Challenges associated with access to recently developed hemophilia treatments in routine care: perspectives of healthcare professionals

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Abstract

The treatment landscape for hemophilia continues to rapidly develop, and expectations for future treatment success are high. There is limited information on the challenges of accessing new and innovative therapies. The aim of this study was to explore challenges of accessing hemophilia treatment from the perspective of healthcare professionals (HCP). A cross-sectional study design was used. A pilot-tested, online survey was distributed to hemophilia treatment centers in Australia, Canada, France, Italy, New Zealand, Republic of Ireland, Turkey, USA and UK. The questionnaire covered questions on product access, economic considerations, health technology assessment requirements, and patient organization involvement. The results were analyzed descriptively using SPSS. A total of 154 HCP completed the questionnaire. There was heterogeneity across countries, regions, and centers regarding HCP knowledge of access to novel recently developed treatments. Notable limitations to access were reported such as differences in access based on age of patient and type of product, economic considerations, and the growing influence of health technology assessment bodies. Many countries have a hemophilia patient organization that does not have a vote at the decision-making table. There is a need to empower HCP to better understand national healthcare structures and decisions that lead to access limitations. Requirements from health technology assessment bodies must be understood to optimally design clinical studies and value generation of treatment options. This may strengthen the hemophilia treatment center's voice to collectively mandate for exchange with key involved individuals, such as the payers and politicians for the provision of optimal therapy.

Introduction

Hemophilia is a rare inherited bleeding disorder affecting more than 800,000 people, worldwide.[1] The condition can be life-threatening, with joint bleeding being the most common complication, which can result in major disability and mobility issues and, in turn, reduced quality of life.[2,3] To prevent mortality and morbidity, in many regions, prophylactic treatment is the current standard of care, and discussions on its optimization are ongoing.[4] The landscape of recently developed novel therapeutic products, based on new mechanisms other than the replacement of deficient factor, have progressed rapidly in recent years.[5-7] There are several hemostatic therapies (e.g., enhanced half-life clotting factor concentrates, non-factor hemostatic therapies, and gene therapy) that are already in place or are about to enter the therapeutic landscape.[8] These treatments, however, are cost intensive and not necessarily universally accessible.[9-10] Due to high development costs, recently developed treatments are generally more expen-

sive than standard treatments.[5,11] Despite the significant improvements that have been afforded by the use of factor prophylaxis, many persons with hemophilia do not have access to such therapies (e.g., ~20% to 30% in low- and middle-income countries).[12]

For hemophilia healthcare professionals (HCP), the primary goal of access is being able to receive optimal therapy for their patients. As recently developed treatments with the potential to greatly improve the clinical- and patient-reported outcomes of patients with hemophilia enter the therapeutic landscape, payers will require evidence on the added value and associated economic impact. A clear understanding of processes and evidence requested from decision-makers is a prerequisite to minimize potential hurdles that limit access to recently developed therapies.[13,14] In many countries, benefit and value (i.e., costs/outcomes) dossiers are required to be submitted for review by payers and/or health technology assessment (HTA) bodies before market launch. Information on potential benefits and harms of new treatments compared to available treatment options, which is often based upon these assessment processes and value demonstration, is taken into consideration when determining the reimbursement status and/or price negotiations of new therapies. The provision of requested evidence on benefits, based on scientific and pre-defined methodological requirements, is crucial for rare diseases, such as hemophilia.[15] Despite a growing number of registries and other data sources, there is a lack of information on epidemiology, patient pathways, treatment patterns, and patient-relevant outcomes for patients treated with standard of care hemophilia treatment, which is the basis for comprehensive value assessments of recently developed treatments. Lastly, clinically relevant hemophilia treatment outcome measurements in clinical studies, and patient-reported outcome measurements, have to meet standards required by HTA bodies.[16,17]

Due to recognized national and regional variabilities in access to hemostatic agents for use in persons with hemophilia, the objectives of this study were to understand HCP awareness of (i) which factors affect access to these recently developed treatments and (ii) whether access is limited due to lack of reimbursement or availability.

Methods

Design

A cross-sectional study design consisting of an internationally distributed survey was used. This study was granted ethics approval by the Hospital of Sick Children's institutional review board in September 2021.

Procedures

The questionnaire was developed through iterative rounds of review by clinical and health services research experts. The online questionnaire was distributed electronically through Research Electronic Data Capture (REDCap©), a secure institutional data management system. The questionnaire was made available from December 2021 through November 2022.

Target countries of this initial survey of the International Prophylaxis Study Group (IPSG) Access Expert Working Group were selected based on having access to long-term prophylaxis within varying healthcare systems.[18] As such, the following countries were selected based off this criterion, while also acknowledging feasibility and the exploratory nature of this work: Australia, Bulgaria, Canada, Croatia, Czech Republic, Estonia, France, Germany, Hungary, Italy, Lithuania, Latvia, Macedonia, New Zealand, Poland, Romania, Serbia, Slovakia, Slovenia, Turkey, UK and USA. To be eligible, while the survey was sent to hemophilia treatment center directors, any staff member of the recognized registered hemophilia treatment center could complete the questionnaire on behalf of that center. The survey was available in English. Given it was an online survey, some individuals may have used an electronic translation platform to translate the webpage. No individuals indicated that the survey not being available in their country's primary or official language would be an issue, and no participants emailed the study coordinator indicating challenges in comprehension due to the survey only being available in English.

