

ORIGINAL ARTICLE

Clinical haemophilia

Challenges and key lessons from the design and implementation of an international haemophilia registry supported by a pharmaceutical company

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Abstract

Introduction: Real-world data are lacking regarding the relationship between prospectively collected patient-reported outcomes (PROs), clinical outcomes and treatment in people with haemophilia (PWH). The Expanding Communications on Hemophilia A Outcomes (ECHO) registry was designed to address this data gap, but a range of difficulties led to early study closure.

Aim: To describe the challenges faced and lessons learned from implementing a multinational haemophilia registry.

Methods: The Expanding Communications on Hemophilia A Outcomes was planned as a five-year observational cohort study to collect data from 2000 patients in nine countries. Based on direct observations, feedback from patients enrolled in ECHO, challenges of the study design and input from study-sponsor representatives, the ECHO Steering Committee systematically identified the challenges faced and developed recommendations for overcoming or avoiding them in future studies.

Results: The study closed after two years because few countries were activated and patient recruitment was low. This was related to multiple challenges including delayed implementation, stringent pharmacovigilance requirements, objections of investigators and patients to the burden of multiple PROs, data collection issues, lack of resources at study sites, little engagement of patients and competing clinical trials, which further limited recruitment. At study closure, 269 patients had been enrolled in four of nine participating countries.

Conclusions: Researchers planning studies similar to ECHO may want to consider the barriers identified in this global registry of PWH and suggestions to mitigate these limitations, such as greater patient involvement in design and analysis, clearer assessment and understanding of local infrastructure and potential changes to the administration of the study.

KEYWORDS

clinical outcome, haemophilia, multinational, patient-reported outcome, registry, study design

1 | INTRODUCTION

Haemophilia A is typically treated with infusions of factor VIII (FVIII), on demand when a bleeding episode occurs, or as prophylaxis to prevent bleeds and development of chronic arthropathy.¹ The emergence of new treatment options for haemophilia² and a growing population of ageing patients have led to wide variations in treatment patterns and associated outcomes. Clinical and sociodemographic data are needed to establish how haemophilia is treated worldwide and to serve as a control when new treatments are introduced. In rare diseases such as haemophilia, Health Technology Assessment (HTA) agencies and regulatory authorities increasingly consider the benefit of disease registries for regulatory decision-making and risk-benefit assessments.³

Cross-sectional data on health-related quality of life and other patient-reported outcomes (PROs) in clinical trials in haemophilia are available.⁴ However, there is a lack of real-world data exploring the relationships between longitudinal changes of PROs, clinical outcomes and treatment patterns/products across different countries. Haemophilia registries and observational cohort studies can capture large amounts of data on a broad range of products in a real-world setting, in contrast to clinical trials, which tend to be smaller and provide limited data.⁵ The Patient Reported Outcomes, Burdens and Experiences (PROBE) study⁶ and the World Bleeding Disorders Registry (WBDR)⁷ are new global initiatives set-up to gather prospective real-world PRO data or clinical data, respectively, from people with haemophilia (PWH). PROBE is a patient-led research project, and WBDR is a World Federation of Haemophilia database that had not been launched when the Expanding Communications on Hemophilia A Outcomes (ECHO) registry was initiated; both independent, investigator-led projects are funded by research grants from multiple pharmaceutical companies.

Several haemophilia registries have been established worldwide, but tend not to collect PRO data.^{5,8} PRO data have been reported in small, cross-sectional studies and in the large, multinational, cross-sectional Haemophilia Experiences, Results and Opportunities (HERO) survey⁹⁻¹¹ as well as the Advate® in HaEmophilia A outcome Database (AHEAD), which was limited to patients receiving a single haemophilia product.¹²

The prospective ECHO registry, sponsored by Bayer, was designed to explore how differences in disease course, clinical outcomes, global treatment practices, healthcare delivery systems and treatment options affect long-term PROs in moderate or severe haemophilia A. The broad nature of the data to be collected from different legal and regulatory environments presented challenging obstacles, ultimately leading to the early closure of ECHO in December 2017.

