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FORUM

# Guidelines for management of hemophilia—why, what, and how?

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## 1 | INTRODUCTION

Clinical practice guidelines (CPGs) are systematically developed statements from available evidence that help healthcare professionals decide on the most appropriate management options for achieving the best outcomes of care in those specific circumstances and support shared decision-making processes [1,2]. They can also help formulate policies for healthcare [3]. They become particularly significant for the management of rare conditions like hemophilia, where evidence from comparative efficacy trials is insufficient. However, framing practice recommendations in these circumstances can become even more challenging in the setting of rapidly emerging novel treatments. There is increasing recognition of the rigor of methodologies required and transparency of strategies applied in the development of guidelines to ensure the validity of the recommendations, as well as their successful implementation [4,5]. Criteria have, therefore, been enunciated for judging the quality of guidelines [6]. After their initial crafting >2 decades ago, the framework for guideline formulations has gradually evolved [7], with the most recent being the Appraisal of Guidelines for REsearch & Evaluation II (AGREE II) instrument (Supplementary Table). In this commentary, we reflect on the why, what, and how of hemophilia CPGs.

## 2 | EVOLUTION OF HEMOPHILIA CPGS

The World Federation of Hemophilia (WFH) developed the first internationally applicable guidelines for the management of hemophilia in 2005 [8]. This brief consensus document, based mostly on previous national and regional guidelines, emerged from a limited literature review and expert opinion. The next edition, published in 2012, was the result of systematic literature review and extensive stakeholder consultations led by multidisciplinary teams of domain experts [9]. This second edition was endorsed by the International

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Society on Thrombosis and Haemostasis (ISTH) and was the first hemophilia CPG to be included in the National Guidelines Clearinghouse. By 2020, it had >2500 citations and >1.5 million downloads across several languages. A few major practice-changing therapeutic advances since 2012 led to the development of the third edition of the WFH guidelines, which was published in 2020 [10]. In this edition, the process followed was more stringent, and a chapter describing it in detail was included in the guidelines document. A considered decision was made to avoid using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess available evidence for formulating these guidelines, as its strict application would have led to exclusion of a significant body of clinical trial and practice data and potentially erroneous conclusions [11]. Instead, the evidence-derived trustworthy consensus-based approach was selected to draft recommendations after systematic review of the literature to include data from comparative controlled clinical trials, well-designed cohort studies, and expert opinions [12,13]. Its success and acceptance by the community are again evidenced by >1000 citations and >0.5 million downloads since publication. In fact, the uptake of the recommendations by the stakeholders of the hemophilia community is a reflection of the validity of the processes adopted and resultant quality of these guidelines. It should also be noted that the third edition of the WFH guidelines has been designated as "living" guidelines, which are being updated as the field advances in a practice-changing way.

## 3 | ADVANCING GUIDELINES—WHEN AND WHY?

Given the resource-intensive nature of the processes required by contemporary standards for creating unbiased, trustworthy evidence-based guidelines, the decision to embark on this path should be carefully considered. The European Reference Networks Guidelines Methodological Handbook suggests a good approach to making such decisions [14]. Two important considerations should guide decisions to prepare new guidelines or advance existing ones: first, significant advances in the field that make existing recommendations unsuitable for the desired outcomes, and second, integrating new products into clinical practice and confirming their usefulness and applicability from both clinical trial and real-world practice data. Data from pivotal clinical trials, which lead to market authorization alone, are best not translated to practice guidelines, as there are possibilities of such products not entering clinical practice for various reasons, including sustained efficacy or access, even if highly innovative [15]. CPGs should also not be initiated just to enhance organizational status or the perceived position of leadership in the field [16].

## 4 | FRAMING GUIDELINES—THE PROCESS

The most important consideration in the process of framing CPGs is the constitution of the guideline panel, both from the content and methods perspectives. It should be recognized that a checkbox completion of a multidisciplinary nature of the panel may not yield the same results as having recognized domain experts who also have a good global context of practice, especially for complex situations like that of the management of hemophilia and its complications. The next important step is to frame the Population, Intervention, Comparator and Outcomes questions to conduct necessary literature search to prepare the evidence tables. These Population, Intervention, Comparator and Outcomes questions and collection of related evidence should be comprehensive and include all relevant clinical aspects, including patient-reported outcomes and lived perspectives of those affected by the condition [12].