Survey distribution began with the involvement of local country 'champions' (i.e., a local hemophilia treater known by the research team). A member of the research team connected with the 'champions' in each country to determine the optimal method of survey distribution for each included country. Members of the IPSG were asked to identify a champion in their respective countries. The champions in the field of hemophilia were selected as first contacts within each of the selected countries. For many countries, clinicians holding key roles of local hemophilia organizations were selected. After an initial meeting with the 'champion', optimal methods for distributing the survey in their country were decided upon. Following the meeting, 'champions' were asked to provide a list of all hemophilia treatment centers in their country along with the contact information of a lead physician working in each hemophilia treatment center. Methods included having the local 'champion' distribute a letter introducing the survey to a member of each hemophilia treatment center in the country, or the 'champion' provided the research team with an email list to distribute the survey to the local clinicians directly.

While there are no established cutoffs regarding 'good' or 'acceptable' response rates for surveys specific to healthcare providers, existing literature demonstrates response rates in physician surveys tend to be low. The response rate of our online survey is in the range of other published HCP-specific surveys. A recently published review paper in Annals of Surgery titled "Global overview of response rates in patient and HCP surveys in surgery" presented

an average response rate of 53% for web-based surveys.[19] Another study on response rates for physician web-based surveys reported an overall response rate of 35% (42% internal medicine).[20] Outside of clinical research, the average response rate for online surveys is approximately 44%.[21]

Measures

Demographic characteristics were limited to job title of the respondent and hemophilia treatment center characteristics (i.e., name of center and type of patients followed at center). The authors were aware of the discordance between products being licensed and their availability for access by patients. Therefore, the survey (see the *Online Supplementary Appendix*) included questions on coverage of products and economic considerations (e.g., 'In your country, who covers the expenses of hemostatic replacement therapies [factor and non-factor], including emicizumab outside of clinical trials?'), access to products and product restrictions (e.g., 'Access to recently developed therapeutics is limited to certain indications'), ethical issues experienced (e.g., 'Please provide any ethical issues that may influence how you prescribe factor [e.g., cost]'), HTA bodies (e.g., 'Does the HTA body in your country have a well-defined and transparent process in terms of methodological requirements and assessment methods for recommending/approving reimbursement of hemophilia treatments?'), and the presence and role of hemophilia patient organizations for access (e.g., 'Does the patient organization have a vote at the decision making table regarding the funding for a hemostatic agent that has regulatory approval and support from a formal HTA or equivalent?'). Response options varied depending on the question, including yes/no/I don't know options, ranking from 1 'most important' to 4 'least important', multiple choice responses, open-ended responses, as well as a Likert scale ranging from strongly agree to strongly disagree.

Statistical analysis

The data from countries with few responses were excluded from the analysis due to the small sample sizes. The reporting of the survey results follows the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).[22]

Results

As shown in Table 1, the survey was distributed to 377 HCP and a total of 154 complete responses were collected (overall response rate 40.8%). Countries that were included, as well as those recruited but not included within the data analysis due to a low response rate are provided in Table 1. Specifically, 78% (N=120) of responses were from countries where mainly government health agencies pay for hemophilia therapies, compared to a heterogeneous funding system in the USA (21.4%, N=33) and Turkey (0.6%, N=1). Out of 154 hemophilia treatment centers, 29 had only pediatric patients, 26 had only adults and 99 reported both pediatric and adult patients. The results were summarized into four categories that highlight the challenges the included countries are facing in terms of access to recently developed hemophilia treatments: (i) differences in access based on age of patient and type of product, (ii) economic considerations and cost of products influence access, (iii) lack of transparency of the HTA recommendation and approval process for treatment reimbursement, and (iv) the role of the hemophilia patient organization.

Differences in access based on age of patient and type of product

Many respondents (119 HCP, 77.3%) reported that, from their perspectives, access to products, in general, was the same for both adults and children. A total of 12 (8%) respondents reported that they perceived access was greater for adults, and 17 (11%) respondents reported that access was greater for children (see Figure 1).

As shown in Figure 2, a total of 98 HCP (64%) reported that

Table 1. Survey distribution and completion by country.

Country	Distributed N	Completed responses N	Response rate %
Included respondents			
Australia	17	12	70.6
Canada	34	22	64.7
France	30	10	33.3
Italy	51	27	52.9
New Zealand	6	6	100.0
Republic of Ireland	4	5[a]	125.0
Turkey	40	17	42.5
UK	33	22	66.7
USA	162	33	20.4
Excluded respondents			
Germany	80	5	6.3
Bulgaria	3	0	0
Croatia	2	0	0
Czech Republic	10	1	10.0
Hungary	4	1	25.0
Estonia	3	0	0
Lithuania	2	0	0
Latvia	2	0	0
Poland	5	0	0
Romania	2	0	0
Slovakia	5	1	20.0
Slovenia	2	1	50.0
Macedonia	1	0	0
Serbia	2	0	0

[a]Two individuals completed the survey at 1 center. Given the survey asked the healthcare providers' perspectives of access, there were variations in the responses between these 2 survey responses, and the research team deemed it was not appropriate to select the 'better' response. Because of this, both survey responses were included, and the number of responses is 1 greater than the total number of centers.

access to recently developed therapies (e.g., extended half-life [EHL] FVIII/FIX, non-factor therapy [i.e., emicizumab], and/or gene therapy) was limited to certain indications. This was reported by the majority of respondents from Canada (91%, N=20/22), Italy (63%, N=17/27), New Zealand (100%, N=6/6), Turkey (65%, N=11/17), England (63%, N=10/16), Northern Ireland (50%, N=1/2), Scotland (100%, N=2/2), Wales (50%, N=1/2), and the USA (61%, N=20/33). Specifically, 54 HCP (35%) and 47 HCP (31%) reported limited access to EHL-FVIII and EHL-FIX, respectively. The highest percentage of respondents who agreed or strongly agreed with this statement of limited access to EHL was from Turkey (59%, N=10/17). Additionally, 76 HCP (49%) reported limited access to non-factor therapies, including 100% of HCP from New Zealand (N=6/6) and Northern Ireland (N=2/2). Lastly, 74 HCP (48%) reported limited access to gene therapy, including 100% of HCP from Northern Ireland (N=2/2).