Assessing PROs and the impact of care are important goals to further the treatment of haemophilia. Here, we describe the obstacles encountered in ECHO and discuss alternative strategies to provide insights for researchers undertaking similar registries or studies in the future. Cross-sectional data available at the time of registry closure will be published in a different paper and are in preparation.

2 | MATERIALS AND METHODS

2.1 | The Expanding Communications on Hemophilia A Outcomes registry study overview

The Expanding Communications on Hemophilia A Outcomes was a multinational, prospective, observational cohort study (NCT02396862) initiated and funded by Bayer, with a planned duration of five years and target enrolment of 2000 patients.^{13,14} The registry aimed to explore the association of different variables with PROs and clinical outcomes in people with moderate or severe haemophilia A. All treatments were at the discretion of the physician and patient, with no mandated clinical tests, treatments or interventions. Study sites obtained appropriate independent ethics committee/institutional review board (IEC/IRB) approval before the study started. Clinical investigators from Canada, China, Italy, Japan, Mexico, Spain, Taiwan, the UK and the United States were invited to participate. Further details of the ECHO protocol are provided in the Appendix.

2.2 | Patient focus groups and feasibility testing

During the design phase, input from patient focus groups was used to identify aspects that are important to haemophilia patients. The focus groups were conducted in the UK, United States and Germany and included men aged ≥ 18 years who had moderate or severe haemophilia A or B.^{15,16} All participants completed either a semi-structured group or individual phone interview that explored their treatment experience and the physical, psychological and social effects of haemophilia. Although patients were involved in the identification of the aspects to be investigated, they did not contribute to the selection of the final nine PRO instruments that subsequently led to the development of ad hoc questionnaires concerning sociodemographic and clinical data, health behaviour and resource use.

Interview transcripts were analysed using the mixed-method data analysis system, which used both qualitative and quantitative data to understand participants' experiences. This analysis was used to identify several themes (physical function, home and daily life, work life, social/psychological and economic) important to patients with haemophilia that would be explored in ECHO.

Once ECHO was underway, feasibility testing was undertaken to evaluate the PROs included in ECHO.¹⁶

2.3 | Identifying study obstacles and recommendations for future studies

The ECHO Steering Committee received input from investigators, patient representatives, operational project team members and study-sponsor representatives in each participating country, as well as patients from the prestudy focus groups and on-study feasibility testing. Using this feedback and direct observations of ECHO,

Steering Committee members identified the main challenges and developed recommendations for overcoming each of these obstacles during a face-to-face discussion in 2018.

3 | RESULTS

3.1 | Overview of challenges faced in the ECHO registry

The Expanding Communications on Hemophilia A Outcomes recruited the first patient in the UK in December 2015 and began enrolment in the United States, Spain and Japan 1.5 years later (recruitment had not started in other countries when the study was closed). At the time of study closure in December 2017, 269 patients (13% of target recruitment) had been enrolled in four of nine participating countries (Table 1). Problems were also encountered with low completion rates of patient-reported outcomes (PROs) (Table 2).

The ECHO Steering Committee and Project Team identified multiple factors that delayed country and site set-up and that limited recruitment and data collection, ultimately leading to study closure. The challenges faced, and observations and recommendations for overcoming these in future research are summarized in Table 3 and further described in Supplementary Material available on-line.

Some sites needed additional support to meet the pharmacovigilance requirements of a single-sponsor registry^{17,18} in order to comply with regulations and legislation¹⁹ and the industry code of practice.²⁰ Delays were encountered in obtaining IEC/IRB approval and in navigating the complex negotiations between the sponsor and the contracting parties.

Patient enrolment was limited, and there were few opportunities to communicate the benefits of participating in the registry with

TABLE 1 The Expanding Communications on Hemophilia A Outcomes study enrolment

	Active sites	FPFV	Planned enrolment ^a	Actual enrolment
Canada	0	NA	25	0
China	0	NA	200	0
Italy	0	NA	150	0
Japan	2	14 June 2017	160	76
Mexico	0	NA	150	0
Spain	8	17 Feb 2017	170	25
Taiwan	0	NA	250	0
UK	6	9 Dec 2015	250	144
USA	7	1 Dec 2016	250	24
Total	23		1605	269

Abbreviations: FPFV, first patient first visit; NA, not applicable.

