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CLINICAL PRACTICE

Personalising haemophilia management with shared decision making

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The current standard of care for treating people with haemophilia (PWH) in the developed world is prophylaxis with regular infusions of clotting factor concentrates. Gene therapy is being investigated as a new treatment paradigm for haemophilia and if approved would potentially eliminate the need for chronic, burdensome infusions. In recent years, shared decision making (SDM) has become increasingly common in patient care settings. SDM is a stepwise process that relies on reciprocal information sharing between the practitioner and patient, resulting in health care decisions stemming from the informed preferences of both parties. SDM represents a departure from the traditional, paternalistic clinical model where the practitioner drives the treatment decision and the patient passively defers to this decision. As the potential introduction of gene therapy in haemophilia may transform the current standard of care, and impact disease management and goals in unique ways, both practitioners and PWH may find their knowledge tested when considering the appropriate use of a novel technology. Therefore, it is incumbent upon haemophilia practitioners to foster an open, trusting, and supportive relationship with their patients, while PWH and their caregivers must be knowledgeable and feel empowered to participate in the decision making process to achieve truly shared treatment decisions.

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With the availability of novel therapies and gene therapy on the horizon, it is essential that the relationship between people with haemophilia and health care practitioners empowers them to make informed joint decisions about their treatment options

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When patient-centred care was conceived nearly 30 years ago, the practice of medicine began a slow shift away from thinking of the disease as an isolated entity and back toward the patient and family [1]. This shift involved practitioners becoming better acquainted with patients' needs, values, and individual experiences of their illness [1]. The patient-as-partner approach is becoming more and more important in medicine and recognises the patient's experiential knowledge, gained from living with a disease, as complementary to that of health care professionals [1,2]. The recent evolution known as shared decision making (SDM) is one of the tools of the patient partnership model. Under this model, health care decisions are based on informed preferences of both the practitioner and patient [3]. SDM advances medicine beyond the traditional 'one size fits all' regimens typical of the customary paternalistic clinical model, by promoting a more symmetrical and equitable partnership between the practitioner and patient, moving from a transactional interaction to a true and equitable relationship between the patient and members of the health care team. This is achieved through integrating the practitioner's expertise and experience with the patient's autonomy, right to information, treatment goals, and involvement in all treatment decisions [4,5]. In certain circumstances, such as acute injury or other emergent medical need, an immediate autonomous decision by the practitioner may be required. However, a new diagnosis, a non-life-threatening condition, or ongoing care for a chronic condition provide ideal opportunities to integrate the patients' – and in many cases caregivers' – preferences into the clinical experience [1,6].

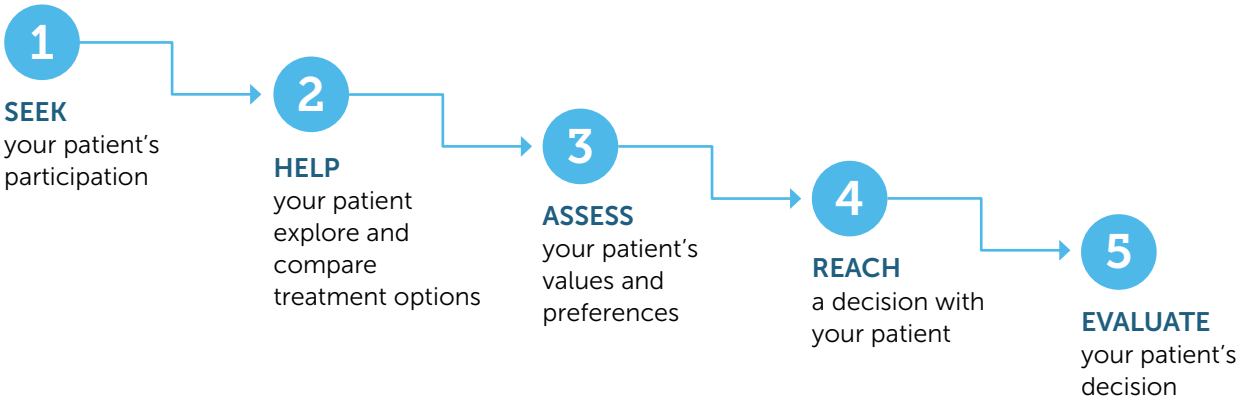
SDM is a stepwise yet fluid process that includes discussion of patient goals, values, and desires, focusing on what matters to patients and their families. This results in treatment decisions arising from the balanced consideration of risks, benefits and alternatives between available management options and patient preferences. The approach assumes a two-way flow of information between the patient and practitioner, assuming that the patient is capable of understanding the risks, benefits and alternatives associated with available management options [6]; in the case of young children, parents/guardians must assume the role of the patient in SDM.

