The European Haemophilia Network (EUHANET)

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Introduction

Haemophilia A and B are rare inherited bleeding disorders due to reduced factor VIII (FVIII) or factor IX (FIX) activity, occurring in 1 in 10,000 and 1 in 50,000 of the population respectively[1,2]. Several other bleeding disorders such as deficiencies of factors I, II, V, VII, X, XI and XIII are even rarer. When the deficiency is severe these disorders present with spontaneous bleeding whilst for milder disorders traumatic bleeding is observed[3]. When bleeding occurs patients are treated with clotting factor concentrates which can be plasma derived or recombinant. Individuals with inherited bleeding disorders are cared for in Haemophilia Centres. There is major disparity in patient access to Haemophilia Centres throughout Europe[4], although it must be appreciated that this publication was based on data from the individual country patient organisations and was not based on national registries. There is a need for harmonisation of the data available in care centres, national data sources and patient organisations and these activities are planned to be improved by the European Haemophilia Network (EUHANET) project. There is also variation in the number of Haemophilia Centres within European countries and whilst in some there are over 80 Haemophilia Centres in others there is only a single centre.

The use of clotting factor concentrates has been associated with major adverse effects. Patients treated with plasma derived clotting concentrates prior to 1985 had an almost 100% risk of being infected with hepatitis C (HCV) and a 30-60% risk of Human Immunodeficiency Virus (HIV) infection[5]. Although the HCV/HIV viruses were eliminated following the introduction of viral inactivation, improvements in diagnostic tools used for the biological qualification of blood donations and the use of recombinant concentrates, other adverse events such as alloantibodies to FVIII or FIX remain[6]. The rarity of these disorders makes it difficult to determine the precise frequency of the adverse events because large numbers of patients are required which are not available in single centres. To overcome this problem, the European Haemophilia Safety Surveillance (EUHASS) system was set up in 2008[7]. This was a collaboration of over 70 European Haemophilia Centres in 26 countries which agreed to prospectively report adverse events occurring in their patients. The project was funded by the European Commission with pharmaceutical industry support. The EUHASS project demonstrated the willingness of these Haemophilia Centres to work together so the EUHANET was set up. This is a collaboration in four separate areas, the certification of Haemophilia Centres, the set up of a haemophilia website, the expansion of the EUHASS system and the establishment of a prospective project on afibrinogenemia and FXIII deficiency.

Organisation of the project

The lead partner of the EUHANET project is the University of Sheffield in the United Kingdom. The other main partners are the European Haemophilia and Allied Disorders organisation, the European Haemophilia Consortium, the University Medical Centre Utrecht, Fondazione IRCCS Ca' Granda in Milan and Medical Data Solutions and Services Ltd in Manchester. In addition there are 84 collaborating partners in 26 European countries. The project has eight work packages and is overseen by a steering committee with a representative from each of the main partners as well as four representatives from the collaborating partners.

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Certification of Haemophilia Centres

There is wide variation in the availability of Haemophilia Centres in different countries as well as in the range of services provided by individual centres. Many names are used by centres such as Haemophilia Centre, comprehensive care centre, Haemophilia Treatment Centre, Haemophilia Reference Centre, national haemophilia centre, etc. There is no agreed definition of what constitutes a haemophilia centre and whilst some centres care for more than 350 patients with severe haemophilia, others have less than 5 patients. Furthermore the laboratory support of haemophilia centres varies enormously.

Patients with inherited bleeding disorders have no way of knowing how comprehensive the care provided by a particular haemophilia centre is. This knowledge is important both for patients within a geographical region where several haemophilia centres are located, as well as for patients from other countries or areas who are travelling and are looking for emergency care. As a haemophilia community we have been looking at standardising the labelling of European Haemophilia Centres and categorising them. At the same time the European Commission has provided guidance for countries to develop centres for rare diseases[8]. Therefore a part of the EUHANET project is the standardisation of the labelling of Haemophilia Centres in Europe.

