



Journal of The Ferrata Storti Foundation

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Haematologica 2020 [Epub ahead of print]

Citation: Flora Peyvandi, Karin Berger, Rainer Seitz, Anneliese Hilger, Marie-Laure Hecquet, Michael Wierer, Karl-Heinz Buchheit, Brian O'Mahony, Amanda Bok, Mike Makris, Ulrich Mansmann, Wolfgang Schramm, and Pier Mannuccio Mannucci. Kreuth V initiative: European consensus proposals for treatment of haemophilia using standard products, extended half-life coagulation factor concentrates and non-replacement therapies.

Haematologica. 2020; 105:xxx

doi:10.3324/haematol.2019.242735

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Kreuth V initiative: European consensus proposals for treatment of haemophilia using standard products, extended half-life coagulation factor concentrates and non-replacement therapies

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Abstract

This report contains the updated consensus recommendations for optimal haemophilia care produced in 2019 by three Working Groups (WG) on behalf of European Directorate for Quality of Medicines & Healthcare in the frame of the Kreuth V Initiative.

WG1 recommended the access to prophylaxis for all patients, the attainment of plasma factor trough levels of at least 3-5% when extended half-life FVIII and FIX products are used, treatment regimen personalisation and choice of chromogenic assays for treatment monitoring. It was also emphasized that innovative therapies should be supervised by Haemophilia Comprehensive Care Centres.

WG2 recommended mandatory postmarketing data collection to assure the long-term safety and efficacy of new haemophilia therapies, the establishment with adequate support under public control of national patient registries including the core data recommended by EMA and ISTH, and more collaboration to facilitate comprehensive data evaluation in Europe.

WG3 discussed methodological aspects of haemophilia care in the context of access decisions particularly for innovative therapies, and recommended that clinical studies should be designed to provide the best possible evidence needed by regulatory authorities, HTA bodies and healthcare providers. The dialogue between all stakeholders in haemophilia care and patient organizations should be fostered to implement these recommendations.

Introduction

The Wildbad Kreuth Initiative started in 1999 with a seminar including experts from 15 European Community member states, which was followed in the next few years by a series of four meetings. Treatment of haemophilia has always been the focus of the initiative, given the increasing number of diagnosed patients and the importance of providing them with optimal therapies. Goals of the Initiative were to evaluate the state of haemophilia therapy, identify areas with need of further studies and provide updated recommendations for optimal use of blood products for patient treatment. The first Kreuth meeting also dealt with the optimal use of the available products in haemophilia therapy, emphasising that the main priority was the safety of blood and blood products and furthermore the need to guarantee an effective treatment, ensuring that all people with coagulation disorders can benefit from these lifesaving therapies.¹

The following Kreuth meetings were periodically convened under the joint auspices of the Ludwig-Maximilian University of Munich (LMU), the Paul Ehrlich Institute (PEI) and the Council of Europe through its European Directorate for the Quality of Medicines & Healthcare (EDQM), under the aegis of the European Committee on Blood Transfusion (CD-P-TS). The latter institution provides resolutions that are non-binding but yet are strong indications for member states. The second Kreuth meeting in 2009 was attended by 110 transfusion medicine experts, haemophilia clinicians and regulatory authority representatives from 38 countries. New recommendations were provided regarding the best clinical practice on haemophilia, home treatment, genetic counselling and equal treatment across European member states.²

The following two meetings in 2013 and 2016 focused on the optimal use of coagulation factors and provided the opportunity to review trends in the use of factor concentrates.^{3,4} A total of 12 recommendations were made in 2016, dealing with national protocols or guidelines for the management of ageing patients with haemophilia; the minimum utilization of FVIII and FIX concentrates in each country; treatment for hepatitis C with direct-acting antiviral agents; genotype analysis for all patients with severe haemophilia; access to bypassing agents and immune tolerance

for those with inhibitors; individualisation of treatment regimens with extended half-life products and the attainment of the highest possible rate of bleeding prevention by increasing the trough plasma factor levels. The recommendations emerging from the 2013 and 2016 Kreuth meetings were subsequently incorporated by the EDQM into proposals for resolutions adopted by the Committee of Ministers of the Council of Europe, with the goals to increase their visibility and provide official weight. The 2017 Resolution [Resolution CM/Res(2017)43 on principles concerning haemophilia therapies]⁵ listed 17 principles.

