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## **The current state of adverse event reporting in haemophilia**

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## **Abstract**

**Introduction:** Replacement of the missing clotting factor is the mainstay of haemophilia treatment. Whilst historically many haemophilia patients were infected with blood-borne viruses transmitted via plasma-derived products, nowadays the formation of alloantibodies against the missing clotting factor is the main adverse event of treatment.

**Areas covered:** This paper provides an overview of the current national and international adverse event reporting systems, what these surveillance schemes taught us about side effects of the products presently in use, and elaborates on how to adapt these systems to the challenges we face with the changing treatment landscape.

**Expert commentary:** Treatment of inherited bleeding disorders was accompanied by severe complications in the past, resulting in major morbidity and mortality. Current products are much safer, but still require monitoring via efficient safety surveillance systems. Adverse events are reported in national and international systems. With many new products entering the market, as well as non-factor replacement therapies, new safety issues may arise. It is important to identify potential adverse events early by making surveillance systems suitable to pick up unknown or unexpected effects, and to recognize and communicate patterns of adverse events rapidly.

**Keywords:** bleeding disorders, haemophilia, safety, surveillance, concentrate

## **1. Introduction**

Safety surveillance is important in identifying, evaluating and communicating treatment-related adverse events as early as possible. This is particularly important for a life-long disease like haemophilia, with a history of severe treatment-related complications.

Haemophilia is an inherited bleeding disorder, affecting around 400.000 individuals worldwide. The X-linked inheritance results in deficiency of clotting factor VIII (FVIII) in haemophilia A and of FIX in haemophilia B. Haemophilia represents the most well-known inherited bleeding disorder, a group of which also includes deficiency or defect of fibrinogen, FII, FV, FVII, FXI, FXIII, and von Willebrand factor, as well as platelet disorders. Lack of FVIII or FIX results in impaired thrombin generation and clot formation, which clinically translates into spontaneous or traumatic bleeding.

### *1.1 Clotting factor concentrates*

The mainstay of haemophilia treatment is the replacement of the deficient clotting factor. Initially, fresh frozen plasma was used, but later specific concentrates were produced from plasma pools, followed by the development of recombinant factors. The introduction of recombinant products in the early 1990s changed haemophilia management greatly with prophylactic treatment becoming the standard of care in patients with severe haemophilia (<1% clotting factor activity). This dramatically improved health outcomes and life-expectancy for haemophilia patients. Table 1 shows the currently available clotting factor concentrates. Treatment can be given ‘on demand’, i.e. at time of a bleed, or ‘prophylactic’ to prevent bleeding [1].

## **2. Treatment complications**

### *2.1 Viral transmission*

The unfortunate contamination of blood products in the past has left a heavy legacy of concerns about safety of treatment for haemophilia. Cryoprecipitate and plasma-derived concentrates introduced respectively in the 1960s and 1970s resulted in transmission of hepatitis C (HCV) and human immunodeficiency virus (HIV). Plasma-derived products, each batch of which was manufactured from pools of 20.000 to 30.000 blood donations, were associated with a 30% risk of HIV [2], and 46%-90% of HCV infection [3, 4, 5]. These infections can lead to major and significant complications: 20% of HCV infected patients develop cirrhosis, and progression to end-stage liver disease is accelerated by coinfection with HIV [6]. This had major impact on survival of haemophilia patients, especially before the introduction of effective antiretroviral therapies [2].

Viral inactivation steps for plasma-derived products [7], and the introduction of recombinant products (with third generation recombinant products being manufactured without the use of any animal or human plasma protein additives during the entire process) [8], have eliminated the risk of HIV and HCV transmission. On the other hand, concern remains for the possible transmission by plasma-derived products of parvovirus B19, Creutzfeldt-Jakob disease, hepatitis E, as well as for a number of new pathogens (West Nile, Zika, Dengue) and currently unknown agents [9].

