

Improving patient informed consent for haemophilia gene therapy: the case for change

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Abstract

Adeno-associated virus-based gene therapy points to a coming transformation in the treatment of people living with haemophilia, promising sustained bleed control and potential improvement in quality of life. Nevertheless, the consequences of introducing new genetic material are not trivial. The perceived benefits should not minimise the challenges facing patients in understanding the long-term risks and providing a valid and meaningful informed consent, whether in a research or clinical setting. Informed consent is a fundamentally important doctrine in both medical ethics and health law, upholding an individual's right to define their personal goals and make their own autonomous choices. Patients should be enabled to recognise their clinical situation, understand the implications of treatment and integrate every facet of their life into their decision. This review describes informed consent processes for haemophilia gene therapy clinical trials, factors affecting patients' decision making and the availability of patient-centred decision support interventions, to ensure that patients' interests are being protected. Regulatory guidance has been published for physicians and manufacturers in haemophilia on informed consent, including for gene therapy, while best-practice recommendations for patient-physician discussions are available. In all settings, however, communicating and presenting highly technical and complex therapeutic information is challenging, especially where multiple barriers to scientific knowledge and health literacy exist. We propose several evidence-informed strategies to enhance the consent procedure, such as utilising validated literacy and knowledge assessment tools as well as participatory learning environments over an extended period, to ensure that patients are fully cognisant of the consent they give or deny. Further research is needed to define new, creative approaches for patient education and the upholding of ethical values in the informed consent process for gene therapy. The lessons learnt and approaches developed within haemophilia could set the gold standard for good practice in ensuring ethical preparedness amidst advances in genetic therapies.

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Plain language summary

Improving the informed consent process for people living with haemophilia considering gene therapy.

Gene therapy is the process of replacing faulty genes with healthy ones. In haemophilia, gene therapy involves introducing a working copy of the gene for the clotting factor that patients are missing. Following treatment, patients should begin producing their own clotting factor normally. However, people living with haemophilia (PwH) need to be fully informed regarding the potential benefits and risks of gene therapy and what this means for them, whether as part of a research study or routine medical care.

Patients must be respected and supported to make decisions about their own health and wellbeing, recognising their legal and moral right to set personal goals and make treatment choices. For this to happen in practice, patients should be aware of their individual health needs, understand the effects of treatment and consider lifestyle preferences in relation to their decisions. This article attempts to describe how informed consent is obtained in haemophilia gene therapy clinical trials, what affects a patient's ability to make decisions and the availability of information and support to respect and protect the interests of PwH.

Regulators responsible for approving medical products have published guidance on informed consent for physicians and pharmaceutical manufacturers in haemophilia, including for gene therapy. Recommendations have been made about the best ways for PwH to discuss gene therapy with their physicians. Yet, poor communication of complex topics, such as gene therapy, can be problematic, especially if patients lack the skills and confidence to understand and discuss the science, or for physicians with limited time in clinic.

We propose strategies to improve the consent process, so patients can feel more able to make informed decisions about new treatments. Further research is needed to find new, creative approaches for educating patients and ensuring that the informed consent process for gene therapy in haemophilia is ethical.

Keywords: ethics, gene therapy, haemophilia, informed consent, patient education, shared decision making

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Introduction

Current generations of people living with haemophilia (PwH) have been promised that a 'cure' by gene therapy is within touching distance in their lifetime.^{1,2} Haemophilia, a rare inherited bleeding condition, is considered an attractive target for gene therapy because of its monogenic causation, opportunities to easily assess the effectiveness of circulating clotting factor (F)VIII (haemophilia A) or FIX (haemophilia B) levels and straightforwardly measurable clinical endpoints (i.e. bleeding rate and treatment consumption). Additionally, interest in gene therapy for haemophilia is enhanced by an ability to ameliorate bleeding symptoms with relatively small increments in factor levels.^{3,4}

Development of gene therapy has been inspired by the appreciation that – at least in principle – a single treatment could produce durable, possibly curative, clinical benefit, minimising or even eliminating the symptoms of a condition for the whole lifetime of a recipient.⁵ In 2020, the regenerative medicine and advanced therapy sector raised nearly US\$20bn in capital, a record

amount, to progress disruptive technologies.⁶ The US Food and Drug Administration (FDA) predict that by 2025, between 10 to 20 cell and gene therapy products will be approved for use per year,⁷ with the global market size expected to grow from currently US\$2.26bn to US\$10bn by 2028.⁸

In 2011, the Nathwani group at University College London were the first to successfully trial a one-off gene transfer in 10 adults with severe haemophilia B (<1% of normal FIX activity). A decade later, all continue to benefit from a significant reduction in both spontaneous bleeding episodes (these can cause severe pain, joint disease and disability) and annual use of FIX replacement therapy. Reportedly, their quality of life (QoL) has improved dramatically and activities once restricted for fear of bleeding are now doable.⁹ At the time of writing there are approaching 20 active clinical trials, including several pivotal trials, alongside the first pending licensing application.¹⁰ While gene-based therapeutic strategies suggest a future transformation of treatment for haemophilia, the potential ramifications of introducing

new genetic material are not trivial. The perceived advantages over approved products today (where treatment burden remains significant) should not minimise the challenges that the clinical and patient community are facing in understanding the long-term risks.^{4,11}

