Review

Beyond patient benefit: clinical development in hemophilia

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Historically in hemophilia, outcome measures have not been collected systematically. Hence, there are insufficient clearly defined, evidence-based measures that can be applied consistently across hemophilia trials. This review focuses on some key challenges to evaluating patient outcomes and performing trials identified by experts at the *Fourth* and *Fifth Zurich Haemophilia Forums*. As procedures appear inconsistent across Europe, guidelines require modification to be more appropriate and/or realistically achievable. The outcome measures utilized, and the timing of their collection, should also be standardized, and more objective measures used where feasible. Implementation of outcome measures could be refined through greater understanding of patient heterogeneity, and tailored to differentiate between hemophilia- and aging-related disease effects. Furthermore, robust outcome measures that can also inform health-economic decisions are increasingly needed. Lastly, as patient recruitment poses a challenge, the panel proposed a call for action to motivate physicians and patients to participate in clinical trials.

Keywords: Endpoints, Hemophilia, Inhibitors, Outcome measures, Health-related quality of life

Introduction

Although the hemophilia community is relatively well served, treatment is not yet optimal and different approaches are needed to address unmet needs and improve patient health-related quality of life (HRQoL), particularly in inhibitor patients.[1,2] Clinical research in Europe is, however, regulated by increasingly rigorous guidelines, including different requirements for adults and children, and performing clinical trials is challenging from the perspectives of physicians, their patients and the pharmaceutical industry.

Regulatory requirements comprise a multistage, clinical trials process, each step of which needs information on a large number of outcome measures. However, many of these measures are not clearly defined, standardized and/or feasible to achieve in hemophilia. Furthermore, different patient/bleed characteristics may influence whether an outcome measure is applicable to individual patients. Thus, consensus definitions and validated assessment tools for outcome measures in hemophilia clinical research are urgently needed.

These issues were discussed by hemophilia experts at the *Fourth* and *Fifth Zurich Haemophilia Forums* (2009 and 2010). This review reflects the personal opinions and consensus views of participants in these forums, which aimed to outline key challenges in evaluating patient-outcome measures in hemophilia and identify areas that need to be re-evaluated and/or revised to make them more applicable to clinical research.

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Current challenges of performing clinical trials in hemophilia

The panel agreed that meeting European Medicines Agency (EMA) requirements for outcome measures in hemophilia trials at pre-authorization and post-marketing is difficult. Some aspects of the guidelines may be inappropriate and/or not realistically attainable (Table 1). General challenges identified included the complexity of trial protocols, lack of guidelines for developing products in inhibitor patients and, most notably, that key outcome parameters (e.g. bleeds, re-bleeds) are poorly defined. In addition, procedures are not standardized across Europe, and EMA and US Food and Drug Administration requirements differ, so the same trial cannot easily be run in different countries.

Another important issue raised was that participation in clinical trials is time consuming for patients, their carers and physicians. Many trials have a long duration. Thus, the disruption to ongoing therapy of previously treated patients to enable them to participate in a trial often presents a dilemma for all parties. Physicians rightly prioritize enrollment of their patients to trials that are most likely to benefit the individual patient and offer potential advances to clinical practice. However, interruption to a patient's lifestyle through trial participation counters the drive in some countries to keep hemophilia patients in school or work, and reimbursement for travel expenses and time spent travelling to hemophilia centers is not always possible. The burden on physicians' time was a key obstacle to panel members' participation in clinical trials, with concurrent involvement in more than one trial being difficult in addition to their other commitments.

Furthermore, the number of patients with hemophilia (particularly inhibitor patients) is limited. Recruitment is therefore challenging for trials of new therapeutic innovations that may directly benefit patients, but is especially difficult for trials of step innovations or biosimilar therapies, although these may appeal to patients and reduce product costs, respectively. These trials are often needed before trials of more innovative treatments can be undertaken. To increase recruitment, many pharmaceutical companies will be forced to perform trials in developing countries where patients/parents may be in a situation of dependence, presenting an ethical issue. In addition, the panel commented that participation in trials is sometimes used to save money as the product is free; this drives recruitment in times when money is tight, but can enhance recruitment for the wrong reasons at an ethical level. The panel proposed a call for action to revitalize physicians' and patients' enthusiasm to participate in clinical trials (Table 2).

