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Proposal of an Integrated Patient Journey roadmap for the introduction of the first gene therapy for haemophilia B in Spain – The BHEMOGEN project

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ABSTRACT

Background: The approval of the first gene therapy for haemophilia B represents a disruptive innovation in its management. Its practical integration into the Spanish national healthcare system presents unique challenges and opportunities, requiring the development of a structured, coordinated and multidisciplinary patient journey roadmap to ensure high-quality patient care and outcomes measurement.

Methods: A multidisciplinary panel of 10 experts was established. The project involved a literature review, structured questionnaires, individual interviews, practical exercises and validation of results by focus group with nominal group methodology.

Results: No specific patient journey for haemophilia B or for gene therapy were identified in Spain. Associated changes required for current treatment of haemophilia B were identified and proposals made: 1) selection of candidates to receive gene therapy involves individualised assessment of eligibility criteria by a multidisciplinary committee including additional profiles; 2) providing adequate training on gene therapy to healthcare professionals is a must to ensure quality of care; 3) the generation of a specific informed consent document and processes involving hepatology and psychology are essential, with the patient association playing a crucial role; 4) centres without prior practical experience in gene therapy must adapt specific areas to ensure correct preparation and administration; 5) short- and long-term patient follow-up should incorporate continuous monitoring of the patient's liver health and inclusion in registries for evaluation of outcomes.

1. Introduction

Haemophilia B is a rare hereditary bleeding disorder characterized by a deficiency of coagulation factor IX (FIX), resulting in an increased tendency to bleed [1,2]. This condition significantly impacts on the quality of life of patients due to spontaneous bleeding episodes, which can affect both the neurological and musculoskeletal systems [3]. The recent approval of gene therapy for the treatment of haemophilia B in Spain represents a significant advancement in the management of this disease [4].

Despite the considerable experience in treating haemophilia B within the Spanish National Health System (NHS), gene therapy presents

Abbreviations: ANEH, National Association of Haematology Nursing; AAV5, Adeno-Associated Virus Serotype 5; FEDHEMO, Spanish Federation of Haemophilia; FIX, Factor IX; GMOs, Genetically Modified Organisms; LPRL, Occupational Risk Prevention; NHS, Spanish National Health System; RFVE, Royal Victoria Eugenia Foundation; SECA, Spanish Society for Healthcare Quality; SEHH, Spanish Society of Haematology and Hemotherapy; SEDISA, Spanish Society of Health Directors; SETH, Spanish Society of Thrombosis and Haemostasis; WFH, World Federation of Haemophilia.

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unique challenges. A previous initiative was developed to advocate for the development of a national gene therapy strategy within the Spanish Healthcare System. However, this was never deployed in practice [5]. Currently, there is no specific patient journey roadmap tailored for any gene therapy in Spain. Developing a structured care process that promotes a coordinated and multidisciplinary approach is crucial to ensure that those haemophilia B patients candidates to receive gene therapy do so in an effective and safety manner.

The BHEMOGEN project "Designing the best way to incorporate gene therapy for the treatment of haemophilia B in Spain" aims to address these challenges and propose practical actions by designing a comprehensive patient journey roadmap. This involves creating a practical and effective proposal, shaped by the insights and consensus of a multidisciplinary group of experts for implementation in hospital settings. Furthermore, the project seeks to contribute to foster further discussion and ongoing work on the practical and contextual aspects of introducing and managing gene therapy in Spain, identifying necessary activities to facilitate its incorporation to the therapeutic portfolio in haemophilia B.

2. Methods

2.1. Literature review, definition of scope and objectives

A targeted literature review was performed in November 2023 to identify and synthesize relevant evidence. The review focused on key steps and aspects of current haemophilia B patient management, as well as on the experience from the introduction of the other only gene therapy available at present (Zolgensma®) [6] in Spain.

The search was performed under the scope of the NHS, focusing on documents in Spanish and English, using grey literature sources such as: Google Scholar [7], Spanish clinical practice guidelines/protocols, Spanish national and regional plans or strategies regarding gene therapies and/or rare diseases, documentation issued by Spanish Scientific Societies and documentation issued by relevant Spanish Patient Associations. No time limit on the literature review was set.