Regardless of the quality of the evidence available, randomized controlled trials (RCTs), cohort studies, or expert opinion, it is important to understand that the steps beyond this require consensus-based finalization of several steps in the process: the practice issues to be considered for the final list of recommendations, the evidence to be included, interpretation of the data from the evidence selected (including those from RCTs), and final wording of the recommendations [12,17]. The significance of framing the draft recommendations, which also consider lived experiences of patients, in a language that is clear and precise with no ambiguity, and which can be subjected to a Delphi process, cannot be overemphasized. It requires tremendous personal clinical experience and familiarity with global practices and possibilities to be able to do so.

## 5 | CPGS FOR HEMOPHILIA—CURRENT STATUS

Taking the widely accepted and used WFH guidelines for the management of hemophilia as the benchmark for providing comprehensive guidance for the management of all aspects of global hemophilia care, an important question is whether they will measure up to AGREE II criteria. If one carefully reads the description of the processes followed and the content of this third edition as described within the WFH guidelines, particularly chapter 12, which provides a detailed description of the methods, nearly all the criteria in the 6 domains seem to be fulfilled, even though this was not specifically aimed for at the time of its formulation.

The recently published ISTH CPGs for the treatment of congenital hemophilia are not intended to be comprehensive, as they are limited to the use of hemostasis products for prevention and treatment of bleeding in specific circumstances [18]. If we measure these guidelines against the AGREE II criteria, both from the process and content perspectives, it is clear that these guidelines do not comply with several domains of these criteria. From the time they were circulated for public comments in October 2023, with the statement that "Comments on content are welcome, however, the recommendations—developed using a structured process, formal management of conflict of interest, and anonymous voting by the panel—cannot be altered at this stage," the bleeding disorders community has expressed

**TABLE** Issues with the International Society on Thrombosis and Haemostasis clinical practice guidelines for congenital hemophilia[a].