^aTotal planned enrolment at study start was 2000, but estimates were updated for each country during recruitment. The numbers in this column reflect planned enrolment for each country at the time of study closure in December 2017.

TABLE 2 PRO measures used in the the Expanding Communications on Hemophilia A Outcomes registry and completion rates

Domain	Type of instrument	PRO instrument	Number of items	Number (%) of patients with data available	
				Initial visit (n = 269)	Follow-up visit (n = 66)
Function	Haemophilia-specific	Hemophilia Activities List (HAL) ³²	42	210 (78.1)	33 (50.0)
Work productivity	Generic	Work Productivity and Activity Impairment (WPAI): v2.0—English for UK ³³	6	205 (76.2)	33 (50.0)
HRQoL	Haemophilia-specific	Haemo-QoL-A ³⁴	41	20 (7.4)	2 (3.0)
	Generic	Short Form of the SF-36 Health Survey (SF-12) ³⁵	12	207 (77.0)	33 (50.0)
Health status	Generic	EuroQoL 5-Level 5-Dimension (EQ-5D-5L) ³⁶	5	207 (77.0)	33 (50.0)
Treatment satisfaction	Haemophilia-specific	Hemo-SAT _A ³⁷	34	205 (76.2)	33 (50.0)
Adherence	Haemophilia-specific	Validated Hemophilia Regimen Treatment Adherence Scale-On-Demand (VERITAS-PRN) ^{38 a}	24	36 (13.4)	4 (6.1)
		Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) ^{39 a}	24	166 (61.7)	27 (40.9)
Symptoms	Generic	Brief Pain Inventory (BPI) Short Form ⁴⁰	11	209 (77.7)	33 (50.0)
Other aspects		Ad hoc questionnaires concerning the following aspects: sociodemographics, clinical data, health behaviour and resource utilization	62		
		Total number of items	237		

Abbreviations: HRQoL, health-related quality of life; PRO, patient-reported outcome.

^aPatients filled in VERITAS-PRN or VERITAS-PRO according to their treatment.

TABLE 3 Lessons learned from the the Expanding Communications on Hemophilia A Outcomes registry

