Accreditation model of European Haemophilia Centres in the era of novel treatments and gene therapy

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Updated European certification of haemophilia treatment and haemophilia gene therapy centres

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ABSTRACT

Introduction: The international certification of haemophilia centres in Europe is run by the European Association of Haemophilia and Allied Disorders (EAHAD) and European Haemophilia Consortium (EHC) since 2013. The centres are designated as European Haemophilia Comprehensive Care Centres (EHCCC) or European Haemophilia Treatment Centres (EHTC), based on the specific requirements which evaluate centres' ability to provide care for patients with haemophilia and allied disorders. Aim: The emerging of novel treatment options, non-replacement and gene therapy for management of haemophilia necessitates the update of the centre's needs and requirements. Methods: To facilitate the realization of these changes, EAHAD, in collaboration with EHC, has taken the steps to define necessary measures to safeguard quality and improvement of bleeding disorders care throughout Europe, to build a novel model for implementation of gene therapy and to provide a new Auditing and Certification protocol. Results: The updated guidelines for the certification of European Haemophilia Centres include all the requirements regarding facilities, laboratory and personnel needed for optimal management of novel treatment options, including the introduction of the hub-and-spoke model for delivery of gene therapy. To verify the implementation of requirements issued by the guidelines, an on-site audit process has been designed. Conclusion: Implementation of the novel certification protocol of the haemophilia treatment and haemophilia gene therapy centres has been made to further improve the quality of care for patients with haemophilia and other inherited bleeding disorders.

1. INTRODUCTION

Haemophilia is a rare inherited bleeding disorder characterised by spontaneous bleeding and chronic impairment of musculoskeletal system. Due to its rarity and complexity, haemophilia is best managed by a multidisciplinary teams organized in specialized centres [1]. The comprehensive care model was developed in the second half of 20th century in Europe, United States, Canada and Australia [2-8], and has since become the standard of care for PWH, as it has been shown to have a positive impact on treatment outcomes and quality of life [3, 9-12]. Haemophilia centres are not limited to the treatment of haemophilia, but include patients with other inherited and acquired deficiencies of coagulation factors, von Willebrand disease and inherited platelet defects.

There are 409 known HCs in Europe, and their size and services offered vary enormously [13]. One hundred fifty-nine HCs are certified as European Haemophilia Centres, a certification process run by European Association for Haemophilia and Allied disorders (EAHAD) and European Haemophilia Consortium (EHC).

The international certification of haemophilia centres in Europe was launched in 2013 with the aim to define criteria for the designation of Haemophilia Centres within Europe, in order to provide standards for an expected level of care for haemophilia and other inherited bleeding disorders and to encourage centres to use these standards for benchmarking and identification of areas for improvement [14].
The project was led by the European Haemophilia Network (EUHANET) and was done in coordination with EAHAD and EHC.
The main objective of EUHANET was ensuring equity of haemophilia treatment and care throughout Europe [15]. The project was funded by the Executive Agency for Health and Consumers (EAHC) of the European Commission, but also with the support of the pharmaceutical industry. The partners of the project were EAHAD, EHC and the Universities of Sheffield, Utrecht, and Milan, together with the 84 collaborating partners in 26 European countries. It was established in June 2012 and emerged from

the European Haemophilia Safety Surveillance (EUHASS). EUHASS system was set up in 2008 was based on collaboration of 70 European Haemophilia Centres from 26 countries that prospectively collected adverse events occurring in PWH [16]. EUHANET project extended the objectives to four separate areas, certification of Haemophilia Centres, setup of a haemophilia website, expansion of EUHASS system and establishment of a prospective project in afibrinogenemia and FXIII deficiency [16]. The project ended in 2015 after successful completion of its objectives and was succeeded by the EAHAD.