| No. | ISTH-HGP recommendation | Comment |
|---|---|---|
| 1 | In individuals with severe and moderately severe hemophilia A without inhibitors, HGP recommends prophylaxis over episodic treatment. (Also for those with FVIII ≥ 2 IU/dL + severe bleeding phenotype). | The term "severe bleeding phenotype" is undefined and open to interpretation, particularly for those with FVIII ≥ 2 IU/dL. The word "recommends" appears only here, and only "suggests" in all other "recommendations" can make clinical implementation confusing. |
| 2 | In individuals with severe and moderately severe hemophilia A without inhibitors, the HGP suggests either prophylaxis with EMI or prophylaxis with FVIII concentrates. | Equates EMI and all CFCs (SHL/EHL) against documented superiority of EHL CFCs and EMI over SHL CFCs. Significance of no. 1 can be confusing, with it being categorized as "conditional and of low certainty[b]." |
| 3 | In individuals with severe and moderately severe hemophilia A without inhibitors, the ISTH suggests prophylaxis with either SHL or EHL recombinant FVIII concentrates. | Equating SHL and EHL CFCs for prophylaxis is harmful—all individuals with hemophilia benefit from higher trough. Omitting EMI could cause confusion about its role in prophylaxis for hemophilia A. |
| 4 | In resource-limited settings in which use of standard dose prophylaxis for severe hemophilia A without inhibitors is not possible, the HGP suggests prophylaxis with low-dose FVIII over episodic treatment of bleeding events. | As no actual doses are mentioned, the terms "low" and "standard" doses can be confusing. Omits the mention of "intermediate dose" prophylaxis as another option between low and standard dose for which there is significant long-term data[b]. |
| 5 | In previously untreated individuals with severe hemophilia A who will start prophylaxis with a plasma-derived or SHL recombinant FVIII concentrate, the HGP suggests initial prophylaxis with plasma-derived FVIII over SHL recombinant FVIII concentrate. | The recommendation of plasma-derived FVIII is inappropriate without specifying "VWF containing pdCFC"—it also ignores the advantages of widely used EHL CFCs and EMI in this setting. |
| 6 | In individuals with severe and moderately severe hemophilia A without inhibitors undergoing a major invasive procedure, the HGP suggests either continuous or bolus infusion of plasma-derived or SHL recombinant FVIII concentrates. | The relevance of mentioning only 2 options without describing their nuances is unclear. Why only SHL CFC? What if the patient is already using EHL CFC or EMI? |
| 7 | In individuals with severe hemophilia A with inhibitors, the HGP suggests prophylaxis over episodic treatment of bleeding events. | The use of the word "suggests" and NOT "recommends" when there is overwhelming evidence of superiority of prophylaxis makes this one of the most contentious recommendations[b]. |
| 8 | In individuals with severe hemophilia A with inhibitors, the HGP suggests prophylaxis with EMI over bypassing agents. | As above, using the word "suggests" and NOT "recommends" in this setting is unjustified and represents a misinterpretation of the strength of evidence already available[b]. |
| 9 | In individuals with severe hemophilia A with high-responding inhibitors who will start immune tolerance induction, the HGP suggests immune tolerance induction with either low- or high-dose FVIII concentrates. | Without clear definition of low- and high-dose ITI, this recommendation can be confusing. Given the well-documented higher bleed rates with lower-dose FVIII ITI (50 IU/kg 3×/wk), it is important to recommend concomitant prophylaxis with EMI until ITI is successful. |
| 10 | In individuals with severe hemophilia A with inhibitors undergoing invasive procedures requiring treatment with bypassing agents, the HGP suggests either rFVIIa (eptacog alfa) or aPCC. | By omitting mention of EMI in this setting for baseline hemostasis, this becomes another very contentious recommendation and potentially dangerous for such patients. Mentioning only 1 bypass agent and omitting other approved products also restricts options. |
| 11 | In individuals with severe hemophilia A with inhibitors who present with joint bleeding and will be treated with rFVIIa (eptacog alfa), the HGP suggests treatment with either 3 doses of 90 μg/kg at 3-h intervals or a single dose of 270 μg/kg. | This dose recommendation without nuances of age and severity of bleeding is unjustified. It is unclear why aPCC (FEIBA) was omitted when RCT data showed equivalence with rFVIIa and another RCT showed superiority of high-dose rFVIIa in treatment of joint bleeding. |
| 12 | In individuals with severe and moderately severe hemophilia B without inhibitors, the HGP recommends prophylaxis over episodic treatment of bleeding events. | Unlike hemophilia A, bleeding phenotype is not mentioned here. The word "recommends" appears only here, not in recommendation 13. This can make clinical implementation confusing. |
| 13 | In individuals with severe and moderately severe hemophilia B without inhibitors, the HGP suggests prophylaxis with purified plasma-derived FIX or standard or EHL recombinant FIX concentrates. | Equating all available CFCs completely ignores the extensive data on the vastly superior outcomes of prophylaxis with EHL FIX CFC in achieving higher trough levels and prevention of bleeding with much lower treatment burden[b]. |

aPCC, activated prothrombin complex concentrate; CFC, clotting factor concentrate; EHL, extended half-life; EMI, emicizumab; FEIBA, factor 8 inhibitor bypass activity; FIX/FVIII, factor IX/VIII; FVIIa, activated factor VII; HGP, hemophilia guideline panel; ISTH, International Society on Thrombosis and Haemostasis; IU, International Units; ITI, immune tolerance induction; pdCFC, plasma-derived clotting factor concentrate; RCT, randomized controlled trial; rFVIIa, recombinant activated factor VII; SHL, standard half-life; VWF, von Willebrand factor.

[a]Adapted from Rezende et al. [18].

[b]Lack of clinical equipoise could make an RCT unethical.

serious concerns with many of the recommendations. As these stakeholder concerns could not be considered within the process chosen for guidelines, critiques were recently published in 2 detailed commentaries with authorship reflecting a wide spectrum of international healthcare professionals and lay opinion leaders [19,20]. From the process perspective, based on the descriptions provided within the ISTH CPGs [18] and the subsequently published clarifications [21], significant deviations are apparent from criteria 4, 5, 6, 11, 12, 13, 15, 16, 19, and 21 from several domains of AGREE II (Supplementary Table). The content-related critique of these guidelines is summarized in Table.