SDM typically occurs through a series of steps [7]. Once a patient is faced with a new management option or change in care, the first step is a planning phase during which they are introduced to the concept of choice to help them, or their family/caregiver(s) if actively involved in care (e.g. for young children), understand that they will play a major role in deciding how they wish themselves or their child to be treated. The patient's values and preferences are elicited, his or her treatment goals are discussed and understood, and the patient is introduced to the available management options and their risks, benefits, and alternatives. At this stage, the patient is ostensibly provided with sufficient information to effectively compare different management options [7,8]. The practitioner's role is to ensure that the patient is well informed about the options, and to stay neutral while providing decision support, which may occur through dialogue and/or decision aids such as printed materials, audio and video, and/or interactive web-based tools that help simplify concepts and issues around treatment choices [9,10]. The SDM process concludes with arriving at a decision at this point in time. The practitioner may offer the patient additional information or support before confirming the treatment choice, including reassurance that there is an opportunity to review the selected treatment before starting it, and that modifying or withdrawing from the initial treatment plan is always possible and will also follow a SDM approach [7]. Furthermore, the patient and practitioner must both realise that a decision made today regarding a treatment may be revisited in the future as additional options become available and/or the patient's expectations evolve.

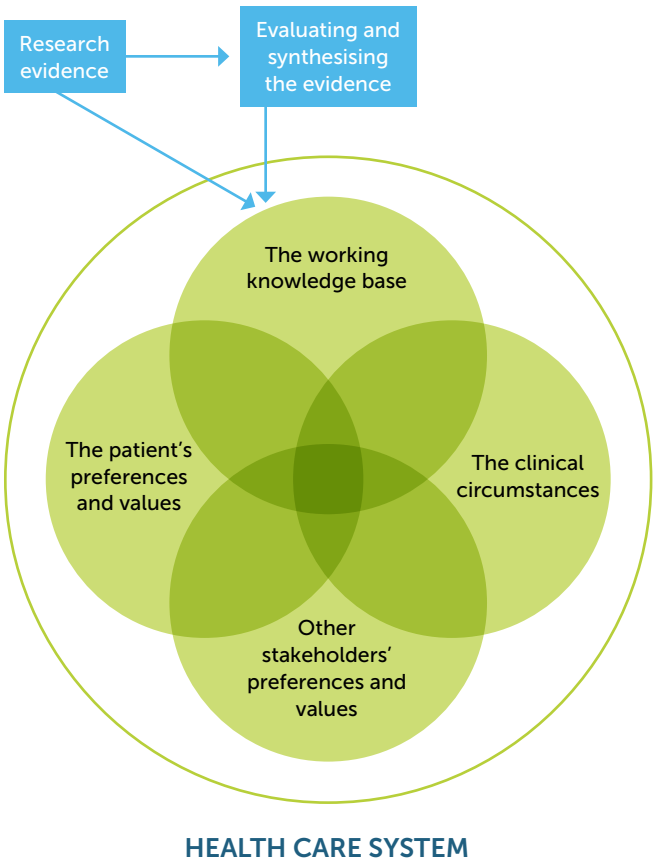
Several structured models of SDM have been proposed. A three-step model published by Elwyn and colleagues proposes stages broken down as choice talk (planning), option talk (introduction to available management options), and decision talk (move to the final decision) [7]. The US Agency for Healthcare Research and Quality offers a similar method referred to as the SHARE approach (Figure 1A), consisting of **S**eeking the patient's participation, **H**elping the patient explore and compare management options, **A**ssessing the patient's values and preferences, **R**eaching a decision with the patient, and **E**valuating the patient's decision [11]. Other approaches generally follow the same flow of seeking the patient's input, assessing their preferences and values, deciding on a treatment, and reviewing the decision (Figure 1B) [12,13].

Figure 1. Models of SDM

1A. The five-step SHARE approach [11]



1B. The Analytic Hierarchy Process [13]



SDM may improve patient outcomes for several reasons, including increased patient satisfaction and improving treatment adherence [8,14]. To accomplish such goals using SDM, care providers need to establish open communication and a trusting relationship with their patients, and present information in a neutral manner, free of overt and implicit or unconscious bias. Overt bias may be introduced by the practitioner who is more familiar with one treatment versus another. On the other hand, the patient may have a bias towards a therapy that is familiar to them and be reluctant to embrace a treatment that presents a new mechanism of action, for example. In both cases, education is vital. It is essential that the practitioner learns about and presents all options to the patient and family in a fair and balanced manner. Likewise, patients must be prepared to embrace new information with an open and thoughtful approach. Unconscious bias on the part of the practitioner can lead to false assumptions and negative outcomes for patients. As it is difficult to omit unconscious bias from interpersonal interactions, it is important that medical professionals take active steps to learn about unconscious biases and acquire skills and techniques to reduce them, especially when interacting with minority group patients. This may require consideration of patient characteristics (e.g. race, ethnicity, culture, educational level, and knowledge base) and potential biases that may affect their values and decision making process, while avoiding stereotyping, to individualise treatment plans for each patient [3,15]. The overall goal is to empower patients to understand their vital role in the process and the consequences of their decisions. One means by which practitioners can facilitate this empowerment is by reinforcing that the patient's values, preferences, and questions can be safely expressed [1,16]. Effective communication also helps keep the patient engaged and ensures that they are adequately educated about the treatment options to confidently share in the treatment decision [16]. Knowledge alone is insufficient for patients to participate in SDM; the power to influence the decision making process must also be assured and this power can be more difficult to attain [17].