Economic considerations and cost of products influence access

Overall, 62 HCP (40%) 'agreed' there are existing situations in routine care where economic considerations impact therapeutic choices of the treating physician (see Figure 3). Additionally, 69 HCP (44.8%) reported that the price of hemostatic agents (factor and non-factor) outside of clinical trials influences access to treatment (see Figure 4). The impact of price of products influencing access was largely reported amongst HCP from Canada (59.1%, N=13/22), New Zealand (66.7%, N=4/6), Turkey (52.9%, N=9/17), England (62.5%, N=10/16), and the USA (60.6%, N=20/33).

Lack of transparency of the health technology assessment recommendation and approval process for treatment reimbursement

Most countries included have a national HTA body, or equivalent, that is responsible for evaluating new drugs and treatments, and most of these respondents (90.08%, N=109/121) reported they were aware of the national HTA body in their country. Of those with an HTA or equivalent, many respondents (79.44%, N=85/107) reported the HTA body in their country has a well-defined and transparent process in terms of methodological requirements and assessment methods for recommending and approving reimbursement of hemophilia treatments. Some, however, reported the HTA body does not have (8.41%, N=9/107), or did not know if the HTA body has (12.15%, N=13/107), a well-defined or transparent process (see Figure 5). Evaluating the type of evidence used as a driver in the benefit assessment for reimbursement recommendations or decisions of hemophilia treatments in each included country, randomized controlled trials were scored as the most important by 76 HCP (49.3%). Besides randomized controlled trials, real-world evidence and systematic literature reviews were scored as the most important evidence used as a driver in the benefit assessment for reimbursement recommendations/decisions of hemophilia treatments by 13 HCP (8.4%) and six HCP (3.9%), respectively. In evaluating the type of health economic aspects considered by the HTA, 95 HCP (61.7%) reported cost-effectiveness analysis and 60 HCP (38.9%) reported budget impact analysis. More specifically, a total of 66 HCP (42.9%) confirmed that budget impact analyses of new hemophilia treatments are requested by

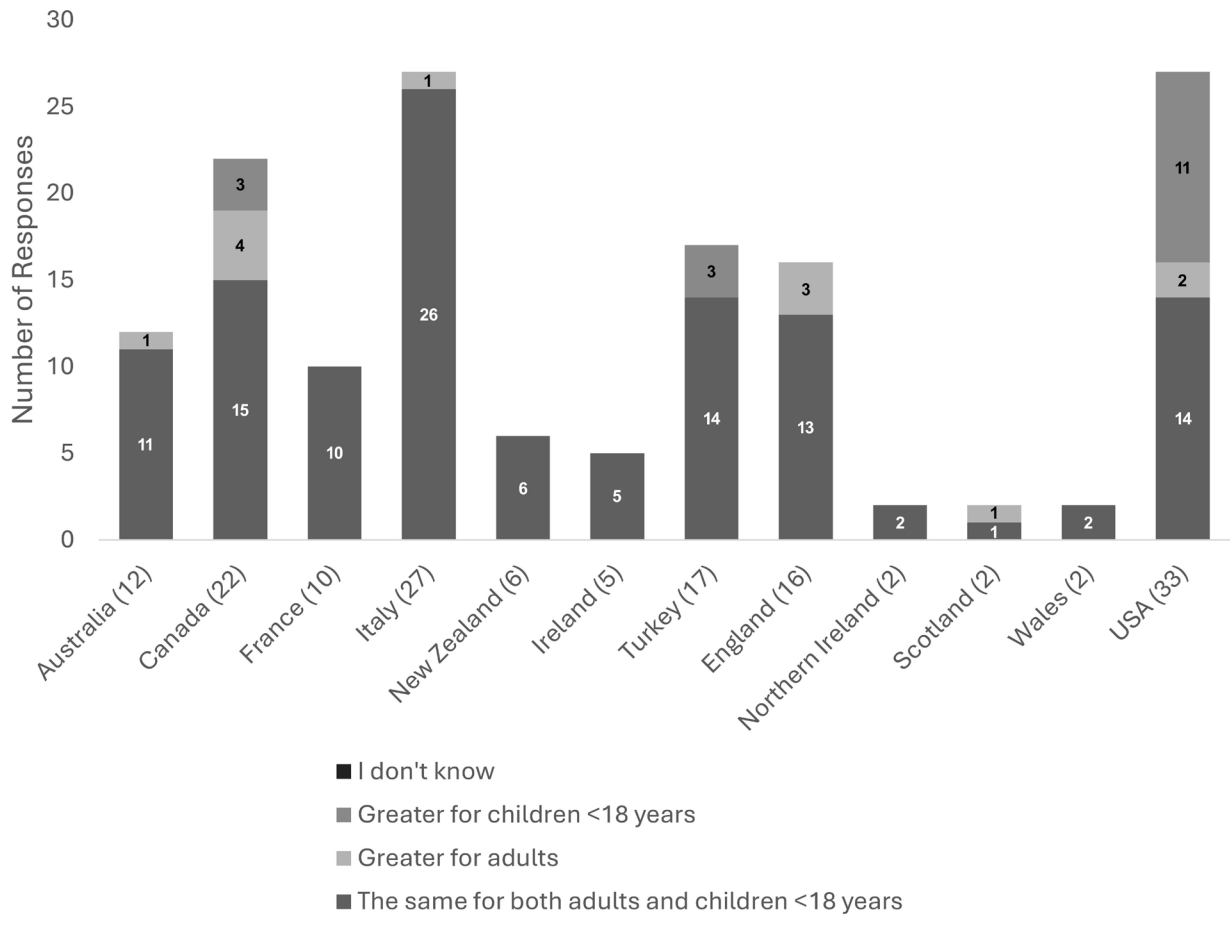

Figure 1. Age-related differences in access to hemostatic agents at the respondents' hemophilia treatment centers.

payers of hemostatic therapies in their country.