Adeno-associated virus (AAV) is the most extensively utilised vector for gene therapy studies, including in haemophilia. One key reason is its apparent safety.¹² Yet, despite large-scale trials nearing completion, a number of issues and uncertainties with the technology persist, prompting a mismatch in patients' expectations *versus* the reality of the available data.^{1,13} In August 2020, the FDA issued a complete response letter to BioMarin Pharmaceutical's biologics license application for their AAV5-based gene therapy for haemophilia A, demanding more data on its durability having observed substantial year-on-year declines in FVIII expression during the phase I/II study. This loss in FVIII levels is compounded by a lack of scientific understanding of the underlying cause.^{13,14} More recently, UniQure, which is running a phase III AAV5-FIX gene therapy study, reported a case of hepatocellular carcinoma (HCC) in a trialist. Initially, it was unclear whether the gene therapy had contributed towards the HCC, even though this subject had prior exposure to hepatitis B and C viruses, which can cause liver damage.¹⁵ However, an independent investigation found no evidence to suggest that the AAV vector played a pathogenic role.¹⁶

Although AAV is considered a non-integrating viral vector (i.e. it should not permanently enter into host cell chromosomes), this remains relatively unexplored, with some evidence linking AAV integrations to genotoxic consequences.^{12,17} To improve understanding, study sponsors/investigators of haemophilia gene therapy are now being encouraged to incorporate, liver biopsy sub-studies in at least one cohort of patients, at a minimum.¹⁸ One such study is already registered within ClinicalTrials.gov (NCT04817462).¹⁹

Certain unresolved issues make the decision to undergo first-generation gene therapy complex for eligible adult PwH.^{1,13} To date, minors are excluded from haemophilia gene therapy trials because of the theoretical concern that a large quantity of the AAV vector could be lost during substantial childhood liver growth.^{3,4,11,20,21} Another obstacle is that, with AAV neutralising

antibodies persisting over many years post-treatment, if the first dose is inadequate, this might preclude redosing with the same vector or even employing different serotypes as an alternative due to cross-reactivity.^{1,3-5,11,13,20-22} Given, then, the enormity of weighing-up the 'irreversible step' of genomic medicine *versus* traditional medicine (i.e. where doses can be altered or stopped),²³ PwH are entitled to make an informed decision before undergoing the potentially life-altering infusion. Ethical considerations both pre- and post-marketing remain of central importance, including robust patient education and discussion of the *known knowns* (such as, the variability of transgene expression), *known unknowns* (for instance, the risk of insertional oncogenesis) and alternative treatment options prior to/after the gene therapy.^{24,25} In particular, gene therapy raises significant questions around the practice of patient informed consent; a widely accepted ethical, legal and regulatory requirement for the majority of research and healthcare interactions, and ultimately, a fundamental component of modern clinical provision.²⁶⁻²⁸

Innovative developments in healthcare and clinical research necessitate greater efforts to understand and address existing and newly emergent challenges regarding informed consent, such as: what/how information should be disclosed, the level of detail an individual providing consent should comprehend and how explicit consent is required to be. Furthermore, informed consent practices vary by context and the reality often fails to live up to the theoretical ideal. A considerable body of literature substantiates a sizable gap between the execution of informed consent and its projected aims, indicating many unresolved conceptual and practical questions.²⁸ Gene therapy faces additional challenges as an investigational modality with large degrees of uncertainty concerning risk, owing to the experimental nature of its composition and mode of action.^{1-4,10-14,17,20-25}

The purpose of this review is to characterise informed consent processes for haemophilia gene therapy clinical trials, factors affecting patients' decision making capacity and the availability of patient-centred decision support interventions. The implications will serve as a focus for future research to ensure that patients' decision making is meaningful and valid and that their interests are protected, whether it be for research or accessing an approved product.

Overview of informed consent

Ethical and legal principles

A fundamentally important doctrine, in both medical ethics and health law, is one of informed consent and the dignity of all patients, tracing its legal and regulatory roots to the 1947 Nuremberg Code and the 1964 Declaration of Helsinki. In theory, informed consent is when a patient provides authorisation of an activity based on a complete understanding of what that activity entails and without any coercion by others. Specifically, informed consent involves valuing, respecting and upholding a person's right to define their personal goals and make their own autonomous choices, particularly in relation to all types of health-related interventions, including life-sustaining measures.^{28–30} The World Medical Association Declaration of Lisbon (1983) on the Rights of the Patient emphasises that patients everywhere have a right to information and self-determination.²⁵

What constitutes 'adequate' informed consent?

