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ORIGINAL ARTICLE

International Society on Thrombosis and Haemostasis Clinical Practice Guideline for Treatment of Congenital Haemophilia—A Critical Appraisal

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ABSTRACT

Introduction: Evidence-based clinical practice guidelines drive optimal patient care and facilitate access to high-quality treatment. Creating guidelines for rare diseases such as haemophilia, where evidence does not often come from randomized controlled trials but from non-randomized and well-designed observational studies and real-world data, is challenging. The methodology used for assessing available evidence should consider this critical fact. In formulating guidelines, it is essential to include treatment goals and patient preference.

Aim: This paper comprehensively critiques, against this background, the recommendations of the ISTH clinical practice guidelines for the treatment of haemophilia.

Methods: Each recommendation was critically reviewed against available evidence as well as existing guidelines and commented upon for its scientific validity, impact on clinical practice and access to care globally. The validity of the way in which the GRADE methodology was applied to existing evidence was also assessed.

Results: The critique provided shows that these recommendations have major limitations: they did not state treatment goals and contradict existing guidelines; opportunities for providing access to innovation were missed when the therapeutic benefits of the products approved in the last decades were not included. A major reason for this is the inappropriate adoption of the GRADE methodology without adaptations and without considering treatment goals and patient-relevant outcomes.

[Correction added on 19 December 2024, after first online publication: The COI and Plain language summary was added to the article.

Authors are listed in alphabetical order because all these authors contributed equally to this study.

Conclusion: These recommendations may mislead healthcare professionals, payers and governments and therefore cannot serve the patient community well. They setback the advances made in haemophilia care because they overlook important available evidence and do not guide clinical practice to contemporary standards.

1 | Introduction

Clinical practice guidelines are the cornerstone of optimal patient care using evidence-based recommendations, where possible, which facilitate access to quality treatment. Creating such guidelines, which can be relevant for the diverse healthcare settings around the world for haemophilia care, is challenging. From the historical perspective, the first attempt came through the initiative of the World Federation of Haemophilia (WFH) in 2005. The subsequent evidence-based editions in 2013 (endorsed by the International Society on Thrombosis and Haemostasis, ISTH) [1] and the most recent in 2020 [2] have continued to address these international needs. These comprehensive guidelines cover all aspects of haemophilia care, from diagnosis to prevention of bleeding and treatment of complications and comorbidities. Their wide acceptance and impact in the bleeding disorders community is demonstrated by the number of citations in publications (> 2500 so far) and downloads (> 1.5 million so far) in several languages. A very important component of these guidelines is the use of therapeutic products to prevent and treat bleeding.

Prophylaxis is now the established standard of care for patients with severe haemophilia or severe bleeding phenotype [2]. This is based on a series of natural history studies, elegant observational studies and randomized controlled trials (RCTs). This goal has been greatly aided by the advent of more effective clotting factor concentrates (CFCs) and other innovative haemostatic agents [2].

With the extensive data from clinical experience and outcomes, it has become possible to aspire to almost complete prevention of bleeds and to pay attention to patients' relevant outcomes as compared only to the simple reduction of bleeding rates. The licensure of multiple advanced treatment options for PwH has elevated treatment ambitions: to move from 'prophylaxis for all' to the aspiration for 'zero bleeds' and potentially 'normalisation of haemostasis,' which could lead to maintenance of joint health with a 'haemophilia-free mind' [3] and broader health equity no matter age, race, gender or haemophilia severity. This important paradigm change in haemophilia care was possible due to increased access to advanced therapeutic products for prophylaxis combined with the recognition of the impact of haemophilia on women/girls and persons with non-severe disease and the continuous generation of large amounts of clinical and health-related outcomes data from clinical trials, and national and international registries (e.g., American Thrombosis and Haemostasis Network, ATHN; European Haemophilia Safety Surveillance system, EUHASS; European Paediatric Network Haemophilia Registry, PedNet; FranceCoag Network; World Bleeding Disorders Registry, WBDR) [4–7].