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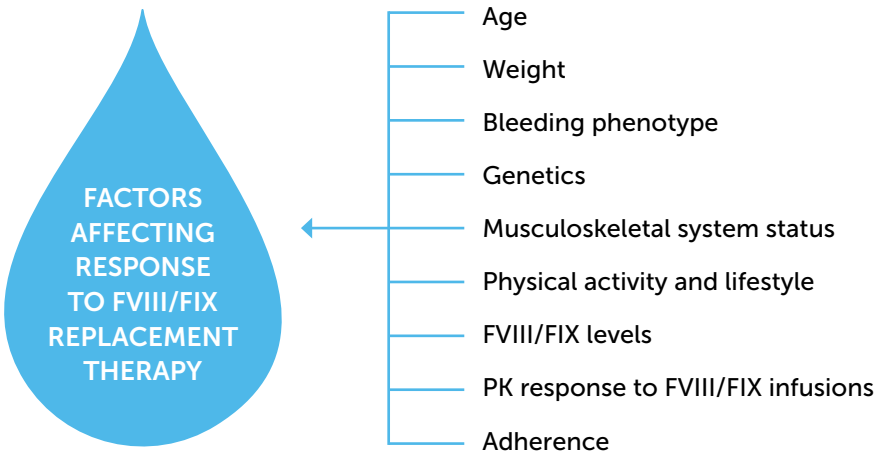
Despite the benefits of SDM, the concept is not without limitations. First, considering the shared nature of SDM, there is the potential for 'conflict decision' whereby a patient's choice may be challenged by the practitioner or vice versa [18,19]. This can occur if/when an informed patient's preference is not supported by the practitioner or organisational policies [20]. Furthermore, some practitioners are sceptical of the value of SDM and may be resistant to adopt the process [17]. This scepticism may extend to healthcare systems as a whole where SDM is not viewed as the standard of care [17]. Healthcare systems may impose specific procedures or limitations counterproductive to SDM, such as incentivising certain practice targets and limiting interaction time between patient and practitioner, limiting available treatments, or refusing (in a number of countries) to reimburse treatments jointly selected by the patient and practitioner [19,21]. These considerations may disproportionately affect uptake of newer therapies where more education and dialogue may be required between the practitioner and patient [17,19].

HAEMOPHILIA CARE

Until recently, the standard of care for treating people with haemophilia (PWH) A and B with and without inhibitors, especially those with severe disease, was the regular administration of safe, virus-inactivated plasma-derived or recombinant clotting factor concentrates [22,23]. Although this approach can be effective, there is a high level of variability in dose and frequency of infusions and treatment response based on product specific characteristics (e.g. product half-life), individual patient characteristics (e.g. age, weight, bleeding phenotype, immunogenicity; Figure 2), and environmental or lifestyle considerations (e.g. level of physical activity, access to homecare, caregiver capabilities) [23-26]. Infusions may be required several times a week on an ongoing basis to maintain therapeutic factor levels, and bleeding can still occur even under such a demanding schedule [27,28]. Additionally, formation of anti-drug antibodies (inhibitors) occurs in up to one third of people with severe haemophilia A and 5% with severe haemophilia B, which can render clotting factor replacement ineffective and require different treatment options or products [29].

The high level of variability in dose and frequency of infusions and treatment response provides an opportunity for the patient, family/caregiver(s) and the practitioner to engage in SDM to better understand the goals for therapy and opportunities to meet the expectations of PWH in terms of efficacy of the therapy and burden of the treatment. Education regarding new treatment products should be undertaken. This may include recently introduced extended half-life (EHL) products, or regimens such as using an EHL product to increase the trough factor activity level or increasing the interval between infusions to reduce the burden of treatment. The licensure of emicizumab-kywh (ACE910) in the US, Europe and other countries affords another choice of haemostatic agent for prophyalxis to prevent bleeding in PWH [30]. This is particularly important for PWH who have developed inhibitors against factor VIII [30], and provides another opportunity to engage in SDM. Once PWH, their family/caregiver(s), and also the practitioner are educated on the product's safety and efficacy profile, its novel mechanism of action and unique pharmacokinetics, the discussions will again focus on how it may meet therapeutic goals and treatment expectations.