Implementing ICH Good Clinical Practice Guidelines[3] can therefore be difficult, but must be followed in all trials. There was broad agreement among the panel that the guidelines should be revisited and, where possible, revised to make them more workable in hemophilia without compromising patient safety. Practical, scientific discussions are needed to determine the best outcomes for trials in the 'real world,' with clear, frequent communication between investigators and industrial sponsors.

Table 1 Examples of challenging aspects of EMA guidelines for clinical trials in pediatric patients with hemophilia

Study	Patients	Challenge
Pre-authorization	PTP	• Clinical trials of pharmacokinetics, safety, clinical efficacy and immunogenicity required • Difficult to perform due to inclusion of two age cohorts of children • Pediatric PTPs are very difficult to recruit as participation in trials disrupts ongoing therapy, and exposes patients to new risk profiles. Clear potential benefits of new agents are therefore needed
Pre-authorization	PUP	• Clinical efficacy, immunogenicity and safety trials of 50 pediatric PUPs for >50 exposure days required • Generally easier to recruit pediatric PUPs than PTPs, but still difficult to recruit the number of PUPs needed
Post-marketing	PTP	• Clinical efficacy, immunogenicity and safety assessment are problematic as 200 PTPs are required – Many post-marketing trials compete for limited number of patients – Investigators generally prefer to participate in trials of new drugs rather than post-marketing studies, or trials of biosimilar agents or confirmatory trials

EMA, European Medicines Agency; PTP, previously treated patient; QoL, quality of life; PUP, previously untreated patient.

Table 2 Suggested ways to motivate physicians and patients in order to increase patient recruitment in clinical trials

- Build closer relationships between well-respected pharmaceutical companies and investigators to better understand and meet the needs of physicians and their patients, and to provide investigators with more information on clinical trial programs
- Generate attractive pipelines of products with clear potential benefits for hemophilia patients
- Develop less complex trial protocols, which are more feasible and less time consuming to perform
- Improve trial-site management
- Provide training for trial participants (physicians, study nurses) to help study centers to perform trials more easily and effectively
- Harmonize EMA and FDA regulatory requirements so the same study can be run in more countries to maximize the potential for recruitment, and thus speed up trial progression, and perhaps reduce the burden per physician/center

EMA, European Medicines Agency; FDA, US Food and Drug Administration.

Evaluating patient outcomes: what kind of data are needed for reliable clinical outcome measures in hemophilia trials?

Although many outcome measures are available, the panel thought that clinical research is hampered by the paucity of clearly defined, precise, evidence-based and objective measures that can be applied consistently across hemophilia trials.

Assessment of efficacy currently uses surrogate measures, but these are often not objective or commonly accepted for evaluating hemostasis. Pharmacokinetic data are accepted as surrogate measures of efficacy for agents with a therapeutic action based on the principle of 'replacement therapy'. However, no surrogate efficacy measures are available for bypassing agents that have an action based on pharmacologic activity in hemostasis.

Definitions of individual efficacy measures vary markedly depending on the product, study center, project and its objectives,[4] and clearer guidance is needed on their use in EMA-regulated trials (Table 3). Commonly used short-term efficacy outcome measures include joint bleeds or the total number of bleeds, for which the types of bleeds to include is not always apparent (or consistent between trials). Patients therefore interpret and record their bleeds differently. It should also be clarified who should determine the type of bleed – the patient or physician – and whether a clinical examination is required, and if so, by which method. The panel agreed that it is difficult to determine when a joint bleed has occurred in an inhibitor patient who has experienced multiple joint bleeds and may have chronic synovitis, as pain may be due to a joint bleed or synovitis. As such, unambiguous definitions of a joint bleed are needed for inhibitor patients. There was also some debate on definitions of a re-bleed versus a new bleed, and the need to differentiate between the two, particularly in chronic arthropathy. Clarification of life-threatening bleeds is also required, including definitions of blood loss or the need for transfusion.