It is with this background that the recent ISTH guidelines [8] are being critiqued regarding their applicability within the current therapeutic landscape. These guidelines focus on the use of some (and not all) available therapeutic products in congenital haemophilia A and B (HA, HB) and used the GRADE system for assessment of evidence without any adaptation to the available evidence [8]. Moreover, there are no recommendations on treatment goals or individualized prophylaxis that aim to take into account both treatment relevant outcomes and patient preferences.

After their first release for public comments in October 2023, there have been widespread concerns in the community about the scientific validity of several recommendations, the methods followed to reach those recommendations, and the potential negative impact on haemophilia care worldwide, including access to therapy and on further research and development of therapeutics.

Hence, the authors of this manuscript felt strongly that a critique of the recommendations was urgently needed. This paper reviews the ISTH recommendations and comments briefly on the scope and methodology of these ISTH guidelines, their similarities and differences with previous guidelines and their potential impact on haemophilia practice and access to care globally. It is the result of a collaborative effort of all authors to provide not only a simple rebuttal but a practical point-by-point discussion of the recommendations.

1.1 | Analysis of the 13 Recommendations of the ISTH Haemophilia Treatment Guidelines

The ISTH haemophilia treatment guidelines consist of 13 recommendations that focus on the use of some (not all) available therapeutic products, mainly in HA—11 recommendations and HB—2 recommendations [8]. These recommendations are listed below, followed by a constructive commentary as mentioned above.

> **#1**. In individuals with severe and moderately-severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel recommends prophylaxis over episodic treatment of bleeding events. (Strong recommendation–moderate certainty evidence).

Prophylaxis is indeed the standard of care for all PwH with a severe bleeding phenotype irrespective of the baseline factor levels because of the clear and undeniable beneficial impact of this approach on arthropathy prevention, prevention of life-threatening bleeds as intracranial haemorrhage (ICH) and quality of life (QoL) improvement [2, 9–13]. Considering the bulk of published literature, including RCTs, large cohort studies and real-world experience (RWE) data establishing the benefits of prophylaxis over many decades, the level of certainty of this strong recommendation should be considered high and not moderate. Furthermore, it is not clear why only severe and moderately

Summary

- The International Society on Thrombosis and Haemostasis (ISTH) recently released new guidelines for the treatment of haemophilia, addressing the effectiveness and roles of various haemostatic agents for patients with or without inhibitors. These recommendations were developed using a methodology known as GRADE, which, in its most strict application, considers only observations from randomized clinical trials as valid, where patients are randomly assigned to two treatments for comparison.
- The stringent application of this strategy resulted in 13 recommendations with significant practical implications. For example, these guidelines suggest that:
  - Prophylaxis should be reserved for patients with severe or moderately severe haemophilia (≤2% factor levels).
  - Various clotting treatments—including recombinant, short or long half-life agents, as well as non-replacement subcutaneous therapies—are considered equivalent.
  - Low-dose prophylaxis is viewed as an acceptable option when resources are limited.
  - The use of plasma-derived FVIII concentrates is favoured to start treatment to reduce the risk of inhibitor development.
  - Emicizumab is mentioned only as a *potential* prophylactic option for hemophilia A patients with inhibitors.
- However, extensive data from observational clinical studies, registries, and the global clinical experience with various haemophilia treatments challenge these guidelines, which are based on an analysis deemed unsuitable for the full scope of available scientific evidence. This article, authored by numerous experts, highlights the weaknesses and inadequacies of this approach. Its primary aim is to remind the community that guidelines should also enable and motivate all relevant stakeholders to advocate for broader access to a diverse range of treatments and improve the health outcomes for individuals with haemophilia worldwide by incorporating all available scientific data and patients' perspective.

severe PwH have been included in this recommendation as well as in recommendations #2, #3, #12 and #13, which exclude many PwH for whom prophylaxis is recommended.

> **#2**. In individuals with severe and moderately-severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests either prophylaxis with emicizumab or prophylaxis with factor VIII concentrates. (Conditional recommendation–very low certainty evidence).