The 2019 meeting was the most recent opportunity for the official delegates nominated by 26 Council of Europe members and observer states - along with members from the academia, the European Haemophilia Consortium (EHC) and the European Medicines Agency (EMA) - to review trends in the use of standard half-life coagulation factor concentrates but also of the new extended half-life products and non-replacement therapies.

Methodology

During the “Wildbad Kreuth Initiative V – Optimal Treatment of Haemophilia symposium” in June 2019 clinicians, regulators and patient organisations from 26 European countries were involved.

The participants are experts invited by the Scientific Programme Committee as well as delegates appointed by the Council of Europe (CoE) Member States upon invitation by the EDQM, plus delegates from the patient organizations European Haemophilia Consortium (EHC) and World Federation of Hemophilia (WFH) and the European Medicines Agency (EMA). Several of the participating experts are active members of the European Association for Haemophilia and Allied Disorders (EAHAD) or other scientific societies. Industry representatives had the opportunity to participate in the open sessions, but were excluded from the discussion and formulation of the recommendations.

The topics of the symposium were defined by the Scientific Committee on the basis of the results and recommendations of the previous symposia and the latest developments in the field of therapies for haemophilia. Subsequently, in the open plenary sessions, the invited experts presented an overview of the current state-of-the-art on haemophilia therapy in Europe and treatment progress on the topics predefined by the Scientific Committee. It was important that the chosen delegates (see above under 2) had not only a good scientific background but also knowledge about the peculiar situation of haemophilia treatment in their own countries, which was crucial to elaborate the recommendations to be addressed to the Health Authorities of the CoE Member States.

The experts met in three different working groups to discuss and develop the new recommendations. Each working group was responsible for one of the following areas of discussion:

- Clinical evaluation of haemophilia therapy;
- Data collection for haemophilia therapy;
- Methodological aspects of haemophilia therapy.

An interim report was prepared by each working group, and then discussed with the general assembly and when full and unanimous consensus was obtained a report was presented for final approval. Based on the final report, this manuscript was prepared and circulated among all participants of the three working groups. Literature research was based on articles published in peer reviewed journals. Medline and PubMed were also searched for all articles published in English language in the last 10 years. Furthermore, data was extracted from the abstracts of the more recent International Congresses.

Recommendation 1

Prophylactic treatment should be available to all haemophilia patients, with or without inhibitors, and access to physiotherapy should be provided.

Prophylaxis in haemophilia is considered the standard of care to prevent joint bleeding and related arthropathy, with the objective to preserve a normal musculoskeletal function. Manco-Johnson established the superiority of prophylactic versus on-demand therapy in a randomized clinical trial in 2007.⁶ Primary prophylaxis in haemophilia should start at a very young age (≤ 2 years) before joint disease develops and usually warrants coagulation factor infusions 2–3 times per week, whereas secondary prophylaxis begins after the onset of joint disease.⁷ There are many prophylactic schedules, although the optimum dosing regimen remains to be defined. Prophylaxis with standard half-life coagulation factors products is usually given at a dose of 25–40 IU/kg 2–3 times per week,^{7,8} whereas with the extended half-life products prophylaxis regimens with intervals from 3 up to 5 days in haemophilia A and once every 7–14 days in haemophilia B can be effectively implemented.^{9–11}

Currently, the availability of a non-replacement therapy administered subcutaneously such as emicizumab makes prophylaxis accessible to all patients with haemophilia A, including those with FVIII inhibitors, and this may help to reduce bleeding events as well as to improve quality of life.^{12,13}

For the optimal care of haemophilia the multidisciplinary team of specialists should include physiotherapists. Their involvement should begin at the time of diagnosis and deal with the functional recovery after each musculoskeletal bleeding, but also involves a rehabilitation program tailored to tackle all the problems related to a chronic condition such as hemophilia.¹⁴

Recommendation 2

With increased treatment options, appropriate instruments should be developed to personalise treatment regimens for all patients with haemophilia A and B.