The panel also concluded that defining when a bleed has stopped is difficult, and it is critical who defines the number of infusions needed to stop bleeding. For trials of recombinant activated Factor VII (FVII), it is mainly decided by patients at home, which increases the inter-patient variability of the outcome. The number of treatments used may also depend on factor availability in the country.

Table 3 Commonly used efficacy outcome measures identified by the panel as areas needing clearer guidance for use when EMA guidelines are applied

Efficacy measure	Comments
Bleeding	• Identification of a bleeding episode is subjective • Symptoms vary according to the type of bleed • Onset and relief of symptoms are used to indirectly assess bleeding • It is often unclear whether diagnosis is by the patient or physician, and which methodology is used • Cessation of bleeding is difficult to observe, describe and quantify in a standardized way
Re-bleeding	• Results of individual trials are difficult to compare: – Inter-trial differences in the definition of re-bleeding – Confounding effects due to the use of concomitant hemostatic measures and medication
Pain	• Indicator of active bleeding evaluated by pain scales as part of global evaluation and QoL assessments • Descriptions of pain differ for children and adults • Reporting of pain is subjective, especially in children • Difficult to know if pain is due to bleed or synovitis • High inter- and intra-patient variability in pain perception in relation to the need for additional hemostatic agents can make it an unreliable surrogate outcome measure for hemostasis • Other conditions also cause pain in older patients, and thus compromise evaluation of hemophilia-specific pain
Mobility and circumference of joint	• Joint circumference and joint range of motion are not clinically sensitive or specific surrogate outcome measures for hemostasis • High inter- and intra-patient variability • Objectivity may be improved by educating patients on the use of this outcome measure at specific time points
Magnetic resonance imaging or radiographic assessments	• Assessment of the impact on these parameters requires very long studies, which is not suited to the development of new agents • Expensive in terms of the relative costs of performing the investigations and time costs
Need for additional hemostatic medication	• Dependent on the choice and behavior of the patient and physician, and is thus inherently subjective
Combined evaluation scales	• Not widely accepted, e.g. the FDA has expressed opposition to composite outcome measures
Global evaluation/3- or 4-point scale	• Judgment remains subjective • Definitions differ between trials • Global evaluations are often performed at non-standardized time intervals • May be of interest as a secondary outcome measure, but not a key outcome measure

EMA, European Medicines Agency; QoL, quality of life; FDA, US Food and Drug Administration.

Further direction in clinical trials is needed on the definitions and timing of clinical assessments by the physician and patient (short-term outcomes), including consensus recommendations on the timing and most appropriate methods of pain assessment.

Among the long-term efficacy outcome measures, results for the number of days lost from school/work are limited by their dependence on social attitudes and country-specific regulations. Although the panel considered days in hospital to be a better outcome measure, its applicability varies depending on the healthcare system and hospital location. The following outcomes were viewed to be more objective, depending on which joints are examined and the equipment available: Haemophilia Joint Health Score 2.0[5,6] (valid for children 4–18 years of age, but not yet validated for adults with established joint disease); magnetic resonance imaging (Compatible score, Denver progressive, European additive);[5,7] X-ray (Pettersson additive, Arnold-Hilgartner progressive);[5,7–9] Haemophilia Activities List;[10,11] Functional Independence Score in Haemophilia;[12,13] and HRQoL measures (for children: Hemo-QoL, CHO-KLAT, QUAL HEMO; for adults: Hem-A-QoL, Hemo-QoL-A, QUAL HEMO, A36 Hemofilia-QoL, HemoLatin-QoL).[14]

Measurement of HRQoL was considered essential to fully understand the success of particular treatments/interventions in the patient's terms, and to compare interventions for the same disease. Because HRQoL is a subjective assessment of the impact of disease and treatment,[15] it needs to be measured directly by the patient (or carer for young children) using the appropriate HRQoL instrument. Nowadays, several hemophilia-specific HRQoL measures are available (see above),[14,16] which have greater sensitivity for detecting differences in HRQoL of hemophilia patients than generic questionnaires (e.g. SF 36, EQ-5D).

