12 METHODOLOGY

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12.1 | Background

The World Federation of Hemophilia (WFH) developed the first edition of the Guidelines for the Management of Hemophilia in 2005.[1] These guidelines were updated in 2012[2] and have since seen global print and online distribution of more than one million (including downloads from the *Haemophilia* journal and WFH websites, WFH print distributions, and WFH and National Member Organization translations). For this third edition, the WFH decided to adopt a different method for development, incorporating evidence-based and Trustworthy Consensus-Based Statement (TCBS)[3] approaches in conformance with established international standards for clinical practice guidelines.[4,5]

In rare diseases such as hemophilia,[6] there are limitations in developing evidence-based guidelines due to gaps in the evidence base related to small sample sizes and the paucity of methodologically rigorous data stemming from randomized controlled trials. The wide range of hemophilia treatments and practices used globally also contributes to the disparate research foci in the current state of hemophilia science. Quantitative analyses of the data for several aspects of management (e.g., direct meta-analyses or network meta-analyses) are not feasible under these circumstances.

When the evidence is not sufficiently evolved to support quantitative analyses for evidence-based recommendations, it is important to provide physicians and other healthcare providers, people with hemophilia, and advocates with advice they can trust.[4,7] The TCBS approach[3] produces unbiased, scientifically valid, and trustworthy recommendations through a transparent process that incorporates both the available evidence, identified using a systematic approach to reduce biases, and expert clinical advice.

This chapter describes the methodology used to develop the third edition of the WFH Guidelines for the Management of Hemophilia.

12.2 | Methodology

The TCBS process produces evidence-informed recommendations supported by a comprehensive and systematic search for relevant scientific literature, which is first screened based on predetermined inclusion/exclusion criteria, then followed by data extraction of the available and relevant evidence. The Delphi technique is a widely used and well-accepted process for soliciting feedback and achieving consensus.[8] There are several variations,[9-12] but the modified Delphi approach for guideline recommendations allows consideration of the evidence base as well as expert opinion while suppressing the introduction of group interaction bias. The WFH adopted the TCBS approach, already in use by several medical professional societies,[13,14] as this type of guideline brings thoroughness and transparency to the guideline development process for the expert panel's evidence-informed and consensus-based recommendations.[7] As with fully evidence-based guidelines, the TCBS approach includes a rigorous review of both methods and content by internal

and external stakeholders of all types. This approach is based on five important pillars:

- confidence in the panel composition and screening;
- systematic and comprehensive evidence searches;
- formal consensus achievement;
- transparency of data and methods throughout; and
- rigorous review process.

Composition of the panels: structure and review

The WFH appointed an overall content lead (AS) and an assistant content lead (GP), both highly experienced in the field of hemophilia, and a methodology consultant (SZL) with extensive experience in developing guidelines and expertise in the TCBS approach. A WFH Guidelines Process Task Force (GPTF) was established to provide objective oversight of the process. The GPTF was composed of members of the WFH Education Committee, including patients and a hematologist not involved in the development of the guidelines.

The content lead and the previous WFH Vice President, Medical, offered initial invitations to the expert and representative panel to meet the criteria described below. An important goal, not always achieved by guideline and research organizations,[15] was to ensure that no serious topic-related conflicts of interest existed for the leads and to minimize the percentage of the panel with relevant conflicts.

This third edition of the WFH guidelines comprises an extensive revision of the existing seven chapters of the 2012 edition, as well as several new chapters. Each chapter was assigned to a panel composed of 7-10 members, including a chapter lead, healthcare professionals with clinical expertise, and patients/caregivers, with the latter making up at least 25% of each chapter panel. A total of 50 panelists were assigned to the 11 content chapters, with some panelists serving on more than one panel. The WFH drew upon its international volunteers and wide stakeholder network to recruit experts from diverse healthcare disciplines (hematologists, orthopedic surgeons and other musculoskeletal specialists, physical and occupational therapists, laboratory scientists, nurses, dentists, and psychosocial professionals). The panel also included a broad representation of people living with hemophilia including those with related complications such as inhibitors, musculoskeletal complications, and diverse comorbidities, as well as parents of children living with these conditions. Panelists were recruited from diverse demographic, geographic, and socioeconomic contexts to ensure the global relevance of these guidelines.