Informed consent is an active process involving a two-way dialogue between the healthcare professionals (HCPs)/researchers and a patient/research participant with sound decision making capacity, culminating in the latter's intentional decision to accept or refuse a specific intervention or participate in a research study.^{28,30,31} Patients should be enabled to recognise their clinical situation, understand the consequences of the treatment being offered and alternative options, appreciate the precise implications for their future and integrate every facet into their *informed* decision.²⁸

An informed consent process consists of multiple elements: information disclosure, comprehension, voluntariness and authorisation and can be understood as complete, meaningful and valid if all of these key criteria are effectively satisfied.^{28,30,32} Neither medical nor research interventions should begin until valid informed consent has been secured, unless in exceptional circumstances (e.g. emergencies). If a patient or trial participant is a child or an incapacitated adult, permission is often sought from a substitute decision maker, such as a caregiver. There remains much debate amongst both academics and practitioners regarding aspects of consent, including: (1) the extent of detail provided, (2) managing and maintaining disclosure, (3) whether/how to assess comprehension, (4) what accounts for

necessary/sufficient understanding, (5) methods for determining individuals' capacity to consent with strategies in place if judged to be lacking, (6) ensuring a level of voluntariness of choices, and (7) matters concerning developing effective consent documentation.²⁸

Somewhat unique to gene therapy research (across many genetic conditions) is how a patient's judgement could be easily clouded by both the extent of disease burden as well as its treatments (or lack of). Also, patients' desire for improvement in health-related QoL in feasibly desperate medical circumstances can undermine their decisional capacity.^{27,33} In addition, thorough understanding may be problematical given the complex and highly technical aspects of the science of gene therapies as well as the limited data related to benefit–risk profile, particularly in early-phase human trials and consequences for the longer-term.^{27,34}

Current challenges

Information presentation. Patients' evaluations of benefit–risk can be greatly swayed by how the information is presented to them. Variations have been observed, depending on the type/degree of detail of information provided, in patient understanding and in how their decisions are made.^{28,35} Gain- *versus* loss-framed messaging (i.e. the 'message framing effect'), reading/discussion order ('natural' *versus* 'fed'), subsequent information coming to light and narrative/numerical explanation of relative *versus* absolute risk, can all result in subjective perceptions of benefit–risk that vary considerably from actual data. For example, patients can make very different decisions towards participating if the risk of death from a treatment is explained at the beginning of the consenting process, as opposed to at the end. Even minor aspects of how information is presented can lead to big variations in the way benefit–risk is conceptualised and understood.³⁵

Support for patients' autonomy is of the utmost importance and requires advanced skills in delivering information in a balanced, equitable manner to enable fully informed choices. HCPs can be influenced by their own experiences and biases, whether consciously or not, which may be transferred to patients through tone or emphasis on particular words and phrasing. Moreover, it has been shown that, when patients decide to undergo

certain procedures, having trust in their physicians is one of the major influencing factors.³¹ However, sometimes roles can be blurred whereby the physician is also the researcher and/or investigator, calling into question their objectivity of recruitment and view of the individual in front of them (i.e. as a research subject or patient). There can be a greater likelihood of physician-investigators misleading their patients into clinical trials (albeit complicated and not always intentionally) if they are themselves invested in the ongoing success of the research.²⁷ Besides the challenges of processing information, other variables shaping an individual's appreciation of benefit-risk include the context of their situation and what matters most to them for both clinical and lifestyle needs.³⁵ It cannot be assumed that clinical goals will always outweigh or satisfy patient holistic demands and choices.

Patient comprehension. Effective informed consent relies on a patient's capabilities to understand the information provided on the medical treatments being offered, or the research aims/protocols of a trial, together with alternatives and the risks associated with them. Factors including age, disease severity, cognitive abilities or impairment (particularly in older patients) and patients affected by mental health conditions or significant psychological distress as well as anxiety or denial (possibly due to their health condition or concerns surrounding a new procedure), may affect a patient's decisional capacity.^{23,28,31,32,35} Inadequate understanding around treatment outcomes can lead to differences in patient expectations of therapeutic interventions.³¹ What's more, patients' acquisition and application of complex scientific information is further complicated by cultural, linguistic and/or health literacy barriers.^{26,28,30-32,34,36}

Despite numerous definitions of health literacy in existence, most interpret the same core elements: skills that enable individuals to seek, obtain, understand, appraise and use information in choices and take appropriate actions.³⁷ The impact of health literacy on health outcomes is widely accepted. Nevertheless, many patients have difficulty understanding and interpreting their discussions with HCPs, attributed in part to the language used. Similarly, healthcare providers do not always recognise health literacy difficulties among adults in spoken conversations.³⁸ Patients with poorer general skills in literacy, numeracy and verbal communication are already at a disadvantage in

functioning effectively within health contexts.³⁹ The European Health Literacy Survey in 2011 noted that nearly half of Europeans have insufficient and problematic health literacy skills.⁴⁰ In the United States, the reporting of 'fair' or 'poor' health is four times more likely amongst adults with low literacy levels.⁴¹