This recommendation mirrors #1 but includes all available products without distinguishing between older products from the late 1960s (e.g., plasma derived CFCs, pdCFCs) and newer ones approved in the last decade (e.g., extended half-life, EHL and emicizumab). It overlooks extensive clinical trials and real-world practice data showing that newer products with better pharmacokinetic (PK) profiles provide much higher trough levels and longer periods of time spent over a certain level (e.g., EHL products) or stable haemostasis (e.g., FVIII mimetic emicizumab) compared to standard half-life (SHL) products. As such, the WFH Guidelines went on to advise trough levels of 3%–5% or higher with EHL CFCs or the equivalent with other haemostasis products that make that possible [2]. The higher trough level was also reflected in the recommendations made in 2020 by the European Directorate for Quality of Medicines and Healthcare (EDQM) [9]. Such an unqualified recommendation for prophylaxis can confuse or misguide physicians, healthcare authorities and payers regarding the choice of products, and adversely affect the quality of haemophilia care. The decreased annualized bleeding rates (ABR), including high numbers with 'zero bleeds,' as well as improved QoL from better haemostasis and enhanced adherence due to decreased treatment burden, have all been achieved only through these advanced products and not SHL CFCs. No guidance has been offered on the desired outcomes and how both product choice and intensity of prophylaxis, have an impact on the protection against bleeds. Making this a conditional recommendation based on low-certainty evidence further detracts from the robust clinical data published on using EHL FVIII CFCs and emicizumab prophylaxis [14] and could also adversely affect the quality of haemophilia care and outcomes if healthcare authorities choose to equate these products with SHL CFCs, resulting in restricted access to new therapies.

> **#3**. In individuals with severe and moderately-severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with either standard or extended half-life recombinant factor VIII concentrates. (Conditional recommendation–very low certainty evidence).

The advent and adoption of EHL FVIII products stemmed from the need to increase protection against bleeds with higher trough levels to better prevent arthropathy and reduce treatment burden by decreasing the number of intravenous injections [2, 9, 15] because regular prophylaxis with SHL products still resulted in bleeds and joint damage [16, 17]. The availability of EHL FVIII allowed for recommendations on minimum troughs of 3%–5% or higher as opposed to 1% with SHL CFCs [2, 9, 15]. EHL FVIII allows for more flexible and feasible treatment schedules, improving adherence and reducing treatment burden, crucial elements to attain improved therapeutic outcomes [18, 19]. Although it is possible to achieve equal levels of protection with SHL CFCs, this would require very frequent injections—in many cases daily—which most PwH are unable to do. As the superiority of FVIII EHL products' PK properties has been demonstrated through head-to-head PK trials [20–24], any further RCT aimed at demonstrating better outcomes with FVIII EHL products, as proposed by the ISTH guidelines (Table 3 of the document) [8] would be unethical and unwarranted.

With such extensive data showing clear superiority of EHL products over SHL products in terms of bleeding prevention, that is, clinical outcome, the rationale for not distinguishing between SHL and EHL in this recommendation is not evident.

> **#4**. In resource-limited settings in which the use of standard-dose prophylaxis for severe hemophilia A without inhibitors is not possible, the ISTH Hemophilia Guideline Panel suggests prophylaxis with low-dose factor VIII over episodic treatment. (Conditional recommendation–very low certainty evidence).

While this concept is indeed widely accepted and practiced [2], without specification of what is low dose versus standard dose, it can be confusing in clinical practice. The remarks sections alludes to reducing bleeding risk, but there is no mention of the optimal outcomes with various prophylactic regimens, with no differentiation offered between the various regimens. To the average physician who relies on authoritative guidelines for practice, it might appear any prophylaxis is the same.

It should also emphasize that complete bleed prevention should be the goal everywhere in the world. The effort to introduce prophylaxis as much as possible worldwide, even in CFC-access limited situations, has led to the adoption of low-dose regimens, also utilized by the WFH humanitarian aid program in some countries [25]. However, low-dose regimens are not ideal long-term therapies because they may slow progressive musculoskeletal damage but will not prevent it [26]. They are only meant to be superior to episodic treatment at similar annual doses. Furthermore, this recommendation overlooks the effectiveness of intermediate-dose prophylaxis supported by long-term data from the Netherlands [27].

> **#5**. In previously untreated individuals with severe hemophilia A who will start prophylaxis with a plasma-derived or standard half-life recombinant factor VIII concentrate, the ISTH Hemophilia Guideline Panel suggests initial prophylaxis with plasma-derived factor VIII over standard half-life recombinant factor VIII concentrate. (Conditional recommendation–very low certainty evidence).