The role of the hemophilia patient organization

Most HCP (97.4%, N=150) reported the presence of a hemophilia patient organization within their country. Additionally, 123 HCP (79.9%) reported that the hemophilia patient organizations lobby for access. Despite having a presence and lobbying for access, only 29 HCP (18.8%) reported these hemophilia patient organizations have a vote at the decision-making table regarding the funding for a hemo-

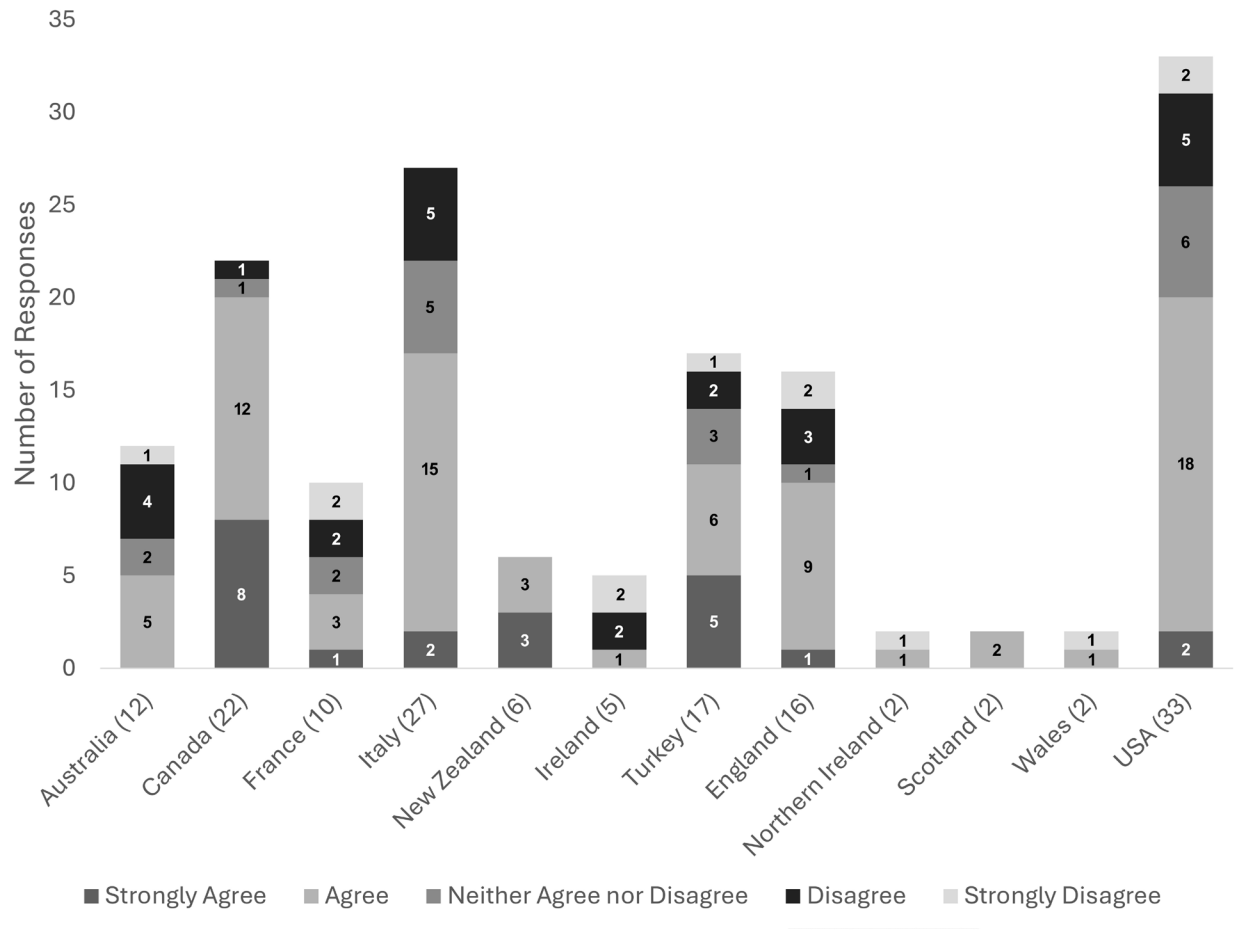

Figure 2. Access to innovative therapies is limited to certain indications.