## 2.2 Inhibitors

At present, the most important adverse event of haemophilia treatment is the development of alloantibodies, rapidly eliminating the infused exogenous factor, thus reducing or neutralizing the concentrate efficacy. This occurs in around 30% of patients with severe FVIII deficiency (highest risk within the initial 50 exposure days) and in about 3-4% of severe FIX deficiency patients [10]. In previously treated patients (PTPs) the incidence of inhibitor development is much lower (1-5 per 1000 patient/years) [11] (table 2). Once a patient develops a high-titer

inhibitor, the available treatment is with one of two bypassing agents (activated prothrombin complex concentrate (aPCC) and recombinant FVIIa (rFVIIa)) or with recombinant porcine FVIII.

The pathophysiology of inhibitor development and the different risk factors have been extensively studied [12, 13, 14, 15]. Several risk factors are identified in previously untreated patients (PUPs) (family history, gene defects, intensity of treatment), whilst for PTPs the risk factors for antibody development remain unknown [15].

The antigenic properties of different concentrates remain matter of investigation. Among PUPs, a number of observational retrospective/prospective studies and systematic reviews [16, 17, 18, 19] investigated the rate of inhibitor development in plasma-derived and recombinant products, generating conflicting results. Variables such as study design, study periods, therapeutic indications and other methodologic factors complicate the interpretation of the results. The most recent study in this field is SIPPET, a randomized controlled trial prospectively comparing plasma-derived and recombinant products, that reports a higher immunogenicity of recombinant products [14], opening a debate on the best treatment approach for PUPs.

Differences in the rate of inhibitor development among different generations of recombinant products constitutes another current debate. The RODIN study [18] showed a higher rate of inhibitor development in PUPs with severe haemophilia A treated with a specific second-generation product. This was also found in two other cohort studies [20, 21]. Analysis of data from the multicenter European Haemophilia Safety Surveillance (EUHASS) registry, after excluding overlapping data with the aforementioned studies [18, 20, 21], did not demonstrate differences in inhibitor development according to concentrate in PUPs [22, 23]. The Pharmacovigilance Risk Assessment Committee of the European Medicine Agency (EMA) performed a meta-analysis of the published studies and concluded that the currently available

evidence does not support the perceived increased risk of inhibitors associated with some specific recombinant FVIII products [24].

Although it had been suggested that in PTPs a B-domain deleted recombinant FVIII product was associated with a higher inhibitor risk [25], this was not confirmed in a subsequent meta-analysis [26].

There are many new treatments for haemophilia currently under development, and particularly non-factor replacement strategies could help in reducing the risk of inhibitor development, by eliminating the exposition to exogenous factor replacement.

### 2.3 Thrombogenicity

Although patients with inherited bleeding disorders suffer from bleeding, and evidence suggests that they are relatively protected from thrombosis [27, 28], both arterial and venous thromboses do occur, especially after abolishing the relative protection by replacing the deficient clotting factor. Data from a systematic review confirmed that the risk of thromboembolic adverse events is low, with an overall prevalence of 3.6 per 1000 patients [29]. Superficial thrombophlebitis accounted for 18 of the 20 reported thrombotic adverse events, but two major venous thromboembolic episodes occurred, both in patients with von Willebrand disease related to surgery. Risk factors for thrombosis were prolonged replacement in case of severe bleeding or major surgery, or co-existing risk factors (age, estrogen intake, obesity), and high peak FVIII levels. In patients with central venous access devices, the rate of thrombosis-related complications was 10.8% [29]. Administration of bypassing agents (aPCC, rFVIIa) in haemophilia patients with high-titer inhibitors is also considered as an important trigger for thrombosis [30, 31].

Although the risk of thrombotic adverse events after clotting factor administration is low, as the life expectancy of haemophilia patients and comorbidities increases the risk of thrombosis

is likely to raise accordingly in future [32]. Finally, as factor concentrate consumption grows over time, ongoing surveillance is essential.

#### 2.4 Allergic reactions and minor adverse events

Anaphylaxis after concentrate infusion is extremely rare, but minor allergic reactions represent the most common non-thrombotic, non-inhibitor adverse events associated with haemophilia treatment. A systematic review of all prospective registration studies in patients with haemophilia A identified only a single anaphylactic episode in the last 20 years [33]. The overall number of adverse events was 732, with 240 allergic reactions reported, including site-reactions, nausea, vomiting and headache. No difference between plasma-derived or recombinant products in terms of adverse event association was reported [33].