This statement is based on a single RCT executed more than 10 years ago that compared a group of recombinant products, including some that are no longer manufactured, and a group of pdFVIII products selected based on their von Willebrand factor (VWF) content—the SIPPET study [28]. This recommendation should thus specify 'only VWF containing pdFVIII products,' which was the comparator in that specific study; without which this recommendation has no validity. Moreover, results from this study only showed a significantly lower risk of inhibitor development in a small subgroup of PwH treated with pdFVIII if they had a *F8* non-null mutation [29]. Cumulative incidences of inhibitor development with new recombinant products that became available after the SIPPET study are similar to inhibitor rates with pdFVIII in the SIPPET study [30]; however, this data was not considered in the ISTH document. Treating previously untreated patients (PUPs) is complex and should not focus solely on inhibitor development. In fact, in very young children, venous access is challenging and often requires central venous lines with possible complications (e.g., bleeding, infections, thrombosis) [31] and pdFVIII concentrates have large volumes of injections, almost double if compared with any recombinant product. Moreover, pdCFCs use deserves continuous biological surveillance due to the theoretical potential for transmission of blood-borne infectious pathogens [32].

Another important point is related to the source of evidence pertaining to inhibitor risk in PUPs because regulatory authorities (both FDA and EMA) now prefer data from well-designed registries and not clinical trials for PUPs [33].

While inhibitor development in PUPs remains a challenge, the perception and management nowadays are very different than in 2014–2016 when EHL products and non-replacement therapy were not widely available. The extra benefits of EHL FVIII products (less infusions, higher trough levels) are particularly important for PUPs. Furthermore, emicizumab (not mentioned in this recommendation) has gained considerable acceptance in paediatrics worldwide since it enables very early initiation of prophylaxis even in infants and, thus, protection from bleeding, including the critical ICH [34], regardless of inhibitor status.

By ignoring EHL FVIII products and emicizumab as two possible agents to commence PUPs on prophylaxis, this recommendation moves practice to choices between two old product types that are clearly less effective.

> **#6**. In individuals with severe and moderately-severe hemophilia A without inhibitors undergoing a major invasive procedure, the ISTH Hemophilia Guideline Panel suggests either continuous or bolus infusion of plasma-derived or standard half-life recombinant factor VIII concentrates. (Conditional recommendation–very low certainty evidence).

Without mentioning any advantage or disadvantage of the only two ways of administration of CFCs, the relevance and the need for this recommendation are unclear. Furthermore, this recommendation does not mention the need for special pumps for continuous infusion (CI) and considerations around product stability during CI [35]. The main issue with this recommendation is that it ignores the existence of EHL products entirely. With EHL CFCs, especially for HB, there is minimal need for CI. Moreover, the recommendation, as written, suggests that in the surgical setting the choice is only between pdCFCs and SHL CFCs, when in fact that is not true given the availability of EHL products for 10 years.

> **#7**. In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis over episodic treatment of bleeding events. (Conditional recommendation–low certainty evidence).

Despite the evidence [36–37], the guideline indicates this is a conditional recommendation supported by very low-certainty evidence. For this PwH population, prophylaxis with emicizumab is strongly recommended over any other treatment, despite the lack of an RCT proving its superiority over episodic treatment. In fact, given its transformational impact on the lives of these

patients, such a study would be unequivocally unethical and will never happen given the extensive clinical trials and RWE already available [14]. Moreover, the presence of inhibitors results in the restriction of the therapeutic products that can be used, but the underlying biology of the disease does not change.

> **#8**. In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with emicizumab over by-passing agents. (Conditional recommendation–very low certainty evidence).

The main issue with this recommendation is that it has been categorized as conditional based on very low-certainty of evidence. Emicizumab licensure trials demonstrated unprecedented bleeding control in this patient population [14, 36, 37]. The intra-patient comparison presented in the HAVEN trials demonstrates the large differences in bleeding rates compared to prophylaxis with bypassing agents (BPA) [36, 37]. It is not clear why the HAVEN 2 study was not included in the list of cited literature [37].