The aim of prophylaxis is to minimize or abolish bleeding events and thus improve quality of life in patients. Prophylaxis regimens with standard and extended half-life products have been shown to be

effective at preserving joint function and preventing bleeding episodes, although a significant variability was seen among individuals exposed to the same treatment regimen.¹⁵ Inter- and intra-individual variability in coagulation factor pharmacokinetics (PK) is thought to be the main determinant of uncertainty in the standardization of prophylaxis regimens. Appropriate tools must be developed to personalise treatment regimens, taking into account each patient's individual lifestyle and pharmacokinetic profile.¹⁶ The individualization of prophylaxis is the optimal strategy that could improve patients' quality of life with the ambitious goal of zero bleeding in the next future.

Recommendation 3

With extended half-life therapies, a minimum trough level of 3-5% should be achieved to preserve joint status.

Patients with severe haemophilia suffer from repeated and prolonged spontaneous bleeding episodes, mainly in muscles and joints, that result in disabling musculoskeletal damage and chronic arthropathy. The aim of prophylaxis in haemophilia is the reduction of the risk of bleeding in order to preserve a normal musculoskeletal function. Prophylaxis dosing regimens using standard half-life FVIII and FIX products can obtain trough plasma levels of 1-2%,¹⁷ but the introduction of extended half-life products significantly improves efficacy by achieving higher trough levels. A further improvement due to the forthcoming second-generation extended half-life products and gene therapies might lead to a further increase in the achievement of almost lower limits of normal factor levels. At the time being, with the opportunity provided by the availability of extended half-life products, a minimum trough level of 3-5% should be aimed in order to preserve joint function.

Recommendation 4

For the post infusion measurement of extended half-life products chromogenic assays should be used.

Haemophilia patients must be monitored by laboratory testing in order to assess the optimal plasma factor levels after concentrate infusion. One-stage clotting or chromogenic substrate assays have been used for monitoring post-infusion levels, but with the introduction of extended half-life products discrepancies between one-stage and chromogenic assays have been recognized. The choice of APTT reagents in the one-stage assays, and particularly the source of the contact activator, can influence assay sensitivity to the extended half-life products. This may lead to over- or underestimation of factor levels in patients depending on the assay used for monitoring, with the potential of adversely affecting management. Therefore, experts recommended as a pragmatic solution to switch from one-stage clotting assays to chromogenic assays.^{18,19}

Recommendation 5

When using non-replacement therapies, for example for patients on emicizumab, some laboratory issues should be considered to correctly measure the procoagulant activity, FVIII levels after infusion of FVIII concentrate and in the estimation of FVIII inhibitors.

Novel non-replacement therapies that decrease the effect of natural anticoagulants rather than replacing the deficient factor have been developed. One approach is based upon the use of a monoclonal antibody (concizumab) against tissue factor pathway inhibitor (TFPI), another emerging class is based on small interference RNA (siRNA) that reduces antithrombin expression. A different approach is represented by a bispecific antibody (emicizumab) that mimics the cofactor function of FVIII by bridging FIXa and FX. Special consideration should be given to laboratory monitoring in patients on the aforementioned novel approaches, especially for emicizumab, since this is the first non-replacement drug approved by both European and American medicine

regulatory agencies (EMA and FDA) for prophylaxis in adult and paediatric patients with haemophilia A with and without inhibitors and is currently used in clinical practice.