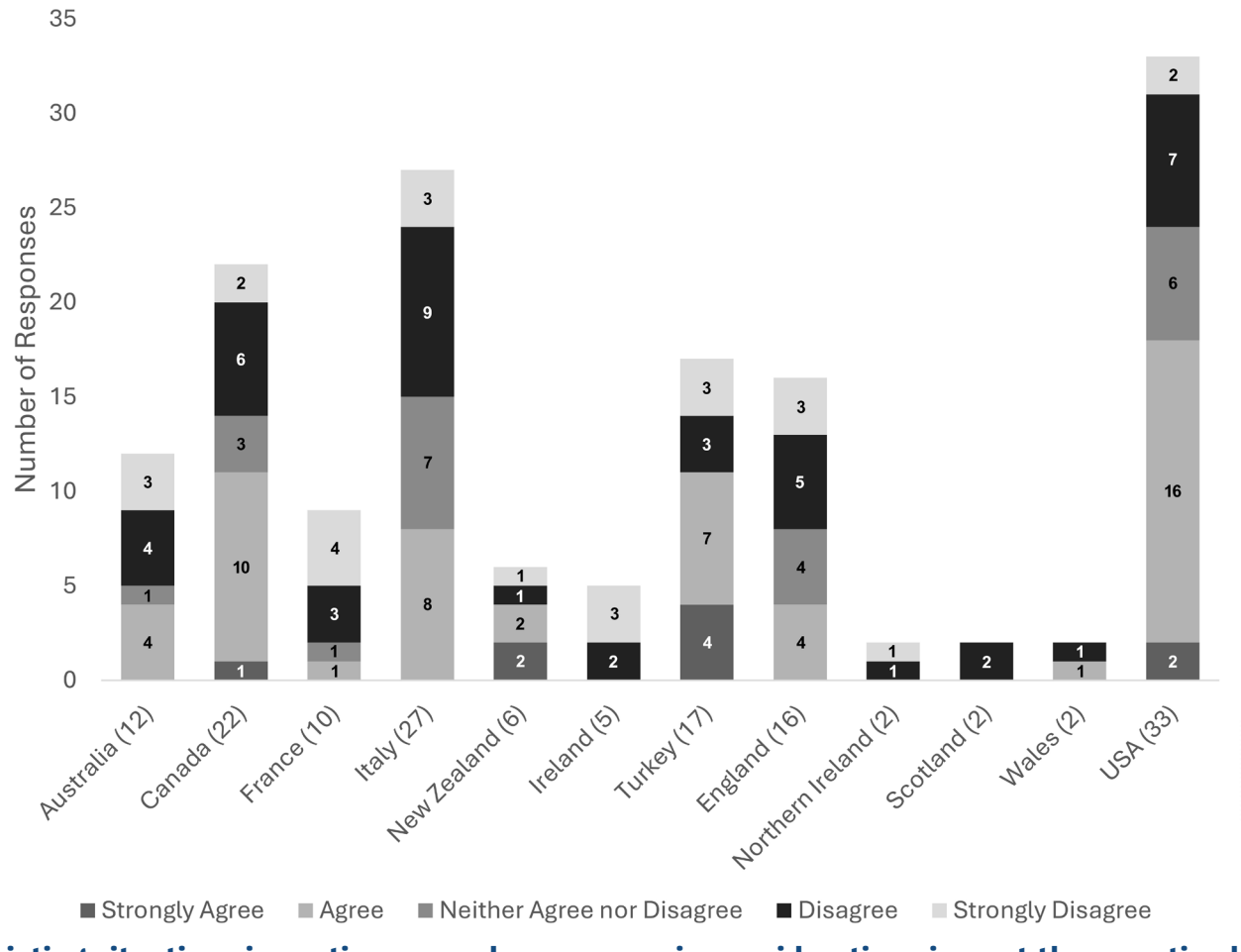

Figure 3. There are existing situations in routine care where economic considerations impact therapeutic choices.