Moreover, emicizumab is licensed for all PwHA and inhibitors irrespective of disease severity, with RWE showing outcomes comparable to PwHA without inhibitors [14]. Hence, to conclude that this is a conditional recommendation with very low-certainty evidence is particularly problematic and could adversely affect the care of PwHA with inhibitors. This statement should instead be a strong recommendation based on high-certainty evidence. Likewise, an RCT comparing emicizumab and BPA will be unethical due to lack of clinical equipoise.

> **#9**. In individuals with severe hemophilia A with high-responding inhibitors who will start immune tolerance induction, the ISTH Hemophilia Guideline Panel suggests immune tolerance induction with either low- or high-dose factor VIII concentrates. (Conditional recommendation–very low certainty evidence).

There is no universal definition of low-dose or high-dose immune tolerance induction (ITI). The lack of such a definition can confuse clinicians unless linked to specific studies.

For example, the International ITI (I-ITI) study compared success rates of 50 IU/kg 3 times/week (defined as low-dose) versus 200 IU/kg/day (defined as high-dose) [38]. However, high-dose ITI in other literature includes protocols like the Bonn Protocol (100-150 IU/kg twice daily), while low-dose can mean 50 IU/kg/day [39]. Moreover, the results of the I-ITI study apply only to PwH with good predictors of ITI response and not to all PwH with inhibitors. Despite achieving similar success rates, the longer duration of the low-dose regimen resulted in more bleeding events as compared to the high-dose regimen [38]. Accepting either regimen without considering these differences could increase treatment burden and misdirect resource allocation. Payers might prefer low-dose regimens for their apparent low economic burden, overlooking the extended treatment duration and higher bleed rates while awaiting successful tolerization. On the other hand, if, in the context of ITI, emicizumab prophylaxis is included for bleed prevention, the FVIII dosing regimen chosen for ITI might have less consequences.

> **#10**. In individuals with severe hemophilia A with inhibitors undergoing invasive procedures requiring treatment with bypassing agents, the ISTH Hemophilia Guideline Panel suggests either recombinant VIIa (eptacog alfa) or activated prothrombin complex concentrate (aPCC). (Conditional recommendation–very low certainty evidence).

This recommendation may be dangerous for those unfamiliar with subtle nuances in this literature. It is widely acknowledged in the existing literature that surgical procedures performed in PwHA and inhibitors during emicizumab prophylaxis can be managed with shorter courses and lower doses of concomitant BPA [40]. In patients concomitantly treated with emicizumab, it is crucial to distinguish between major and minor procedures: for minor surgeries, no additional product is usually required. However, for major surgeries, while recombinant activated FVII (rFVIIa) is preferable, it should be mentioned that activated prothrombin complex concentrate (aPCC) may also be used with careful dose calculations remaining within 100 IU/kg/day due to the risk of thrombosis and/or thrombotic microangiopathy if administered at higher doses and for prolonged periods [41]. Additionally, in the case of procedures at very high risk of bleeding complications, if inhibitor titers allow, there is the option of exploiting the haemostatic efficacy of FVIII at least until the anamnestic response occurs. This option is indeed always valid in the case of low-responding inhibitors. Furthermore, eptacog beta and the pdFVIIa/FX concentrate, other BPA effective in both bleeding control and prevention of bleeding complications after surgery are not mentioned as possible alternatives [42–44].

> **#11**. In individuals with severe hemophilia A with inhibitors who present with joint bleeding and will be treated with recombinant factor VIIa (eptacog alfa), the ISTH Hemophilia Guideline Panel suggests treatment with either three doses of 90 μg/kg at 3-hour intervals or a single dose of 270 μg/kg. (Conditional recommendation–very low certainty evidence).

This indication may be misleading because (i) the use of the two alternative dosages has been included in the label of the drug only for mild to moderate joint bleeds and (ii) the high-dose is not indicated for elderly PwH, and it is not licensed worldwide (e.g., USA). Moreover, the NODOP study (which is an RCT) is missing in the cited literature [45]. This study demonstrated comparable efficacy and safety but a lower treatment burden with the high single dose regimen [45]. Another concern is the lack of aPCC not being mentioned as a treatment option for bleeding events in PwHA and inhibitors. In fact, the FENOC study, a RCT comparing rFVIIa and aPCC efficacy for the treatment of bleeding episodes in PwH and inhibitors prior to the advent of emicizumab, proved the equivalence of those BPA [46], but was not included among the cited literature.