Figure 2. Factors affecting response to prophylaxis for haemophilia [25,56]



Other considerations can negatively impact the standard of care for haemophilia therapy. Notably, treatment nonadherence is common among PWH [31-33], and one third of US haemophilia practitioners do not prescribe and/or have stopped prophylaxis based on concerns about adherence in their patients [34]. The cost of treatment is another important consideration for haemophilia care. Under the current treatment paradigm, more than 80% of the overall costs of care for haemophilia is due to clotting factor concentrates [35,36]. Furthermore, given the advancing treatment paradigm of gene therapies, where lifetime treatment costs are offset due to the potentially curative nature of the therapies, value-based prices resulting from cost-effectiveness analysis often result in high up-front prices. This is evidenced in the Institute for Clinical and Economic Review (ICER) evidence report, which found spinal atrophy gene therapy treatment Zolgensma's $2.1 million price to be cost-effective at quality-adjusted life-year (QALY) thresholds often considered appropriate for evaluating ultra-rare diseases [37].

Treatment nonadherence presents another opportunity to engage in SDM. The practitioner must seek to identify the underlying basis for individual PWH's behaviour, to understand the barriers, real or perceived, that impair compliance with their treatment plan, and provide potential solutions to overcome these barriers. For example, cost may be a concern and the practitioner may be able to provide advice regarding available programs that could assist with the high costs of their haemophilia treatment. It also may be determined that the nonadherence reflects a lack of alignment between individual PWH and practitioners in terms of their treatment goals. In this case, a revision to the treatment plan can be undertaken to realign both parties and meet the patient's expectations.

As scientific breakthroughs result in the emergence of potentially one-time treatment modalities, methods of cost-effectiveness evaluation will also need to evolve to best measure the cost and outcomes of these treatments [38,39].

NEW THERAPIES IN HAEMOPHILIA

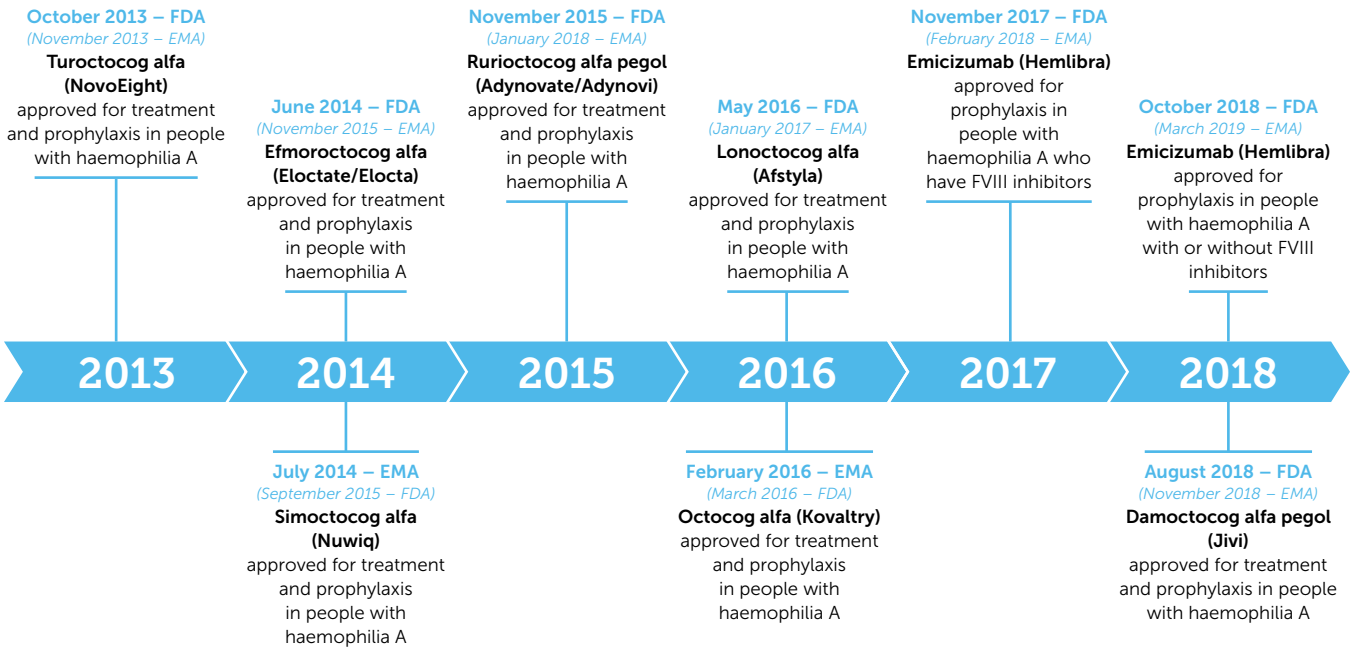
Recent advances in haemophilia treatment may overcome some of the drawbacks of chronic factor infusion therapy and ease the burden on PWH (Figure 3). In 2017, the monoclonal antibody emicizumab-kxwh was approved in the US to treat haemophilia A with inhibitors and extended to all haemophilia A in 2018 [40]. This is a bispecific antibody that binds activated factor IX and factor X to mimic the cofactor activity of activated factor VIII and restore haemostatic function. This approach allows PWH to transition from intravenous infusion to a subcutaneous injection as infrequently as once every four weeks [41]. The discovery and characterisation of the anticoagulant protein tissue factor pathway inhibitor (TFPI) led to the development of medicinal anti-TFPI molecules that can restore functional haemostasis in factor VIII or IX-independent manner. A small interfering RNA (siRNA) approach (fitusiran) is also under investigation, which potentiates the coagulation pathway by inhibiting plasma antithrombin production (specifically antithrombin 3) and therefore activity to 'rebalance' the system [42]. Each of these advances represents potential opportunities to engage in SDM should one or more receive regulatory authorisation.