2.2. Constitution of the focus group

The study was carried out through the setup of a multidisciplinary panel of 10 experts, representing 5 different regions (Andalucía, Cataluña, Galicia, Madrid and Valencia), with experience in haemophilia B and gene therapy management, assessment and decision-making in Spain. The panel included 3 haematologists and 1 nurse specialised in haemophilia B, 2 hospital pharmacists, 1 regional specialist in advanced therapies, 1 representative from a regional healthcare service, 1 hospital manager and 1 patients' representative from the Spanish Haemophilia Federation (FEDHEMO).

2.3. Development of a structured questionnaire and data analysis

A structured questionnaire was developed to obtain additional relevant information and validate each step of the proposed patient journey roadmap for gene therapy in haemophilia B. The questionnaire included detailed sections on current haemophilia B patient management, the patient journey for Zolgensma® (both estimated and constructed from findings from the literature review and individual consultations with experts) and the proposed patient journey roadmap for gene therapy in haemophilia B. Experts were asked to propose and justify changes to current management and make proposals to address them, specifying human, structural and economic resources required to implement these changes.

The questionnaire was distributed to and completed via email by the experts who returned it providing feedback based on their expertise and practical experience.

Experts were also requested to identify key challenges and propose actions. They were asked to rate each action in terms of its relative importance and feasibility of short-term implementation. A scale from 1 to 4 was employed, where '4' represented the highest importance or feasibility, and '1' the lowest.

The practical exercise was distributed via email to the experts, who completed and returned their evaluations.

Individual interviews were performed afterwards with all expert group members to validate and complete their responses.

The responses were analysed using descriptive statistical tools in Microsoft Excel 2016. Parameters such as mean, standard deviation, and minimum and maximum values were calculated for the assigned scores.

2.4. Group discussion and consensus session

An online workshop was held in March 2024 with the focus group using nominal methodology to present, discuss and validate the final patient journey roadmap and to propose the prioritisation of key action points identified.

3. Results

3.1. Proposed patient journey roadmap for gene therapy in haemophilia B in Spain

The proposed patient journey roadmap for the introduction of the gene therapy in Spain is illustrated in Fig. 1. The patient journey is structured into six sections, detailing the experts involved at each step and the differential aspects resulting from the introduction of gene therapy in the treatment of haemophilia B: 1) Diagnosis: the current haemophilia B diagnostic process remains unchanged; 2) Eligibility criteria for candidate patients; 3) Informed consent: generation and obtaining informed consent; 4) Initiation of treatment, ensuring safe infusion preparation and post-infusion monitoring; 5) Short-term and 6) Long-term patient follow-up, encompassing both liver health monitoring, FIX level assessment, treatment dispensing and patient registration.

Across the different steps of the care process, the Haemophilia Unit is the main driver of the various actions, supported by the other profiles acting as consultative elements, and supported by the hospital medical management and the hospital manager to ensure a cohesive approach within the facility.

Differential elements and necessary changes introduced at each step of the patient journey with the implementation of gene therapy for haemophilia B are presented below:

3.1.1. Diagnosis

The introduction of gene therapy for the treatment of haemophilia B, considering its approved indication, [8] does not imply any changes in the current diagnostic process since it is indicated for patients over 18 years old who have already been diagnosed and treated with conventional therapies.

3.1.2. Eligibility criteria

3.1.2.1. Experts involved in patient selection. Currently, experts involved in the selection of treatment for patients with haemophilia B include haematology (coordinator of the Haemophilia Unit), hospital pharmacy and nursing. With the introduction of gene therapy, it is proposed to add the additional profiles of infectiology or immunology to this step.

The hepatologist plays a consultative role in assessing the patient's baseline liver function before starting treatment. Meanwhile, infectious disease specialists and immunologists act as consultants in evaluating and determining the level of preexisting neutralizing antibodies against the vector, adeno-associated virus serotype 5 (AAV5) [9]. The involvement of these specialists will depend on the organizational structure of each hospital.

