



The 1st WFH Gene Therapy Round Table: Understanding the landscape and challenges of gene therapy for haemophilia around the world

Glenn F. Pierce  | Donna Coffin  | Members of the WFH Gene Therapy Round Table Program Committee and Organizing Committee^a

World Federation of Hemophilia, Montreal, Québec, Canada

Correspondence

Donna Coffin, The World Federation of Hemophilia, Montreal, QC, Canada
Email: dcoffin@wfh.org

In this first in a series of round table meetings, the 1st World Federation of Hemophilia Gene Therapy Round Table was convened to initiate a global dialogue on the expected challenges and opportunities that a disruptive therapy, such as gene therapy, will bring to the haemophilia community. Perspectives from key stakeholder groups, including healthcare professionals, regulators, payors, people with hemophilia and pharmaceutical industry representatives, were sought in the identification of the key issues we expect to face. Didactic presentations and open discussion covered the clinical development of gene therapy in haemophilia; regulatory perspectives of gene therapy; making informed decisions; accessibility, affordability and pricing of gene therapy; and ethical issues of gene therapy clinical trials. These were followed by small group work. This manuscript outlines the key issues identified and the path forward.

KEYWORDS

challenges, gene therapy, global, haemophilia, roundtable, world

1 | INTRODUCTION

Most haemophilia is caused by a mutation in one of two genes, *F8* or *F9*, and is inherited in an x-linked recessive pattern. These genes encode proteins that work in concert to contribute to clot formation at a break in a blood vessel wall, and their absence results in prolonged bleeding. Clinical manifestations include severe arthropathy from repeated bleeding into joints, and increased mortality if untreated.^{1,2} An estimated 1 in 5000 males are affected by haemophilia; however, identification of these patients is a challenge, which

disproportionately affects developing countries. While high-income countries have identified the majority of patients, this is not the case in lower income countries, where as few as 8% of expected patients have been identified.³ Tragically, up to 70% of patients, reflecting those living in low- and middle-income countries (LMIC)⁴ do not have access to adequate care.^{5,6} Without a minimum of care, patients suffer from the long-term sequelae of chronic bleeding and early mortality.^{1,7,8}

This gap in access to treatment between high- and low-income countries is driven mainly by the high cost of clotting factor concentrates (CFC),⁸ with approximately 15% of the world (ie, North America and Europe) using approximately 66% of the total CFCs available.³ It is thought that even if CFCs could be provided to all regions of the world, industry would not be able to manufacture sufficient amounts to meet the global demands of patients.⁹ Clearly, the World Federation of Hemophilia's (WFH) vision of Treatment for All will need to include options outside of the CFC protein replacement paradigm.

^aMembers of the WFH Gene Therapy Round Table Program Committee were: David Lillicrap, Canada; Margareth Ozelo, Brazil; John Pasi, UK; Dawn Rotellini, USA; Carlos Safadi Marquez, Argentina; Thomas Sannié, France; Alok Srivastava, India; Marijke van den Berg, The Netherlands; Alain Weill, France; and members of the WFH Gene Therapy Round Table Organizing Committee were: Antonio Almeida, Canada; Alain Baumann, Canada; Mark Brooker, Spain; Luisa Durante, Canada; Mayss Naccache, Canada; Fiona Robinson, Canada

[†]A full list of participants of the 1st WFH Gene Therapy Round Table is outlined in the Acknowledgement section.

Recently, we have seen the introduction of non-factor therapies, including gene therapy, reach late phase clinical trials and the market.¹⁰⁻¹⁶ There are currently several ongoing clinical trials for both FVIII and FIX gene therapy,¹¹ and barring unforeseen safety or efficacy issues, it is expected that at least 1-2 will obtain regulatory approval in the next few years. In anticipation of this, the 1st WFH Gene Therapy Round Table was convened in Montreal in April 2018, to initiate a global dialogue on the expected challenges and opportunities that a disruptive therapy, such as gene therapy, will bring to the bleeding disorders community.

2 | MATERIALS AND METHODS

2.1 | Gene Therapy Round Table

This cross-sectoral one-and-a-half-day meeting included representatives and perspectives of 52 stakeholders from 21 countries, including healthcare professionals (HCP), scientific experts, regulators, payors, people with haemophilia (PWH) and advocates, pharmaceutical industry representatives and a medical ethicist. The round table approach was used to encourage participation and engagement from all stakeholders.