The next innovative treatment option for hemophilia is gene therapy [43]. Gene therapies work by providing a functional copy of the absent or mutated gene responsible for causing disease to restore normal coagulation function. The therapeutic gene (e.g. F8 or F9 for factor VIII and factor IX, respectively) is delivered into target cells (e.g. hepatocytes) using recombinant viral vectors, typically from the adeno-associated virus (AAV) family. The vector is replication defective due to the removal of the rep (replication), cap (capsid) and aap (assembly) genes, which are replaced by the therapeutic gene along with a tissue-specific promoter element, inverted terminal repeats required for genome replication and packaging, and a terminator/polyadenylation signal. This investigational approach may be well suited for conditions like haemophilia that result from the functional absence of a single gene [29]. The first marketed gene therapy, alipogene tiparvovec (Glybera; uniQure, Amsterdam, Netherlands), was approved by the European Medicine Agency (EMA) in 2012 to treat patients with lipoprotein lipase deficiency. More recently, voretigene neparvovec-rzyl (LUXTURNA®; Spark Therapeutics, Philadelphia, PA, US) was approved in the US and the European Union for the treatment of an inherited retinal dystrophy [44], followed by Zolgensma (Novartis, Basel, Switzerland) for paediatric patients with spinal muscular atrophy [45].

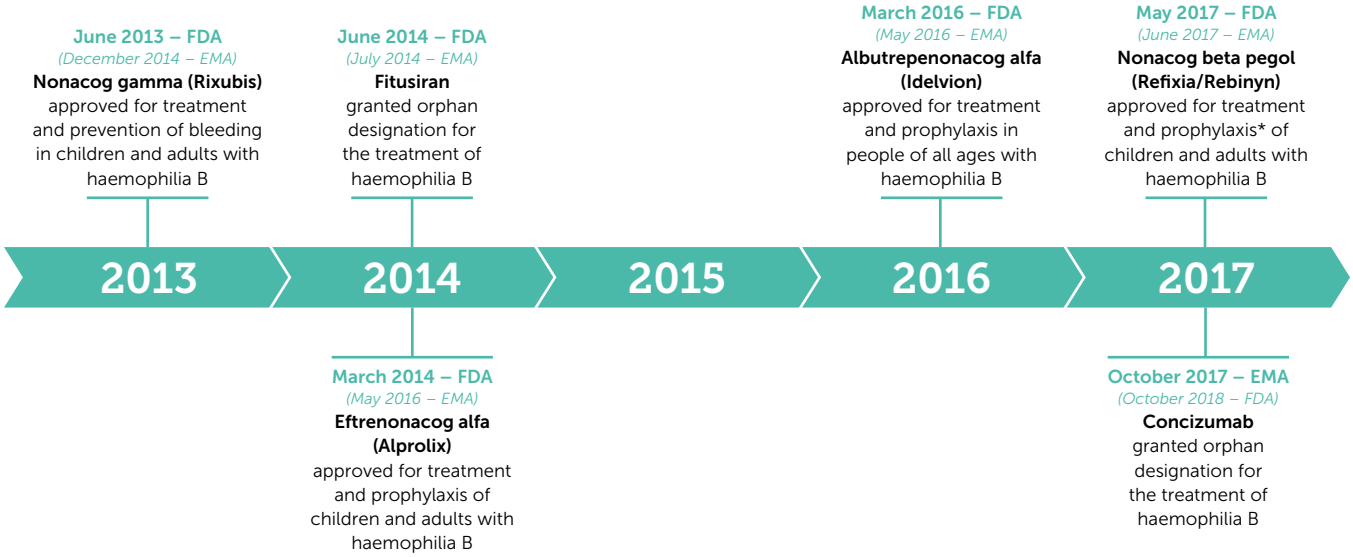
Gene therapy is now under investigation in phase 3 clinical trials for the treatment of haemophilia A and B, representing a potential major shift in how haemophilia is treated. A summary of the currently known benefits and risks of gene therapy in haemophilia is provided in Table 1. Gene therapy is especially promising for this condition as the bleeding phenotype can respond to a broad range of factor levels, which eliminates the need for precise expression levels, and factor proteins