There is a vast body of research demonstrating that patient comprehension is suboptimal and retention of information is fragmentary and often selective, with patients more likely to recall benefits over risks.⁴² A cross-sectional survey of hospitalised patients consenting before undergoing a procedure reported not remembering being provided with information on risks or any alternative treatments, emphasising challenges with patient recall of consent discussions or that the information was omitted altogether.⁴³ A systematic review concluded that, in general, patients demonstrated lower levels of comprehension regarding aspects of consent, whilst crucial information, including benefit-risk, voluntariness and the relation between clinical trials and standard therapy are poorly understood by many participants; severely compromising existing practices intended to provide a sound ethical rationale for research with human subjects.⁴⁴

Therapeutic misconceptions. Research participants, often with pre-existing conditions, may be susceptible to overestimating the benefits/underestimating the risks of early phase trials and may misunderstand the distinctions between research and individualised care, -a concern referred to as the 'therapeutic misconception'. A strong evidence-base demonstrates how therapeutic misconceptions can influence both patients' and researchers' decisions towards study participation, which can invalidate informed consent.^{23,27,28,30,32,42,45,46} It is this dichotomy between research practices conflicting with the traditional aims of clinical medicine that can lead to patient misunderstanding: the former primarily seeks to answer scientific questions without necessarily compensating medical benefits for the participant, whereas the latter's purpose is to provide the best medical care.⁴⁶

The therapeutic misconception has ethical and wider social impacts (e.g. eroding confidence in biomedical research amongst the public), not least seriously undermining informed consent should patients fail to distinguish the goals of research participation from those of medical treatment.^{28,46}

Consent forms. Informed consent within research is more stringently regulated and comprehensive than within clinical practice. As such, a consent form is a legal document designed to record both that researchers have provided sufficient information to patients (relevant to help in decision making) and whether the patients have understood the proposed trial therapy. Despite oversight and governance from an institutional review board (IRB) or research ethics committee (REC) (to ensure research interventions are carefully defined and explained to prospective participants), institutional dynamics, underlying subjectivities, inconsistencies in opinion and inflexible submission requirements can affect IRB/REC assessment of consent forms and their subsequent accessibility and usability by patients.^{47–49} They can be anywhere from 10 to 20 or more pages in length, formatted in a legal prose to satisfy regulatory compliance and loaded with complex scientific terminologies and technical jargon; it is generally assumed that patients will read the consent forms and fully comprehend them. The reality, however, is far from certain and not empirically documented.^{27,28,31,32,35}

There are often several different consent documents that participants need to declare they have read, understood and signed (e.g. biobank repository, qualitative data forms), which can compound the confusion and ‘information overload’.³¹ Individuals may not be given adequate time, space or support to read, comprehend and reflect on the content of consent forms. Studies have suggested that participants may not comprehend the research they are involved in, nor their rights, even after signing a consent form.³² Another important factor is the readability (a measure of the ease with which a passage of text can be read). Although recommendations have been made to simplify the language used (e.g. the US National Institutes of Health recommend language understandable at an 8th grade reading level – equivalent to UK school year 9 – or lower), most consent forms continue to grow in length and are written for much more advanced levels of readability.^{32,39,50} In research analysing oncology consent forms, only 6% out of 137 forms had readability at or below 8th grade; notably a person’s reading-comprehension (the reader’s active extraction and construction of meaning from text) might be a far lower score than the last result they achieved at school.⁵¹ Accordingly, it has been recommended that consent forms should aim to be accessible for at least

three grades lower than the average educational level of the target audience.⁵²

Therapeutic optimism and hype. To increase interest and garner support about research progress, patient advocacy groups (PAGs), the media and public relations agencies sometimes convey compelling and emotional family stories in an over-exaggerated way, leading to patient and public misunderstanding. This tendency to hype positive findings evolves throughout clinical trials and subsequent public discussion of novel treatments often overestimates and overstates benefits, whilst underestimating potential harms.⁵³ Such unrealistic therapeutic optimism may influence how patients apply the information appropriately and misconstrue the benefit-risk assessment of the research or new drug.⁴⁶ Although necessary to report and celebrate therapeutic progress, it is similarly important that all stakeholders – scientists, physicians, journalists, families, PAGs, the pharmaceutical industry and the public – remain diligent in distinguishing between justified hope and excessive hype.⁵⁴

Informed consent in haemophilia gene therapy

Managing patient expectations

As part of the informed consent process, physicians and nurses are expected to be primary educators to PwH about gene therapy, with the responsibility to set patient expectations surrounding eligibility, access and treatment outcomes – both for clinical trials and for approved treatment options.^{55–58} In a mixed methods study involving 63 caregivers of PwH aged <18 years, haemophilia nurses were seen as the most trusted source for advice on gene therapy.⁵⁹ Furthermore, the provision of additional psychosocial support has been suggested to manage and reduce any stress and anxiety that patients and their families/caregivers may express related to risks and areas of uncertainty.^{56,57} In an evaluation study of patient-relevant treatment attributes, 20 PwH ranked ‘uncertainty regarding long-term safety of gene therapy’ in the top three of an opinion poll.⁶⁰ Also, when six PwH in the UK were asked retrospectively about their experiences of receiving an investigational gene therapy, all noted that pre-infusion they had been worried about some of the possible side effects.⁵⁸