The first day comprised didactic presentations and open discussion covering the following topics (a) clinical development of gene therapy in haemophilia; (b) regulatory perspectives of gene therapy; (c) making informed decisions; (d) accessibility, affordability and pricing of gene therapy and (e) ethics of gene therapy clinical trials. At the end of the first day, a list of key issues and considerations in achieving gene therapy for all was agreed upon (Table 1). Each of these key issues was then expanded in subgroup sessions on the second day. Stakeholder sub-groups were tasked with developing the priority, urgency and feasibility of addressing each issue, a proposed means to address each issue, the resources required, and expected risks and benefits of addressing each issue.

2.2 | Pre-meeting survey

To better understand the global needs and knowledge level of our community, a pre-round table survey was completed by 103 patient

organizations (national member organizations [NMO]) from different countries (78% response rate) and 109 treating physicians from 76 countries (60% response rate). Overall, most patients reported a "basic" understanding of gene therapy (n = 69, 68%) and treaters had a "basic" or "intermediate" understanding (n = 48, 44%), with very few respondents claiming an "advanced" understanding (6% and 12% for patients and treaters, respectively). This gap in knowledge amongst patients and treaters, and the need for education at all levels, was a salient point throughout the round table sessions. It was noted that not only is there a lack of education and knowledge of gene therapy, but mis-information on gene therapy is readily available on the Internet, which may be a higher priority issue to address. Education has a key role to play in informing realistic expectations across the community. The knowledge stemming from the round table will inform the WFH educational program on gene therapy and advocacy efforts.

3 | RESULTS

3.1 | Key issues and considerations

Six key issues were identified as important by the round table participants (Table 1).

3.1.1 | Key issue: efficacy endpoints for gene therapy: need for a standardized, objective and non-surrogate efficacy endpoint with consensus of regulators

At the time of the round table, neither the US Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) had recommended a primary efficacy endpoint for phase III gene therapy trials in haemophilia. As at least one phase III clinical trial had started, establishing one standardized primary efficacy endpoint for all gene therapy trials accepted by both the FDA and the EMA was deemed a high and urgent priority. Failure to establish this, runs the risk of different trials reporting different primary endpoints, making between trial comparisons impossible. HCPs viewed annual bleeding rate (ABR) as imprecise and subjective and argued factor activity level to be an objective and non-surrogate endpoint, corroborating published recommendations that factor level, versus ABR, be the primary efficacy endpoint.^{17,18} Patients, in general, believed factor level was a more accurate reflection of their quality of life than ABR. Some discrepancies between assays and assay reagents notwithstanding, it was agreed that the haemophilia community should establish a minimally acceptable factor level and a minimum durability of treatment, for gene therapy to be considered successful. Several studies have demonstrated that a reduction in bleeding and factor use can be achieved with FIX expression levels of <10%^{15,16}; however, a minimal acceptable level still needs to be determined. Subsequent to the round table, the FDA issued draft guidelines specifying that factor levels may be utilized as the primary endpoint for breakthrough therapy

TABLE 1 Key issues

Key issues identified
Efficacy endpoints for gene therapy: need for a standardized, objective and non-surrogate efficacy endpoint with consensus of regulators
The known and unknown long-term safety concerns associated with gene therapy
Gaining access to gene therapy for all patients around the globe
Paradigm shift in treatment goals, and organization and delivery of care for people with haemophilia
Maintaining the solidarity and security of the local and global haemophilia community
Expanding the indication from the "ideal" patients enrolled in phase 3 trials

approval, but ABR was proposed as the primary endpoint for the regular approval process.¹⁹ This issue is not resolved and is complicated by factor assay variations in both FVIII and FIX gene therapy trials. Patient leaders and HCPs also made the point that if gene therapy leads to a reduction in bleeds close to zero, haemostatic outcomes may no longer be the most relevant outcome for patients. Endpoints such as improvements in quality of life, activity level and participation may be the new measure of success.²⁰

Participants also proposed that all phase III trials use a common core set of outcomes, with data collected on additional outcomes at the discretion of investigators. Agreement on a core data set and standard definitions by all stakeholders was assessed as high priority and urgent. The benefit of this approach is that it allows different decision makers to use different components of the same core set of clinical outcomes.