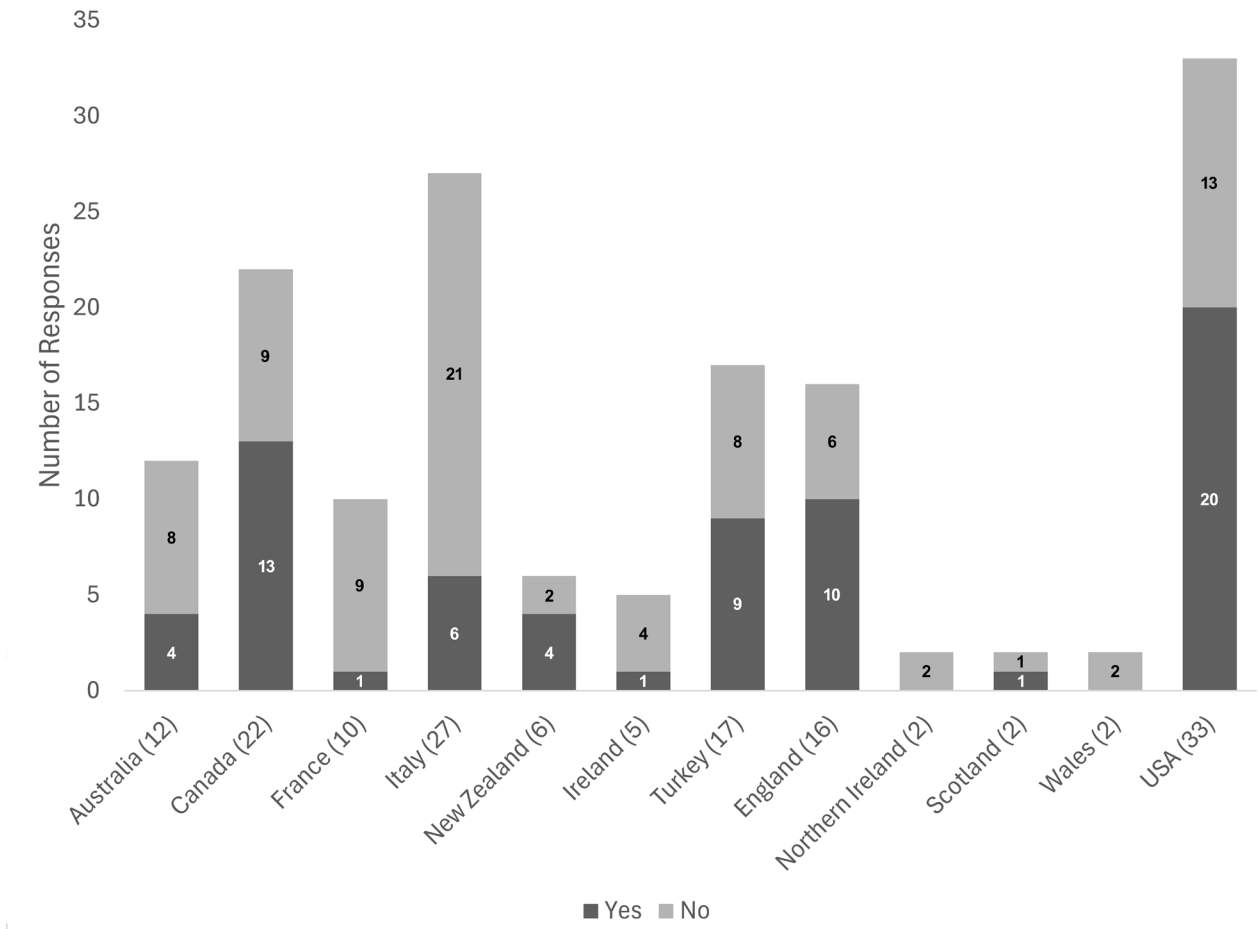

Figure 4. Does the price of hemostatic agents (factor and non-factor) outside of clinical trials influence the access to treatment?

static agent that has regulatory approval and support from a formal HTA or equivalent (see Figure 6).

Discussion

This survey is one of the first in the field of hematology to address the awareness of access to recently developed treatments from the HCP perspective. The topic of access, specifically concerning recently developed treatments, from the viewpoint of HCP is an identified gap of knowledge in the literature. Seeking the subjective opinions of HCP who work with patients with chronic health conditions, such as bleeding disorders, is crucial to identify timely challenges and perceptions regarding access to resources. Without the HCP perspective, there are limitations in enhancing infrastructure, bettering patient interactions, as well as improving clinical- and patient-reported outcomes, such as health-related quality of life. As the landscape of recently developed innovative treatments with promising clinical- and patient-reported outcomes for persons with hematological diseases has progressed rapidly in recent years, we used hemophilia as a use case for a rare hematological disorder. This survey serves as a temperature check to assess HCP awareness, experiences, and perceptions of access to optimal hemophilia treatment in their daily routine care.[18]

The results demonstrate that a majority of the respondents are aware of access in their respective countries. However, it has to be highlighted that the variation and heterogeneity of knowledge on access was evident, both between and within countries. Further, findings indicated that, in most of the included countries, there are added barriers to optimal access to hemophilia treatment (e.g., differences in access based on age of patient and type of product or certain indications). As such, there may be a need to generate more information on the topic of access to newly licensed therapies in routine care. In addition, the findings highlight a need to empower HCP to understand and observe national healthcare structures that lead to limitations in access to optimal therapy. This can potentially empower hemophilia treatment centers to collectively mandate for the provision of optimal therapy. This is in contrast to clinical trials for which multinational trials are the standard, where access to therapies, especially those expensive, is limited by the structures and processes of the respective national healthcare systems.

The results of the survey demonstrate the need to know about requirements of established HTA processes, or their equivalent, which are an add-on to established licencing and approval processes. In the center of most HTA processes is the value assessment for decision making regarding reimbursement, primarily from the payer's perspective. Although a drug may be licensed, it does not guarantee subsequent access. If the value assessment does not demonstrate the added value of a new drug, payers will not be willing to reimburse premium prices. Therefore, despite a drug being licensed, no reimbursement from the payers contributes to

a limitation in access for patients. Within this survey, 90% of respondents reported being from a country with an HTA body, or equivalent. Of these respondents, 80% reported that the HTA body in their country has a well-defined and transparent process for recommending and approving reimbursement of hemophilia treatments. When evaluating the type of evidence used as a driver in the benefit assessment for reimbursement recommendations or decisions