The European Guidelines for the certification of Haemophilia Centres were developed with the main objective of implementing a common and shared European strategy for a certification system that involved two levels of haemophilia care. Haemophilia Centres were designated as either European Haemophilia Comprehensive Care Centres (EHCCC) or European Haemophilia Treating Centres (EHTC), distinguished according to the functions and activities they carry out [14]. The document was produced by adopting a rigorous methodological approach and involving different stakeholders (National Health Authorities, Health Professionals, Patient Organisations and EUHANET Project Partnership). It was based on the key reference documents including the European principles of Haemophilia care published in 2008 [17], three recommendations on rare diseases drafted by the European Union Committee of experts on rare Diseases (EUCERD) and data on the existing certification systems in use in Europe [18]. The operational steps started with the review of the literature on available standards and certification systems in Europe and sharing of principles and criteria with the collaborating partners in a form of questionnaires. A draft of the guiding document was shared with more than two hundred European stakeholders, and agreement was achieved for the great majority of standards. The final release of the document was approved on the 7th of June 2013.

The development of haemophilia treatment centres throughout history has been largely influenced by the development of therapy and advancement of treatment modalities, evolution of haemophilia management and its specific requirements. Now, in 2023, we are experiencing a new revolution in the management of haemophilia. Novel treatment possibilities, long-acting factor products and

innovative non-factor therapies are improving the outcomes of prophylaxis and provide better quality of life for PWH [19]. However, these treatment options require increased medical expertise, education of patients, information exchange and adoption of structure of haemophilia centres. More than other novel treatments, gene therapy requires the implementation of new set of practices, reassessment of the infrastructure and an update of current processes in haemophilia centres [20].

To facilitate the implementation of these changes, EAHAD, in collaboration with EHC, has taken the steps to define the quality standards for improvement, the standards of service and resources for the application of the gene therapy, and create the new European certification and auditing protocol.

2. UPDATE OF THE EUROPEAN GUIDELINES FOR THE CERTIFICATION OF HAEMOPHILIA CENTRES (2020 – 2023)

The new options of prophylactic treatment for PWH, extended half-life factor concentrates and non-replacement therapies, are aiming to improve the quality of protection and lessen the treatment burden [19, 20]. In addition, several novel molecules have been investigated in clinical trials and are expected to become available in clinical practise in the next couple of years [21-25]. The modification of molecules and the discovery of new drugs enable us to think about a new era in haemophilia management and the possibility of more ambitious treatment goals [26]. However, the implementation of new treatment options will require education and adoption of new skills for the members of the multidisciplinary team, as well as a close collaboration between haemophilia treatment centres.

Moreover, haemophilia patients with life expectancy close to the general population suffer from similar diseases like hypertension, atrial fibrillation, cardiovascular and diabetes as they age [27]. The management of all these disorders in the era of novel therapies requires a proper multidisciplinary approach.

The updated European Guidelines for the certification of Haemophilia Centres address these challenges and aim to set the standards for modern haemophilia care. They define updated

requirements for the designation of EHCCC and EHTC [28], but also hub and spoke centres for gene therapy [20].

a) Comprehensive care

The fundamental characteristics and determinants of haemophilia care in Europe have not been changed in comparison to our previous European guidelines (Table 1). All PWH and patients with other inherited or acquired bleeding disorders should be registered and treated in EHTCs and EHCCCs with a comprehensive care programme including access to prophylaxis and modern treatment.

Comprehensive care has been defined as continuing supervision of all medical and psychosocial factors affecting PWH [11]. The multidisciplinary team of experts consists of the core haemophilia team and the affiliated medical specialists who address the specific needs and comorbidities of PWH. The functioning pathways should be defined to ensure the access to all the specialists involved in the comprehensive care.

