Received: 31 August 2022 | Revised: 3 October 2023 | Accepted: 3 October 2023

DOI: 10.1111/hae.14887

Haemophilia WFH WILEY

ORIGINAL ARTICLE

Clinical haemophilia

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

Ana Boban[1,2] | **Fariba Baghaei**[3] | **Fijnvandraat Karin**[4] | **Robert Klamroth**[5,6] | **Wolfgang Miesbach**[7] | **David Stephensen**[8] | **Mary Kavanagh**[9] | **Declan Noone**[10] | **Miguel Crato**[10] | **Flora Peyvandi**[11,12] | **EAHAD Accreditation and Audit of Haemophilia Centres Working Group**

[1]Haemophilia Centre, Department of Haematology, University Hospital Centre Zagreb, Zagreb, Croatia

[2]School of Medicine, University of Zagreb, Zagreb, Croatia

[3]Coagulation Centre, Department of Medicine, Section of Haematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden

[4]Amsterdam UMC, Emma Children's Hospital, Pediatric Hematology, University of Amsterdam, Amsterdam, Netherlands

[5]Department of Internal Medicine – Vascular Medicine and Haemostaseology, Haemophilia Treatment Centre, Vivantes Clinic im Friedrichshain, Berlin, Germany

[6]Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany

[7]Department of Haemostaseology and Haemophilia Centre, Medical Clinic 2, Institute of Transfusion Medicine, University Hospital Frankfurt, Frankfurt, Germany

[8]Kent Haemophilia and Thrombosis Centre, East Kent Hospitals University NHS Trust, Canterbury, UK

[9]Paediatric Coagulation Centre, Children's Health Ireland at Crumlin, Dublin, Ireland

[10]European Haemophilia Consortium, Bruxelles, Belgium

[11]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi, Hemophilia and Thrombosis Center, Milan, Italy

[12]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Correspondence
Ana Boban, Haemophilia Centre, Department of Haematology, University Hospital Centre Zagreb, Kišpatićeva 12, Zagreb, Croatia.
Email: bobanana@gmail.com

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: To establish the new protocol for accreditation of European Haemophilia Centres.

Methods: EAHAD, in collaboration with EHC, established Accreditation Working Group with the aim to define necessary measures to safeguard quality and improvement of bleeding disorders care throughout Europe and to build a novel model for accreditation of European Haemophilia Centres.

Results: The European guidelines for certification of haemophilia centres have been updated to guidelines for the accreditation and 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. A pilot project for the accreditation of haemophilia centres including on-site audit has been designed.

Conclusion: Implementation of the novel accreditation 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.

KEYWORDS
accreditation, certification, gene therapy, haemophilia, haemophilia centres, on-site audit, von Willebrand disease

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 organised in specialised 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 had 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, either as European Haemophilia Comprehensive Care Centre (EHCCC) or European Haemophilia Treatment Centre (EHTC). The certification process is run by European Association for Haemophilia and Allied disorders (EAHAD) and European Haemophilia Consortium (EHC).

The certification program of haemophilia centres on European level started in 2013. The program aimed to provide standards for expected care and management of haemophilia as well as other inherited bleeding disorders, and to encourage centres to use these standards for benchmarking and identification of areas for improvement.[14]

The program was led by the European Haemophilia Network (EUHANET) in coordination with EAHAD and EHC. EUHANET project started in June 2012 as a part of the European Haemophilia Safety Surveillance (EUHASS). Institution of EAUHASS aroused out of necessity to monitor and collect data on adverse events related to management of haemophilia[15] and was based on the partnership between HC from different European countries.

However, EUHANET project extended the objectives to couple of distinct matters, one of them being the certification of Haemophilia Centres, led by EUHANET.[15]

The funding of the EUHANET project came from the Executive Agency for Health and Consumers (EAHC) of the European Commission, but also the pharmaceutical industry. The main goal of the project was to help assuring equal level of haemophilia care throughout Europe.[16] The partners of the project were EAHAD, EHC and the Universities of Sheffield, Utrecht, and Milan, together with the 84 collaborating partners from 26 European countries.

The product of this collaboration was publishing of the European Guidelines for the Certification of Haemophilia Centres. The main objective of the guidelines was to apply mutual strategy for a certification system of HC throughout Europe. The two levels of haemophilia care have been defined, comprehensive care centre or treatment centre. HC were designated as either EHCCC or EHTC based on the number of patients followed in the centre and the level of haemophilia care.[14] Preparing of the guidelines included different stakeholders involved in haemophilia care; authorities, health professionals and patient representatives, but also a methodologist. The document was based on current principles and recommendations on care of haemophilia and rare diseases in Europe,[17,18] as well as the experience of the national certification systems that have already been in use in Europe.[18]

In 2020, EAHAD recognised the need for renewal of the HC certification process and formed a new Working Group with the aim of having the new accreditation protocol of European HC in balance with the latest clinical practices offered in European HC.