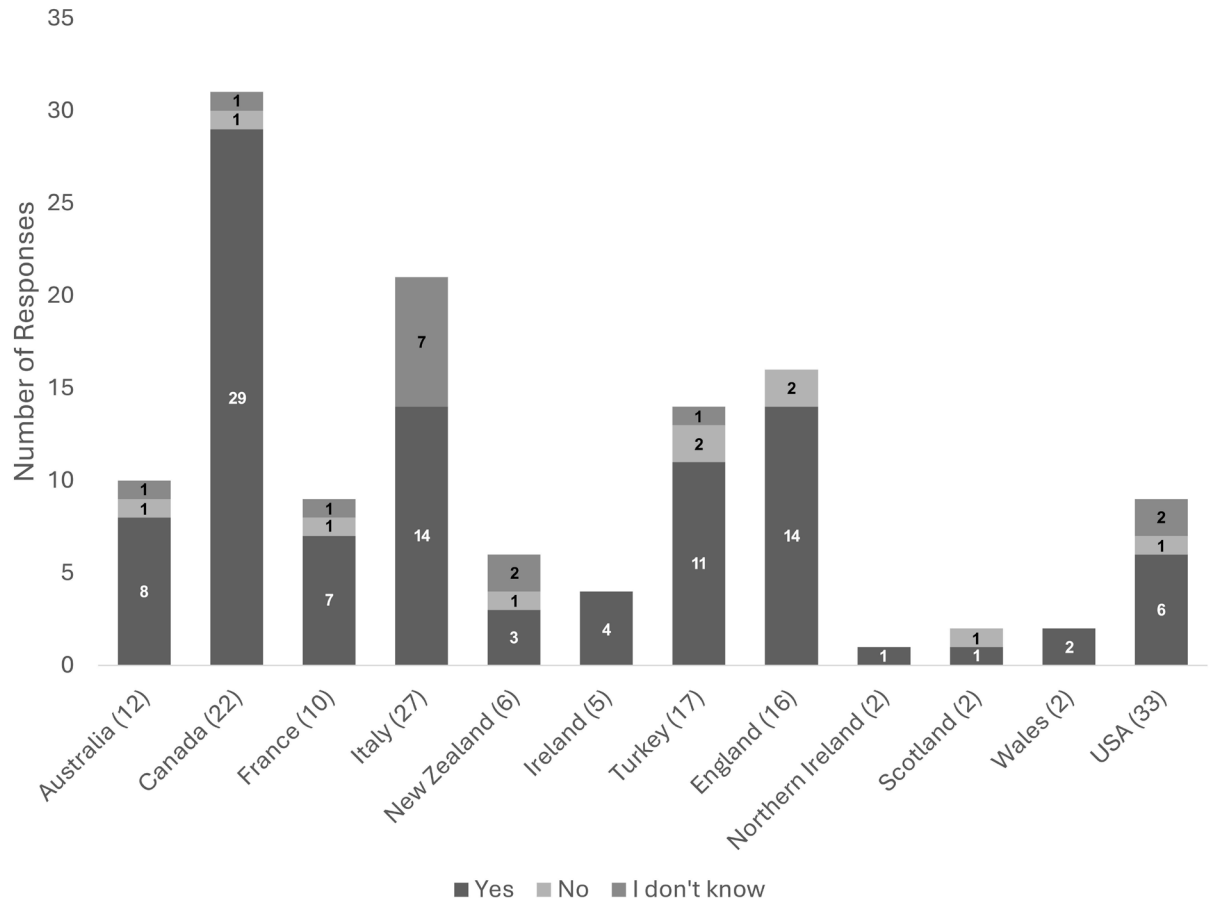

Figure 5. Does the health technology assessment body have a well-defined and transparent process in terms of methodological requirements and assessment methods for recommending/approving reimbursement of hemophilia treatments?

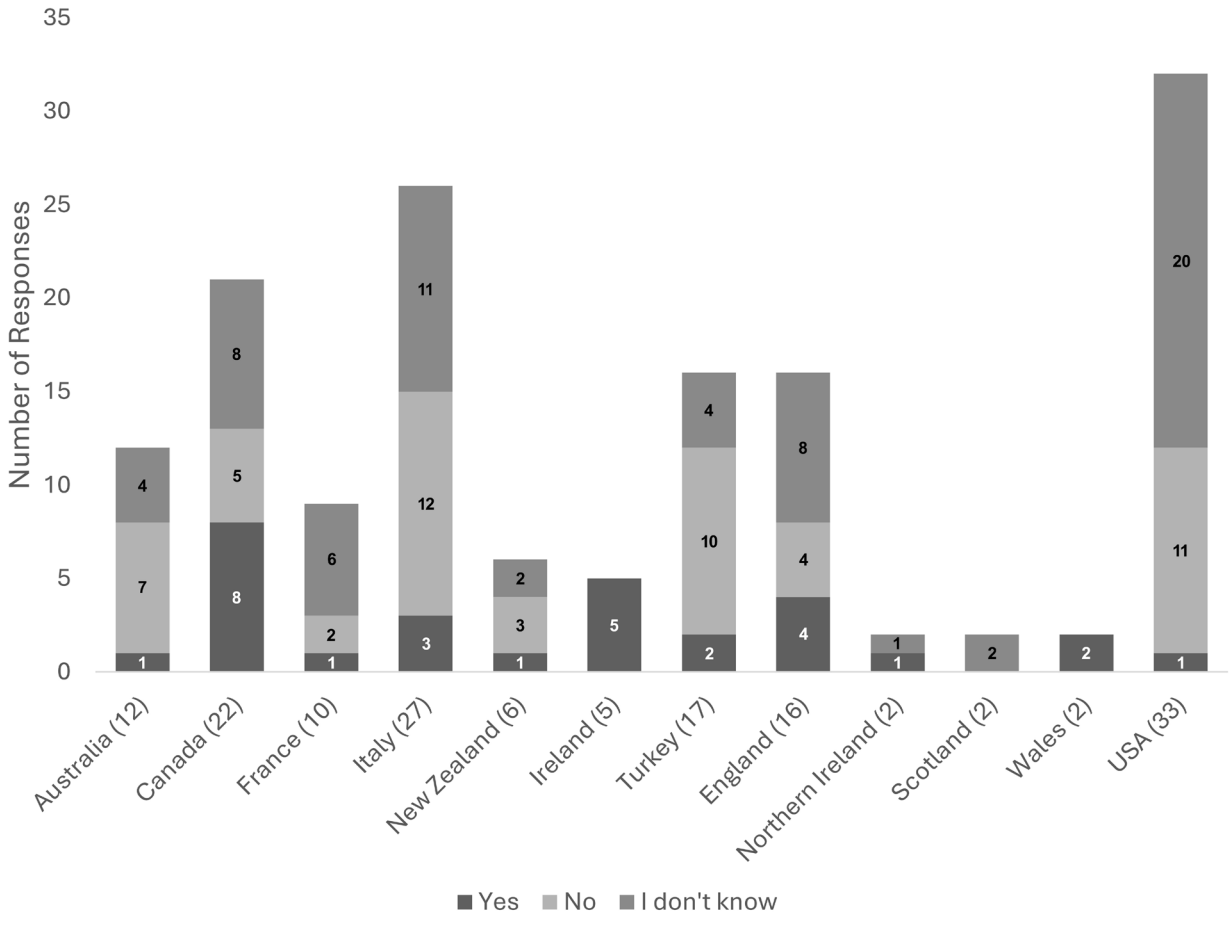

Figure 6. Does the patient organization have a vote at the decision making table regarding the funding for a hemostatic agent that has regulatory approval and support from a formal health technology assessment or equivalent?