Identified issue	What we did	What we observed	Recommendations for future research
Patient involvement	<ul style="list-style-type: none"> • Interview/focus group of patients to identify aspects of interest (early) • Feasibility testing (late) 	<ul style="list-style-type: none"> • Inclusion of large number of questionnaires • Inadequacy of communication materials for patients • Suboptimal patient motivation 	<ul style="list-style-type: none"> • Involve patients at all stages of study design
Costs	<ul style="list-style-type: none"> • Budget built according to number of patients, time commitment and fair market value for each participating country 	<ul style="list-style-type: none"> • Participant expectations about budget were high because of pharmaceutical company sponsoring • Fair market value constraints may prevent participation in certain countries 	<ul style="list-style-type: none"> • Consider study administration through a not-for-profit organization
Infrastructure and human resources	<ul style="list-style-type: none"> • Assumed that investigators would use local resources to enter data 	<ul style="list-style-type: none"> • Clinical research fatigue amongst patients and investigators—many competing clinical trials and infrastructure targeted towards clinical research rather than registries 	<ul style="list-style-type: none"> • Clear assessment and understanding of local infrastructure, capacity and limitations • Perform due diligence at a deeper level
Questionnaire administration format and length	<ul style="list-style-type: none"> • Expected most patients to complete questionnaires online at home 	<ul style="list-style-type: none"> • Investigator preference was to gain patient feedback on paper • Online questionnaires were incompatible with some computer systems • Online system was not available at study start • Compliance was much higher when questionnaires were completed in clinic 	<ul style="list-style-type: none"> • Ensure alignment of patient preference with questionnaire administration format and length • Adopt efficient way of ensuring questionnaires are completed (eg use tablet computer in the clinic) • Budget accordingly and consider patient incentive where appropriate
CRO	<ul style="list-style-type: none"> • Expectation that CRO would perform continuous checks on data quality and questionnaire completion rate 	<ul style="list-style-type: none"> • Frequency of data readout did not allow for remedial action 	<ul style="list-style-type: none"> • Establish a data management plan for real-time monitoring and feedback
Licensing and linguistic validation of PRO questionnaires	<ul style="list-style-type: none"> • Task delegated to CRO and then subcontracted 	<ul style="list-style-type: none"> • Licensing complexity exceeded expectations • Length of time for translation and validation exceeded expectations • Large number of PROs may configure as interventional study 	<ul style="list-style-type: none"> • Only use questionnaires that are validated in each country or account for time/cost needed for translation • Consider labelling study design as interventional
Bleeding diaries	<ul style="list-style-type: none"> • Planned to use Haemtrack across all study centres 	<ul style="list-style-type: none"> • Preference for the locally used patient bleeding diary 	<ul style="list-style-type: none"> • Ensure alignment with patient preference and local custom • Try to harmonize bleeding diary administration and analyses across countries
Communications plan	<ul style="list-style-type: none"> • Over-reliance on investigator initiative 	<ul style="list-style-type: none"> • Patient information leaflet was not distributed because of need for ethics committee approval 	<ul style="list-style-type: none"> • Ensure patients understand the need for, and value of, the study • Establish a mechanism early on for patient follow-up on form completion • Collaborate with patient advocacy organization • Identify/train local champion
Ethics committee submission	<ul style="list-style-type: none"> • Submitted and tried to adhere to requests of the ethics committees • Underestimated complexity of the ethics approval process for an international registry study 	<ul style="list-style-type: none"> • Concerns about pharmaceutical company involvement, use and ownership of data, and budget delayed process in some countries • Feedback from ethics committees in some countries necessitated updates to trial documents • In the United States and the UK, ethics approval was required before a contract could be generated 	<ul style="list-style-type: none"> • Consider the complexity of the ethics process in advance • Consider labelling study design as interventional

(Continues)



TABLE 3 (Continued)

Identified issue	What we did	What we observed	Recommendations for future research
Logistics	<ul style="list-style-type: none"> Adopted the same approach as for a clinical trial Expected site selection and contracting would take 3–6 months 	<ul style="list-style-type: none"> Negotiation of site contracts took 1 year Site assessment was inappropriate and inefficient for a registry study 	<ul style="list-style-type: none"> Carefully evaluate whether the study should be corporate- or investigator-led Ensure site evaluation is appropriate for a registry study
Study integration with existing studies and databases	<ul style="list-style-type: none"> Set up a completely new prospective data entry system 	<ul style="list-style-type: none"> Data fatigue—unwillingness to perform multiple data entry Lack of harmonization between databases Competing agendas with coexisting studies and databases 	<ul style="list-style-type: none"> Consider more collaborative work between databases
Difficulties with recruitment of centres and patients	<ul style="list-style-type: none"> Principal investigator in each country in collaboration with Bayer affiliates for recruiting centres 	<ul style="list-style-type: none"> Lengthy gestation of study/loss of enthusiasm of participating centres 	<ul style="list-style-type: none"> Plan for a simple, clear study design with fast start-up

Abbreviations: CRO, contract research organization; PRO, patient-reported outcome.

patients and caregivers. No specific recruitment or educational materials were distributed, patient organizations were not engaged in recruitment efforts, and the initial global investigator meeting did not include patients, mainly because of legal and compliance issues within the pharmaceutical industry. Recruitment was further complicated by regulations in participating countries that prohibited the contract research organization (CRO) and the registry sponsor from communicating directly with patients.

The logistics of data collection and return were complicated by the high number of PRO instruments and the diversity of bleeding diaries used. Allowing patients to fill out questionnaires at home led to a delay in study sites becoming aware of poor compliance and the subsequent need for staff follow-up with patients, such that timely remedial action could not be taken.