Advances in haemophilia treatment have led to an improved life expectancy of PWH, raising necessities to include care for ageing persons and comorbidities related to the older age, including cardiologists, nephrologists, oncologists, geriatrists and other specialists. Moreover, the introduction of gene therapy might require the addition of new members to the team, and the redefinition of the roles of current members, as hepatologist and immunologists [29]. Psychological support has been strongly recommended during the process of gene therapy within the EHCCC, from the pre-therapy assessment and screening to the follow up period and facing with the positive and the negative outcomes of treatment [30].

b) Coagulation laboratory services

The coagulation laboratory plays a crucial role in diagnosis and monitoring of treatment of inherited bleeding disorders and is a mandatory part of each EHCCC and EHTC, either internal or external to the centre. Each EHTC should be associated with a coagulation laboratory which can provide diagnostic and monitoring laboratory support during working hours. On the other hand, the coagulation laboratory within the EHCCC should offer the full repertoire of tests for the diagnosis and monitoring of inherited disorders of haemostasis, but also provide a 24-hour laboratory service for the clotting factor assays and inhibitor testing. EHCCC should provide a comprehensive review of the results by an expert haematologist.

Laboratories should be able to measure activity of FVIII and FIX in plasma by both one-stage clotting assay (OSA) and chromogenic substrate assay (CSA). Moreover, as modifications in FVIII and FIX molecules in the extended half-life (EHL) concentrates (fusion with the Fc fragment, albumin fusion and pegylation) alter the effect of FVIII and FIX in the laboratory tests, specific assays and reagents should be used for monitoring EHL-products. Due to the significant differences between products, coagulation tests should be validated specifically for the particular EHL-product [31].

Moreover, the non-factor product emicizumab, a bi-specific antibody mimicking the co-factor function of FVIIIa, artificially shortens activated partial thromboplastin time–based clotting times, making standard OSCAs inapplicable for analysis of samples from patients treated with this drug [32]. Therefore, a specific set of assays should be used in PWH receiving emicizumab. A modified FVIII OSA has been developed for the determination of emicizumab levels in plasma, and FVIII CSA with bovine FX in kit reagents for the measurement of residual FVIII activity and the presence of inhibitors [32].

Discrepancies in the assays measuring activities of FVIII and FIX following gene therapy have been also described, with OSCA results approximately 1.5 times higher than CSA in both haemophilia A and haemophilia B [33, 34]. Therefore, laboratories providing testing for patients receiving gene therapy should be able to perform modified chromogenic test for the gene therapy program and follow-up of patients.

The minimal requirement for the coagulation tests that should be provided by the laboratories are listed in Table 2.

c) Introducing the hub and spoke model for gene therapy

Gene therapy for haemophilia A and haemophilia B has been recently approved by the European Medicines Agency (EMA). It represents a fundamental paradigm shift in the treatment of haemophilia [35]. It promises long-term expression of FVIII or FIX after a single intravenous administration of the gene therapy construct, thus providing independence from the standard prophylaxis [36].

Among the novel treatments of haemophilia, gene therapy represents the biggest challenge to both medical staff and haemophilia centres, since this approach to haemophilia treatment differs significantly from all other current treatment protocols. Even more, experience with gene therapy has been to date exclusively gathered in clinical trials, which implies inclusion of restricted number of carefully selected haemophilia centres and experience built on a rather small number of patients. Inclusion criteria, dosing and follow-up of patients have been carried out according to previously defined strict and regularly monitored criteria. Consequently, the transition of gene therapy into clinical practice outside of clinical trials poses challenges to the entire gene therapy process, form patient selection and information, to dosing of the gene construct, and the organisation of care before and after gene therapy. Furthermore, a number of uncertainties still exist regarding the implementation of gene therapy, including inclusion criteria, durability and level of factor expression, safety issues, short-term and long-term complications, and their management.

In conclusion, the implementation of gene therapy should be led by highly experienced and well-educated experts in both haemophilia and gene therapy but should also be carried out in adequately equipped haemophilia centres, in which requirements may go beyond standard capabilities of haemophilia centres.

A “hub-and-spoke” model has been developed to ensure access to gene therapy for all patients, to facilitate the delivery of gene therapy and to better qualify haemophilia centres to address all aspects of gene therapy [20, 37]. The model was designed as a modifiable network of haemophilia centres that coordinates gene therapy from patient counselling and informed consent through preparation and administration of the gene therapy product to close monitoring of the immediate post infusion period and long-term follow up.