On the whole, the total rate of adverse events was calculated at 0.13%, confirming the high degree of safety of the products currently used for replacement therapy.

Specific for haemophilia B is the occurrence of allergic and anaphylactic reactions to FIX concentrate infusion occurring at time of inhibitor development [34]. The exact pathophysiologic mechanism is unclear, it occurs more frequently in patients with a large deletion in the FIX gene, but overall the incidence is low.

### **3. Current adverse event reporting in haemophilia**

#### 3.1 Adverse events during clinical trials

Adverse events, however minor, are formally reported during clinical trials used for registration purposes. Such studies are performed at good clinical practice (GCP) standard and the problem for the clinician is that so many events are reported that it is difficult to know which are the important ones. Once a drug is marketed the manufacturer has to perform post-marketing safety surveillance studies but these rarely involve more than 150 patients.



### 3.2 Generic national schemes

Many countries have generic schemes by which doctors, other health professionals and often patients can report adverse events for any medicinal product [9]. In the UK the scheme is known as the yellow form scheme, named after the color of the form used for submission of the adverse event information. The information initially provided is brief but the reporting individual subsequently receives a request asking for much more information that is often time consuming to complete. Often the enthusiasm for reporting to this scheme wanes once the first report has been submitted.

### 3.3 Specialized haemophilia national schemes

National schemes for reporting adverse events exist in the UK, France, Netherlands, Italy, Canada, USA and Australia [9]. These schemes vary in the detail of the information collected and the length of time they have been in existence. Although traditionally the regulatory authorities depended on clinical trials for adverse event reporting, there is a move that could result in registry data being accepted in the future [35].

The UK Haemophilia Centre Doctors Organisation (UKHCDO) scheme is the most developed and has been in existence for almost thirty years. The scheme is particularly strong in the reporting of inhibitors and deaths and has resulted in a number of high impact publications [2, 21, 36, 37, 38, 39]. The quality of the data is based on the fact that the UK has a good quality registry of all patients with inherited bleeding disorders and all their treatments that has been running since 1968. Clinicians in the UK report inhibitors, thromboses, malignancies, deaths as well as all treatments with concentrate.

In France, the FranceCoag network collects high quality data on inhibitor development in all patients with haemophilia [20]. The reported data are checked by auditors that visit the centers to confirm the accuracy of the information.

In the Netherlands, the KWARC system collects prospective adverse events, but no publications have so far been sought. Most Dutch haemophilia centers also participate in international adverse event reporting efforts such as RODIN and EUHASS.

Canada has adopted four years ago a system very similar to EUHASS, called CHES, which actually uses the same software infrastructure (CHES). The intention is to combine CHES and EUHASS data in the future, taking advantage of the similarities of their process.

In the USA the ATHN collaboration is collecting data on the treatment of patients with inherited bleeding disorders, including adverse events but so far nothing has been reported on the adverse event. Important publications from previous collaborative studies in the US coordinated from the Centre for Disease Control have been published [40, 41, 42].

### 3.4 Specific multicenter schemes

#### a) RODIN

The RODIN (Research Of Determinants of Inhibitor Development) study is being carried out by the PEDNET group. In the RODIN registry patients with haemophilia are registered at diagnosis and followed up to their 75<sup>th</sup> exposure day. The participating centers are mainly in Europe with some centers in Canada and Israel. Among the important publications from this study were a report suggesting that one second generation recombinant FVIII concentrate was associated with a higher rate of inhibitors [18, 43], and papers on the risk factors for inhibitor development in PUPs [44, 45]. In terms of adverse events the RODIN study collects data only on inhibitor development.

#### b) EUHASS

The European Haemophilia Safety Surveillance (EUHASS) was set up in 2008 to monitor adverse events in the treatment of inherited bleeding disorders in Europe. Currently 85 haemophilia centers from 26 European countries are participating. Events are reported as they occur or by three months at the latest, and centers have to confirm that they have not had any events, if this is the case. Annually each haemophilia center reports on the number of patients with the different types of bleeding disorders and also on the number of patients treated with each specific concentrate. All bleeding disorders and all concentrates are included in EUHASS [9, 46, 47]. Table 3 shows the type of events reported in EUHASS, and table 4 shows the events reported up to 10<sup>th</sup> October 2016.