Process for panel workflow and oversight

The content and chapter leads guided the panels through the chapter development process and provided content expertise. The responsibilities of the chapter leads, with help from other healthcare professionals on their panels, included developing a comprehensive set of important subtopics per chapter, advising the medical librarians on relevant search terms, drafting initial recommendations, and developing the manuscripts including citation of important research. The responsibilities of the chapter leads also included ensuring that the patient/ caregiver panelists' perspectives were solicited and addressed. Even though the vast majority of recommendations address the care and management of patients, rather than treatments, content and chapter leads also ensured that no specific products or brand names were mentioned; with the exception of the Laboratory Diagnosis and Monitoring chapter, wherein the therapeutic products may not be recognized by their international nonproprietary names (INN) by the community and brand names were included for all products, without which medical errors could inadvertently be made. For the diagnostic reagents, the specific brand names for which published evidence of assay validation is available were included within each category of the reagents.

All panelists were involved throughout topic organization, evidence generation, consensus achievement of recommendations, and manuscript drafting and reviews. Meetings, communications, and trainings were conducted via videoconferences, emails, and electronic surveys. Recordings and slides of training sessions and calls were made available to all members afterward. All panelists were afforded the opportunity to review all of the chapters before finalization and external reviews.

The equal status of all panelists (whether healthcare professional or patient/caregiver), the importance of each individual's expertise, and the imperative for all panelists to work together to solicit and validate all perspectives were emphasized in the trainings. Under the direction of the GPTF, a patient partner facilitator was hired to contribute training on the value that this approach adds to guideline development and the practicalities of its application, and assist with the implementation of this philosophy. The patient partner facilitator supported the patient/caregiver panelists throughout the guideline development process with monthly calls and guidance and non-financial support as needed.

Funding
The sole source of funding for these guidelines was the World Federation of Hemophilia.

12.3 | Evidence generation

A team of qualified and experienced medical librarians, screeners, methodologists, and data extractors was assembled to update the evidence base. Separate systematic reviews of the published literature were conducted on 10 of the 11 content chapters. A review of the literature was deemed not relevant for one chapter, Principles of Care, which focuses on ideal goals and aspirations given the current understanding of hemophilia and available science and technologies. Additional searches were developed specifically to target dental procedures, planned and emergent surgical and invasive procedures, and the emerging area of genetic assessment, resulting in a total of 11 reviews conducted. Details of the search strategies, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the extracted evidence are provided in the online supplemental materials.

Study eligibility criteria

Population, interventions, comparisons, and outcomes
For all chapters, studies that included patients with hemophilia A or B were retained. Additional population criteria were established for each chapter. There were no exclusions based on sex or age. Eligibility of included studies was not restricted by interventions, comparisons, or outcomes for any content area.

Search strategies and information sources
All search strategies were developed by a medical librarian in collaboration with content experts involved in each of the chapters and the overall content lead. All searches were restricted to English language and human-only studies. No exclusions based on geography or type of care setting were implemented. Searches were run in PubMed, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE, covering the period from January 1, 2000, to the date of the search between May and November 2019. The complete search strategies can be found in the online supplemental materials.

No crawling or searching of reference lists of identified systematic reviews was conducted. One exception was made for the new review on Outcome Assessment, for which the reference list of one generally well-respected landmark paper was crawled. Chapter leads and panelists were invited to propose any directly relevant literature that was not identified through formal searching to be reviewed for inclusion.