Hub centres are defined as EHCCCs that are experienced in comprehensive care and additionally specialized in gene therapy. Designation of being a hub centre does not imply a separate classification besides EHCCC and HTC, but an additional characterisation of the EHCCC. This centres, named European Haemophilia Gene Therapy Centre (EHGTC), would take the lead in delivery of gene therapy, especially the preparation and infusion of the gene therapy construct (Table 3). The responsibilities of hub centres would be to confirm the eligibility criteria, conduct the final discussion with the patient and provide informed consent, to prepare, store and dose the gene construct, and to be actively involved in counselling the spoke centres during the short-term follow-up period. The medical team in hub centres should have experience obtained in previous gene therapy trials or via specific knowledge transfer through a mentorship program. Mentorship program should be designed to ensure best practice methodologies in the delivery of gene therapy from centres with previous experiences in gene therapy and could be organized as a national or international program.

Spoke centres are usually, but not necessary, patients’ home centres where PWH receive initial information and counselling about their treatment options and are evaluated according to inclusion and exclusion criteria, but are also the centres that should offer long-term follow-up to patients that have received gene therapy. Short-term and long-term follow-up includes determination of coagulation and immunological parameters, monitoring of joint score and function, and liver health [37], and should be carried by close collaboration and information exchange between hubs and spokes. PWH will be encouraged to do the regular visits to the spoke centre, with communication

between centres carried by the medical personnel. Moreover, all the supportive services should be available in the spoke centres.

Well-defined and structured protocols for the follow-up period are necessary to assess the outcomes of treatment, detect reduction or loss of factor expression and to monitor possible side-effects, including liver toxicity. Immunologists and hepatologists should be consulted when appropriate.

3. THE NEW AUDITING PROTOCOL FOR CERTIFICATION OF HAEMOPHILIA CENTRES

a) The current certification of haemophilia centres in Europe

The current auditing process for the certification of HCs in Europe is conducted by EAHAD and EHC and relies on a self-assessment process performed by the centres that apply for the certification. The application document is built on the criteria defined by the European Guidelines for the certification of Haemophilia Centres, which is accessible through the EAHAD official web page [28]. The thorough and detailed evaluation sheet is fulfilled in and signed by the medical director of the applying centre, and revised by the European Haemophilia Centre Certification Group, consisting of four members, including a patient representative. Based on the necessary requirements, the centre is designated as EHTC and EHCCC. The process finishes by the issue of the certificate for the period of three years, after which the process can be renewed.

The Certification of haemophilia centres in Europe by EAHAD is entirely voluntary. By the definition, certification is a voluntary procedure attesting the fulfilment of set of technical or organisational specifications which are developed based on consensus among all interested parties. Accreditation is, on the other hand, a formal procedure that finds its legal framework within certain regulations [38]. Therefore, although not obligatory and not a formal procedure, the certification of the HC by the EAHAD/EHC provides recognition at the European but also global level as high-quality haemophilia centres with specifically defined services, possibilities to offer comprehensive care, and capabilities of performing clinical studies. For patients, certification carries reassurance that the certificated service meets current standards of care and may even encourage them to choose treatment only in those

centres that are certificated [39]. Currently, 159 haemophilia centres from 34 countries have been registered, among which 117 are designated as EHCCC and 42 as EHTC [40].

Besides being certificated by EAHAD and EHC, some European countries like Netherlands, Italy, Germany and United Kingdom have a long-standing well-established per-review process of HCs on the national levels [41-43]. The certification process differs from county to county, but is usually performed by trained external peers, haemophilia experienced clinicians and nurses, and patient representatives. In some countries, like The Netherlands, officer from a specialized auditing company joins the audit team [41]. The certification process in the United Kingdom has been described as a highly effective mean of improving the quality of care for patients with bleeding disorders [43].

b) The need for new certification procedure for haemophilia centres on the European level

The current certification process of HCs in Europe has limitations. In the program run by EAHAD and EHC the evaluation of the HC applying for the certification is based solely on the description of the centre provided by the applicant, while no documentation corroborating the given information is neither provided nor required. The process is lacking objective verification of the presented data by independent party. On the other hand, countries that have established national certification process are duplicating the work if they choose to apply for both types of certifications. To overcome these unsolved issues, the new auditing protocol for certification of haemophilia centres has been proposed by the EAHAD in collaboration with EHC.