Emicizumab does not affect the prothrombin and thrombin time, but tests based on intrinsic coagulation are affected by this drug.^{19,20} Conventional one-stage clotting assay overestimates the procoagulant activity of emicizumab, so that a modified FVIII one-stage clotting assay should be used to monitor this activity. The chromogenic FVIII assay is sensitive to emicizumab and provides an indirect measure of the procoagulant activity and drug concentration when reagents of human origin are used. However, there is no evidence that the procoagulant activity nor emicizumab concentrations are correlated with its hemostatic efficacy when assessed by the chromogenic assay employing human reagents. Because the measurement of plasma FVIII levels after in vitro addition of FVIII concentrate and the measurement of anti-FVIII inhibitor titre by the conventional Bethesda method employing human reagents are affected by the drug in treated patients, in order to measure post-infusion FVIII levels and accurately detect the inhibitor titre it is possible to employ a chromogenic assay but only with reagents of bovine origin that are insensitive to the presence of the drug.¹⁹⁻²³

Recommendation 6

The management of patients with haemophilia, particularly those using non-replacement therapies and gene therapies, should be supervised by Comprehensive Care Centres, such as the certified European Haemophilia Comprehensive Care Centres (EHCCC).

Haemophilia patients with and without inhibitors in Europe will be using more and more novel subcutaneous and innovative non-replacement therapies such as emicizumab. Haemophilia specialists must manage these patients in comprehensive care centres, particularly at the time of a major intercurrent bleeds or surgery, because the involved physicians must have adequate knowledge of the novel drugs and be able to handle any side effect. The need of additional

haemostatic drugs such as bypassing agents at the time of breakthrough bleeding and surgery may increase the risk of thrombosis, that must be carefully evaluated. In general, patients should be managed by EHCCC. The objective of these expert centres should be in the future the preparation and standardization of specific healthcare packages integrating comprehensive procedures for the management of haemophilia patients (with and without inhibitors) using emicizumab and other novel drugs during prophylaxis, with or without the addition of other haemostatic drugs during intercurrent bleeds or at the time of a surgery. The European Association for Haemophilia and Allied Disorders (EAHAD) and the European Haemophilia Consortium (EHC) need to update their joint European certification system, moving from the current self-documentation provided by each centre to the implementation of audit visits that are going to be the basis for decision on whether or not a certificate is issued.

Recommendation 7

Postmarketing data collection for the long-term safety and efficacy of all products should be mandatory. Every country should establish a national patient registry for haemophilia and other inherited bleeding disorders, covering all treatment modalities and patient-relevant outcomes.

Since its beginning the Kreuth Initiative for optimal use of blood products has been producing recommendations for haemophilia treatment,⁴ but so far the issue of data collection was not addressed. Clinical registries are important tools, particularly in the context of rare diseases such as haemophilia characterized by a limited number of patients available for clinical trials. Registries may also help to collect long-term real-life data on the usage of products and patient-relevant treatment outcomes, thus providing valuable safety information. Registries should be set up in each European country on a national basis, including ideally all patients with inherited bleeding disorders.

Although recent EMA guidelines set standards for clinical studies,²⁴ the design and conduct of the currently available studies are characterized by several differences which prevent comparative data analysis. Registries may provide relevant complementary real-life data across a variety of products.²⁵ Notwithstanding the reporting obligations according to the pharmacovigilance legislation, registries should also collect comprehensive postmarketing safety information on all treatment modalities.

Recommendation 8

Dedicated data governance, evaluation and reporting should be implemented with adequate sustainable financial support under public control. Core data elements as recommended by European Medicines Agency (EMA)^{24,26} and minimal dataset for post-registration surveillance should be implemented according to the communication from the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Subcommittee (SSC) on Factor VIII, Factor IX and Rare Coagulation Disorders.²⁷

Although there are a number of ongoing registries in Europe, their organisation and status, as well as the amount and quality of collected data, is quite variable.²⁸ There are various models of registries and promoters may be patient organisations, scientific societies, networks of treatment centres or governmental institutions. Important questions need to be answered and solutions must be found for each registry. How is the collection of data organised, preferably as user-friendly online portals? How is data integrity and quality assured? Who owns the data? Who performs which analysis? How and by whom are results reported and eventually published? Additional challenges may also be some degree of reluctance from haemophilia caregivers to share the data of their patients and to implement the effort needed for entering the data into a registry. To tackle these challenges, the German Haemophilia Register participation was recently made mandatory in Germany by an update of the Transfusion Act. The organisation of registries is far from being trivial, and needs thorough planning and substantial and sustainable support. Given the relevance of

the data for scientific evaluation of haemophilia treatment by regulatory agencies and the peculiar sensitivity of patient data, registries and their funding need to be under public control. In order to enable meaningful evaluation and comparative analysis, a minimum set of common data elements should be included, as recently recommended by EMA.²⁶ Detailed guidance concerning the data set required for post-registration surveillance was also previously communicated by the ISTH Scientific and Standardization Committee on Factor VIII, Factor IX and Rare Coagulation Disorders.²⁷