A core data set for gene therapy trials, known as coreHEM, with patient, clinician, regulator, healthcare professional, payor and manufacturer input, was in development at the time and has since been published.²¹ Through a Delphi process, frequency of bleeds, factor activity level, duration of factor expression, chronic pain, healthcare resource use and mental health were identified as the core outcomes to be measured, in addition to regulatory-mandated adverse effects. It is now up to the community to ensure these core data outcomes are incorporated into the clinical framework of gene therapy trials to ensure appropriate and relevant appraisals demonstrating the value of gene therapy are possible. Work is underway in selecting the most suitable measurement tools for the identified outcomes, where needed.²¹

3.1.2 | Key issue: the known and unknown long-term concerns associated with gene therapy

Collecting long-term safety and efficacy data was identified as a high priority with an urgent timeframe as well. Consensus by the round table participants was that lifelong follow-up of gene therapy patients is crucial to monitor both known and unknown safety issues (eg, risks of hepatocellular carcinoma) and durable efficacy. The list of known and unknown risks in gene therapy is vast,²² and only through long-term monitoring of a large number of patients can many of these risks be detected. The round table participants agreed that these data should be captured in a long-term, international registry providing real-world evidence, ideally stored by a neutral, accessible body within the haemophilia community. Because haemophilia is a rare disease and gene therapy recipients will be scattered around the world, the international component was viewed as essential to ensure the inclusion of a maximum number of patients, to increase the likelihood of identifying low-incidence events. A simple, but robust global database with multi-stakeholder involvement in the development was proposed, with a suggestion of modelling it similar to the Center for International Blood and Marrow Transplant Research platform.²³ Representatives suggested leveraging the WFH World Bleeding Disorders Registry (WBDR)²⁴ as the global database, as a viable option.

The feasibility of establishing a registry was rated as high, with important consequences associated with not pursuing a registry: lack of long-term follow-up data, and incomplete or low-quality safety and efficacy data after the short 5-year FDA recommended follow-up period of clinical trials. Without long-term safety and efficacy data, collected in one global system to maximize number of patients, identification of rare adverse events may be difficult. Additionally, it was noted that participating in a patient registry may provide an opportunity for PWH to maintain community connections, and for treating physicians to retain contact with patients, who may be less inclined to follow-up with clinic visits.

3.1.3 | Key issue: gaining access to gene therapy for all patients around the globe

Gaining access to gene therapy for patients globally was a core theme that anchored the round table discussions. Creating a strategic roadmap forward was identified as a high-priority issue, realizing that a multi-pronged approach to accommodate the various environments will be necessary. Amongst other factors, the economics of a country and their national health policies will influence the strategic approach. The focus for high-income countries will be on cost: reimbursement and payment models; the focus for lower income countries will be access models used by other international healthcare organizations as a source of inspiration (eg, The Gates Foundation, The Rockefeller Foundation). Current standard of care treatment for PWH in developed countries remains out of reach for up to 70% of PWH globally, making the idea of leapfrogging over the current treatment gaps straight to gene therapy for PWH in developing countries an attractive option.⁶

Regardless of country-specific paths forward, a multitude of common issues to consider in parallel were identified. The deployment of gene therapy was them. Manufacturing of gene therapy will require scaling up to meet the demands of commercialization.²⁵ Access to sufficient amounts of adeno-associated virus (AAV), the vector commonly used in gene therapy for haemophilia, will be required for widespread access to become a reality. As will overcoming the persistent barriers to these AAVs, namely, their high rate of pre-existing antibodies in the general population.^{6,25,26} Present gene therapies could be considered first-generation, viewed as a bridging therapy to the next generation of gene therapy vectors that will be developed over the next 15-20 years. There will also be demands on the medical infrastructure to identify, treat and monitor patients. Determining which patients will benefit most from gene therapy is another consideration. Younger patients could be considered a priority, with the potential to prevent the long-term morbidity associated with chronic bleeding; however, paediatric studies are first needed. Beyond access, acceptance may differ based on a patient's current access to non-gene therapy products. Access to an efficacious and safe non-gene therapy treatment regime may diminish the appeal of gene therapy, given the current unknown risks of gene therapy.⁶

Multiple stakeholder involvement will be essential in the development of access strategies to ensure the best prospect for

equitable and mutually beneficial approaches for all. The process may be driven by manufacturers and regulators, but HCPs, PWH, NMOs, payors and healthcare organizations will also be necessary to enable the process.