The Certification and Audit Working Group has been found within the EAHAD with the aim to establish the new protocol for certification of HCs. The first step of the process was to update the European Guidelines for the Certification of Haemophilia Centres, as described before, and the second step to established the on-site peer-audit as a part of the standard certification protocol.

The on-site audit has been chosen as it has demonstrated as highly effective on the level of national certification processes of HCs. Audit is posited to increase accountability and improve the quality of care through systematic monitoring and evaluation. Moreover, the audits have demonstrated to

create quality improvement awareness, trigger active participation by healthcare professionals, audit data support healthcare professionals in raising issues in their dialogues with dose in leadership positions and finally, audits legitimise the provision of feedback to colleagues, which encourages constructive collaboration [44]. The advantages over web-based audits is also in providing opportunities for interaction, discussion and sharing of ideas, while the sense of community contributes to implementation effectiveness [44]. Finally, audit creates opportunities for feedback on multidisciplinary issues that affect all stakeholders involved in the care process, and open possibilities for exchanging views about potentials for improvement.

c) Pilot project of the certification of haemophilia centres

The pilot project of on-site auditing HCs has been prepared by the EAHAD/EHC Certification and Audit Working group. The results will be used for establishing the EAHAD/EHC certification procedure but can be also used as a model for different auditing processes on national or international levels.

The process will be conducted by the Certification committee consisting of multidisciplinary professionals, physicians, nurses, physiotherapists, laboratory specialists, and patient's representatives. In that way, every member of the audit team will be responsible for the area of her/his expertise. Involvement and participation of patient representatives as members of the inspection team, or as a promotor of the process, is common element in the most national certification of HCs [45]. The members of the audit team will be recruited from EAHAD and EHC. The audit groups that will visit the centres will consist of at least three members, a physician, a nurse or a physiotherapist, and a patient representative, which may be a patient or patient's parents. All team members will receive training by the external experts in the quality control of health care systems to ensure the equity and harmonisation of the certification process. The visits to the centres will be based on the pre-defined quality standards and will include interviews with the staff members, analysis of a random sample of medical records, onsite auditing of the operating procedures and the review of the

facilities. Interviews with patients and caregivers are equally important to determine the patients' opinions and their satisfaction with the care provided.

The new certification process will therefore consist of three steps.

1. The first step is the application by the haemophilia centre, including sending the completed thorough and detailed application/self-assessment form.
2. The on-site audit team will visit the centre after verifying and confirming that all criteria based on the application form are met. The structured and detailed on-site audit process would include the interviews with the medical staff and the patients and the evaluation of the centre's facilities and documentation.
3. The certification committee will review all the data gathered and make a final decision. The process will end by producing the report and sending the feedback to the audited centre.

The detailed report will be provided by the Certification committee at the end of the auditing process. The centres will be designated as EHCCC or EHTC, while EHCC may get additional designation of being EHGTC. In case that some of the standards defined by European Certification of haemophilia treating centres are not met, the centre will receive the document describing discrepancies and could re-apply after undertaking necessary measures for improvement. Regular re-certification process is planned to be performed every five years.

The collaboration between EAHAD/EHC and national auditing organisations will be proposed for the countries with the existing national certification system to ease the process of certifications and to avoid unnecessary reauditing. A national certification process and requirements will be assessed and compared with EAHAD/EHC auditing process, and if necessary, audit of the selected requirements will be performed.

All the documentation regarding the certification process will be securely stored by EAHAD, as it has been since the onset of certification process in 2013. Designation of the certified centre will be available on EAHAD web page [40], howe14ver, all the other information will not be publicly available.

CONCLUSION

The new EAHAD/EHC audit and certification procedure has been developed with the aim to help haemophilia centres (EHCCCs and EHTCs) to achieve a harmonized European standard of haemophilia care. The updated European guidelines for the certification of Haemophilia Centres include all the novel requirements regarding facilities, laboratory and personnel needed for optimal management of the treatment that is currently available, and those expected in the near future, including the need for introduction of the hub-and-spoke model for delivery of gene therapy.