Setting and study designs
Due to the volume of literature identified, post hoc restrictions on included studies (e.g., by publication year and study design) were applied without knowledge of the literature identified. Most studies selected for extractions were limited to publication dates after January 1, 2010 (preceding the search date limit for the previous edition of the guidelines), with the exception of the new chapter on Outcome Assessment, for which the inclusion date extended back to January 1, 2005. Additional papers and qualitative reviews were referenced when relevant, but data extraction was not performed. Study designs retained were randomized controlled trials, quasi-randomized controlled trials, and prospective comparative studies. In some cases, retrospective studies were included at the request of individual chapter leads. Some included studies were later confirmed as retrospective during extraction. These were retained in the evidence tables and marked as retrospective in the study design column. Cross-sectional studies were included in the evidence base for the Laboratory Diagnosis and Monitoring chapter. Systematic reviews were included for reference only.

Study selection
For each of the 11 search strategies, screening criteria were developed based on pre-specified criteria as defined during the chapter's search development calls and in collaboration with the chapter leads. Identified references were screened for chapter-specific eligibility using the reference management software Distiller SR®.

A team of seven trained reviewers screened titles and abstracts. Pilot testing was conducted prior to screening of each chapter, with all reviewers screening the same 50 references, followed by discussions and modifications to the screening forms when required for clarification. The remainder of title and abstract screening was completed by single review for all chapters. Dual screenings were not performed. For 8 of the 11 chapters, a secondary round of title and abstract screening of those studies deemed potentially eligible was conducted for two reasons. First, as the screening team became more familiar with the literature identified by the searches and through further discussions with the chapter and content leads, additional screening criteria were applied for subsequent rounds of review. Screening

decisions were made without the panelists' knowledge of the identified literature to avoid biasing the results. Second, a secondary title and abstract screening allowed the team to efficiently eliminate irrelevant references, providing time- and cost-saving measures. References not eliminated during title and abstract screening were reviewed for eligibility at full-text screening.

For further details related to the flow of references in PRISMA diagrams, please see the online supplemental materials.

Data extraction and development of evidence tables

Evidence tables were created for each chapter. Relevant outcomes were determined with the help of the chapter leads.

A senior methodologist (TS) provided oversight and organization of the evidence tables. A team of 15 methodologists and data analysts extracted the relevant data from all included studies. Dual extractions were not performed. The evidence tables and the underlying research articles for each chapter were shared with the entire chapter panel and used by the chapter leads and healthcare professionals to inform the recommendations. The evidence tables are available in the online supplemental materials.

Risk of bias in individual studies

No formal quantitative analyses were conducted, and no critical assessments were made of individual study quality. It should be noted that hemophilia is classified[6] as a rare disease which results in inherent limitations of primary research studies; thus, most assessments would have resulted in low or very low levels of evidence. Other than the study design limitations placed on the literature search and screenings, no additional exclusions were made based on methodological quality of the research studies.

By design, no recommendations were graded as the vast majority of the evidence base in the field, given the barriers to clinical research and data collection in rare diseases, is insufficient to support meta-analyses. Grading is based on two components, the quality of the evidence and the balance of benefits to harms and/or risks. The former is an assessment of the quality of the evidence supporting the recommendations specific to each outcome. When low-level evidence is partitioned by outcomes, the remaining data are not feasible to support quantitative analyses. Attempting to grade such recommendations can be misleading to the target audience of healthcare providers.[16] The second component is not explicit in the absence of the quality assessments, so we did not assign a level of strength to the recommendations. Therefore, in the interest of transparency, the WFH guideline recommendations were not graded but were clearly marked "CB" for consensus-based.

12.4 Formal consensus achievement through Delphi techniques

A priori rules and processes

Following the drafting of the recommendations by the assigned healthcare professionals, each set of recommendations went through the modified Delphi consensus process.

Several *a priori* decisions guiding the modified Delphi process were determined by the GPTF:

- Up to three rounds of Delphi surveys were permitted to achieve consensus.
- The minimum response rate for each survey round was set at 75% of eligible voting panelists.
- The threshold for achieving consensus was 80% of the respondents indicating agreement or strong agreement.
- Statements achieving consensus in the first or second round were not subjected to subsequent rounds.
- No minority reports were permitted.

Drafted recommendations that did not achieve consensus after three rounds do not appear as recommendations in the final guidelines. However, the underlying topics may be included in the relevant chapter text, often with a call for additional research in these areas to help resolve some of the controversies.