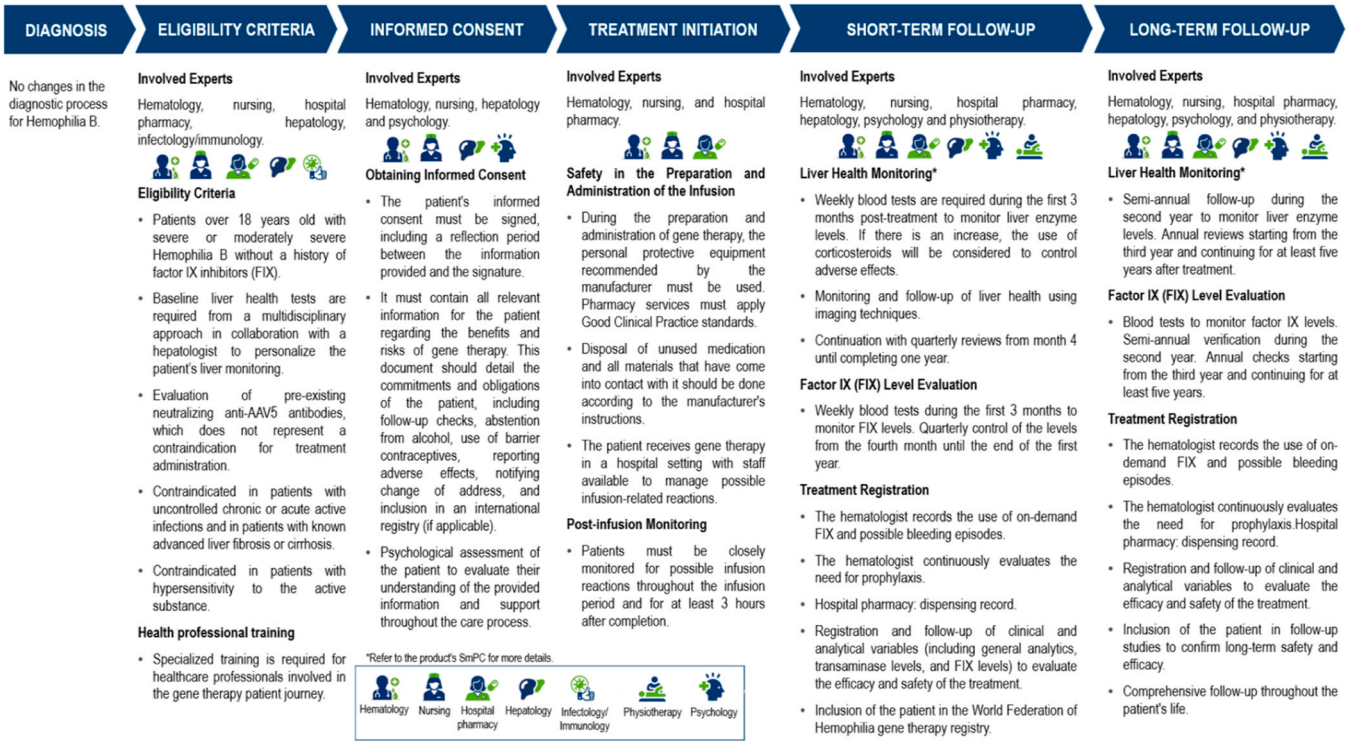

Fig. 1. Patient journey roadmap for gene therapy in haemophilia B in Spain.

3.1.2.2. Eligibility criteria for patients candidate to receive gene therapy. An individualized assessment and coordinated care by a multidisciplinary committee are required, ensuring an inclusive and comprehensive dialogue regarding selection of patients for treatment with gene therapy, as well as throughout the entire patient journey to guarantee comprehensive and high-quality care. Given the specific characteristics of this therapy, including the complexity and plurality of potential candidates, the hospital management/medical director is involved in the final approval and validation of the patient who receives gene therapy as treatment for haemophilia B.

3.1.2.3. Training of healthcare professionals. Due to the innovative nature of gene therapies in general and the first opportunity for its application in haemophilia B, along with the differential aspects compared to current treatment, provision of adequate training in gene therapy to all the healthcare professionals involved in patient management is required to ensure adequate quality of care. This training should be provided by the corresponding scientific societies.

3.1.3. Informed consent

3.1.3.1. Generation of the informed consent. With the incorporation of the first gene therapy into clinical practice, it is proposed to include the roles of hepatologist and psychology in drafting the informed consent document. The hepatologist provides insight into the therapy's implications for liver health, while the psychologist provides emotional and psychological support, helping the patient understand and manage the implications of undergoing a new treatment modality with long-term impact.

Additionally, the patient association plays an essential role performing readability tests to ensure patients' understanding of the language used in the document.

3.1.4. Obtaining informed consent

It is essential to develop a robust, specific and detailed process to obtain the informed consent from the patient including provision of comprehensive information on risks, benefits and commitments expected from the patient, thereby enabling the patient to make an autonomous, conscious, and informed decision.

The haematologist is responsible for obtaining the informed consent supported by psychology, providing emotional support to the patient; hepatology who evaluates the therapy's implications for liver health; and nursing facilitating patient's understanding of the information and accompanying the patient throughout the process.