The development of new therapeutics and the arrival of novel treatment possibilities had a significant impact on the management of haemophilia, presenting a major paradigm shift in haemophilia care. Consequently, these changes will have major impact on the management and organisation of haemophilia centres but will also change the principles governing the planning and philosophy of haemophilia treatment.

CONFLICTS OF INTEREST

Ana Boban received honoraria as a member of advisory boart and/or speaker form Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Takeda. Fariba Baghaei received honoraria as a member of advisory boart and/or speaker form Bayer, Octapharma, Pfizer, Novo Nordisk, Shire/Takeda, Roche, BioMarin, uniQure, Sobi. Karin Fijn van Draat received unrestricted research grants from CSL Behring and NovoNordisk and consultancy fees from SOBI, Grifols, Takeda, Novo Nordisk and Roche. Wolfgang Miesbach acted as a paid consultant for Bayer, Biomarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda/Shire, uniQure. Robert Klamroth received research funding and consultancy from Bayer, Biomarin, Biotest,

CSL Behring, Grifolds, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, Takeda/Shire. David Stephenesen: nothing to declare. Mary Kavanagh: no conflict of interest. Declan Noone: no conflict of interest. Miguel Crato: no conflict of interest. Flora Peyvandi: speaker at educational symposia organized by Grifols, Roche, Sanofi, Sobi and Takeda. Member of Advisory Board of Biomarin, Roche, Sanofi, Sobi, Takeda.

AUTHOR'S CONTRIBUTIONS

Ana Boban, Fariba Baghaei, Karin Fijn van Draat, Robert Klamroth, Wolfgang Miesbach, David Stephensen, Mary Kavanagh, Declan Noon, Miguel Crato and Flora Peyvandi are members of the centre certification working group of EAHAD. Ana Boban and Flora Peyvandi produced the first draft of this manuscript, which was subsequently revised and finalized with all authors. All authors approved the final manuscript.

REFERENCES:

1. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, Carcao M, Mahlangu J, Ragni MV, Windyga J, Llinás A, Goddard NJ, Mohan R, Poonnoose PM, Feldman BM, Lewis SZ, van den Berg HM, Pierce GF; WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020 Aug;26 Suppl 6:1-158.
2. Levine PH. Delivery of health care in hemophilia. Ann N Y Acad Sci. 1975 Jan 20;240:201-7.
3. Levine PH, McVerry BA, Segelman AE, Cranford CM, Zimbler S. Comprehensive health care clinic for hemophiliacs. Arch Intern Med 1976; 136: 792–4.
4. Kerr CB. Comprehensive care for haemophilia. J R Coll Physicians Lond. 1971 Apr;5(3):263-7.

5. Biggs R, Macfarlane RG. Treatment of Haemophilia and Other Coagulation Disorders. Oxford, UK: Blackwell Scientific;1966.
6. Kasper CK. A total program for the patient with hemophilia. J Am Phys Ther Assoc. 1966;46:1268–1285.
7. Street A. Developing models of haemophilia care. Haemophilia. 2012 Jul;18 Suppl 4:89-93.
8. Evatt BL, Black C, Batorova A, Street A, Srivastava A. Comprehensive care for haemophilia around the world. Haemophilia. 2004 Oct;10 Suppl 4:9-13.
9. Smith PS, Keyes NC, Forman EN. Socioeconomic evaluation of a state-funded comprehensive hemophilia-care program. N Engl J Med. 1982 Mar 11;306(10):575-9.
10. Smith PS, Levine PH. The benefits of comprehensive care of hemophilia: a five-yea study of outcomes. Am J Public Health 1984; 74: 616–7.
11. Yeung CH, Santesso N, Pai M, Kessler C, Key NS, Makris M, Navarro-Ruan T, Soucie JM, Schünemann HJ, Iorio A. Care models in the management of haemophilia: a systematic review. Haemophilia. 2016 Jul;22 Suppl 3(Suppl 3):31-40.
12. Soucie JM, Nuss R, Evatt B, Abdelhak A, Cowan L, Hill H, Kolakoski M, Wilber N. Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. Blood. 2000 Jul 15;96(2):437-42.
13. https://eahad.org/european-haemophilia-centres-certification/acessed Nov 8th 2022
14. Giangrande P, Calizzani G, Menichini I, Candura F, Mannucci PM, Makris M. The European standards of Haemophilia Centres. Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s525-30.
15. Makris M, Calizzani G, Fischer K, Gatt A, Gilman E, Hollingsworth R, Lambert T, Lassila R, Mannucci PM, Peyvandi F, Windyga J. The European Haemophilia Network (EUHANET). Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s515-8.
16. Makris M, Calizzani G, Fischer K, Gilman EA, Hay CR, Lassila R, Lambert T, Ludlam CA, Mannucci PM. EUHASS: The European Haemophilia Safety Surveillance system. Thromb Res. 2011 Jan;127 Suppl 2:S22-5.