In order to clarify the use of the terms Accreditation and Certification, hereby EAHAD/EHC as organisation is giving Accreditation as an official approval stating the Haemophilia centre has achieved required standard and is designated as HTC or HCCC. The Certification is the process of checking, auditing and approving or declining the status of the Haemophilia centre. This implies that EAHAD/EHC would issue the Accreditation to HC as an official approval stating the HC has achieved required standard and is designated as HTC or HCCC.

The EAHAD/EHC project for establishing the new accreditation procedure consisted of two steps. The first step of the process was to update the current European Guidelines for the Certification of Haemophilia Centres. The document is now titled European Guidelines for Accreditation of Haemophilia Centres and includes quality standards adopted for novel treatment modalities including gene therapy. The second step was to build a new protocol for the accreditation of HC including the on-site peer-audit. To facilitate accreditation project, a pilot project for the new European accreditation protocol has been created.

2 | UPDATE OF THE EUROPEAN GUIDELINES FOR THE ACCREDITATION 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 may 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 accreditation of HC address these challenges and aim to set the standards for contemporary haemophilia care. They define updated requirements for the designation of EHCCC and EHTC,[28] but also hub and spoke centres for gene therapy.[20]

2.1 | Comprehensive care

The fundamental characteristics and determinants of haemophilia care in Europe have not been changed in comparison to our previous European Guidelines for the Certification of Haemophilia Centres (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.

The core members of multidisciplinary team have not been changed, however, improved management of haemophilia increased life expectancy of PWH raised the need for closer collaboration with specialists who take care of comorbidities related to ageing, such as cardiologists, nephrologists, oncologists and geriatrists. 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, such, as hepatologist and immunologists.[28] 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.[29] The functioning pathways should be defined to ensure the access to all specialists involved in the comprehensive care of PWH.

2.2 | Coagulation laboratory services

The coagulation laboratory plays a crucial role in diagnosis and monitoring of treatment of inherited coagulation disorders and is a mandatory part of each EHCCC and EHTC. The minimal requirement for the coagulation tests that should be available in the laboratories are listed in Table 2, including the standards needed for clinical use of novel

TABLE 1 The functions and activities carried out by the EHTC and EHCCC[a].

EHTC and EHCCC

- Provides care for patients, including diagnosis, treatment, follow-up and rehabilitation
- Provides basic diagnostic and monitoring laboratory support during normal working hours for the more common inherited bleeding disorders
- Provides patients with safe and effective treatment products
- Offers specific treatment for patients with inhibitors and immune tolerance in collaboration with an EHCCC
- Provides a 24-h emergency treatment service
- Has access to multidisciplinary support, locally or in conjunction with EHCCC
- Provides advisory service, including genetic counselling, to patients and healthcare professionals
- Promotes information and training programs on inherited bleeding disorders to patients and healthcare professionals

EHCCC

- Co-ordinates the delivery of haemophilia services
- Provides a 24-h advisory service for patients, families, hospital doctors, general practitioners and affiliated EHTCs health care professionals
- Provides specialist care for patients with inhibitors, including surgery
- Provides a diagnostic and reference laboratory service with a full repertoire of tests for the diagnosis and monitoring of inherited disorders of haemostasis
- Provides a 24-h laboratory service for clotting factor assays and inhibitors testing
- Has access to multidisciplinary support:
  - ➢ Orthopaedic and/or rheumatological service with provision of surgery
  - ➢ Physiotherapy service
  - ➢ Obstetric and gynaecological service
  - ➢ Paediatric facilities if children are treated
  - ➢ Dental service
  - ➢ Hepatology and infectious diseases service
  - ➢ Professional psychological support
  - ➢ Social worker and welfare advice
- Has access to a genetic diagnosis service providing also carrier detection and antenatal diagnosis

Abbreviations: EHCCC; European Haemophilia Comprehensive Care Centre; EHGTC, European Haemophilia Gene Therapy Centre; EHTC, European Haemophilia Treating Centre.

[a]The table is reproduced from the European guidelines for the certification of haemophilia centres.[37]

treatments. 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.[30]

Furthermore, the non-factor product emicizumab, a bi-specific antibody mimicking the co-factor function of FVIIIa, artificially shortens

TABLE 2 Minimal requirement of the coagulation test required by the EHCCC and EHTC.