3.2 | PRO challenges

The 13 patients who participated in the feasibility testing of the ECHO registry took a mean \pm standard deviation of 70.7 ± 31.2 minutes (median, 60 minutes; range: 35–150 minutes) to complete the PRO instruments and ad hoc questionnaires. Some patients considered the PRO instruments to be too lengthy, with repetitive questions that were not applicable to UK health care. Although patients in the feasibility testing considered the PROs easy to complete and relevant, some items in the ad hoc PRO questionnaires were not completed, including those referring to income, personal health behaviour or status information.¹⁵

After ECHO began enrolment in the United States, one questionnaire, the Psychological General Well-Being Index (PGWBI),²¹ had to be removed from the PRO instruments because legal advice indicated that the predefined responses could have been perceived as providing life-threatening information related to suicidal intent.

The highest completion rates were in Japan, where patients were asked to complete PRO questionnaires during their clinic visit. In general, patients who began the PRO questionnaires completed most items, but a considerable number of patients did not begin them at all. Only the longer, ad hoc, questionnaires had some skipped items. Completion rates did not improve when deadlines were extended from two weeks to six months.

3.3 | Logistic challenges

Multiple logistic challenges were encountered in ECHO. The case report forms (CRFs) completed by research staff were lengthy and contained redundant items (eg several instruments to measure joint status, which were not always feasible in clinical practice). In some countries, study start was delayed by contracting issues, including the need for IEC/IRB approval before contracts could be initiated and the need for PRO licences and linguistic validations with related additional costs; using multiple PROs in an industry-sponsored study required payment of licence fees that were generally higher than those charged for academic research. Delays in IEC/IRB or data protection approvals resulted from uncertainty as to whether PRO collection studies using many PROs should be considered interventional or non-interventional; IEC/IRB approvals can sometimes take longer for non-interventional studies because of the greater priority typically given to interventional studies.

PRO questionnaires were originally requested to be completed within two weeks, or the patient would be electronically locked out; strict deadlines for PRO completion proved to be unrealistic for real-world studies. Allowing PROs to be completed on paper, which many patients preferred, rather than electronically was inefficient and more difficult to administer across multinational sites. The timings of PRO completion did not always coincide with clinic visits.

The electronic Haemtrack system which was used was established in the UK²²; however, other countries were reluctant to adopt this system. A shortened version of the UK Haemtrack diary was designed to collect only study-specific data, which made it quicker to use but reduced its clinical utility for normal clinical practice.

Since implementation was slow, the study infrastructure and enthusiasm suffered at some sites. Higher investigator fees/greater financial support for some sites could not be implemented because they exceeded the possible fair market value in the countries involved.

3.4 | Patient-investigator interaction challenges

A patient brochure, describing the registry for prospective participants, was started late in the study design process, required IEC/IRB approval and could not be finalized before study closure. Other efforts to generate patient enthusiasm for ECHO were complicated by prohibitions against direct communication with patients by the CRO and registry sponsor so all communication had to be routed through the investigators and site staff.

4 | DISCUSSION

4.1 | Investigator perspective

For investigators, participation in ECHO required a considerable time commitment for administrative paperwork, CRF completion and interaction with multiple consultants. Investigators were unaware of PRO instrument completion rates because electronically completed PROs were submitted directly to the CRO managing ECHO, and paper questionnaires completed by patients at home could not be monitored by investigators. Consequently, staff follow-up with patients regarding PROs was delayed. However, patients had the option to complete PROs on paper during clinic visits, which allowed investigators to verify that the instruments had been completed.

4.2 | Patient perspective

In ECHO, the use of fewer PRO questionnaires or validated shorter versions, if available, might have improved the completion rate. The use of tailored materials rather than generic PRO instruments might have been preferable for capturing data and avoided question repetition. With hindsight, materials to improve understanding of the long-term value of participating in ECHO may have increased patient engagement and participation.