Recommendation 9

Collaboration at the European level should be encouraged, by strengthening and harmonising existing registries in order to facilitate pooling and comprehensive evaluation of data.

In order to increase the amount of evaluable data and to enable pooling and a comprehensive evaluation of data across all treatment modalities at the European level, enhanced collaboration is essential. Notwithstanding the fact that the performance, cooperation and outputs of the registries already existing in Europe is not satisfactory,²⁸ the way forward is not to advocate a single new, pan-European super-registry, but to strengthen and harmonise existing registries, as well as to encourage the establishment of common tools and strategies for their optimal use. This is an important and ambitious task which requires support by all stakeholders, including patients, haemophilia treaters, academia, regulatory authorities and policymakers involved in health care.

Recommendation 10

Data collection should include direct reporting from patients using appropriate electronic industry-independent tools. Its use should be supported by education, user-friendly applications, and positive feedback to the patients.

The ultimate success of any kind of haemophilia registry depends on the participation and commitment of the caregivers and the willingness of patients to provide their data. In particular, the accuracy and completeness of the collected data is closely related to the tools made available for data reporting to the registry. Data collection by direct reporting from patients through electronic tools is an attractive avenue provided bias due to industry-developed applications is excluded and supervision and quality control by the treating physicians is implemented. Of particular importance is the appropriate information and education about the background, instruments and goals of each registry, and provision of user-friendly applications. It is also important to provide patients with a positive feedback, with the goal to demonstrate the value of their contributions.

Recommendation 11

Clinical studies should be performed to provide the best possible evidence needed for regulatory authorities, health technology assessment (HTA) bodies, academia and healthcare providers.

Clinical trials conducted during the drug licensing process provide the most important information for predicting the efficacy and value of new medicines. While clinical trial data are the gold-standard of the evidence-based efficacy needed by regulatory authorities and health care providers, their usefulness has often limitations with respect to HTA and value determination within the frame of cost-effectiveness studies, primarily done in the interest of the decision-making processes of payers. The purpose of most clinical trials is to test hypotheses about the efficacy and side effects of medications, compared against placebo or a selected comparator therapy. HTA aims at answering questions about how these findings can be translated into clinical practice and change the standard of care, but also on how to estimate cost-effectiveness, with the goal to inform decisions intended to ensure value for money. Most clinical trials often do not focus on endpoints such as the patient relevant outcomes requested by HTA bodies and/or payers. These limitations have become more relevant after regulatory authorities introduced new initiatives such as adaptive licensing in order to

accelerate access to innovative treatments, particularly in the context of orphan or rare diseases. Smaller and shorter trials may be able to provide faster evidence, but they will fail to generate enough information for patient assessment of relevant outcomes and for cost-effectiveness. To minimise these gaps of knowledge and provide sufficient evidence in order to optimize usefulness for HTA and cost effectiveness analysis, clinical trial designs for innovative therapies should be optimised to reduce uncertainty, eliminate bias, decrease costs and accelerate patient access.

Recommendation 12

A process to reach better agreement on relevant indicators and methods should be started in order to meet the needs of regulatory authorities, HTA bodies, academia and healthcare providers, that have different foci, responsibilities and requirements.