The certification work package undertook the development of this work and the process is described in the other manuscripts in this supplement of the Blood Transfusion journal. Briefly, the current regulations and processes within all European countries were reviewed and a document of standards of haemophilia care was prepared. Extensive consultation during several stages of the process led to modification of the document. The final standards document was approved in May 2013 and it was launched at a meeting in Rome in July 2013[9]. Two types of Haemophilia Centres are recognised by the standards document, the European Haemophilia Treatment Centre (EHTC) and the European Haemophilia Comprehensive Care Centre (EHCCC).

Because of the length of the standards document, a pro-forma of the key areas was developed for centres to use when applying for certification. This asks for the number of patients registered, the services offered, the emergency care facilities as well as the laboratory backup. Both the standards document and the application pro-forma are available on the EUHANET project website (www.euhanet.org).

The application process was launched in December 2013 and any Haemophilia Centre in Europe can apply for certification into EHTC or EHCCC. Although the standards for the two types are different, there are certain minimum requirements that have to be satisfied before one of these two titles are awarded to a centre. Once an application is made, it is reviewed by a five member committee which has representatives from medical and nursing staff as well as patients.

The certification process is based on data supplied by the centres and there are no site visits to check the accuracy of the data. Because of this, several parts of the application form will be made publically available. This is a first step and it is anticipated that in future audit visits will be incorporated into the process, although political, geographical and language differences have to be addressed to achieve this.

Haemophilia Central website

Although there is a lot of information about inherited bleeding disorders on the web, it is spread over many sites and its accuracy is often unclear. In the EUHANET project we set out to develop a website with all the information in a single place. The site is called Haemophilia Central and can be found at www.haemophiliacentral.org. Several components will be developed during the project but those currently publically available are:

1. News - this is produced in collaboration with Dr Uwe Schlenkrich. The site is regularly updated with haemophilia and other bleeding disorder related news;
2. Guidelines - here readers can select guidelines by subject and language. For most guidelines the reader is redirected to the site of the original publication;
3. Clinical trials - this is a search engine for any trials registered on www.clinicaltrials.gov in the field of acquired or inherited bleeding disorders;
4. Concentrate directory - this section contains details of all the available clotting factor concentrates in Europe. Once a concentrate is selected, the details of the manufacturer, production and characteristics of the product as well as publications relating to the products are provided;
5. Database of centres and organisations. A fully functional database assists the user in locating Haemophilia Centres and patient, doctor, nurses and physiotherapy organisations based in Europe;
6. Frequently asked questions section for queries relating to the EUHANET project as well as to bleeding disorders more specifically;
7. Links - contains links to the journals Blood, Haemophilia and Journal of Thrombosis and Haemostasis, and to an information site for very rare coagulation disorders.

Haemophilia Centre Locator (www.hclocator.org)

The EUHANET project has developed a search engine that can be accessed by all devices including

personal computers, tablets and mobile phones using any software. Once a user accesses www.hclocator.org they can enter any address or choose their current location. The site generates a map with the nearest five Haemophilia Centres. Clicking on the name of any of these centres will give information on location and phone numbers about how to get emergency care from the centre during normal working hours or in an emergency. Currently the system works only for Europe but it is intended to expand it so it covers Haemophilia Centres worldwide.

European Haemophilia Safety Surveillance (EUHASS)

The EUHASS project began on 1st October 2008 and currently 84 European Haemophilia Centres from 26 countries are participating. A report on the initial experience has been published[7]. The original EUHASS project has been extended and incorporated into the EUHANET in 2012. Prior to participation all centres have to obtain clearance from the Ethics Committee (Institutional Review Board) of their organisation. All adverse events are reported anonymously online either when they occur or within a maximum of three months. Every three months all centres have to actively sign off the quarter even if no events have occurred in their centre. The patients included in the surveillance are those with inherited deficiency of factors I, II, V, VII, VIII, IX, X, XI, XIII, von Willebrand disease, Glanzmann thrombasthenia, Bernard Soulier syndrome, platelet storage pool disease, acquired haemophilia and acquired von Willebrand disease.