4.3 | Industry sponsor perspective

With hindsight, the feasibility and relevance of administering multiple PRO instruments in ECHO were not adequately assessed until

after the registry had started. Implementing even minor amendments to the ECHO protocol required substantial administrative effort (eg resubmission to IEC/IRB and changing site contracts). Delays in setting up the registry in each country also increased the opportunity for further discussions and requests for protocol amendments by different internal and external stakeholders.

Before selecting a site, an evaluation may need to be performed to ensure that there are adequate resources and to guarantee that any competing studies at the participating centre will not interfere with the development of the study.

Use of PROs in an industry-sponsored registry creates potential legal and safety issues, since pharmaceutical companies are required to monitor any adverse events. Considerable time was spent in each country discussing pharmacovigilance and timely collection and reporting of adverse events of special interest and how the sponsor could fulfil its safety obligations.

4.4 | Insights from other disease registries

Other disease registries have faced similar obstacles to ECHO, such as difficulty in attracting participants, failure to maintain continued patient involvement, suboptimal data quality control and missing data.²³⁻²⁵ Some disease registries have mitigated these obstacles, including the Cystic Fibrosis Foundation Patient Registry (CFFPR) in the United States and the European Cystic Fibrosis Society Patient Registry (ECFSPR) in Europe.^{26,27} The CFFPR can be used by clinicians to prepare for appointments and discuss treatment plans with patients, and provides a searchable database of > 800 documents.²⁶ The ECFSPR, although initially facing many of the same obstacles as ECHO, was ultimately successful.²⁷ Related to haemophilia specifically, the WBDR, which was launched in April 2018 after the ECHO study registry was already initiated, records real-world patient-level data on global clinical outcomes. The pilot study indicated good feasibility and a high level of patient interest,⁷ and the first report was produced in 2019.²⁸ This registry has a privacy-protected, web-based data entry system that allows for the collection of individual patient data, providing a clinical profile for each PWH. Unlike ECHO, these registries did not focus exclusively on PRO data,^{7,26} the collection of which can potentially create additional hurdles. For example, in Spine Patient Outcomes Research Trial (SPORT), which evaluated PROs in > 600 patients with lumbar spinal stenosis over 8 years, only 53% of initial participants supplied data at final follow-up. This may have confounded results, because significant differences in patient characteristics were observed between patients who were lost to follow-up and those who continued throughout the study.²⁹

National registries are a potential source of cross-sectional real-world data; however, different registries may collect similar data in different ways and may have a limited history of aggregating data or making comparisons across countries. Until there is greater collaboration between national registries, a preferred approach may be to encourage investigator-led multi-company collaborations.



Although the multinational ECHO haemophilia registry was closed early, the global PROBE project is currently underway to collect PROs in PWH and control subjects without bleeding disorders. PROBE may overcome some common registry obstacles by administering a short questionnaire and employing a cross-sectional design.⁶ Indeed, initial results suggest that the PROBE questionnaire is a reliable tool for assessing PROs in PWH and control populations from many countries.^{30,31} An initiative has recently been launched by the European Medicines Agency (EMA) to leverage disease-specific registries for postmarketing regulatory as well as HTA decision-making for rare diseases.¹⁸

4.5 | Lessons learned from the ECHO registry

Upon reflection, there are numerous ways in which the ECHO registry could have been improved. Firstly, setting clear and limited objectives from the beginning and agreeing these amongst potential study investigators would allow for a more focused study. Secondly, involving patients earlier in the process could help to avoid unrealistic expectations of the number of PRO questionnaires they would be willing to complete. This would also allow patient input into the questions being asked. Such a patient-led approach has the potential to generate greater patient compliance by including fewer questions and less repetition. Thirdly, minimizing the workload for the patient and investigators involved in the study could improve compliance and uptake of the study by both parties. Simple data collection strategies, such as using computer-adaptive testing (eg PROMIS), could allow more data collection with less patient/physician burden but would require a calibrated item bank to be developed prior to use in a trial like ECHO. Lastly, starting early to build a robust communication strategy could also improve patient/physician uptake of the study by minimizing the workload and ensuring both parties understand the potential benefits of involvement in the study.