There is a strong need for a multidisciplinary consensus on measurable, patient-relevant outcome indicators which reflect the benefits of new and innovative haemophilia therapies. Consensus on the choice of outcome assessment instruments should also be reached in order to allow for a more effective combination of data from different sources. These goals will be necessary to obtain harmonized and transparent decision-making processes. It should also be discussed if outcomes should be collected in clinical trials or if data from other sources such as observational studies including registries should be complementary sources for benefit assessment in haemophilia care. Furthermore, a minimum set of methods for outcome determination would be helpful for benefit assessment by the different decision makers. Because haemophilia is a chronic rare disease and hard patient-relevant outcomes like avoidance of joint damage cannot be evaluated at the time of market entry of innovative therapies, it is important to identify appropriate surrogate indicators and agree on statistical methods for prognostic calculations, in order to provide estimates also on medium to long-term consequences.

Recommendation 13

A dialogue with agencies and academia should be started in order to reach understanding of relevant outcomes and to ensure comprehensive and consistent reporting.

HTA bodies and/or payers request information on patient-relevant clinical endpoints in order to provide the evidence of therapeutic benefit of new or innovative therapies compared to the standard of care. These hard endpoints are mainly morbidity, mortality and quality of life, but these reflect only partially the benefits associated with innovative haemophilia therapies.²⁹ Even though mortality in haemophilia was very high before the introduction of replacement therapy, nowadays it is almost comparable to that of the general population, so that it cannot be seen as an appropriate outcome to be measured at the time of drug evaluation and market entry. Repeated joint bleeds cause morphological changes and lead to arthropathy on the long run, but many years of follow-up would be required to assess hemophilic arthropathy and its consequences. Multifactorial influences lead to individual variations in a small patient population such as haemophilia pertaining to the bleeding phenotype, development of arthropathy and inhibitory antibodies. Thus, the measurement of health-related quality of life (HRQoL) might be a reasonable indicator of the long-term outcome and effectiveness of the therapeutic intervention chosen. It can also be converted into utility values to enable the assessment of gained quality-adjusted life years (QALYs), and to calculate cost-effectiveness. Both hemophilia disease-specific instruments and generic instruments are available and should be implemented as a standard procedure.

ACKNOWLEDGMENTS:

Co-sponsoring by Paul Ehrlich Institut, the Ludwig-Maximilian University of Munich and the European Directorate for the Quality of Medicines & Healthcare.

To Isabella Garagiola, Ph.D. from Angelo Bianchi Bonomi Hemophilia and Thrombosis Center for helping us in the preparation of the manuscript and to all participants and delegates who actively participated in the discussion with the three working groups, providing their own input and helping to produce this Kreuth V European consensus for treatment of haemophilia.

Conflicts of interest

FP reports participation at advisory board of Bioverativ, Roche, Sanofi, Sobi, Takeda and Grifols.

KB has received a Research grant from Roche.

RS, AH, MLH, MW, KHB, BOM, AB, UM have no competing interests to declare.

MM has acted as consultant or participated in advisory panels for Bioverativ, CSL Behring, NovoNordisk and Shire. MM is also the project leader for EUHASS which receives funding from Bayer, Biotest, BPL, CSL Behring, Grifols, Kedrion, LFB, NovoNordisk, Octapharma, Pfizer, Roche, Takeda and Sobi.

WS has participated in a DSMB for Biotest and received honoraria for lectures from Biotest, Novo, Roche, Takeda and Bio&Bio.

PMM: Member of the scientific board for the Bayer Awards. He has also received honoraria from Bayer, Kedrion and Novo Nordisk for participation at their educational symposia.

REFERENCES

1. Schramm W, von Auer F, Delaney F, Seitz R. Blood Safety in the European Community: An Initiative for Optimal Use. Wildbad Kreuth, 20-22 May, 1999. Conference Proceedings. ISBN 3-00-005705-6.
2. Berger K, Klein HG, Seitz R, Schramm W, Spieser JM. The Wildbad Kreuth initiative: European current practices and recommendations for optimal use of blood components. *Biologicals*. 2011;39(3):189-193.
3. Giangrande P, Seitz R, Behr-Gross ME, et al . Kreuth III: European consensus proposals for treatment of haemophilia with coagulation factor concentrates. *Haemophilia*. 2014;20(3):322-325.
4. Giangrande PLF, Peyvandi F, O'Mahony B, et al. Kreuth IV: European consensus proposals for treatment of haemophilia with coagulation factor concentrates. *Haemophilia*. 2017;23(3):370-375.
5. Council of Europe, Committee of Ministers, Resolution CM/Res(2017)43 on principles concerning haemophilia therapies (replacing Resolution CM/Res(2015)3).
6. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia. *N Engl J Med*. 2007;357(6):535-544.
7. Berntorp E, Astermark J, Björkman S, et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia*. 2003;9(Suppl 1):1-4.
8. Fischer K, Astermark J, van der Bom JG, et al. Prophylaxis treatment for severe haemophilia: comparison of an intermediate-dose to a high-dose regimen. *Haemophilia*. 2002;8(6):753-760.
9. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*. 2016;388(10040):187-197.