17. Colvin BT, Astermark J, Fischer K, Gringeri A, Lassila R, Schramm W, Thomas A, Ingerslev J; Inter Disciplinary Working Group. European principles of haemophilia care. Haemophilia. 2008 Mar;14(2):361-74.
18. Candura F, Menichini I, Calizzani G, Giangrande P, Mannucci PM, Makris M. The methodology for defining the European standards for the certification of Haemophilia Centres in Europe. Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s519-24.
19. Mahlangu JN, Blanchette V, Klamroth R. Redefining prophylaxis in the modern era. Haemophilia. 2021 Feb;27 Suppl 3:21-27.
20. Miesbach W, Chowdary P, Coppens M, Hart DP, Jimenez-Yuste V, Klamroth R, Makris M, Noone D, Peyvandi F. Delivery of AAV-based gene therapy through haemophilia centres-A need for re-evaluation of infrastructure and comprehensive care: A Joint publication of EAHAD and EHC. Haemophilia. 2021 Nov;27(6):967-973.
21. Shapiro AD, Angchaisuksiri P, Astermark J, Benson G, Castaman G, Eichler H, Jiménez-Yuste V, Kavakli K, Matsushita T, Poulsen LH, Wheeler AP, Young G, Zupančić-Šalek S, Oldenburg J, Chowdary P. Long-term efficacy and safety of subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors. Blood Adv. 2022 Jun 14;6(11):3422-3432.
22. Cardinal M, Kantaridis C, Zhu T, Sun P, Pittman DD, Murphy JE, Arkin S. A first-in-human study of the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-06741086, an anti-tissue factor pathway inhibitor mAb, in healthy volunteers. J Thromb Haemost. 2018 Sep;16(9):1722-1731.
23. Pasi KJ, Lissitchkov T, Mamonov V, Mant T, Timofeeva M, Bagot C, Chowdary P, Georgiev P, Gercheva-Kyuchukova L, Madigan K, Van Nguyen H, Yu Q, Mei B, Benson CC, Ragni MV. Targeting of antithrombin in hemophilia A or B with investigational siRNA therapeutic fitusiran-Results of the phase 1 inhibitor cohort. J Thromb Haemost. 2021 Jun;19(6):1436-1446.