3.1.4 | Key issue: paradigm shift in treatment goals, and organization and delivery of care for PWH

Over time, gene therapy may bring a paradigm shift in the organization and delivery of care for PWH. Although gene therapy may necessitate more frequent monitoring visits initially, in the absence of frequent bleeding, over time patients may rely less on HTC for bleed control. However, until gene therapy is available for very young patients, our current model of comprehensive care for pre-existing musculoskeletal damage and progressive arthropathy will still be necessary, even for patients who have gene therapy. Depending on the factor level achieved, patients may continue to have milder forms of haemophilia and experience breakthrough bleeds requiring follow-up and treatment. It will be necessary to create a model of care for gene therapy to manage milder haemophilia, damaged joints, breakthrough bleeds and joint flare-ups, in the absence of frequent bleeds. New types of care may be needed, such as re-building muscle strength surrounding damaged joints. The establishment of centres of excellence for haemophilia and gene therapy was suggested.

Treatment goals may also change: a reduction in bleeds may no longer be a valid goal with gene therapy, while quality of life may become more important.²⁰⁻²² Patients will require education and support on the expected clinical outcomes of gene therapy, and their changing reality within society and the haemophilia community. It was noted that there should be considerable involvement from patient organizations in adapting the current models of care and providing education for PWH. A shift in the organization and delivery of care was identified as a medium priority, requiring education to PWH and HCPs over time.

The traditional model of care for haemophilia will also need to remain in place for PWH who do not receive gene therapy, including our current models of comprehensive care and prophylaxis infusion practices. It is not known what the uptake of gene therapy will be, however, an estimated 40%-80% of the population, depending on AAV vector subtype, are estimated to have neutralizing antibodies to the AAVs commonly used in gene therapy for haemophilia, immediately excluding them from eligibility.^{22,25,26} Patients will also be ineligible for many other reasons. Cost and availability will preclude many patients, and others will choose not to take gene therapy at all, preferring to remain with protein-based therapies.⁶

3.1.5 | Key issue: maintaining the solidarity and security of the local and global haemophilia community

Participants voiced a concern of a potential breakdown in the solidarity and security of the haemophilia community. If gene therapy leads to a reduced reliance on HTCs and NMOs over the long run,

the community may become less relevant as the number of patients getting gene therapy rises. There was concern on behalf of the individual and the family, loss of a lifelong identity of haemophilia, and a sudden loss of a community that has defined them for much of their lives. Other issues raised included losing disability status and having to enter the workforce, which may be difficult for PWH who have not been able to work for many years. There was also a concern of a potential widening of the gap in care globally, and a potential loss of advocacy voice if gene therapy becomes available to only high-income countries.

Participants agreed that although this threat is real, the strong support network of the haemophilia community will still be needed and NMOs should be in the forefront of ensuring their relevance. It was thus prioritized as medium, with an emphasis on the immediate need to create educational and advocacy tools to help NMOs inform and support their haemophilia community.

Gene therapy will not change the genetics of haemophilia and children will continue to be born with haemophilia. It will be important to continue supporting new diagnoses and PWH on all treatments, including gene therapy. Participants highlighted long-term education and training as a vehicle to demonstrate how NMOs can continue to support all PWH, on all types of treatment. This will include managing patient expectations of treatment outcomes, such as possible break-through bleeds and risks associated with an increase in physical activity or sports participation, and continuing to support advocacy efforts to gain access to all treatments for patients globally.

3.1.6 | Key issue: expanding the indication from the "ideal" patients enrolled in phase 3 trials

Initial approval of gene therapy in haemophilia will likely be restricted to otherwise healthy male adults, reflecting the strict eligibility criteria of the clinical trials. While a small number of trials do permit inclusion of patients with human immunodeficiency virus (HIV), hepatitis C or B, or known antibodies to AAV, the majority do not. Participants of the round table identified sub-groups of PWH to consider expanding the indication of gene therapy in haemophilia. These included: (a) persons with inhibitors, both those with past transient inhibitors and those with currently active inhibitors refractory to immune tolerance induction; (b) children under 18 years of age and elderly patients; (c) persons who have HIV, and persons with liver disease post-resolution of chronic hepatitis C and/or B infections; (d) persons with mild or moderate haemophilia; (e) persons with pre-existing neutralizing antibodies; and (f) females with severe or moderate haemophilia.