3.1.5. Treatment initiation

3.1.5.1. Experts involved in the initiation of treatment. There are no changes in the experts involved in administering gene therapy compared to the current care process for haemophilia B. The professionals involved in this step are haematology, nursing and hospital pharmacy.

3.1.5.2. Preparation and administration of the infusion. Hospital pharmacy is responsible for preparing the infusion, while the haemophilia unit nursing staff are responsible for the administration and post-infusion monitoring. The preparation of gene therapy for administration to patients must be conducted in a hospital setting, under the supervision of healthcare personnel to monitor and manage potential adverse reactions after the infusion [8].

Hospitals with prior experience in handling gene therapy for other indications or those involved in clinical trials with gene therapy for haemophilia B already have the necessary facilities in place. Other centres without this practical experience must undertake an assessment and make the necessary adaptations to ensure adequate handling and administration.

Post-treatment monitoring measures must be established to ensure treatment efficacy and safety. Hospital management is tasked with facilitating and ensuring that the necessary infrastructure requirements for both preparation and administration of the treatment are met.

3.1.5.3. Safety in managing gene therapy. Practical management of gene therapy for haemophilia B does not differ from those applicable to any

gene therapy [8].

It is essential that the Occupational Risk Prevention (LPRL) of each hospital reviews, validates, and homologates the procedures related to managing these therapies, ensuring compliance with local and national regulations for biosafety with genetically modified organisms (GMOs).

The head of the haemophilia unit is responsible for implementing any safety measures. Additionally, hospital management must facilitate and ensure compliance with safety requirements, providing the necessary resources and overseeing that all processes adhere to current regulations.

3.1.6. *Short-term and long-term patient follow-up*

In the current short- and long-term follow-up for haemophilia B, professionals from haematology, nursing, hospital pharmacy, psychology and physiotherapy are involved. Gene therapy introduces a new dimension to the care team with the addition of hepatology due to the therapy's mechanism of action, which involves the transfer of genetic material to the liver [8]. Consequently, a differential aspect is introduced in the patient follow-up, which now includes liver health monitoring by a hepatologist.

In the short term, this monitoring includes weekly blood tests and imaging techniques during the first three months post-treatment, followed by quarterly reviews until the end of the first year. In the long term, semi-annual monitoring of liver enzyme levels is conducted during the second year, with annual reviews starting from the third year, extending for at least five years [8].

The evaluation of FIX levels for the current treatment for haemophilia B may vary depending on the severity of the disease, the patient's response to treatment and medical recommendation [10]. With the introduction of gene therapy for haemophilia B, it is also necessary to verify FIX levels to determine treatment efficacy. This is done through weekly blood tests during the first three months following the infusion, followed by quarterly checks until the end of the first year. In the long term, the evaluation of FIX levels continues with semi-annual checks during the second year and annual checks starting from the third year, extending for at least five years.

The haematologist will record the use of FIX on demand and any potential bleeding episodes continuously evaluating the need for prophylaxis in the same manner as with current treatment. A differential element is introduced in this step: the recommendation to include patients in the gene therapy registry of the World Federation of Haemophilia (WFH) for continuous follow-up, obtaining robust data and the possibility of sharing results on clinical outcomes in patients treated with gene therapy for haemophilia B.

The haematologist in charge of the Haemophilia Unit is the coordinator of such activities supported by other roles. Nursing manages the administration of FIX if prophylaxis is needed, while hospital pharmacy is responsible for dispensing records. Hepatologists assess liver health, psychologists provide emotional support to the patient and physiotherapy addresses musculoskeletal complications playing a crucial role in functional adaptation when bleeding is stopped and optimal FIX levels are achieved.

3.2. *Prioritization of activities proposed by the expert working group*

The experts identified and prioritised necessary actions to execute the proposed patient journey roadmap based on their relative importance and the feasibility of implementation in the short term, as shown in Fig. 2 and Table 1.

Most actions received high importance scores, averaging above 2.1. The development of a specific informed consent process was rated the highest with an average score of (3.5 ± 1.1) showing consensus on its relative importance. Specialized training for healthcare professional, while important, received the lowest score of (2.1 ± 1.0).