The events reported are:

1. acute or allergic events;
2. transfusion transmitted infections;
3. inhibitors;
4. thromboses;
5. malignancies;
6. deaths;
7. unexpected poor efficacy;
8. any other possible adverse event.

For each of the above events limited details regarding the event such as the timing of the last clotting factor exposure and exposure days are also collected.

Annually the participating centres report the total number of patients registered at their centre, how many of these have severe disease and how many were treated with concentrate over the previous year. Furthermore the centres report how many patients received each specific concentrate and how many of these patients had severe disease. This information allows the determination of the rates of adverse events per 1,000 treatment years.

The rates of inhibitors in previously untreated patients is traditionally calculated by following a cohort of severely affected patients from first treatment to their 50th exposure day, but such studies take a long time to complete. EUHASS determines the inhibitor rate in previously untreated patients using a novel method which is based on number of patients reaching the 50th exposure day during a specific year[10].

Prospective rare diseases database

The evidence base for the bleeding disorders other than the haemophilias is weak due to the rarity of the disorders and the fact that most patients are to be found in countries without a strong background in research. A significant advance has been the collaboration of several Haemophilia Centres in the previously funded EAHC project led by Professor Flora Peyvandi to set up the Rare Bleeding Disorders Database (EN-RBD)[11]. This database obtained retrospective information on the non-haemophilic RBD. Data was collected on demographics, phenotype, genotype, bleeding manifestations, treatment and their complications. Personal identification data were not entered.

A problem with retrospectively collected data is bias and it would be desirable to collect prospective data. As part of the EUHANET project the EN-RBD database, now applied on a global scale (RBDD) has been revised to create the prospective RBDD (Pro-RBDD, http://eu.rbdd.org), so that prospective information can be collected. Initially this database is collecting data on patients with deficiencies of fibrinogen and factor XIII. Over the three years of the EUHANET project there will be 6 data entry points per patient. Subsequently, prospective data will be collected for all RBD and the data will be used to design clinical trials of treatment modalities. Central laboratory testing for clotting factor levels and genotyping as well as an external laboratory quality control is provided.

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Keywords: haemophilia, EUHANET, reference networks, European, certification.

Funding and conflict of interest

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References

1) Stonebraker JS, Bolton-Maggs PH, Soucie JM, et al. A study of variation in the reported haemophilia A prevalence around the world. Haemophilia 2010; **16**: 20-32.
2) Stonebraker JS, Bolton-Maggs PH, Soucie JM, et al. A study of variations in the reported haemophilia B prevalence around the world. Haemophilia 2012; **18**: e91-4.
3) Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013; **19**: e1-47.
4) O'Mahony B, Noone D, Giangrande PL, Prihodova L. Haemophilia care in Europe - a survey of 35 countries. Haemophilia 2013; **19**: e239-47.
5) Makris M, Preston FE, Rosendaal FR, et al. The natural history of chronic hepatitis C in haemophiliacs. British Journal of Haematology 1996; **94**: 746-52.
6) Weinstein M, Makris M, Ludlam CA. Biovigilance and pharmacovigilance for haemophilia. Haemophilia 2010; **16** (Suppl 5): 17-21.
7) Makris M, Calizzani G, Fischer K, et al. EUHASS: The European Haemophilia Safety Surveillance system. Thrombosis Research 2011; **127** (Suppl 2): S22-5.
8) EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States, 24 October 2011. Available at: http://www.EUCERD.eu/upload/file/EUCERDRecommenda-tionCE.pdf. Accessed on 09/01/2014.
9) International Meeting "Haemophilia Centre Certification Systems across Europe". Centro Nazionale Sangue. Available at: http://www.centronazionalesangue.it/newsbox/seminario-malattie-emorragiche-congenite-mec. Accessed on 09/01/2014.
10) Fischer K, Lewandowski D, Van den Berg MH, Janssen MP. Validity of assessing inhibitor development in haemophilia PUPs using registry data. Haemophilia 2012; **18**: e241-6.
11) Peyvandi F, Palla R, Menegatti M, et al. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. Journal of Thrombosis and Haemostasis 2012; **10**: 615-21.

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