Figure 3. Recent treatment approvals and investigational treatments in haemophilia A and B treatment
Approvals are listed in chronological order from the date first approved (from either the FDA or EMA). Consizumab and fitusiran are agents currently under investigation for the treatment of haemophilia.

HAEMOPHILIA A



HAEMOPHILIA B



*Prophylaxis approved in the EMA only

Table 1. Potential benefit and risk considerations for gene therapy for haemophilia [29,35,51,55]

POTENTIAL BENEFIT CONSIDERATIONS	POTENTIAL RISK CONSIDERATIONS
One-time treatment modality	Novel treatment approach with limited clinical experience to date
Evidence of potential clinical efficacy in clinical trials	Limitations due to patient ineligibility
May decrease cost of treatment over time vs. prophylaxis or standard of care	Potential immune response to treatment
May improve quality of life vs. other treatment modalities	Limited clinical experience precludes availability of long-term safety data and durability

can be synthesised in non-native cells and tissues since clotting factor proteins are secreted into the circulation [29]. Perhaps the most important benefit of gene therapy in haemophilia is that a single treatment may result in long-term therapeutic benefit, eliminating the need for chronic, burdensome infusions [29]. In the absence of long-term clinical trial data in patients with haemophilia A, clinical trials in haemophilia B have demonstrated that this approach is safe and effective with expression of F9 genes maintained for over eight years at last report [46]. Overall, gene therapy may impact treatment effectiveness, and potentially address patient nonadherence to traditional therapy. Moreover, since it is a one-time therapy without the long-term commitment associated with clotting factor or non-factor based therapy, it may expand treatment availability to patients with limited or no access to these haemostatic agents [47,48].

While these considerations are not exhaustive and the optimal benefit-risk profile of gene therapy for haemophilia A is yet to be fully characterised and remains the subject of intense research, it nonetheless follows that an evolved set of evaluation criteria, including a core outcome set [49], would need to be defined for treating clinicians and their patients for assessing the appropriate use of gene therapy and other emerging technologies.

The introduction of new therapies, some with novel mechanisms of action, provide PWH and practitioners with additional opportunities to engage in SDM regarding their appropriateness as a treatment for the individual if and when they become available outside of a clinical trial.

SHARED DECISION MAKING IN HAEMOPHILIA

A chronic condition like haemophilia provides an ideal opportunity for SDM as PWH need knowledge and skills to manage their lifelong condition [16]. Under the existing clotting factor replacement treatment model, data suggest that active patient engagement in designing and evaluating prophylaxis with support from the multidisciplinary treatment team has been effective in reducing bleeding and improving overall quality of life and physical activity [3,23,50].

The introduction of a one-time treatment such as gene therapy into the treatment landscape may challenge the base assumption that prophylaxis, whether with factor concentrates or with chronic administration of a subcutaneous medication, should be the standard of care for all patients with haemophilia. Since gene therapy may present a significantly different treatment choice vs. a chronic therapy (Figure 4), a new set of risk and benefit considerations would need to be evaluated during the treatment decision process [51,52]. For PWH accustomed to clotting factor-based treatments, gene therapy represents a major shift that would require both practitioners and PWH to adopt a new way of thinking about treatment beyond the previous known benefits and risks of clotting

Figure 4. Peaks and troughs of factor levels and haemostasis differ between modalities [51]