Most actions are considered highly feasible in the short term, with a mean rating above 2.7. The identification of relevant clinical variables

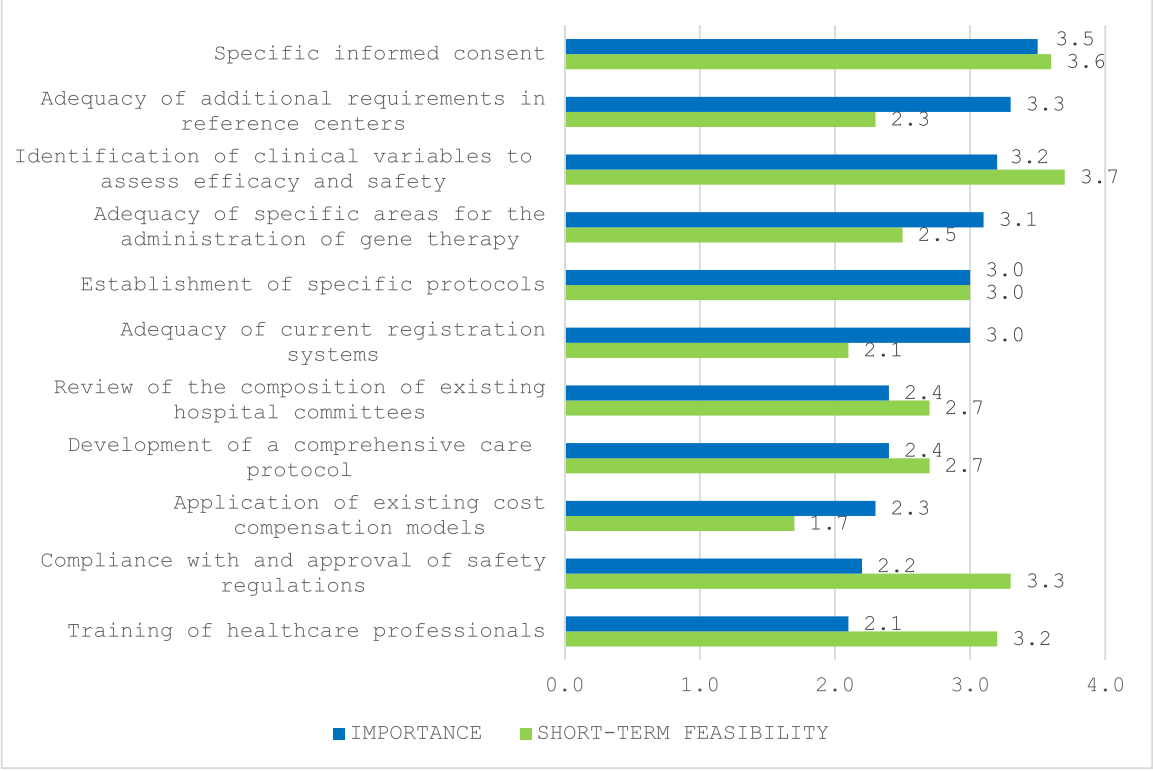

Fig. 2. Prioritisation of actions to execute the patient journey roadmap for gene therapy in haemophilia B in Spain based on their importance and short-term feasibility. **Note**: The scores were provided by 10 participants and show the mean of the results, prioritizing actions based on their importance and short-term feasibility.

Table 1
Results of the prioritization exercise completed by the panel of 10 experts.

STEP OF THE PJ	PROPOSED SOLUTION	IMPORTANCE				SHORT-TERM FEASIBILITY			
		Mean	SD	Min	Max	Mean	SD	Min	Max
3	Specific informed consent	**3,5**	1,1	1,0	4,0	**3,6**	1,0	1,0	4,0
2	Adequacy of additional requirements in reference centers	**3,3**	1,3	1,0	4,0	**2,3**	1,2	1,0	4.0
5 y 6	Identification of clinical variables to assess efficacy and safety	**3,2**	1,0	2,0	4,0	**3,7**	0,7	2,0	4,0
4	Adequacy of specific areas for the administration of gene therapy	**3,1**	1,1	1,0	4,0	**2,5**	0,7	2,0	4,0
4	Establishment of specific protocols	**3,0**	0,9	1,0	4,0	**3,0**	0,9	1,0	4,0
5 y 6	Adequacy of current registration systems	**3,0**	0,9	2,0	4,0	**2,1**	0,7	1,0	4,0
2	Review of the composition of existing hospital committees	**2,4**	1,0	1,0	4,0	**2,7**	1,2	1,0	4,0
2	Development of a comprehensive care protocol	**2,4**	1,0	1,0	4,0	**2,7**	0,9	1,0	4,0
4	Application of existing cost compensation models	**2,3**	1,5	1,0	4,0	**1,7**	1,3	1,0	4,0
4	Compliance with and approval of safety regulations	**2,2**	0,9	1,0	4,0	**3,3**	1,1	1,0	4,0
2	Training of healthcare professionals	**2,1**	1,0	1,0	4,0	**3,2**	0,9	2,0	4,0