Overall, it was concluded that definitions of many outcome indicators need to be less ambiguous in terms of what is being measured, the methodology being used and the timing of the measurements. Clinically relevant, validated robust markers/outcome measures that are widely agreed upon for comparing the efficacy and safety of different hemostatic agents in different trials are needed to provide more standardized, reliable and objective assessments and, hence, more meaningful clinical data. Consensus documents are required that can be adopted by regulatory authorities. The panel also advised that it is imperative to give patients clearer guidance on outcome measures as currently many assessments are subjective and performed at home.

Heterogeneity in bleeding characteristics and responsiveness to treatment: Are different trial designs/outcome measures needed?

There was general consensus that one of the obstacles to defining outcome measures for uniform use in clinical trials is the marked heterogeneity in patient characteristics and unpredictability in bleeding tendencies, including responsiveness to treatment.

The timing of bleed onset varies according to the severity of haemophilia/type of bleed, increasing from a median age of 1 (0.5–2.0) year for the first bleed in severe hemophilia to 6.5 (3.8–18.2) years for mild hemophilia.[17] Mild hemophilia can, however, be diagnosed at any time throughout life, usually occurring in relation to trauma or surgery. Bleeding in children is mostly due to trauma, venipuncture or it develops in the joints, commonly when a child starts to walk. In contrast, the timing of bleed onset in adults is more complicated, suggesting to the panel that different trial designs may be needed for children and adults.

Current outcome measures for bleeding tendency include measuring concentrations of Factor VIII or IX (FVIII/FIX). However, FVIII/FIX concentration does not always accurately predict bleeding: some patients on prophylaxis with trough levels $<1\%$ do not bleed, whereas others bleed despite trough levels $>3\%$.[18] Thus, more guidance is needed on appropriate trough levels to use in clinical practice and trials, perhaps encompassing recent findings showing an association between bleeding risk during FVIII prophylaxis and length of time per week with FVIII <1 IU dL^{-1}.[19] The definitions may need to be revised for factors with prolonged half-lives. Theoretically, bleeding frequency in hemophilia should be correlated to a 'global parameter of coagulation', but recent studies suggest that activated protein C is not well correlated with bleeding type.[20] The thrombin generation assay may provide a more objective measure of bleeding tendency.[21]

In the panel's opinion, more sensitive/accurate outcome measures are needed to detect subclinical hemarthrosis for more precise evaluation of bleeding frequencies. Currently, minimal joint bleeds, especially in children, can escape clinical detection,[22,23] but knowledge of their presence would modify approaches to prophylaxis.

A greater understanding of the factors underpinning the variation in bleeding tendencies and responsiveness to treatment could help guide the use of more appropriate outcome measures, as well as provide markers for predicting difficult-to-treat patients. The large heterogeneity of phenotypes in severe hemophilia, including inhibitor development, appears multi-factorial in origin, comprising genetic as well as non-genetic influences, such as coagulation,

inflammatory, angiogenetic and environmental factors (Table 4).[24,25]

Genetic factors (e.g. type of FVIII and FIX mutation) are major determinants of phenotype in patients with severe hemophilia, with some mutations producing very small (non-measurable) levels of factor that may affect bleeding tendency. This may be important for designing clinical trials because detection of the type of FVIII and FIX mutation may point to a need for earlier prophylaxis. Larger studies are needed to assess this possibility. Genetic determinants of inhibitor development include FVIII mutations, the presence of inhibitors in other family members and ethnic background.[26,27] In addition, co-inheritance of thrombophilia risk factors, including Factor V Leiden or prothrombin mutation PT20210A, may influence the phenotypic expression of hemophilia (bleeding onset, frequency, arthropathy).[28–31]

Although the presence of the disease modifiers, such as Factor V Leiden or prothrombin mutation PT20210A, could potentially impact on the efficacy and safety of treatments, exclusion of these patients from clinical trial protocols was not considered necessary by the panel as this could introduce bias and also lead to exclusion of patients with other contributing factors. Determining the bleeding tendency in these patients before prophylaxis might be more informative than testing for a mutation.