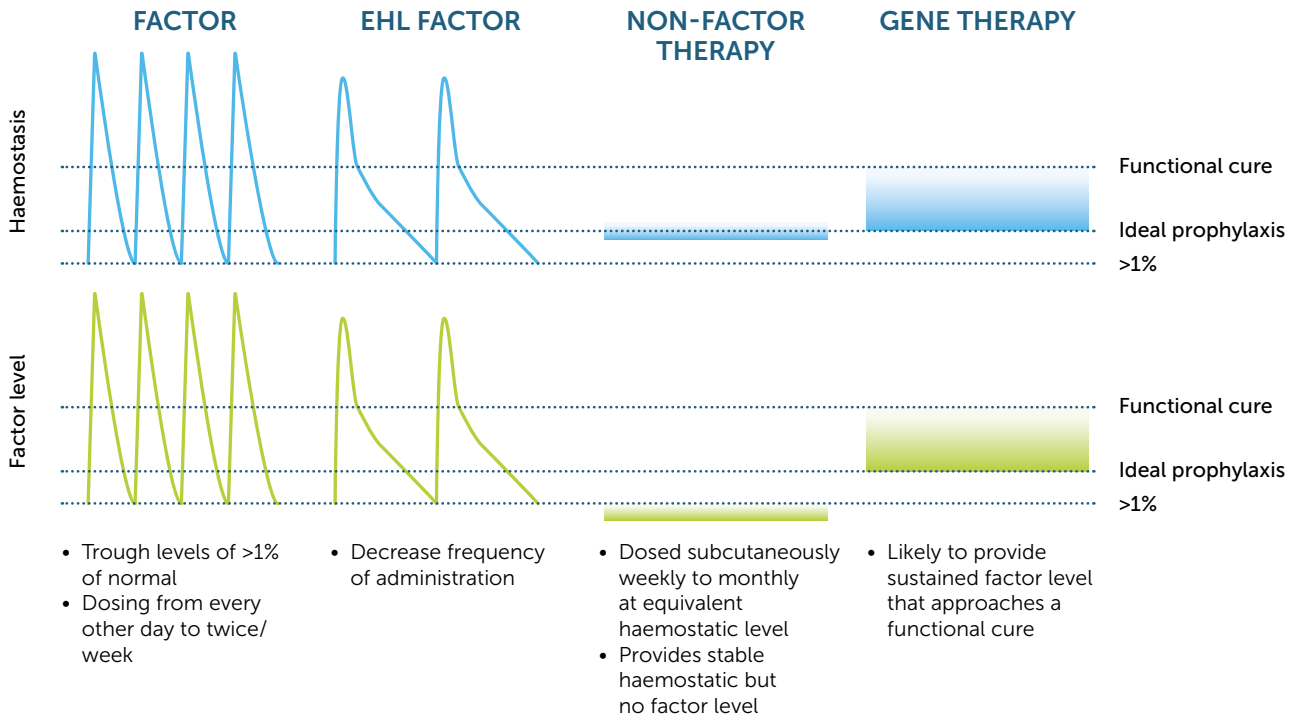


Table 2. Available examples and resources for shared decision making

NAME	DESCRIPTION	URL
Ottawa Personal Decision Guides	Designed to help people identify their decision making needs, plan the next steps, track their progress, and share their views about any health-related or social decisions	*https://decisionaid.ohri.ca/decguide.html*
Laval University and McMaster University	Prepares the clinician to discuss scientific evidence with the patient (or caregiver) so they can make an informed decision together	*https://www.boitedecision.ulaval.ca/fileadmin/documents/Boites_PDF/Prophylaxis/Dbox_prophylaxis_treatment_options_AN.pdf*
The Mayo Clinic Shared Decision Making National Resource Center	Advances patient-centred medical care by promoting shared decision making through the development, implementation, and assessment of patient decision aids and shared decision making techniques	*https://shareddecisions.mayoclinic.org/*
Dartmouth-Hitchcock and the Dartmouth Institute Center for Shared Decision Making	Provides patient decision aids, decision support counselling, and facilitation of advance care planning discussions	*https://www.dartmouth-hitchcock.org/shared-decision-making/resources*
The National Learning Consortium	SDM fact sheet with an overview of the process and links to other resources	*https://www.healthit.gov/sites/default/files/nlc_shared_decision_making_fact_sheet.pdf*

factor therapy. Both parties will need to think differently about what may be possible in order to focus on what matters most to PWH and their families. With the potential introduction of a new treatment modality, practitioners may find their knowledge tested when having a conversation with PWH, while PWH may be unsure how to navigate a conversation about their own therapies. This change in thinking would impact disease management and goals, and further necessitate that PWH receive highly accurate and timely information, empowering them to make educated treatment decisions and, if necessary, inform or influence their health care team about the benefits and risks of gene therapy during the SDM process.

PATIENT SUPPORT IN AN ERA OF GENE THERAPY

Considering the novelty of gene therapy, it may be a challenge for PWH to integrate this new information when establishing (or re-establishing) their preferences. Patient advocacy organisations, such as the National Hemophilia Foundation, World Federation of Hemophilia, or European Haemophilia Consortium, may be helpful in assisting PWH in understanding this complicated new science, its possibilities and risks, and how it may coalesce with individual preferences. Additional resources, such as the educational gene therapy module offered by the American Society of Gene & Cell Therapy [53], may help PWH understand the complexities of gene therapy.