Delphi surveys

The modified Delphi surveys were conducted using SurveyMonkey, with all responses remaining anonymous except to the independent administrator (MG) who created and managed the process. All panelists received two trainings on the TCBS approach, written reminders of the Delphi process and rules, and instructions on the first page of the surveys.

The initial recommendations were drafted by the healthcare professionals, as assigned by the chapter leads. Recommendations were based on the evidence provided in the evidence tables and articles, as well as on the experience and expertise of the panelists. Panelists were trained in writing recommendations. The consultant and editors provided advice and edited the recommendations to make them specific and actionable.

Before the modified Delphi process began, the entire chapter panel, including the patients/caregivers, convened via teleconference to discuss the evidence as a group and receive instructions on the Delphi process. They were not permitted to discuss the drafted recommendations so as to avoid the occurrence or even perception of group interaction bias. Panelists were permitted to suggest topics for additional recommendations that did not appear in the list. When new topics were suggested, the assigned healthcare professionals for that chapter's section were tasked with drafting new recommendations to address the identified gaps.

Panelists were encouraged to respond completely to all recommendations in every round of the surveys. The healthcare professionals were advised to base their level of agreement or disagreement on the evidence and their experience treating patients with hemophilia. The patient/caregiver panelists were asked to make similar judgments based on the evidence and their experience as hemophilia patients/family caregivers in the healthcare system. These guidelines benefitted from the experiences of patient/caregiver panelists. However, some expressed hesitation about being asked to vote on recommendations for which they did not have any expertise or experience. Therefore, if the recommendation addressed an area in which the patient/caregiver panelists were not familiar, they could opt out of the denominator by voting neutral and adding the phrase "No experience in this area" in the comments field. This signaled that their neutral vote should not be added to the denominator when the votes were tallied. Across all chapters, 53 of 344 recommendations (15%) achieved consensus with at least one patient/caregiver panelist selecting this option. These choices were made selectively by individual patient/caregiver panelists on a recommendation-by-recommendation basis and did not impact the votes of others.

For recommendations that did not achieve consensus in the first or second round, the chapter leads drafted revisions based on the comments provided by the respondents. The revised recommendations were submitted for the next round of voting. The topics of any recommendations that did not achieve consensus by the end of the third round could be noted in the manuscripts along with calls for future research in the respective areas. After all Delphi rounds were completed, consensus was not achieved for 13 (<4%) of the recommendations. Research funding agencies are encouraged to prioritize these areas to address knowledge gaps.

Survey tallies with the degree of consensus for each recommendation are available upon request (research@wfh.org).

Diversions from the process

There were a few diversions from the described process requiring additional surveys after the third round. One recommendation in the muscle hemorrhage section of the Treatment of Specific Hemorrhages chapter was resubmitted for voting because new evidence (albeit low level) was brought forth that raised doubts about the timeframe specified in the recommendation. Due to inadvertent group discussion of this recommendation, this section with all three recommendations was then moved to the Musculoskeletal Complications chapter, which was composed of different panelists, to avoid the introduction of group interaction bias. The panelists were informed of the full set of evidence, provided with the relevant papers and extracted data, and voting on the updated recommendation took place. During reviews for consistency and gaps, three additional recommendations (one from the Treatment of Specific Hemorrhages chapter and two from the Inhibitors to Clotting Factor chapter) required additional revisions or the addition of remarks. One recommendation was inadvertently excluded from the original surveys for the Prophylaxis in Hemophilia chapter. All were rectified through additional survey rounds.