> **#12**. In individuals with severe and moderately-severe hemophilia B without inhibitors, the ISTH

> Hemophilia Guideline Panel recommends prophylaxis over episodic treatment of bleeding events. (Strong recommendation–moderate certainty evidence).

As mentioned earlier for HA, prophylaxis is indeed the standard of care for all PwH with a bleeding phenotype because of the clear and undeniable impact of this approach on arthropathy prevention and QoL improvement [10–12]. Considering the bulk of published literature on the benefits of prophylaxis, the level of certainty of this recommendation should be considered high and not moderate. Any RCT with a non-prophylaxis arm would therefore be unethical.

> **#13**. In individuals with severe and moderately-severe hemophilia B without inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with purified plasma-derived factor IX or standard or extended half-life recombinant factor IX concentrates. (Conditional recommendation–very low certainty evidence).

The availability of EHL factor IX (FIX) products brought a significant improvement in the management of PwHB and in their QoL, given the much higher trough levels (5%–10% or more) with much reduced frequency of infusions and a high percentage of those with 'zero bleeds' [47]. The recommendation as written implies that both these choices (SHL and EHL CFCs) are equal, ignoring the huge benefits of EHL FIX. A recommendation as this can be used to wrongly justify not providing EHL FIX and instead relying on pd and SHL FIX alone. This can be very detrimental to patient outcomes.

2 | Methodological Considerations on the ISTH Hemophilia Treatment Guidelines

2.1 | The GRADE System

The ISTH haemophilia treatment guidelines have been developed by applying the GRADE methodology based on an evidence to decision (EtD) framework. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology provides guidance to systematically evaluate the existing evidence on a given topic to develop evidence-based, trustworthy recommendations [48]. Among medical evidence, RCTs are considered the highest level of certainty. However, in specific medical fields, such trials are not common and sometimes hardly feasible; this is the case in rare conditions such as haemophilia and other inherited bleeding disorders [49]. Recognizing these limitations, the GRADE Working Group has proposed a method allowing evidence-based recommendations when the strength of available published evidence is lower or even lacking by using a collective experience approach [49]. This method was successfully used, for example, by the American Society of Haematology (ASH) to develop the guidelines for treatment of paediatric venous thromboembolism and the guidelines for von Willebrand disease management by ASH, ISTH, National Bleeding Disorders Foundation (NBDF) and WFH [50–51]. This positive experience and the recommended approach in situations with no or limited data from RCTs do not seem to have been applied in the development of these ISTH haemophilia treatment guidelines [8]. As stated by Olaf M. Dekkers in a companion commentary with these ISTH guidelines, 'GRADE should not be seen as the magic bullet that removes all uncertainty and resolves all debates' and 'grading the evidence does not automatically generate recommendations' [52].

2.2 | Choice of the Outcomes

The ISTH Guidelines have been generated considering ABR and joint ABR as the only clinically relevant outcomes.

However, it is widely recognized that considering solely a reduction of ABR is neither sensitive nor reliable enough to inform on prophylaxis efficacy. Further, goals of prophylaxis go well beyond ABR reduction and include high protection levels, maintenance of healthy joints and enhanced activities with associated improved QoL. Prophylaxis is a process, but its outcomes are more important than the process itself. In light of all available evidence, all available haemostatic products should not be equated.

2.3 | PICO Questions

Another crucial point about these guidelines is related to the choice of the relevant questions to be answered to produce well-informed, evidence-based and clinically relevant recommendations. In fact, when a guideline development process begins, a series of questions are identified that will form the basis of the recommendations. These PICO (Population, Intervention, Comparator, Outcome) questions drafted by the ISTH guideline panel unfortunately do not reflect the critical current issues in practice and do not accommodate available data with emerging treatment advances. Indeed, some of these data were available in 2019 and were incorporated into the two previous evidence-based guidelines issued in 2020 from the WFH and the EDQM [2, 9] but not in the 2024 ISTH Guidelines.