Test	EHCCC	EHTC
PT, APTT, thrombin time, mixing studies	Yes[a]	Yes
FVIII and FIX (assays for diagnosis)	Yes[a]	Yes
FVIII and FIX (assays specifically validated for modified FVIII or FIX products used in that center)	Yes[a]	
Factor VIII (with human FX in kit reagents) and FIX chromogenic	Yes	
Factor VIII chromogenic assay (with bovine FX in kit reagents)	Yes	
Inhibitor testing	Yes[a]	Yes
fibrinogen, VWF activity, FII, FV, FVII, FX, FXI, FXIII assays	Yes[a]	Yes
VWF antigen	Yes	
Platelet aggregation tests	Yes	

Abbreviations: APTV, activated partial thromboplastin time; EHCCC, European Haemophilia Comprehensive Care Center; EHTC, European Haemophilia Treating Center; FVIII; factor VIII; FIX, factor IX; FX, factor X; FII, factor II; FV, factor V; FVII, factor FVII; FXI, factor XI; PV, prothrombin time; VWF, von Willebrand factor.
[a]Services available 24/7.

activated partial thromboplastin time-based clotting times, making standard OSCAs inapplicable for analysis of samples from patients treated with this drug.[31] 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.[31]

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.[32,33] 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.

2.3 | Introducing the hub and spoke model for gene therapy

Gene therapy for both haemophilia A and B has been recently approved by the European Medicines Agency (EMA). It represents a fundamental paradigm shift in the treatment of haemophilia.[34] It offers the possibility long-term expression of FVIII or FIX after a single intravenous administration of the gene therapy construct, thus providing independence from the standard prophylaxis.[35]

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, from 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.

TABLE 3 Criteria for a haemophilia gene therapy hub centre.

- EHCCC
- Experience obtained in previous gene therapy trials or specialists who can provide timely expertise in gene therapy, or available mentorship program
- Ability to order, store, prepare and administer the gene therapy product
- Provision of informed consent/shared decision making
- Ability to perform diagnostic tests for the gene therapy program and follow-up of patients
- Close cooperation with other EHCCCs and EHTCs
- Knowledge in timely diagnosis and management of adverse events in gene therapy
- Close cooperation with hepatologists and immunologists
- Protocols on different strategies for immunosuppression
- Longitudinal data collection and evaluation in gene therapy (national and/or international registries)

Abbreviations: EHCCC; European Haemophilia Comprehensive Care Centre; EHTC, European Haemophilia Treating Centre.

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 equity of access for eligible patients, to facilitate the delivery of gene therapy and to better qualify HCs to manage all issues of gene therapy.[20,36] 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 specialised 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. These 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 organised as a national or international program.

Spoke centres are usually, but not necessarily, 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,[36] 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 ACCREDITATION OF HAEMOPHILIA CENTRES

3.1 | 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. 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.[37] The thorough and detailed evaluation sheet is fulfilled in and signed by the medical director of the applying centre, and reviewed 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, or not designated if the criteria are not met. The process finishes by the issue of the certificate for the period of 3 years, after which the process can be renewed.

The Certification of haemophilia centres in Europe by EAHAD is entirely voluntary. 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.[38] Currently, 159 haemophilia centres from 34 countries have been registered, among which 117 are designated as EHCCC and 42 as EHTC.[39]

Besides being certificated by EAHAD and EHC, some European countries like Netherlands, Italy, Germany and United Kingdom have a long-standing well-established peer-review process of HCs on the national levels.[40–42] This process differs from county to county, but is usually performed by trained external peers, experienced clinicians and nurses, and patient representatives. In some countries, like The Netherlands, officer from a specialised auditing company joins the audit team.[40] The formal audit process in the United Kingdom has been described as a highly effective mean of improving the quality of care for patients with bleeding disorders.[42]

3.2 | The need for new accreditation procedure for haemophilia centres on the European level

The current certification process of HCs in Europe has limitations. 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 Accreditation and Audit Working Group (AAWG) has been established within EAHAD with the close collaboration with EHC with the goal to produce auditing protocol for accreditation of haemophilia centres.

Members of the AAWG are the experts in the field of haemophilia, physicians, nurses and physiotherapists, and patient representatives. The group is also closely collaborated with EAHAD's Gene Therapy Working Group and the specialist from the coagulation laboratory. The on-site audit of HC with a team of external auditors who will visit the centre has been proposed as it has been 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 those in leadership positions and finally, audits legitimise the provision of feedback to colleagues, which encourages constructive collaboration.[43] Moreover, 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 the implementation effectiveness.[43] 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.