Abbreviations: PJ; Patient Journey.

to assess the efficacy and safety of gene therapy showed the highest consensus in feasibility with a score of (3.7 ± 0.7). The informed consent process achieved a feasibility score of (3.6 ± 1.0) showing a strong consensus on its short-term implementability. While cost offset logistics showed the lowest consensus in both importance (2.3 ± 1.5) and feasibility (1.7 ± 1.3).

4. Discussion

Gene therapy offers unprecedented promise for long-term management and even cure of diseases like haemophilia B. Delivering such promise depends on the collective ability to effect change through initiatives that target scientific challenges, alongside solutions.

This work demonstrates that the development of a patient journey roadmap for gene therapy in haemophilia B is as much about the scientific and clinical components, as it is about the organisational structures, and, more than ever, about placing the patient in the centre of decision-making and care, requiring new levels of collaboration between all stakeholders. Such collaboration will represent a game-changer, turning scientific progress that was once unimaginable into transformative medical practice. The approach followed and the discussions held do also set a precedent for future gene therapies, contributing to improving the processes for the inclusion of this disruptive innovation into the healthcare system.

To our knowledge, this is the first proposal of a patient journey roadmap for the introduction of gene therapy for haemophilia B in Spain. A roadmap generated and agreed upon with all key stakeholders involved in the management of haemophilia B and gene therapy, including patients' association representatives.

This project has also prioritised, from the point of view of the stakeholders, the necessary actions to implement the patient journey in practice, with the aim of establishing the essential pillars that facilitate the introduction of gene therapy into the NHS in the short term and in the context of the upcoming availability of gene therapy for haemophilia B. Its implementation must be accompanied by a process flow that includes a guarantee of timelines to achieve the necessary quality of care and the desired clinical outcomes, representing future areas of work.

Experts agreed that it will be essential to review and adjust the organizational structures of the current reference centres available in most Spanish regions and where patients with haemophilia B are treated, ensuring efficient management of gene therapy and equitable access for patients across the different regions.

Including patients treated with gene therapy in existing international registries, such as the WFH Gene Therapy Registry, will allow correct patient follow-up and collection and analyses of clinical outcomes. This process will require the commitment and active collaboration from healthcare stakeholders at national, regional and hospital level.

This study is not exempt from some limitations, including the reduced number of participants and the scarce prior experience with gene therapy in Spanish hospitals. To mitigate this, experts in haemophilia B management and gene therapy in Spain were selected, ensuring comprehensive coverage of all involved specialties. Another limitation is that this project was designed at national level, and the experts included do not represent all 17 Spanish regions although it was enriched with representatives from regions with reference centres in haemophilia B. Conducting a study with a larger number of participants, while considering the practical solutions proposed, would be beneficial for future studies.

This project has received significant scientific endorsement from a wide range of esteemed societies and organizations, underscoring its value and importance. These endorsements include contributions and support from the Spanish Society of Thrombosis and Haemostasis (SETH), the Spanish Society of Haematology and Hemotherapy (SEHH), the Royal Victoria Eugenia Foundation (RFVE), the National Association of Haematology Nursing (ANEH), the Spanish Federation of Haemophilia (FEDHEMO), the Spanish Society of Health Directors (SEDISA) and the Spanish Society for the Healthcare Quality Research (SECA).

Ethics statement

This submission does not involve human or animal subjects. Hence, there is not ethics statement provided.

Authors contributions

AG: conceptualization, formal analysis, data curation, methodology, supervision, writing – original draft.

CH, DAGD, JBM, JLP, JPQ, MRL, MTAR, SB, SG: writing – review and editing and validation.

IC and IG: funding acquisition– review and editing.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MTAR, SB, CH, MRL, DAGD, SG, JBM, JPQ and JLP, reports financial support was provided by CSL Behring. MTAR reports a relationship with CSL Behring that includes: consulting or advisory. AG reports financial support was provided by CSL Behring SA. IG and IC are CSL-Behring employees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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