of hemophilia treatments, 50% of respondents reported randomized controlled trials to be the most important. Therefore, following recommendation number 11 of the Wildbad Kreuth Initiative, which specifies that "clinical studies should be performed to provide the best possible evidence needed for regulatory authorities, HTA bodies, academia and healthcare providers", clinical trial designs for recently developed therapies are recommended.[23] Clinical trial designs will help to reduce bias, lower financial costs, and improve patient access through providing evidence to promote effective HTA and cost-effectiveness analyses.

The relevance of health economic analyses in terms of cost-effectiveness and budget impact was also emphasized in the findings of this survey. Approximately 40% of HCP 'agreed' that there are existing situations in routine care where economic considerations impact therapeutic choices of the treating physician, with the price of a drug seeming to be an important decision criterion. In Germany, a prior survey among hematologists reported comparable findings.[24]

The reason for treatment decisions with consideration of prices may be manifold, such as internal requirements from the administrative side of the respective institution, complex application processes, expected disputes with the payers for reimbursement, as well as too little transparency and trust in the expected outcomes. However, if those rationing decisions are neither guided by a consensus on what should count as dispensable benefit nor shared with the patient, there is a high likelihood that patients in similar clinical situations will receive different care solely because of the physicians they encounter in the course of their illness. Future research on the reasoning behind decisions made around use of costly treatments, and the associated impact on patient outcomes, is needed. Based on the findings of this study, the field may benefit from a systematically and transparently developed process for engaging all roles involved in the drug licensing, value assessment, and care process to avoid individualized institutional rationing.[25]

A majority also reported that the hemophilia patient organizations present in their country lobby for access, but only a minority reported that these hemophilia patient organizations have a vote at the decision-making table. Patients and patient organizations have much to contribute to the decision-making process as a result of their lived experiences, therefore, patients must be involved within decision-making on new treatments. Despite various efforts in the field of rare diseases, such as the discussions in the policy-engagement workshop in Edinburgh 2026,[26] and initiatives of the World Federations of Hemophilia and European Consortium it seems that, according to the present survey results, further and continuous efforts, especially national ones, are important to give patients an active voice in decision-making processes where this is not yet a reality.

There are a few minor limitations of this survey to note. The representativeness of the survey is limited. While a response rate for each country's respondents could be calculated, we are limited in our ability to state that the findings at the country level are representative of that country's access. To build on the needs and challenges identified in this exploratory study, confirmatory research at the national/international level that includes the perspectives of different types/levels of HCP as well as, importantly, patient representatives, should be a priority within national research agendas. For this kind of research, country-specific representativeness is essential. Additionally, the proportion of different professional groups that provided feedback within each country varied and might lead to an information bias. This is based, among other things, on the different structures of the health systems. Lastly, the countries included within this study are classified as upper-middle- and high-income countries according to the World Bank.[27] While the focus on upper-middle- and high-income countries allowed for some cross-country comparisons to be made within this study, we observed variations in access between the included economically wealthier countries. Future research is needed with representatives from lower-middle- and low-income countries to further understand differences, and barriers, to access.

In summary, these findings can inform HCP, manufacturers, and patients alike. Here, we highlight the key takeaways from the findings of the survey. There is a large amount of heterogeneity across the included countries, regions, and centers regarding HCP knowledge of access. Access to innovative hemophilia therapy is determined by national conditions of the healthcare system in the respective country. This paper provides initial cross-national evidence on access to recently developed hematological therapies from the HCP perspective. Therefore, the value of the findings from this comprehensive survey is the knowledge that there are notable limitations to access and the need to better understand requirements from HTA bodies to optimally design clinical studies and to provide evidence for the value of different treatment options. Knowledge gaps regarding access from the HCP perspective should be filled in future work through providing more information, education, and empowerment. There is a need to empower HCP to understand and observe national healthcare structures in the context of other countries that lead to limitations in access to optimal therapy. Potential avenues for doing so include training and discussion exchange platforms geared towards initiating conversations with decision makers external to the medical area. This can potentially empower hemophilia treatment centers to collectively mandate for exchange with key individuals, such as the payers and politicians for the provision of optimal therapy. Importantly, patient advocacy groups, while involved in conversations on access, are not involved in decision-making processes on access to treatment. Finally, the generated evidence corroborates the need for more interprofessional health services research, outcomes research, and health economics as complements to basic research for access

to optimal hemophilia care. National hemophilia treatment centers should be empowered with information and consensus papers to initiate a dialogue with other key roles, such as agencies, academia, payers, and patients to foster access to optimal hemophilia treatment.

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Contributions

All authors designed the study. KB, RHO, and LA conducted data collection and analysis. KB, RHO, MDM, and LA wrote the initial draft of the manuscript. All authors reviewed the final manuscript.

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Data-sharing statement

Data collected for this study will not be made available to others.

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