

In the study, translating the findings from the US to the Indian context presented significant challenges and introduced uncertainties. As mentioned earlier, the majority of data related to cost-effectiveness, costs and QALYs required for the ICER adjustment were obtained from the full HTA report conducted in the USA by the Institute for Clinical and Economic Review. This introduces the inherent limitations of applying evidence derived from a different healthcare system and population to the Indian setting, along with the assumptions and limitations of each of our adjustment methods as noted above. Differences in healthcare practices, resource availability, disease epidemiology, treatment patterns and cost structures between the USA and India may impact the generalisability and applicability of the findings. Furthermore, the use of different pricing structures, inflation rates and cost variations across countries adds another layer of complexity in estimating the ICERa. These uncertainties should be considered when interpreting the results of this study regarding the implementation of emicizumab prophylaxis in India.

Our diverse team of six researchers, comprising both junior and senior members, successfully conducted this project while managing their other responsibilities, which reflects the real-world challenges of research. The project was completed within a 4-month time frame, with junior researchers dedicating approximately 60 hours each and senior researchers contributing around 20 hours each. Being our first implementation of the aHTA methodology, there was a significant learning curve in planning and executing the research, resulting in the time and duration required for completion. However, with subsequent studies, we anticipate improved efficiency as we leverage our growing expertise. By sharing these insights, we aim to inform readers about the practical considerations, resource requirements and potential for optimisation associated with aHTA studies, promoting their adoption in different country settings.

Strengths and limitations

The strength of this study lies in its uniqueness, methodological rigour, efficient resource utilisation and rapidity in decision-making. As the first study of its kind in India, it provides valuable insights into the cost-effectiveness of emicizumab prophylaxis for patients with haemophilia A and inhibitors. Expanding on the aHTA methodologies, we presented the feasibility of using this approach for rapid HTA assessments in the Indian context by generating timely cost-effectiveness evidence for informed decision-making for policymakers and healthcare professionals.

The efficient utilisation of resources, including manpower and time, further contributes to the study's strengths. Active involvement of stakeholders, including clinicians, at every step of the study improved its relevance and applicability. Additionally, the research question itself was suggested by a clinician, enhancing its direct connection to real-world clinical practice.

The RES methodology used in the study allowed rapid assessment of available evidence in a short time frame, which aligned with the principles of undertaking an aHTA methodology, to provide evidence for any urgent policy decision. Further, the approach of consultations with experts facilitated synthesising evidence from seminal work on the topic and facilitated the judgement on the applicability of the evidence to the Indian settings. These strengths inherent to the RES methodology, combined with

the study's findings, could inform policy deliberations and facilitate the uptake of emicizumab prophylaxis within the Indian healthcare system.

The study also has certain limitations. We acknowledge that this aHTA methodology represents a novel approach, and the methodologies employed in aHTA studies can significantly vary across different settings. This uniqueness presents certain limitations but is balanced by the strengths of the RES and ICER adjustment methods employed in the study. The ICER adjustment methods are also novel and exploratory, and are based on an understanding of key health system factors that differ by setting, such as intensity of resource utilisation, life expectancy, health system costs and technology prices. These formulae have not yet been validated, in part because there is no natural counterfactual de novo economic evaluation conducted in the country of interest. Further work is required to validate their use and confirm their benefit.

Key parameters such as mean duration of treatment, drug costs, life expectancy and bleeding episodes relied on expert opinion, which introduces uncertainty into the estimates. This is mainly due to a lack of Indian-specific evidence from primary studies on emicizumab including randomised controlled trials, potentially impacting the generalisability of the findings.

The ICER adjustments are presented in deterministic fashion in this study and do not carry any quantitative presentation of uncertainty that might have been included in the source HTA report. This may prove to be a challenge if the source estimates are themselves deterministic in nature. If probabilistic estimates are available then adjusted CIs and other quantitative estimates could be generated in future aHTA iterations. In addition, the results of sensitivity analyses conducted in the source report could be adjusted to the local context, and limited sensitivity analyses (eg, price, life expectancy) might even be calculated after local adjustment.

Another limitation is the focus on the reduction in annualised bleeding rates as the primary outcome. Secondary outcomes, such as rates of treated bleeds and treatment for surgical bleeds, were not considered in the analysis, limiting the comprehensive inclusion of the treatment's effectiveness. We lacked the resources for a de novo CEA, and did not conduct a budget impact analysis, which would have provided insights into the financial implications of implementing emicizumab prophylaxis in India.

Methodological limitations in the trials of emicizumab should be acknowledged as various key parameters for the analysis were taken from these. These include the relatively short follow-up duration and lack of head-to-head randomised comparisons with BPAs. Furthermore, the safety of emicizumab in various clinical settings has not been extensively evaluated, which may affect the understanding of its risk-benefit profile. It is important to consider these limitations when interpreting the study findings.

From the methodological front, the RES approach employed could have introduced selection bias, as the expedited nature of RES might not have captured the entirety of existing evidence before commencing the evidence synthesis process. However, it is worth emphasising that the study's iterative process for acquiring evidence, coupled with periodic consultations with experts in the field, could have helped to mitigate this bias.

This study on cost-effectiveness of emicizumab for patients with inhibitors provides valuable lessons for future research and decision-making. Limited availability of full HTA reports underscores the need for more comprehensive evidence generation. Although the RES approach could be considered a pragmatic and efficient way to provide timely decision-making, it comes with a trade-off between comprehensiveness and risk of bias which needs to be considered while interpreting the findings. Further, the absence of cost-effectiveness studies from Indian or Asian settings restricted generalisability of study findings. The lack of primary data on treatment costs highlights the importance of data availability in India. These lessons underscore the need to address data gaps, promote research activities and enhance the availability of robust evidence for informed decision-making.

Conclusion

The findings of the ICERa from this study suggest the potential cost-effectiveness of implementing emicizumab prophylaxis in India for patients with haemophilia A with inhibitors, and the feasibility of using aHTA methods for rapid evidence generation to inform time-sensitive decision-making in India. However, future studies should address the limitations described earlier to strengthen the evidence base on the cost-effectiveness of emicizumab prophylaxis in the Indian context. Additionally, conducting a full HTA on the topic that includes patients with haemophilia with inhibitors, and a comprehensive budget impact analysis are crucial to inform policy decisions in the long term regarding the implementation of emicizumab prophylaxis in India and its funding through public financing.

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