Informed consent for long-term monitoring

The World Federation of Hemophilia (WFH), in partnership with professional societies, regulatory authorities and the pharmaceutical industry, are developing the WFH Gene Therapy Registry (GTR) to capture longitudinal data on all PwH who receive gene therapy globally, *via* clinical trial or post-regulatory approval. This data will be critical to answer questions regarding safety and efficacy over the lifespan of treated patients (collected beyond the 5 years-mandated follow-up requested by the FDA).^{61,62} While the intensity of patient monitoring may reduce outside of trials, regular tests will still be essential, particularly to detect any liver abnormalities.^{61,63} Gene therapy recipients will be encouraged to provide informed consent to participate in the WFH GTR, although the process has not yet been defined.^{61,62} The development of tools to reinforce patients' commitment to follow-up has been proposed,⁶¹ and engagement activities to inform HCPs and PwH about the importance of health-surveillance have already started.⁶²

Bioethicists have drawn critical attention to whether, and through what means, current informed consent practices can accommodate long-term storage and use of data.⁶⁴ When creating a patient registry, consent requirements may not be as stringent when compared with those for participation in clinical studies. However, the sensitive nature of data being collected, together with risks (e.g., potential breaches of confidentiality), still necessitates a robust consent process about: the registry's purpose, how information will be used and data protection.^{65,66}

New challenges arise for consenting to a registry when there is uncertainty about its future purposes. In a qualitative study involving 44 specialist research stakeholders, about half considered some mechanism of re-consent as a requisite for mitigating limitations in information exchange at initial consent. For example, patients treated with Strimvelis, the first approved *ex vivo* stem cell gene therapy for ADA-severe combined immunodeficiency, will be followed for a minimum of 15 years and re-consented as appropriate.⁶⁷ Consequently, participants should, over time, develop in their understanding of the registry, likely leading to increased commitment to the long-term research goals.⁶⁴

Consenting to clinical trial participation

Current regulatory guidance. The majority of novel medicines introduced into clinical practice globally are initially approved by the FDA and European Medicines Agency.⁶⁸ Both regulatory agencies have issued general guidance on informed consent for clinical trials and what type of information should be provided to research participants for oral discussion as well as to be incorporated in consent forms (e.g. purpose of the trial, aspects that are experimental, reasonably expected benefits/risks etc.).^{69,70} Furthermore, in 2019, the European Commission released new guidelines on good clinical practice requirements for advanced therapy medicinal products (ATMPs), such as gene therapy, where they emphasise that participants should receive comprehensive information on the expected benefit–risk of the product, together with the explicit instruction to explain to participants the irreversible nature of ATMPs.⁷¹ In 2020, the FDA published further guidance to the pharmaceutical industry that addresses informed consent in clinical trials involving long-term follow-up observations, notably the commitments expected of participants for regularly reviewing their progress.⁷²

Pre-enrolment procedures to solicit informed consent. Experts in haemophilia – representative of the patient and clinical community – have made best-practice recommendations for patient–physician discussions when considering a trial of investigational gene therapy.^{55,56,73} Sidonio *et al.*⁵⁵ have developed a visual aid of the AAV vector delivery procedure, alongside a glossary of key terms. Similarly, Miesbach *et al.*⁵⁶ have generated a list of possible questions that PwH may want answered. Also, Hart *et al.*⁷³ have created a summary of preferred lexicon in an attempt to standardise and facilitate effective communication about AAV-based gene therapy in haemophilia. In addition, Miesbach *et al.*⁵⁷ have outlined approaches for introducing gene therapy within clinical practice and its implications on haemophilia care models in developed healthcare systems. These initiatives highlight some of the ways in which global multi-stakeholders in haemophilia are tackling problems to ensure informed consent practices are authentic, intentional and genuine within the new paradigm of gene therapy.

Following the initial consultation with their physician, prospective trial participants are advised to

write down any thoughts and queries they may have to be addressed as well as familiarise themselves with the trial protocol.⁵⁶ PwH might choose to participate in a specific trial dependent on the key outcomes which are most important to them (e.g. factor level, durability, reduction in chronic pain, impact on mental health, bleed frequency etc.).^{55,56} As such, one defining mantra is for PwH to be at the centre of decision making, whereby physicians implement timely and transparent information sharing, based on the best available evidence at the time. Participants must fully understand their follow-up obligations, too.^{55–57} Another suggestion is to involve an independent person, not part of the haemophilia treatment centre team, who would give a clear, objective presentation on the benefit–risk when seeking patient consent; however, the skills and expertise of this role have not been outlined, neither is it a requirement for consent in most trials.⁵⁶