Expanding indications was considered a low priority to address, signifying that it will likely occur organically through extension studies, market pressures, and with the generation of post-authorization evidence over time. The participants conveyed that it is necessary to first demonstrate the efficacy of gene therapy in a population where the benefit is very clear and then allow market forces to find a way of expanding studies into smaller sub-groups.

4 | DISCUSSION AND CONCLUSIONS

This 1st WFH Gene Therapy Round Table was a unique meeting that generated a great deal of provocative discussion amongst a multi-disciplinary group of experts. Gene therapy is evolving quickly, with haemophilia at the forefront; however, there remain a number of challenges to overcome before this technology can progress globally. The challenges to this progress are not trivial and many carry opposing interests between stakeholders. Collaboration amongst all stakeholders will be key to ensuring that not only is gene therapy safe and efficacious over the long-term, but that equitable access for patients globally is achieved. As part of the WFH's vision of Treatment for All, we are committed to raising the issues and calling for solutions to these challenges. In this first of a series of round table meetings, a few of the issues our community will face with the introduction of gene therapy have been identified, with initial thoughts on best approaches to address them. Subsequent meetings will focus in more detail on specific issues.

ACKNOWLEDGEMENTS

The WFH thanks Georgia Michael, PhD, for writing and editorial assistance of this manuscript. The World Federation of Hemophilia gratefully acknowledges the sponsors of the 1st WFH Gene Therapy Round Table: Bayer, Biomarin, Pfizer, Shire, Spark Therapeutics, Bioverativ and uniQure. The WFH is grateful for the important contributions to the discussions that took place during the 1st WFH Gene Therapy Round Table: Lisa Bagley, UK; John Chapin, USA; Saliou Diop, Senegal; Magdy El Ekiaby, Egypt; Mathias Flume, Germany; Lindsey George, USA; Jack Grehan, UK; Matt Hawe, USA; Katherine High, USA; Anneliese Hilger, Germany; Bengt Jonsson, Sweden; Joanne Kim, Canada; Jonathan Kimmelman, Canada; Gisela Kobelt, Sweden; Mimi Lee, USA; David Lillicrap, Canada; Adriana Linares, Colombia; Jay Lozier, USA; Johnny Mahlangu, South Africa; Michael Makris, UK; Klaus Marten, Switzerland; Prasad Mathew, USA; Declan Noone, Ireland; Jamie O'Hara, UK; Margareth Ozelo, Brazil; Tsukasa Ohmori, Japan; David Page, Canada; John Pasi, UK; Jed Perry, USA; Glenn Pierce, USA; Enrique Preza Hernandez, Mexico; Margaret Ragni, USA; Magda Rakha, Egypt; Bradley Rayner, South Africa; Ulrike Reiss, USA; Danielle Rollmann, USA; Dawn Rotellini, USA; Paul Ruff, South Africa; Sol Ruiz, Spain; Carlos Safadi Marquez, Argentina; Thomas Sannié, France; Ragothaman Sathyanarayanan, India; Mark Skinner, USA; Alok Srivastava, India; Bartholomew Tortella, USA; Edward Tuddenham, UK; Leonard Valentino, USA; Marijke van den Berg, The Netherlands; Thierry Vandendriessche, Belgium; Alain Weill, France; Renchi Yang, China; Steven Zelenkofske, USA.

DISCLOSURES

Glenn F. Pierce has been a paid consultant to BioMarin, Genentech/Roche, Pfizer, Shire, and is the VP Medical and a member of the

Board of Directors for The World Federation of Hemophilia and a director at Voyager Therapeutics, officer of Ambys Medicines, and entrepreneur-in-residence at Third Rock Ventures. Donna Coffin is an employee of the World Federation of Hemophilia and has no disclosures. Dawn Rotellini sits on the Bayer Healthcare, Inc. Haemophilia Advocacy Advisory Board and all honoraria goes directly to the National Haemophilia Foundation and not to Ms. Rotellini.

DISCLAIMER

The contents of this summary do not necessarily reflect the opinions or policy positions of individual attendees or the organizations they represent.