Another missing step appears to be the lack of community consensus about the relevant PICO questions to be addressed within these guidelines, as answered, for instance, had been done for the guidelines on VWD management [51].

A detailed discussion contrasting the application of the GRADE methodology in these ISTH guidelines and previous guidelines for haemophilia and von Willebrand disease is published elsewhere [53].

2.4 | Acceptability of Proposed Recommendations

The GRADE approach stresses the necessity to consider the balance between desirable and undesirable consequences of guidelines. Further best practice recommends that when guidelines are issued, acceptability of the recommendations to the intended stakeholders should be considered upfront. The strong critical response from the extended scientific community expressing concerns with these recommendations, when put up for public comments in October 2023, indicated the lack of acceptability of such recommendations due to their considerable limitations from both the content and process perspectives. In

addition, the fact that the three patients who had been a part of the panel declined to have their names listed and withdrew from the publication further emphasizes the critical issue of the acceptability of these guidelines.

2.5 | RCTs to Compare Product Efficacy in Haemophilia

The debate about the need for RCT to demonstrate the superiority of a given therapeutic strategy over others has been elegantly summarized by the parachute study published in the British Medical Journal in 2018 [54]. Randomisation has undeniable advantages for unbiased allocation to treatment arms. However, it has been effectively shown that in certain circumstances, non-randomized interventional studies and well-designed observational studies may generate evidence of a level comparable to RCT [55], making RCTs unnecessary [56], especially when the principle of clinical equipoise is not satisfied [57]. For an RCT to be ethical, a genuine uncertainty about the scientific question the trial is supposed to answer must exist; patients' randomization to an intervention known or judged by experts to be inferior to the chosen comparator automatically renders that RCT unethical [58]. There is usually a time window of equipoise when there is still 'sufficient uncertainty' about the benefit or risk of a new intervention. RCTs can and should only be performed within that time window. For many of the above cited products in the treatment of haemophilia, this window has been long shut.

That maintenance of stable high factor levels to prevent bleeding episodes and their long-term sequelae has a strong and direct impact is clear and straightforward from an enormous amount of published literature. Hence any RCT comparing SHL (either plasma-derived or recombinant) with EHL or non-replacement therapy, as proposed in Table 3 of the ISTH guidelines [8], would be unfeasible because they would be unethical.

The available haemostatic products have been proven to have different and unique properties that can address different needs of PwH according to the principle of personalized and individualized treatment [59, 60]. In all the HAVEN studies, which resulted in the licensure of emicizumab, there was a within-patient comparison to a period while PwH were still on their prior treatments through which non-inferiority has been demonstrated in hundreds of PwH [14], and similar results have been confirmed by large cohort studies of RWE [61].

Importantly, regulatory authorities have also declared that single-arm studies with prospective intra-patient comparisons are acceptable to inform on non-inferiority and/or superiority of new treatment strategies [62].

In this light, the strength of most ISTH recommendations should have been assigned after considering non-randomized studies also with patients serving as their own controls, observational studies from registries, RWE and even expert consensus, if needed.

Finally, the proposed list of topics for future research in haemophilia with 30 top priorities, all envisioned to be realized in the frame of RCTs is not realistic and, as mentioned above, may even be unethical. In fact, those RCTs are very difficult, if not impossible, to be accomplished for two main reasons: (i) the nature and prevalence of haemophilia will make the conduct of successful RCTs extraordinarily challenging going forward, especially with new highly effective therapeutic approaches; (ii) the concept of significant clinical equipoise and therefore its ethical acceptability will need to be considered even where such RCTs can indeed be designed.

3 | Will Clinicians and Patients Benefit From These Recommendations?

Looking at the overall conclusion of these 13 ISTH recommendations, it may be perceived by many that pdCFCs, all recombinant CFCs, EHL CFCs, as well as the factor VIII mimetic, emicizumab, are all equivalent in efficacy and safety, meaning one could appropriately and interchangeably choose any of these options for effective prophylaxis. Likewise, for PwHA and inhibitors, the superiority of emicizumab prophylaxis over BPA is presented as based on very low-certainty; hence, either choice could be acceptable. Yet the evidence from non-randomized studies strongly refutes the above, showing superiority of the newer over older treatments for the management of haemophilia.