3.3 | Pilot project of the accreditation of haemophilia centres

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

Accreditation will be run and overseen by the Accreditation committee consisting of multidisciplinary team, three physicians, a nurse, a physiotherapist, laboratory specialist, and patient's representatives. However, a larger audit team will be formed from the members of EAHAD and EHC, also including health professionals as mentioned above, and also patient representative, which may be a patient or patient's parents. 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.[44] 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 accreditation process. Each centre will be visited by a smaller audit group of three to four members. 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. When needed, a professional translator will be included as a part of the team to facilitate the communication between auditors and the centre's personnel, as well as to translate the documentation in the original language.

The new accreditation 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 accreditation 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 Accreditation committee at the end of the auditing process. The centres will be designated as EHCCC or EHTC, while EHCCC may get additional designation of being EHGTC. In case that some of the standards defined by European accreditation of haemophilia treatment centres are not met, the centre will receive the document describing discrepancies and could re-apply after undertaking necessary measures for improvement. Regular re-accreditation process is planned to be performed every 5 years.

The collaboration between EAHAD/EHC and national auditing organisations will be proposed for the countries with the existing national on-site audit to ease the process of accreditation and to avoid unnecessary reauditing. The national certification/accreditation 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 accreditation process will be securely stored by EAHAD, as it has been since the onset of certification process in 2013. Designation of the accredited centre will be available on EAHAD web page,[39] however, all the other information will not be publicly available.

4 | CONCLUSION

The new EAHAD/EHC audit and accreditation procedure has been developed with the aim to help haemophilia centres (EHCCCs and EHTCs) to achieve a harmonised European standard of haemophilia care. The updated European guidelines for the Accreditation 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 modalities 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.

AUTHOR 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 Accreditation and Audit Haemophilia Centres working group of EAHAD. Ana Boban and Flora Peyvandi produced the first draft of this manuscript, which was subsequently revised and finalised with all authors. All authors approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Ana Boban received honoraria as a member of advisory boart and/or speaker form Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi and 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 and 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 and uniQure. Robert Klamroth received research funding and consultancy from Bayer, Biomarin, Biotest, CSL Behring, Grifolds, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI and 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 organised by Grifols, Roche, Sanofi, Sobi and Takeda. Member of Advisory Board of Biomarin, Roche, Sanofi, Sobi and Takeda.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

This review is based on previously conducted studies and does not report any new data; therefore, ethical approval was not required.

ORCID

Ana Boban https://orcid.org/0000-0003-3532-2336
Robert Klamroth https://orcid.org/0000-0003-4194-8183
Wolfgang Miesbach https://orcid.org/0000-0001-8286-5398
David Stephensen https://orcid.org/0000-0002-6175-3343
Flora Peyvandi https://orcid.org/0000-0001-7423-9864