A further possibility hypothesized during the forum was whether hemophilia patients exhibit diurnal variations in bleeding tendencies, and if so, whether this might contribute to variations in responsiveness to treatment. Clinical trial data in inhibitor patients showed differences in bleeding patterns across the day, which were markedly altered during secondary prophylaxis with recombinant activated FVII.[32] The panel was not aware of any publications in hemophilia specifically looking at circadian/diurnal rhythms in blood coagulation factors and the timing of bleeds relative to treatment. However, data in non-hemophilia patients[33–36] indicate that this topic may merit investigation as it could provide further insight into the effectiveness of dosing at different times of day. This, in turn, may perhaps lead to increased stringency concerning the timing of factor administration in clinical trial protocols.

Large-scale studies should investigate further the factors that contribute to the wide heterogeneity of phenotypes in hemophilia. The panel also advocated the need for additional data and outcome measures that can predict bleeding tendency in individual patients. It is also critical to distinguish phenotypes and identify patients with mild disease so that young children do not receive incorrect treatment regimens.

Approaches to meet future challenges

As new challenges in the management of hemophilia continue to emerge, the panel emphasized that clinical trial designs and the use of outcome measures will also need to evolve so that new therapies and clinical scenarios can be evaluated to meet guideline requirements.

Designing clinical trials for new products

It was suggested that existing surrogate efficacy outcome measures may not be acceptable for newer products with different mechanisms of action, such as PEGylated therapies with prolonged half-lives. Defining new, relevant outcome measures is difficult, but will nevertheless be required for determining the efficacy and safety of new therapies.

Meeting the growing need for health-economics outcome measures

The panel agreed that there is an increasing need for reliable outcome measures (including HRQoL) to inform health-economic decisions as current health-economic outcome measures are poorly defined and

Table 4 Potential non-genetic influences contributing to the variability in bleeding tendency, and thus to difficulties in evaluating responsiveness to treatment

Potential influence	Comments
Presence of undetected inhibitors	• Occurs particularly in patients not treated at specialist centers
Use of incorrect dosing schedules	• For example, the need for different doses of recombinant activated FVII in children due to different pharmacokinetic profiles versus adults, incorrect post-surgical maintenance doses, use of continuous infusion
Nature of the patient	• For example, activity levels: – A very active child will have a greater chance of early bleeds than a quieter child – Some adults with hemophilia now have more active lifestyles, and may thus have a higher bleeding tendency than in the past – In contrast, the population of elderly – and potentially more sedentary – patients with hemophilia is increasing
Joint structure	• Differences in joint tissues/reaction between individuals in the tendency to develop arthropathy • Once changes are present, the clinical course of arthropathy is usually progressive and irreversible, so prompt treatment of the first hemarthrosis is paramount
Low factor concentration	• Time spent below the trough factor level during prophylaxis and secondary prophylaxis in adults with severe hemophilia

FVII, Factor VII.

highly variable, depending on the measure used (Table 5). They are also not truly comparable, and hence, not sufficiently robust to enable commissioners and treaters to compare centers or providers if, as is currently the case, each center chooses its own measures.

It is, however, difficult to develop an outcomes model in hemophilia for commissioning purposes and health-economic assessments. Nevertheless, funding by health authorities/budget holders will probably become more dependent on agreed health-economic clinical outcomes that provide evidence of the benefits of new therapies for setting cost-effectiveness values against existing therapies. It should be noted that health-economic data will indicate a current state, but not inform how to reduce costs or improve quality of care, nor can they mirror some important aspects of treatment, such as recombinant safety.

Consensus is needed among physicians, payers and the pharmaceutical industry on a practical set of outcomes that are robust, reliable and easy to measure in both trial and non-trial settings, and directly evaluable for health-economic planning. Research and clinical service outcome measures need to be the same, or at least compatible. A nationally, and ideally internationally, agreed set of outcomes could be drawn up by working groups.