The lessons learned from the ECHO registry could help similar initiatives to find a more workable approach and negotiate practical and regulatory hurdles for large-scale national and international PRO data collection and analysis.

5 | CONCLUSIONS

The multinational ECHO registry was closed early because of administrative delays in its initiation, contracting issues posed by its global reach, the burden of completing multiple PRO instruments, competing studies and a lack of resources at participating sites. ECHO had a complex design, requiring multiple interactions with the CRO and subcontractors. Greater success might have been achieved if ECHO had been designed as an investigator-led research study in which recruitment and data control were managed by an independent CRO. Having narrower research objectives, a single patient diary, fewer PROs or a single instrument covering different aspects of interest and earlier and more widespread

patient involvement in study planning might also have improved ECHO success.

Although ECHO was closed early, the lessons learned from this registry and the recommendations for future research proposed by the ECHO Steering Committee provide valuable guidance for haemophilia researchers undertaking similar registries or studies in the future. The multiple challenges that arose in implementing ECHO illustrate the many potential issues that must be considered in designing multinational registries enrolling patients with haemophilia.

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CONFLICT OF INTEREST










Charles RM Hay attended speaker bureau for Pfizer, Novo Nordisk, Shire, Sobi, and Biotest and advised for Alnylam, Bayer, Shire and Roche. Midori Shima received grants/personal fees from Shire, Bioverativ, Chugai, CSL Behring, Novo Nordisk, Bayer, Kaketsuken, Pfizer and Sysmex and personal fees from Roche, BioMarin, Octapharma and Sanofi. Michael Makris was the project lead of the EUHASS project, which receives partial funding from Bayer. Victor Jiménez-Yuste was reimbursed for attending symposia/congresses and/or honoraria for speaking/consulting and/or funds for research from Shire, Bayer, CSL Behring, Grifols, Novo Nordisk, Sobi, Octapharma and Pfizer. Johannes Oldenburg was reimbursed for attending symposia/congresses and/or honoraria and/or funds for research from Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Swedish Orphan Biovitrum. Kathelijin Fischer received speaker fees from Bayer, Baxter, Biogen, Biotest, CSL Behring, Octapharma, Pfizer and Novo Nordisk; performed consultancy for Bayer, Baxter, Biogen, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche and Sobi; and has received research support from Bayer, Pfizer, Baxter and Novo Nordisk; she is the epidemiologist for EUHASS and PedNet registries. Alfonso Iorio's institution has received funds for research and service agreements from Bayer, Novo Nordisk, Octapharma, Pfizer and Roche. Mark W. Skinner received honoraria for educational presentations and advisory roles with Bayer, BioMarin, Roche, Pfizer, Novo Nordisk and Spark Therapeutics and received research support as the PROBE study principal investigator from Shire (part of Takeda), Bayer, Bioverativ (a Sanofi company), CSL Behring, Novo Nordisk, Roche and Sobi. Elena Santagostino was the member of the speaker bureau and/or advisory boards for Bayer, Shire/Takeda, Pfizer, Novo Nordisk, CSL Behring, Sobi, Bioverativ, Roche, Grifols,

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AUTHOR CONTRIBUTIONS

Charles RM Hay planned, designed and conducted the study as chief investigator, and co-authored the first draft of this manuscript and edited all subsequent drafts. Midori Shima, Michael Makris, Johannes Oldenburg and Kathelijn Fischer were members of the Steering Committee, wrote and designed the protocol, and interpreted and analysed the data. Victor Jiménez-Yuste and Elena Santagostino were members of the Steering Committee, contributed to the study design and protocol, and analysed the data. Alfonso Iorio was a member of the Steering Committee, wrote the original SAP and conceived the idea of the paper. Mark W. Skinner was a member of the Steering Committee, reviewed the study protocol, participated in the evaluation of the study protocol and analysed the data. Sylvia von Mackensen consulted on PRO measures, constructed and analysed the feasibility questionnaire and contributed to the design of the study. Craig M. Kessler was a member of the Steering Committee, enrolled patients, wrote and designed the protocol and analysed the data. All authors were involved in the critical review of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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