#### **4. Future perspectives**

The haemophilia treatment landscape is evolving rapidly, with many new products entering the market or being well along in the pharmaceutical pipeline (see table 5). Whilst it is clear that these developments hold promise to answer currently unmet medical needs, information on their long-term safety is limited. It is unlikely that large trials comparing these products head-to-head will be performed and as such, data from well-designed and well-managed registries will be an important source to assess efficacy and safety of different treatment modalities in a real world setting [48].

##### **4.1 Potential new infectious agents**

The risk of transmission of infectious agents decreased drastically by improvements in the process of purification and viral inactivation of concentrates. Third-generation recombinant products are manufactured without human or animal proteins other than the required factor in the culture medium or final formulation [8]. However, non-enveloped viruses still represent a potential risk by resisting viral inactivation techniques as demonstrated by the continued

transmission of parvovirus B19 through plasma-derived factor concentrates [49]. Another emerging small non-enveloped virus is hepatitis E (HEV), with an IgG seroprevalence up to 30% in Irish male blood donors over 60 years [50]. RNA positivity was detected in 0.02-0.1% of blood donations tested, with the highest incidence in South Asian countries [50, 51, 52]. There are indications that viral inactivation procedures during fractionation are able to clear HEV [53]. Nevertheless, HEV is a small non-enveloped virus, which lends itself to some level of removal by nanofiltration.

Other potential threats are West Nile, Dengue, Ross River, Zika virus, and currently unknown agents [54], indicating the need for continued surveillance.

#### 4.2 Extended half-life products

A number of new treatment options are promising to introduce a new era for haemophilia care. In order to reduce the frequency of infusion, extended half-life products are becoming available with the first products currently licensed, and many others in the pipeline [55, 56]. Different technologies are used to prolong the circulation of recombinant factors, including fusion to recombinant albumin or to the Fc-region of human IgG, attachment of polyethylene glycol (PEG), polysialylated FVIII, and single chain FVIII. These products are equally efficacious in treating acute bleeds and show a good short-term safety [57]. Long-term safety of these modified molecules needs to be monitored, and uncertainty remains about the immunogenicity of these products. Theoretically, these modifications could diminish the immunogenicity via inducing B-cell anergy, tolerance, or masking immunogenic epitopes [58], but whether this outweighs the high immunogenic potential of FVIII in the long-term remains unanswered. For PEG, although assumed to be non-immunogenic, naturally-occurring antibodies are detected in up to 25% of healthy donors [59] and these antibodies may accelerate clearance and compromise therapeutic efficacy [60, 61].

PEGylation could also potentially lead to new issues, since PEG is a chemical compound that cannot be readily metabolized. It might lead to accumulation in the liver with unknown toxicological consequences. Whereas clinical trials with limited follow-up are reporting reassuring results, the lifelong nature of the disease and treatment makes it important to register and record outcomes longitudinally. The introduction of new molecules also introduces the risk of unknown side effects, which prompts to adapt the report systems to ensure that they will pick up these events.

#### 4.3 Alternative therapeutic strategies

A number of technologies attempt to improve hemostasis by mechanisms other than replacing the missing factor. A bispecific antibody specifically binding factor IX and X and mimicking the cofactor activity of FVIII (ACE910) has been produced and is injected subcutaneously [62]. Other approaches exploit the inhibition of natural anticoagulants [55, 63, 64], for instance via a monoclonal antibody (mAb) targeting tissue factor pathway inhibitor (TFPI) [65], a mAb blocking the interaction between FX and TFPI [66], or RNA interference therapeutic targeting antithrombin [67]. These technologies may prevent inhibitor development, and provide a mechanism for reducing or eliminating exposure to the deficient factor. In addition, reduction of dose frequency and subcutaneous administration of treatment may represent a real breakthrough in the routine management of haemophilia. However, inhibiting natural anticoagulants carries the risk of inducing a hypercoagulable state and therewith thrombosis, particularly during rescue treatment with FVIII or FIX. If and when these products are licensed, they will require specific safety monitoring.