10. Berntorp E, Andersson NG. Prophylaxis for hemophilia in the Era of extended Half-Life Factor VIII/Factor IX Products. *Semin Thromb Hemost.* 2016;42(5):518-525.
11. Peters R, Harris T. Advances and innovations in haemophilia treatment. *Nat Rev Drug Discov.* 2018;17(7):493-508.
12. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med.* 2017;377(9):809-818.
13. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med.* 2018;379(9):811-822.
14. Stephensen D, de Kleijn P, Matlary RED, et al. EAHAD Physiotherapists Committee. Scope of practice of haemophilia physiotherapists: A European survey. *Haemophilia.* 2019;25(3):514-520.
15. Collins PW. Individualized prophylaxis. *Haemophilia.* 2012;18(Suppl. 4):131-135.
16. Hazendonk HCAM, van Moort I, Mathôt RAA, et al. Setting the stage for individualized therapy in hemophilia: What role can pharmacokinetics play? *Blood Rev.* 2018;32(4):265-271.
17. Collins PW, Blanchette VS, Fischer K, et al. Breakthrough bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost.* 2009;7(3):413-420.
18. Kitchen S, Tiefenbacher S, Gosselin R. Factor Activity Assays for Monitoring Extended Half-Life FVIII and Factor IX Replacement Therapies. *Semin Thromb Haemost.* 2017;43(3):331-337.
19. Tripodi A, Chantarangkul V, Novembrino C, Peyvandi F. Advances in the treatment of hemophilia: Implications for laboratory testing. *Clin Chem.* 2019;65(2):254-262.

20. Nogami K, Soeda T, Matsumoto T, Kawabe Y, Kitazawa T, Shima M. Routine measurements of factor VIII activity and inhibitor titer in the presence of emicizumab utilizing anti-idiotypic monoclonal antibodies. *J Thromb Haemost.* 2018;16(7):1383-1390.
21. Teichman J, Chaudhry HR, Sholzberg M. Novel assays in the coagulation laboratory: a clinical and laboratory perspective. *Transfus Apher Sci.* 2018;57(4):480-484.
22. 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(9):1384-1393.
23. Collins PW, Liesner R, Makris M, et al. Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving Emicizumab. Interim guidance from UKHCDO Inhibitor Working Party and Executive Committee. *Haemophilia.* 2018;24(3):344-347.
24. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. EMA/CHMP/BPWP/144533/2009 rev. 2
25. Keipert C, Jonker C J, van den Berg HM, Hilger A. Clinical trials and registries in haemophilia: Opponents or collaborators? Comparison of PUP data derived from different data sources. *Haemophilia.* 2018;24(3):420-428.
26. Report on Haemophilia Registries: Workshop 8 June 2018. EMA/487643/2018. https://www.ema.europa.eu/en/documents/report/report-haemophilia-registries-workshop_en.pdf
27. Peyvandi F, Makris M, Collins P, et al. Minimal dataset for post-registration surveillance of new drugs in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost.* 2017;15(9):1878-1881.
28. Keipert C, Hesse J, Haschberger B, et al. The growing number of hemophilia registries: Quantity versus quality. *Clin Pharmacol Ther.* 2015;97(5):492-501.

29. Berger KC, Feldman BM, Wasserman J, et al. Securing reimbursement for patient centered haemophilia care: major collaborative efforts are needed. *Haematologica*. 2016;101(3):266-268.