REFERENCES

1. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020(Suppl6):1-158.
2. Levine PH. Delivery of health care in hemophilia. *Ann N Y Acad Sci*. 1975;240:201-207.
3. Levine PH, McVerry BA, Segelman AE, Cranford CM, Zimbler S. Comprehensive health care clinic for hemophiliacs. *Arch Intern Med*. 1976;136:792-794.
4. Kerr CB. Comprehensive care for haemophilia. *J R Coll Physicians Lond*. 1971;5(3):263-267.
5. Biggs R, Macfarlane RG. *Treatment of Haemophilia and Other Coagulation Disorders*. 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;18(Suppl4):89-93.
8. Evatt BL, Black C, Batorova A, Street A, Srivastava A. Comprehensive care for haemophilia around the world. *Haemophilia*. 2004;10(Suppl4):9-13.
9. Smith PS, Keyes NC, Forman EN. Socioeconomic evaluation of a state-funded comprehensive hemophilia-care program. *N Engl J Med*. 1982;306(10):575-579.
10. Smith PS, Levine PH. The benefits of comprehensive care of hemophilia: a five-yea study of outcomes. *Am J Public Health*. 1984;74:616-617.
11. Yeung CH, Santesso N, Pai M, et al. Care models in the management of haemophilia: a systematic review. *Haemophilia*. 2016;22(Suppl3):31-40.
12. Soucie JM, Nuss R, Evatt B, et al. Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. *Blood*. 2000;96(2):437-442.
13. Accessed Aug 15th 2023, https://eahad.org/european-haemophilia-centres-certification/acessed
14. Giangrande P, Calizzani G, Menichini I, Candura F, Mannucci PM, Makris M. The European standards of Haemophilia Centres. *Blood Transfus*. 2014;12(Suppl3):s525-530.
15. Makris M, Calizzani G, Fischer K, et al. EUHASS: the European Haemophilia Safety Surveillance system. *Thromb Res*. 2011;127(Suppl2):S22-25.
16. Makris M, Calizzani G, Fischer K, et al. The European Haemophilia Network (EUHANET). *Blood Transfus*. 2014;12(Suppl3):s515-518.
17. Colvin BT, Astermark J, Fischer K, et al. Inter Disciplinary Working Group. European principles of haemophilia care. *Haemophilia*. 2008;14(2):361-374.
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;12(Suppl3):s519-524.
19. Mahlangu JN, Blanchette V, Klamroth R. Redefining prophylaxis in the modern era. *Haemophilia*. 2021;27(Suppl3):21-27.
20. Miesbach W, Chowdary P, Coppens M, et al. 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;27(6):967-973.
21. Shapiro AD, Angchaisuksiri P, Astermark J, et al. Long-term efficacy and safety of subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors. *Blood Adv*. 2022;6(11):3422-3432.
22. Cardinal M, Kantaridis C, Zhu T, et al. 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;16(9):1722-1731.
23. Pasi KJ, Lissitchkov T, Mamonov V, et al. Targeting of antithrombin in hemophilia A or B with investigational siRNA therapeutic fitusiran-Results of the phase 1 inhibitor cohort. *J Thromb Haemost*. 2021;19(6):1436-1446.
24. Jiang M, Yang F, Jiang Y, et al. Blocking human protein C anticoagulant activity improves clotting defects of hemophilia mice expressing human protein C. *Blood Adv*. 2022;6(11):3304-3314.
25. Aymonnier K, Kawecki C, Arocas V, Boulaftali Y, Bouton MC. Serpins, new therapeutic targets for hemophilia. *Thromb Haemost*. 2021;121(3):261-269.
26. Lewandowska M, Nasr S, Shapiro AD. Therapeutic and technological advancements in haemophilia care: quantum leaps forward. *Haemophilia*. 2022;28(4):77-92. Suppl.
27. Kempton CL, Makris M, Holme PA. Management of comorbidities in haemophilia. *Haemophilia*. 2021;27(Suppl3):37-45.
28. Miesbach W, Barcenilla SG, Golan G, Lobet S. Implications of haemophilia gene therapy for the changing role of the multidisciplinary team. *Haemophilia*. 2022;28(1):e12-e14.
29. 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;17(1):155.
30. 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;42(04): 248-260. doi:10.1055/a-1665-6232
31. 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.
32. 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.
33. 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.

34. Leebeek FWG, Miesbach W. Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. *Blood*. 2021;138(11):923-931.
35. Miesbach W, Baghaei F, Boban A, et al. Gene therapy of hemophilia: hub centres should be haemophilia centres: a joint publication of EAHAD and EHC. *Haemophilia*. 2022;28(3):e86-e88.
36. Pipe SW, Reddy KR, Chowdary P. Gene therapy: practical aspects of implementation. *Haemophilia*. 2022;28(Suppl4):44-52.
37. Accessed Aug 15th 2023, https://www.eahad.org/wp-content/uploads/2023/02/Euhanet-European_guidelines_for_the_certification_of_Haemophilia_Centres_NEW.pdf
38. Valori R, Rogers C, Johnston D, Ingham J. Developing a strategy for accreditation of clinical services. *Clin Med (Lond)*. 2013;13(6):538-542. doi:10.7861/clinmedicine.13-6-538
39. Accessed Nov 8th 2023, https://www.euhass.org/aspxpages/certcentres.aspx
40. Leebeek FW, Fischer K. Quality of haemophilia care in The Netherlands: new standards for optimal care. *Blood Transfus*. 2014;12(Suppl3):s501-504.
41. Mannucci PM, Menichini I. A certification/accreditation model for Haemophilia Centres in Italy. *Blood Transfus*. 2014;12(Suppl3):s505-509.
42. Wilde JT. The UK Haemophilia Doctors Organisation triennial audit of UK Comprehensive Care Haemophilia Centres. *Haemophilia*. 2012;18(4):491-495.
43. 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;16(3):e0248677. doi:10.1371/journal.pone.0248677
44. 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;12(Suppl3):s492-494.

How to cite this article: Boban A, Baghaei F, Karin F, et al. Accreditation model of European Haemophilia Centres in the era of novel treatments and gene therapy. *Haemophilia*. 2023;29:1442–1449. https://doi.org/10.1111/hae.14887