24. Jiang M, Yang F, Jiang Y, Cheng L, Han J, Yi J, Zhang G, Ma Z, Cao L, Zuo B, Zhou L, Huang L, Niu S, Xia Z, Zhou X, Bai X, Esmon NL, Ruan C, Xia L, Han Y, Esmon CT, Wu D, Xu J. Blocking human protein C anticoagulant activity improves clotting defects of hemophilia mice expressing human protein C. Blood Adv. 2022 Jun 14;6(11):3304-3314.
25. Aymonnier K, Kawecki C, Arocas V, Boulaftali Y, Bouton MC. Serpins, New Therapeutic Targets for Hemophilia. Thromb Haemost. 2021 Mar;121(3):261-269.
26. Lewandowska M, Nasr S, Shapiro AD. Therapeutic and technological advancements in haemophilia care: Quantum leaps forward. Haemophilia. 2022 May;28 Suppl 4:77-92.
27. Kempton CL, Makris M, Holme PA. Management of comorbidities in haemophilia. Haemophilia. 2021 Feb;27 Suppl 3:37-45.
28. https://eahad.org/wp-content/uploads/2020/06/Euhanet-European_guidelines_for_the_certification_of_Haemophilia_Centres_NEW.pdf, accessed Nov 8th 2022
29. Miesbach W, Barcenilla SG, Golan G, Lobet S. Implications of haemophilia gene therapy for the changing role of the multidisciplinary team. Haemophilia. 2022 Jan;28(1):e12-e14.
30. Fletcher S, Jenner K, Pembroke L, Holland M, Khair K. The experiences of people with haemophilia and their families of gene therapy in a clinical trial setting: regaining control, the Exigency study. Orphanet J Rare Dis. 2022 Apr 4;17(1):155
31. Müller J, Miesbach W, Prüller F, Siegemund T, Scholz U, Sachs UJ; Standing Commission Labor (STAEKOLA) of the Society of Thrombosis and Haemostasis Research (GTH). An Update on Laboratory Diagnostics in Haemophilia A and B. Hamostaseologie. 2022 Feb 1. doi: 10.1055/a-1665-6232.
32. Müller J, Pekrul I, Pötzsch B, Berning B, Oldenburg J, Spannagl M. Laboratory monitoring in emicizumab-treated persons with hemophilia A. Thromb Haemost 2019;119(09):1384–1393.

33. Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia A. N Engl J Med 2017;377(26): 2519–2530.
34. Robinson MM, George LA, Carr ME, et al. Factor IX assay discrepancies in the setting of liver gene therapy using a hyperfunctional variant factor IX-Padua. J Thromb Haemost 2021;19(05):1212–1218.
35. Leebeek FWG, Miesbach W. Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. Blood. 2021 Sep 16;138(11):923-931.
36. Miesbach W, Baghaei F, Boban A, Chowdary P, Coppens M, Hart DP, Jimenez-Yuste V, Klamroth R, Makris M, Noone D, Peyvandi F. Gene therapy of hemophilia: Hub centres should be haemophilia centres: A joint publication of EAHAD and EHC. Haemophilia. 2022 May;28(3):e86-e88.
37. Pipe SW, Reddy KR, Chowdary P. Gene therapy: Practical aspects of implementation. Haemophilia. 2022 May;28 Suppl 4:44-52.
38. Giangrande P, Calizzani G, Menichini I, Candura F, Mannucci PM, Makris M. The European standards of Haemophilia Centres. Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s525-30
39. Valori R, Rogers C, Johnston D, Ingham J. Developing a strategy for accreditation of clinical services. Clin Med (Lond). 2013 Dec;13(6):538-42. doi: 10.7861/clinmedicine.13-6-538.
40. https://www.euhass.org/aspxpages/certcentres.aspx, accessed Nov 8th 2022
41. Leebeek FW, Fischer K. Quality of haemophilia care in The Netherlands: new standards for optimal care. Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s501-4.
42. Mannucci PM, Menichini I. A certification/accreditation model for Haemophilia Centres in Italy. Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s505-9
43. Wilde JT. The UK Haemophilia Doctors Organisation triennial audit of UK Comprehensive Care Haemophilia Centres. Haemophilia. 2012 Jul;18(4):491-5.
44. Hut-Mossel L, Ahaus K, Welker G, Gans R. Understanding how and why audits work in improving the quality of hospital care: A systematic realist review. PLoS One. 2021 Mar

31;16(3):e0248677. doi: 10.1371/journal.pone.0248677. PMID: 33788894; PMCID: PMC8011742.

45. Calizzani G, Makris M, Mannucci PM, Taruscio D, Grazzini G, Oleari F. Haemophilia Centre Certification Systems: optional or optimal choice for healthcare systems? Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s492-4.