The ISTH CPGs need not be faulted for not including references to newer nonclotting factor concentrate (CFC) products (other than emicizumab), the high-sustained activity factor (F)VIII concentrate (efanesoctocog alfa), or gene therapy [18]. As clarified within these guidelines, the literature on these products was not available when the process of evidence collection was initiated. However, the outdatedness of these ISTH guidelines, even at the time of its publication, is more related to the exclusion of the extensive literature, including real-world data, which has been available for 5 to 10 years, showing clear superiority of outcomes with extended half-life (EHL) CFC products and emicizumab compared with conventional standard half-life CFC products [22].

A recent commentary also highlights the limitations of nearly all the ISTH recommendations, mostly from the perspective of their applicability in the current clinical context [23]. However, these recommendations should not be modified by "expert opinion" on the basis of clinical trial data on newer emerging products without following due process for developing practice recommendations. Much more data will be needed from real-world utilization of these new products—clotting factor mimetics, hemostasis rebalancing drugs, and gene therapy products—regarding both their efficacy and safety before they can be incorporated into CPGs [22]. The gap between efficacy of products in clinical trials and their adoption in clinical practice is best exemplified by the currently approved adeno-associated virus vector-based gene therapy products [24].

A prominent misconception that seems to have affected the selection of evidence included in these ISTH guidelines is that the GRADE method only allows data from RCTs or similar studies to be included for framing recommendations. As explained in a recent publication on this specific issue in 2021, the GRADE methodology may also be applied even when there is "no evidence," with only the experiences and opinions of the expert panel contributing to the evidence base for framing recommendations [25]. Between these 2 extremes, there is much peer-reviewed literature of well-designed cohort studies in hemophilia, which can and should be the basis of strong practice recommendations. If such data had also been considered by the ISTH CPG panel, it is possible that the recommendations may have been different.

Another critical concept that seems to have been ignored in the ISTH guidelines, as reflected not only in the practice recommendations but also in the aspirational list of future studies recommended, is the clinical equipoise needed to justify RCTs [26]. The remarkable superiority in prevention and control of bleeding already documented in cohort studies with the recent hemostasis products for hemophilia, apart from reduction of treatment burden and improved compliance, would make it unethical to even consider RCTs when there is access to such products. Cost considerations and logistics of such trials would be additional considerations against initiating such RCTs [22].

## 6 | CPGS—BRINGING CONTEXT TO PROCESSES

An ideal product for achieving good hemostasis for people with hemophilia would maintain steady-state hemostasis as close to normal as possible, with no peaks and troughs, have a low treatment burden, may be initiated soon after birth, and have no risk of inhibitor formation. The advances over the last decade with EHL CFCs and the first FVIII mimetic have already moved the bar of hemostatic efficacy in this direction. Several of the newer products, such as efanesoctocog alfa, more FVIII mimetics, and the hemostasis rebalancing drugs such as concizumab, marstacimab, and fitusiran could move that bar even higher [23].

The unique advantages of non-CFC hemostasis products are steady-state hemostatic protection at higher efficacy than what has been achieved with even EHL CFCs. However, in the absence of suitable models for evaluating this phenomenon, the precise level of steady-state hemostasis attained by these products remains unqualified at this time [27]. More data on their efficacy and safety will determine their position in the clinical practice algorithm among other available hemostasis products for patients at various ages with different activity levels, lifestyles, and risk factors (Figure).

Preparation of trustworthy CPGs needs tremendous resources to follow the required processes. With the availability of detailed documents describing such requirements, it may appear that if all the boxes in such lists are checked, a good final product will automatically appear. This would be another huge misconception. Good CPGs do not get autogenerated as a computational output of the process but are indeed steeped deeply in the art of clinical medicine applied to the interpretation of all the evidence gathered and building consensus without bias and with active informed participation of all members around carefully worded final recommendations. The knowledge and experience of the experts in the panel in their own domains and their familiarity with the process of preparing CPGs are also critical to how the final product is presented.