Evaluating treatments in an aging hemophilia population

Advances in hemophilia management have increased life expectancy, leading to new challenges in assessing treatments as more patients develop concomitant age-related disorders, such as malignancy, atherosclerosis, musculoskeletal disorders and ischemic heart disease.[37,38] In addition, it is recognized that age affects HRQoL; as age increases, HRQoL decreases. Separating the effects of the normal aging process from the effects of disease progression or concomitant disorders is necessary, e.g. for evaluating hemophilia-related pain. Bleeding frequencies should be determined across a wider range of patient ages, and outcome measures for bleeding/re-bleeding adjusted accordingly for age.

Decreasing patient psychological barriers to treatment

Another aspect that the panel felt warranted further consideration, now that hemostasis can be better controlled, is an understanding of the psychological reasons that prevent hemophilia patients, and their carers, from maximizing the potential benefits of prophylaxis and treatment. For example, rapid treatment improves clinical outcome,[39–41] but in a study of 459 hemophilia patients/parents, 49% reported that bleeds were not treated early.[42] A recent study of 413 non-inhibitor patients found that 13% of patients (mostly mild hemophilia) never treated a hemorrhage and 48% waited to see if bleeding occurred before treating.[43]

So, what hinders patients from treating immediately or seeking treatment from a doctor/hospital? Key factors appear to be low compliance and adherence to treatment. As the benefits and efficacy of treatment rely on optimal compliance with therapy, patients' lack of adherence to hemophilia treatment becomes relevant.[44] VERITAS-Pro, a new measure of adherence to prophylaxis, showed that only 86.7% of recommended infusions were administered as prescribed and 61% taken at the recommended time.[45] Factors associated with the lack of adherence in hemophilia (Table 6) have recently been described.[43,44] Strategies for overcoming these perceived psychological barriers to treatment require further investigation using standardized methods to evaluate their effectiveness. More could then be done to help patients (and their carers) to manage their disease more positively.

Patient registries, post-marketing surveillance and retrospective analyses of case studies are becoming an increasingly useful source of clinically relevant data in hemophilia. It should, however, be noted that to be of value, patient registries and post-marketing

Table 5 Evaluation of some health-economics outcome measures for assessing the use of Factor VIII (FVIII) in hemophilia patients in relation to commissioning and financing clinical services

Outcome measure	Conclusions
Bleeding	• Definitions are subjective, based on intuitive definitions and vary markedly across hemophilia treatment centers
Joint scores	• Prospective, long-term outcomes, not the short-term outcomes, needed for year-on-year financial planning
Gait/motion analysis	• Potentially more robust, recordable and scoreable outcomes
Magnetic resonance imaging	• Expensive and reflect longer-term outcomes
Days off school	• Data relatively easy to collect
Days off work	• Data difficult to collect and confounded by absences from work for reasons unrelated to hemophilia • Not applicable to retired or unemployed patients • May suffer from geographic variability due to economic variability in different regions
Quality-adjusted/disability-adjusted life years	• Considerable variation in methodologies used • Can only be used to compare health technologies

Table 6 Examples of factors preventing patient adherence from studies in Scandinavia and Spain[43,44]

• Poor knowledge about the disease:
– A bleed may not be considered important
– There is often poor recognition of the early symptoms of a hemophilia-related bleed and/or its severity
• Fear of:
– Inhibitor development
– Virus transmission by factor concentrate
– Stigma associated with self-treatment of an inheritable disease in some cultures
• Difficulties with treatment:
– Problems accessing the health center/hospital for treatment
– Lack of skills with self-treatment/self-care
– Discomfort with injections (pain, conditioned anxiety reactions)
• Interruption to daily life:
– Difficulties for parents in balancing prophylactic treatment with other social and family needs
– Time commitment involved in prophylaxis
• Severity of the disease:
– Significantly more difficulties are experienced by patients with mild or moderate hemophilia than with severe hemophilia
• Economic factors:
– Some patients who develop arthropathy receive economic compensation

surveillance need to comprise standardized, well-defined and, ideally, objective outcomes measures.

Conclusion

In order to provide new therapeutic options, consensus is needed among researchers, physicians and payers on how to measure clinical efficacy, safety and health-economic outcomes, and standards are needed on what is considered a success. Guidelines for clinical trials in hemophilia may need to be modified to make them more achievable.

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