ORCID

Glenn F. Pierce  <https://orcid.org/0000-0002-3310-328X>

Donna Coffin  <https://orcid.org/0000-0001-8372-4474>

REFERENCES

1. Mazepa MA, Monahan PE, Baker JR, Riske BK, Soucie JM. Men with severe hemophilia in the United States: birth cohort analysis of a large national database. *Blood*. 2016;127:3073-3081.
2. Soucie JM, Monahan PE, Kulkarni R, Konkle BA, Mazepa MA. The frequency of joint hemorrhages and procedures in nonsevere hemophilia A vs B. *Blood Adv*. 2018;2:2136-2144.
3. Annual Global Survey 2016. World Federation of Hemophilia, 2016. <http://www1.wfh.org/publications/files/pdf-1690.pdf>. Accessed June 13, 2018.
4. World Bank 2015. World Development Indicators 2015. <http://documents.worldbank.org/curated/en/795941468338533334/World-development-indicators-2015>. Accessed October 25, 2018.
5. World Federation of Hemophilia. <https://www.wfh.org/en/page.aspx?pxmlid=646>. Accessed June 28, 2018.
6. Mahlangu J, Cerquiera M, Srivastava A. Emerging therapies for haemophilia—global perspective. *Haemophilia*. 2018;24:15-21.
7. Mejia-Carvajal C, Czapek EE, Valentino LA. Life expectancy in hemophilia outcome. *J Thromb Haemost*. 2006;4:507-509.
8. Evatt B. The natural evolution of haemophilia care: developing and sustaining comprehensive care globally. *Haemophilia*. 2006;12:13-21.
9. Pierce GF, Weill A. The growing global supply and demand imbalance for factor VIII clotting factor concentrates. Unpublished manuscript. 2018.
10. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Efficacy of emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379:811-822.
11. Brown K, Green G. The haemophilia drug market. *Nat Rev Drug Discovery*. 2018;17:541.
12. Peters R, Harris T. Advances and innovations in haemophilia treatment. *Nat Rev Drug Discovery*. 2018;17:493.
13. George LA, Sullivan SK, Giermasz A, et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. *N Engl J Med*. 2017;377:2215-2227.
14. Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia A. *N Engl J Med*. 2017;377:2519-2530.
15. Nathwani AC, Reiss UM, Tuddenham EGD, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med*. 2014;371:1994-2004.



16. Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. *Blood*. 2018;131:1022-1031.
17. Pierce GF, Ragni MV, van den Berg HM, et al. Establishing the appropriate primary endpoint in haemophilia gene therapy pivotal studies. *Haemophilia*. 2017;23:643-644.
18. Recht M, Konkle BA, Jackson S, Neufeld EJ, Rockwood K, Pipe S. Recognizing the need for personalization of haemophilia patient-reported outcomes in the prophylaxis era. *Haemophilia*. 2016;22:825-832.
19. Food and Drug Administration UDoHaHS. Human gene therapy for hemophilia. Draft Guidance for Industry; 2018.
20. Machin N, Ragni MV. Measuring success in hemophilia gene therapy using a factor level & outcomes yardstick. *Expert Rev Hematol*. 2018;11:83-86.
21. Iorio A, Skinner MW, Clearfield E, et al. Core outcome set for gene therapy in haemophilia: results of the coreHEM multistakeholder project. *Haemophilia*. 2018;24:e167-e172.
22. Pierce GF, Iorio A. Past, present and future of haemophilia gene therapy: from vectors and transgenes to known and unknown outcomes. *Haemophilia*. 2018;24:60-67.
23. Center for International Blood and Marrow Transplant Research. <http://www.cibmtr.org/Pages/index.aspx>. Accessed June 28, 2018.
24. Coffin D, Herr C, O'Hara J, et al. WBDR: the pilot study. *Haemophilia*. 2018;24:e113-e116.
25. George LA, Fogarty PF. Gene therapy for hemophilia: past, present and future. *Semin Hematol*. 2016;53:46-54.
26. Liu Q, Huang W, Zhang H, et al. Neutralizing antibodies against AAV2, AAV5 and AAV8 in healthy and HIV-1-infected subjects in China: implications for gene therapy using AAV vectors. *Gene Ther*. 2014;21:732.

How to cite this article: Pierce GF, Coffin D; Members of the WFH Gene Therapy Round Table Program Committee and Organizing Committee. The 1st WFH Gene Therapy Round Table: Understanding the landscape and challenges of gene therapy for haemophilia around the world. *Haemophilia*. 2019;25:189-194. <https://doi.org/10.1111/hae.13673>