Due to the limited number of haemophilia comprehensive care centres (CCCs) already conducting gene therapy trials, PwH can be transferred from their own treatment centre to participating CCCs elsewhere. Coordinated and integrated models (such as ‘hub-and-spoke’) have been endorsed to oversee all facets of the care pathway for gene therapy.^{56,57,74} However, given that informed consent is shaped and influenced by patient–physician relationships and the trust and rapport built between these two parties, this move could equally unsettle the foundations required for patients to feel able and confident to query, challenge and discuss gene therapy with the newly assigned physician.⁷⁵

Discussion

Gene therapies for rare genetic conditions are now experiencing rapid clinical and commercial development,^{5–8,10,23,25} with an AAV-based vector product for haemophilia likely approved within the next 2 years.²⁰ This may enable some PwH to aspire to, and attain, improved health outcomes and QoL above that achievable with treatments prescribed today, not least sustained control of bleeding and liberation from prophylaxis.^{2–5,9,11,20–22,24} Nonetheless, there remain many unanswered questions, particularly regarding the long-term safety.^{1–5,10–15,17,18,20–22,24,25} This will inevitably impact on the dynamic between treaters and patients, requiring in both actors considerable thought in balancing risks against the health benefits that gene therapy offers.^{1,13,14,20,22,23,25,26}

Scientific knowledge of the biology of AAV delivery has been outpaced by the momentum of clinical studies.¹ While some questions cannot be fully answered premarket authorisation (e.g. long-term data in a real-world setting required),¹³ a patient’s decision to switch to gene therapy should not have to represent a blind leap of faith.^{14,23} Researchers have a responsibility to clearly define the benefit–risk involved and specify exactly how any potential risks will be addressed and minimised.²³ Without scientific consensus about benefit–risk,¹ it is difficult (indeed, arguably impossible) for potential recipients to appraise, understand and control their own risks through processes of ‘informed’ consent alone; challenging the very nomenclature of such supposed ethical safeguards.²³ Although the patient’s signature in a trial setting, or verbal acceptance in a clinical scenario, may signify agreement, it should not be taken to infer understanding; it may be evidence of ‘consent’ but not representative of a valid informed decision.⁵¹ The contaminated blood scandal of the 1970s–1980s makes for a precautionary principle with regard to decision making where uncertainties persist.¹

The basis for an ethically designed informed consent process is one of having good, clear and transparent information – the patient cannot understand what is not disclosed to them.²⁷ Paying close attention to what information to share, the optimum way to do so and how to ensure sufficient understanding is paramount,^{28,30–32,35,42,44,45,51,52} especially in the context of ‘manufactured hysteria’ and sensationalist media coverage in a high-profile research field.^{46,53,76} In all settings, determining how to communicate and present highly technical and intricate therapeutic information makes for a challenging task, particularly if individuals have: limited scientific knowledge and health literacy, diverse sociocultural backgrounds and debilitating conditions, exacerbated by complex physician–patient power-relations and shifting boundaries between healthcare and learning.^{26–28,30–32,34–39,43,45,46,50} Commonly, patient comprehension of what consent is for and their treatment – a key aspect of the informed consent process^{29,31,32,34,36,46} – is low, despite self-reporting that they are happy with the amount of information given.^{42,44} In haemophilia, PwH’s comprehension of different treatment options and knowledge about clinical trials, including gene therapy, is predominantly limited.^{65,77–81} Clinical trials could be considered ethically questionable, or markedly flawed, when

patients with wide ranging education and health literacy needs agree to a medical intervention based on inadequate, or fragmented, understanding of the relevant information; posing a threat to the participant's autonomy (and thus – dignity).⁴⁴

Potential strategies to improve informed consent in haemophilia gene therapy

To ensure informed consent within haemophilia gene therapy is valid and meaningful, a range of strategies are required to better enable PwH to make evidence-informed choices; to protect their freedoms and prospects if eligible for this one-off, non-reversible treatment in a trial or clinical setting. By reviewing the literature on informed consent, (including for gene therapy), and identifying examples of good practice, we have made the following recommendations and suggestions to enhance the consent procedure in this era of genetic medicine.

Making research consent materials fit for purpose. Consent documentation should be specifically designed for gene therapies, being alert and sensitive to the phrasing of content, terminology, reading level as well as translation into local languages. Information should be presented in plain language to assist in decision making and increase positive feelings, which in turn can lead to perceived greater control of information implementation.^{32,34} The leading problem of informed consent materials is the length and vast quantity of text included, yet the conundrum is that much of this detail is critical. Patients who drop out of trials early are twice as likely to say that the consent form was difficult to understand.⁸² More worryingly, over three-quarters of trial participants who sign the consent form within 24h of first receiving it do so having read only certain sections in detail.⁸³