The most important target of the CPGs is the clinical practitioner who is looking for specific guidance on the best possible choice for a specific situation from the available options, regardless of whether the evidence is from RCTs or the "expert consensus opinion" (not individual). While purists in the field may want to differentiate between guidelines and guidance statements in these documents [28], for the average practitioner, both serve the same purpose. These documents are meant to facilitate and enhance individual patient care rather than initiate debate within the healthcare system by creating ambiguity in the choices of available options and advocating further research to

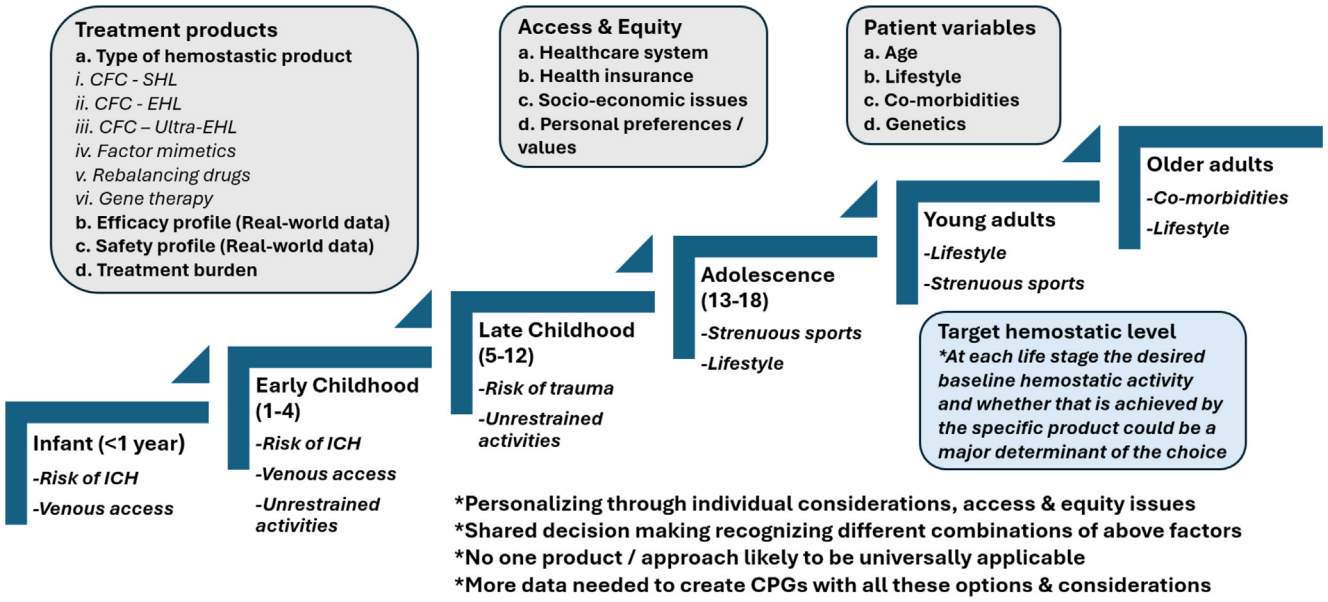



**FIGURE** Looking into the future: choosing hemophilia therapy. CFC, clotting factor concentrate; CPG, clinical practice guideline; EHL, extended half-life; ICH, intracranial hemorrhage; SHL, standard half-life

resolve the situation. It is rather common, even within the context of shared decision-making, for the patient to ask the physician for the "best" choice for him. Clear recommendations in CPGs based on all the available data resolve that situation.

## 7 | CONCLUSION

It is important that before embarking on creating new CPGs, the existing documents be reviewed for gaps to be addressed. Given the stringent current requirements for producing good CPGs, the resource allocation should be justified by the need for revised or new CPGs. There should also be enough scope within the process followed to modify draft recommendations based on external review so that the final recommendations should address the needs of the stakeholders that they are intended for, based on all the existing data, as we continue to strive for better clinical studies to enhance the quality of available evidence.

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## SUPPLEMENTARY MATERIAL

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