#### 4.4 Gene therapy

Ultimately, gene therapy and gene editing have the potential of curing the disease. Small increases in factor activity levels are potentially sufficient to improve the disease phenotype and therefore have a significant clinical impact, especially for resource-limited countries. The first gene therapy studies were carried out in haemophilia B, as the FIX gene is considerably smaller than the FVIII gene. It remains a matter of debate as to what factor level to aim for prevention of joint bleeds without increasing the risk of thrombosis. Moreover, the duration of the therapeutic effect has to be awaited, with currently reported consistent increased levels at a follow-up of 4.5 years [68].

A new strategy to achieve higher sustained levels is the use of a naturally occurring gain-of-function mutated FIX gene (FIX-Padua) that has a ~8-fold greater FIX activity [69]. The first preliminary results in 4 patients showed an increase of FIX activity to 25-35% with a follow-up of 7-26 weeks [70]. Furthermore, a clinical trial is being planned in haemophilia B to investigate the possibility of gene editing by inserting an not mutated copy of the FIX gene into the hepatocytes using a zinc finger protein [71].

For haemophilia A, the first gene therapy study is currently running, with interim results demonstrating FVIII levels >15% in all patients treated with the high dose [72]. In 4 of these 7 patients, levels were >50% at the latest evaluation (7-23 weeks), which raises the concern of thrombogenicity.

Other potential risks of gene therapy are toxicity, inflammatory responses, hepatitis, and insertional mutagenesis. As the effects of a single infusion are potentially everlasting, it also raises the question what time of follow-up is sufficient to state that it is a safe therapy. For this treatment modality, special registries need to be designed as safety follow-up for at least a portion of the patients is likely to be lifelong.

#### 4.5 Registry design

At present, there is a large number of registries with different aims and designs. Registries often focus on different aspects of the disease or treatment and collect different types of data. Whereas it is clear that monitoring in registries is useful, the growing number of registries might come at the expense of overall data quality. Ideally, every patient should be in a registry with a specific patient identifier to avoid overlap and reduce double counting. To ensure consistency across participating sites and registries, data elements should be clearly defined, and changes in definitions over time need to be recorded. For the design of a registry, it is necessary to identify, in advance, potential adverse events and how and when they should be reported. The same holds true for new unexpected events. As most registries try to include as many data elements as possible, the workload increases, with the risk of high rates of discontinuation and missing data. By clearly defining the purpose of the registry and limiting the number of items that can be reported, the quality of the registry will improve and missing data decrease.

To improve quality during data collection, consistent registration over time and between participating sites should be reassured. Standardized training should be provided for all registry personnel. Systematic and frequent data registration is important to prevent recall bias, which requires dedicated (research) personnel and time. To improve outcome from registry data, it is important to consider this during the design phase and obtain sufficient financial support.

At last, a central body should be responsible for surveillance of data and registration, administration and interpretation of the provided data. Registries are of most value if they communicate findings via regular reports.

#### 4.6 Electronic medical records and diaries

Electronic medical records will play an increasingly important role as data source for registries. Structured data like ICD-10 diagnoses and laboratory results can already be collected

automatically. Data extraction of free text is more labor intensive, but new technologies like ‘natural language processing’ [73] may facilitate this, reducing workload and potential human errors.

Moreover, electronic patient diaries are used increasingly to record treatment and bleeds. With the introduction of hand-held devices, patients can record data anywhere, anytime. Although adherence to record keeping is still a problem, data from an electronic diary can more easily be verified and connected to registries.

#### 4.7 Rapid alert systems

An important task of registries is to recognize adverse effects of treatment and to act accordingly. It is important to recognize adverse effects rapidly, and to notify the community immediately if a severe or unexpected adverse event has been reported.