For such reasons, finding more creative and practical approaches through multimedia and interactive formats can have numerous benefits for presenting information in more user-friendly ways, including: personalising the experience (e.g. providing a sense of what participation will look or feel like), synthesising content and minimising 'information overload', plus addressing immediate and long-term understanding through high message recall.^{28,84,85} Known risks and potential safety implications of *known unknowns* of gene therapy must be explicitly addressed,²⁴ even though this may potentially raise

participants' anxiety. Nevertheless, if relayed in a non-threatening way, it could help facilitate opportunities for questions and dialogue to manage personal expectations of benefits and possible harms,^{52,85} particularly when the safety and efficacy of treatment such as gene therapy is unclear or not yet available, thereby reducing therapeutic misconception.⁸⁶

Still, even the most well-designed consent intervention cannot be a substitute for rich, face-to-face conversations.⁸⁵ A multimedia tool(kit) can function as a practical aid for optimising decision making,⁸⁷ but should be used only as an enhancement, rather than a replacement of the entire process; human interaction and relationships are the core of informed consent.⁸⁴ Moreover, it should be mandatory to involve an independent patient expert with technical knowledge and ethical application of gene therapy, to be co-opted as a liaison between prospective trial participants and the research team to ensure a clear and unbiased overview of proceedings.^{23,56} Also, when designing consent forms and information sheets, patient involvement can improve their quality and relevance, leading to improvements in participant informed consent.⁸⁸ Taken all together, participants may gain greater understanding of the study and feel more like a 'partner' in the research activities, be responsive to a natural/feedback setting (i.e. answering multi-choice questions, notating the information, or researchers using techniques such as the teach-back method to ensure explanations are effective) and build a rapport with the researcher.^{52,85,89} Meanwhile, researchers must promote transparency by declaring their conflict of interest; empathy with participants' welfare against meeting enrolment goals.⁸⁴

Assessing health literacy and patient comprehension. There is a pressing need in haemophilia for the development and routine clinical use of validated assessment tools to efficiently collect and assess data (importantly, qualitative as well as quantitative) on patient health literacy, linguistic ability and cultural beliefs, instead of healthcare providers and researchers relying on gut feelings and historical profiling based on past interpersonal exchanges.^{36,89} Screening questions relating to health literacy have been shown to be practicable, even within busy clinical spaces, to assist in developing ways to overcome barriers to patients accessing information (e.g. utilising diagrams and graphical communication styles).⁹⁰

Likewise, for a more complete picture of how people access, understand, appraise and apply health information, measuring specific health and treatment knowledge may be necessary, rather than assuming that the level of education completed represents their cognitive ability.^{42,52,91} As such, the research team and referring physicians could be better guided away from unconscious biases (i.e. holding back information on the assumption a patient will not understand or explaining things they already know) to instead, tailoring their communication on treatments such as gene therapy to fit patients' informational needs,^{36,92} with focus and support given to those disproportionately affected by low health literacy or socioeconomically disadvantaged.^{37,91} Gathering such insights could even shorten aspects of clinical or study encounters,⁹² and serve to guide the design and utility of interventions to advance patient comprehension of the informed consent process. The use of interactive features and those that encourage active patient involvement and dialogue are especially helpful in enhancing patient understanding as opposed to non-interactive interventions (e.g. patient leaflets, densely worded documents, etc.).⁹³ Giving patients access to clinical notes has been shown to strengthen health literacy and there are opportunities to draw on the growing 'eHealth' movement to educate and empower.⁹⁴

Promoting therapeutic patient education programmes. Increasing calls have been made for greater efforts to raise awareness of and properly educate and prepare PwH for gene therapy, to facilitate an improved informed consent process.^{3,21,26,57,73} Patients are already expected to become more adept at managing their own health across the life-course to optimise their QoL. This necessitates not only treatment knowledge but also effective skills in medical, behavioural, emotional and self-management.³⁹ Yet, the rapidly changing biomedical landscape is driving health system demands for improvements in patients' comprehension of, and engagement in, the fundamental science and application of biotechnology, as well as a grounding in bioethical principles.³⁴ Undertaking gene therapy is currently a once in a lifetime decision and requires accessible education and support, with consistent and translatable language. It cannot be assumed that all PwH will seek and learn about new treatment options,⁵⁸ particularly those that are less activated/hardest to reach and, therefore, face numerous obstacles to

sustained engagement in accessing educational provision and related services.²⁶ Already a key barrier to adherence to prophylaxis is a lack of understanding about the underlying condition – access to education is integral to achieving optimal outcomes through democratising decision making *via* informed consent.⁵⁸

Haemophilia PAGs and umbrella groups, pharmaceutical companies as well as professional membership societies have produced several standalone educational initiatives for patients to take part in fact-based discussions on gene therapy.^{26,34} These, however, can only scratch the surface in their function and utility to empower and inform PwH, who may differ in their ability to learn and will respond to varying forms and delivery of content in diverse ways.³⁷ Notably, many of these health promotion activities will more than likely be consumed by the same groups of activated and engaged PwH, who are already cognisant of the value of knowledge acquisition.²⁶ Thus, great care must be taken so that these initiatives do not simultaneously risk marginalising those who are not currently engaged or in possession of high levels of health literacy.