In embarking on SDM that includes the possibility of gene therapy, a starting point is determining whether the approach is right for an individual with haemophilia and what they want to achieve (i.e. the outcomes that matter most to them) rather than focusing specifically on which specific treatment to use. This may be particularly beneficial for PWH who have already switched between several factor-based therapies and/or emicizumab and may be resistant to switching again. Prioritising treatment goals and discussing how each therapy option may enable or challenge the individual to achieve these goals may help simplify the decision.

Specific decision aids and health information tools, all of which are designed to facilitate SDM, have been developed in the form of paper or electronic media, including pamphlets, brochures, videos, patient testimonials, two-sided decision tools, decision boxes for physicians, and decision aids for individuals with haemophilia. Several of these are available online and are briefly summarised in Table 2.

LIMITATIONS

Despite the promise of gene therapy, there are challenges that would make SDM conversations about gene therapy in haemophilia difficult. A common challenge to effective SDM is the need to routinely engage patients to take an active role in the process. A certain level of patient motivation,

knowledge, and ability to understand the available information is required, while conversely, health care professionals must have the knowledge and mindset to educate and empower their patients towards an informed conversation about their treatment options. Caution must be exercised to aid patients who may be overwhelmed, disinterested and/or wish to take a passive role in SDM [15,19], particularly if a new treatment modality is complex and requires considerable education to make informed decisions. PWH, especially the older generation, may feel intimidated or confused by the science, especially after becoming accustomed to clotting factor replacement therapy over many years. This shift in thinking may lead to anxiety, affecting the individual's ability to receive information, make effective decisions, or effectively express their assumptions and expectations [19,54]. However, PWH over time have proven their resource and capacity to go through important difficulties: the HIV and hepatitis C crisis, lack or shortage of treatment, and constant adjustment in their daily life. That is why an open, trusting, and supportive relationship between the practitioner and patient is requisite for achieving a truly shared treatment decision [3]. This is achievable in the setting of a chronic condition such as haemophilia, where clinical management presents many opportunities to integrate SDM into the clinical experience [6].

As each innovation moves through the clinical development process, we, as a community will learn more about the safety, efficacy, durability, and predictability of each product. As this information becomes available, it is incumbent that PWH and practitioners absorb this information so that, if approved, they can engage in a productive dialogue using the principles of SDM outlined in this manuscript.

Since SDM is based on information sharing and adequate understanding of the risks and benefits on both sides, discussions between practitioners and patients around a novel therapy may be more challenging if the practitioners themselves lack the information and experience required to properly advocate for these therapies. PWH may be uncertain about which therapy to pursue if several options are available and none clearly stands out as the best for them, and information provided by guidelines, population studies, or clinical trial data may be difficult to translate to their individualised needs [21]. Therefore, education and skilled communication on behalf of the practitioner and/or health care team are required for effective SDM, especially for a new and complex treatment paradigm. Moreover, there are still many unknowns regarding the risks and benefits to novel treatments due to the lack of long-term (5–10 years) clinical efficacy and safety data; in addition, patients and practitioners may differ in risk tolerance.

Finally, several ethical issues would need to be addressed if gene therapy for haemophilia becomes available. There will undoubtedly be debate regarding who should be offered gene therapy. Some patients may not be eligible based on circumstances such as age, health status, or lack of insurance coverage. Moreover, testing may be required to determine if/which gene therapy option may be available as up to 40% of people in the general population have neutralising antibodies to AAV [51], potentially excluding them from the option of gene therapy. Although a desired treatment option may be unavailable or limited within a health system, or an individual with haemophilia may be ineligible for a given treatment and limited to prophylactic therapy, an SDM discussion including all treatments is still a useful process in empowering PWH with valuable information.

CONCLUSION

SDM can be a powerful approach in the era of multiple therapeutic options for PWH. The focus of SDM is on understanding the patient's treatment goals, and on assisting both the patient and practitioner to jointly arrive at a decision that takes into consideration the risks, benefits and alternatives to the proposed intervention on a case by case basis. Yet, despite the benefits of SDM, there are also barriers to overcome, such as the need for accurate and current information, and the desire by both the practitioner and patient to engage in the process. Considering the recent innovations in haemophilia and choices of approved therapies, SDM is a useful tool in determining treatments approaches, and may also set the stage for advocacy for access to novel therapies such as gene therapy.

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This paper does not contain any studies involving human participants or animals performed by any of the authors.

Declaration of interest

Dr Victor Blanchette reports that he is the Chair of a non-profit organisation, the International Prophylaxis Study Group (IPSG). He has received fees for

participation in advisory boards/education events from Amgen, Bayer, Novo Nordisk, Pfizer, Roche and Takeda. He is a recipient of investigator-initiated grants from Bioverativ, Novo Nordisk and Takeda and has received fees for participation in Data Safety Monitoring Boards (DSMB) from Octapharma and Takeda.

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