### 5. Expert commentary

Safety surveillance is an important issue in all diseases and treatments, but specifically in inherited bleeding disorders, as these patients were disproportionally affected by adverse events in the past. Inherited bleeding disorders are rare diseases, adverse events in their treatment even more rare, and the number of treatment modalities increasing. It is therefore important to collaborate in monitoring adverse events. Creating a network of treatment centers who collaborate in reporting adverse events has the advantage of recognizing adverse event patterns rapidly and notifying the community if any safety issue arise. To ascertain commitment to report long-term and completeness of data, a balance between quantity and quality in the number of parameters and registries must be found. Harmonization and transparency of registries is necessary to enhance its benefit for patients, health care providers and regulatory authorities.



## **6. Five-year view**

In the next few years interfacing registries with electronic medical records and electronic diaries will become more important. This will pose new issues in confidentiality, privacy, security, and data access.

With the introduction of new treatment modalities, especially non-replacement strategies and gene therapy, it is likely that new types of adverse events will occur. Registries need to be adapted to this challenge, to ensure that unknown side effects will be picked up. Post-marketing surveillance will serve as an important data source to compare efficacy and safety of the new treatment modalities. Long-term surveillance is imperative to warrant the safety of treatment in haemophilia, as the past has taught us that safety needs to be confirmed rather than assumed.

## **7. Key issues**

- The mainstay of haemophilia treatment is to prevent bleeding and its sequelae by replacement of the deficient clotting factor.
- In the past, major morbidity occurred due to transmission of viral infections by plasma-derived concentrates.
- At present, the most important adverse event in haemophilia treatment is the development of alloantibodies (inhibitors).
- Prospective adverse event reporting in (inter)national registries is essential to monitor treatment safety and efficacy in inherited bleeding disorders.
- In the future, surveillance systems need to be adapted to monitor the safety of new products such as long-acting agents, and new treatment-strategies including gene therapy.

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## Tables

**Table 1.** Currently available clotting factor concentrates

<b>Clotting factor</b>	<b>Plasma-derived concentrates</b>	<b>Recombinant concentrate</b>
Fibrinogen	Yes	No
II	Yes (as PCC)	No
VII	Yes	Yes
VIII	Yes	Yes
VIII – porcine	No	Yes
VIII-EHL	No	Yes (Fc fusion; PEGylated)
IX	Yes	Yes
IX-EHL	No	Yes (Fc fusion; albumin fusion)
X	Yes	No
XI	Yes	No
XIII	Yes	Yes
VWF	Yes	Yes

EHL, extended half-life; PCC, prothrombin complex concentrate; VWF, von Willebrand factor

**Table 2.** Risk of inhibitor development according to the number of exposure days (EDs)

<b>Exposition to factor concentrates</b>		<b>Risk of inhibitor development</b>
PUPs	Previously untreated patients: no previous exposure to factor concentrates	High risk – first 50 exposure days
MTPs	Minimally treated patients: < 3 – 5 exposure days *	
PTPs	Previously treated patients: > 50-150 exposure days *	Low risk – more than 50 exposure days

\* definition varies among studies

**Table 3.** Adverse events reported in the EUHASS scheme

Allergic and other acute events
Transfusion transmitted infections
Inhibitors
Thromboses
Malignancies
Deaths
Unexpected poor efficacy
Any other possible adverse events



**Table 4.** Adverse events reported to EUHASS by 10<sup>th</sup> October 2016

<b>Event type</b>	<b>Number reported</b>
Allergic and other acute events	153
Transfusion transmitted infections	0
Inhibitors – first occurrence	380
Inhibitors – recurrence	46
Thromboses	172
Malignancies	446
Deaths	746

**Table 5.** Therapies in development

<b>Therapy</b>	<b>Route of administration</b>	<b>Status of clinical trial</b>
Plasma-derived FV	Intravenous	In vitro
PEGylated FVIII	Intravenous	Phase 3
PEGylated FIX	Intravenous	Phase 3
Antibody against TFPI	Subcutaneous	Phase 1
siRNA against AT	Subcutaneous	Phase 1/2
Bispecific antibody against FIXa and FX	Subcutaneous	Phase 1/2
FVIII gene therapy	Intravenous	Phase 1/2
FIX gene therapy	Intravenous	Phase 1/2
FIX gene editing	Intravenous	Phase 1

AT, antithrombin; siRNA, silencing RNA; TFPI, tissue factor pathway inhibitor