Consent is a *process*, rather than an event.⁵² Therefore, a successful consent approach warrants education and engagement taking place over an extended period of time, rather than as a one-off interaction; giving space for answering questions, addressing misconceptions and allowing participants a 'cooling-off' period for further consent discussions.^{23,34,45} Embedded in the process should be a well-vetted, unified educational strategy – one that has already identified patients' knowledge gaps and priorities²⁶ – based on a multidisciplinary, collaborative framework that provides clear direction for learning goals and implementation; enabling prospective gene therapy recipients equitable access to tailored, age-appropriate education and to promote gene therapy literacy competency.^{34,59} Only by creating participatory learning environments where individuals are treated as active subjects of their own learning – to change and resist patterns of dependency and passivity by providing and reinforcing inclusive and empowering experiences⁹⁵ – can PwH build critical consciousness, become mobilised and 'arm' themselves with the knowledge-base,^{95,96} to lead informed shared decision making discussions about gene therapy. Meanwhile, relevant stakeholders can feel satisfied that they have

done everything in their power to ensure that the patient has an all-round understanding and is fully aware of the consent they give or deny. It could be argued that these extra precautionary measures may risk convoluting the consent process. Nevertheless, safeguarding the rights of PwH should remain the top priority.

Clarifying the role of PAGs. Patients can gain knowledge about investigational treatments through multiple routes, including turning to PAGs.⁹⁷ PAGs are uniquely positioned to facilitate patient education through partnering with physicians, other healthcare professionals and industry, to further the cause of science and help improve the care of their members for the future.⁹⁸ As well as advocating for patients' safety and well-being, the quantity and quality of resources PAGs provide can sway patient decision making.⁹⁵ PAGs in haemophilia have a moral responsibility to provide an engagement pathway to nurture and support PwH at each milestone in their gene therapy decision making journey. This should include a peer mentoring programme to connect prospective trial participants or clinical patients with those who have already received gene therapy, particularly in respect of the practicalities of treatment administration and what to anticipate during follow-up.⁵⁶ The PAGs could also play a central role in the formation of a 'Patient Charter' for gene therapy, to educate patients and research participants on their rights and why they matter, including the right to demand a dialogue with the physician and to be treated as an individual with consideration, dignity and respect.^{29,57}

Conclusion

The race towards commercialising AAV-liver directed gene therapy for haemophilia must be tempered by the absolute protection and safeguarding of the rights, interests and autonomy of research participants or patients to have a complete, meaningful and valid informed consent process, with an emphasis on all round patient knowledge and comprehension. In contrast to conventional medicine, pharmacological treatments based on human gene therapy have extremely complex characteristics and modes of action that are unpredictable and not clearly understood, contributing to remaining scientific evidence gaps. As such, this will demand enabling PwH to achieve higher levels of competence, capacity and health literacy to engage in benefit–risk discussions;

integral to shared decision making for each step of their gene therapy journey. There are numerous factors, including the role of the patient, researcher, physician/physician-investigator, together with cultural and socio-economic conditions, that can influence decision making and challenge the ethical foundations for obtaining consent. Bringing the theoretical and practical aspects of informed consent closer together is essential – good ethics requires transparent and consistent communication to help foster a sense of both trust and empowerment for PwH choosing to/not to undergo gene therapy. Consent is a *process*, rather than a one-time event, so ongoing assessment of patient understanding, followed by enhanced consent forms and use of diverse multi-media interventions – designed through community-based participatory research – as well as peer support mechanisms, can all aid information delivery, tailored to the assessed learning needs and preferences of the individual. An independent patient expert with technical knowledge and ethical application of gene therapy should also be mandatorily co-opted in as an unbiased voice to give confidence to PwH and prevent possible coercion in the proceedings. Further research is needed that incorporates the views and perceptions of key stakeholders in haemophilia to continue defining new, creative strategies for patient education and the upholding of ethical values in the informed consent process. The lessons learnt and approaches developed within haemophilia could set the gold standard for good practice in ensuring ethical preparedness amidst advances in genetic therapies.

Author contributions

In accordance with SAGE's authorship criteria, Laurence Woollard is responsible for 'conceptualisation', 'writing – original draft', and 'writing – review & editing'. Richard Gorman is responsible for 'conceptualisation' and 'writing – review & editing'. Dakota J. Rosenfelt is responsible for 'writing – review & editing'.

Conflict of interest statement

Laurence Woollard is the sole owner of and runs On The Pulse Consultancy Ltd, which provides independent, strategic advice on global patient activation campaigns to the commercial and third sectors in haemophilia and rare diseases, including Pfizer, Sobi, Freeline and Roche. LW has also served as an advisory board consultant for haemophilia-related educational purposes for BioMarin, bluebird bio, UniQure and Roche, and

has received honoraria for educational presentations with Pfizer, Novo Nordisk, Shire, Roche and Spark Therapeutics. LW is also a member of the Patient Advisory Board of Therapeutic Advances in Rare Disease.

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