The only strong recommendation of the ISTH guidelines pertains to the use of prophylaxis over on demand treatment, while specific product recommendations for different treatment classes to carry out prophylaxis are all conditional, based upon 'low- or very low-certainty of evidence.' Yet even intensive prophylaxis with conventional SHL CFCs does not ensure the protection provided by newer agents [17].

Surprisingly, the recommendation rated as 'strong' for prophylaxis of severe HA and HB is based upon a 'moderate' certainty of evidence despite the universally recognized benefits of prophylaxis that derive from decades of clinical experience, many interventional clinical trials, including RCTs, and data from numerous registries.

Guidelines should cover the entire patients' journey; hence, they should be based on all available evidence, especially in fields where RCTs are not common, as in rare diseases; moreover, they should be as comprehensive as possible to guide clinicians and serve the community, considering the nuances of individualized care. The ISTH guidelines are not comprehensive as they are limited to the use of some products. Furthermore, no dosing guidance across different scenarios has been provided.

4 | How Might These Recommendations Impact Policy Makers and Affect Access?

It is particularly surprising that these recommendations, which should be intended to help policy makers develop initiatives to reduce the burden of a given disease, do not consider the advances offered by all the treatments developed over the past decade.

As these recommendations become available to governments, private payers, and medical authorities around the world, they

could legitimately question why they should be paying for newer, often higher-priced products, when plasma derived and first-generation (SHL) recombinant CFCs are considered equally effective for the treatment of haemophilia, including prophylaxis. The proposed recommendations contradict many professional medical societies' goals and existing guidelines for haemophilia treatment, including the objective of zero bleeds, trough levels above 3%–5% or higher, improved physical and emotional outcomes, and economic productivity of PwH in countries of all incomes throughout the world [2, 9, 63]. It could be argued that some of this evidence has been included in the remarks and other sections of the ISTH Guidelines document; however, it should have been referenced within the recommendations and not elsewhere in the text to make secondary considerations. At a time when some of these advanced products are yet to become available in many parts of the world, these guidelines could delay or prevent access to those products that can improve outcomes for all PwH. This can harm haemophilia care and reverse hard-won health equity gains in the long term. They may also negatively impact research on new treatment strategies and distract or interrupt future investments in haemophilia research for the development of new therapeutics, which has been so fruitful over the last decades. These collateral effects ('unintended consequences') appear to have been ignored in these ISTH guidelines. It is important that when developing such guidelines, the potential benefits, harms, and acceptability by all stakeholders of the recommendations are carefully considered. Continued advocacy for investing in therapeutics that have been proven to offer long-term benefits, such as EHLs, even ultra EHL CFCs, FVIII mimetics, rebalancing agents and gene therapy, is crucial. These recommendations appear not to favour this important process.

5 | Conclusions

As summarized above, the methodological approach used and subsequent categorization of available evidence as weak, mostly due to the exclusion of many relevant clinical studies and other available evidence to date, the ISTH recommendations fail to recognize the tremendous advantages of the modern haemostatic products in the treatment of haemophilia. Moreover, the recommendations do not touch on the variability in response to a given therapeutic approach and the need for personalised prophylaxis for individual optimal outcomes. Overall, in the context of a rapidly changing treatment landscape, these recommendations may misguide haemophilia treaters, payers and governments and cannot serve the patient community well as they overlook important evidence and incorporate obsolete treatment principles.

To that extent, they are already outdated at the time of their publication and do not add value or relevant information to existing evidence-based guidelines.

Moving forward, great caution is needed when making recommendations for management of haemophilia from an international perspective. A more innovative and realistic methodological approach is warranted in the future for preparing guidelines as well as for designing clinical trials that can be informative, feasible, ethical and of high quality. An urgent need is for the methodologists to propose alternative strategies moving away from the dogma of RCTs as the only gold-standard and incorporate other study designs that can provide reliable evidence in the context of haemophilia in a feasible and ethical way involving all relevant stakeholders from the community.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.