12.5 Finalization of the recommendations and manuscript development

At the conclusion of the final round of the modified Delphi surveys, the chapter leads finalized the manuscripts for their assigned chapters. All recommendations that achieved consensus were incorporated within the relevant section of the manuscript, bolded, and numbered accordingly. All remarks are considered integral to the recommendations themselves and therefore included as part of the recommendations. *The WFH advises that as recommendations are uploaded into digital platforms, incorporated into separate lists, or otherwise removed from this full guideline publication, the remarks should always be kept with the rest of the recommendation as a single unit.*

These guidelines have an intrinsic navigation system for the chapters, sections, recommendations, and supplemental materials. The numbering system uses the chapter number as the initial number, followed by the section numbers. Recommendations are numbered according to the chapter and section in which they appear. This will help readers locate the background information that builds the case for the recommendations themselves. For example, a recommendation

numbered 4.2.3 represents the third recommendation in Chapter 4, section 2.

Review and finalization

Each chapter manuscript underwent extensive review. Final manuscripts were reviewed by the chapter lead and panelists; the content lead and co-lead; the GPTF; key members of the WFH senior management team; followed by an external team of highly experienced healthcare professionals with expertise in the care of people with hemophilia, and well-informed expert people with hemophilia from around the world, ensuring a global perspective. Finally, the entirety of the guidelines was submitted to several organizations for their review and consideration for endorsement. Comments at each stage of review were considered by the chapter leads, and modifications were made when relevant. No editing or changes to the recommendations or remarks were permitted. A final independent peer review was also done through the *Haemophilia* journal and the extensive comments were addressed.

12.6 | Methodology limitations

As is common in guideline development, methodological processes have to be pragmatically adjusted to accommodate challenges with the available evidence, organizational matters, and other constraints. Similarly, with these guidelines, compromises were required in order to provide the best guidance possible in a clinical area with limitations in the evidence base.

The panels were organized by invitation and without a declared review of conflicts of interest (although current disclosures accompany this publication). All panelists were invited to participate in the scope of the chapter searches, which was accepted as a proxy for *a priori* established PICO (Population/Intervention/Comparators/ Outcomes paradigm) questions.

Search strategies were then developed by highly experienced medical librarians based on the scope discussions and early drafts, although they were not peer-reviewed. Since the last guidelines were published in 2012, the searches were restricted to the years 2010-2019 for the chapters which are revisions from the previous edition. However, since that edition did not include a formal systematic review, future searches may have to be extended further back in time.

Studies identified as retrospective by the screeners were excluded, except where specified above. For a rare disease, especially for the more subjective topics, a more comprehensive and reliable evidence base would have included these reviews.

Due to the high yield of references from the searches for the Prophylaxis in Hemophilia chapter, references were limited to studies with a minimum sample size of 40. Sample size is not a proxy for quality, but alternative options to limit the number of studies to meet the timeframe did not exist.

Both single screening, rather than dual screening with adjudication, and single data extractions, rather than dual extractions with adjudication, were necessary compromises.

There were no critical appraisals of the quality of the evidence or assessments of the feasibility of quantitative analyses as these had been ruled out in advance due to previous efforts to conduct systematic reviews in this rare disease.

Considerable support was provided to reduce the burden on the volunteer panelists in the literature searches, screenings, data extractions, and drafting of the manuscripts. Like all multi-chapter guidelines, the level of consistency of writing varied across chapters, but the medical editors strove to reduce duplication and ensure standardization. This helped to ensure a final consistent format in these important guidelines for all users.

12.7 | Future plans for updates

With this third edition, the WFH Guidelines for the Management of Hemophilia have advanced considerably and comply with current standards for guideline development using the TCBS approach.[3] As additional research is conducted in the field of hemophilia, as methods standardize, and knowledge grows, published data should become more homogeneous and quantifiable, permitting more evidence-based guideline updates by the WFH in many of the content areas. This will also increase the methodological rigor and allow the evolving science to guide future recommendations, especially in areas where the research is growing, such as diagnostic methods, hemostatic agents, regular replacement strategies, and management of inhibitors apart from curative treatments. Additional efforts will follow the advancing work of several international initiatives to provide recommendations for digital platforms and repositories and to increase implementation, especially at the point of care.

12.8 | Conclusion

Even though this third edition of the WFH Guidelines for the Management of Hemophilia is primarily intended for

use by healthcare professionals, it will also be useful for people living with hemophilia and healthcare agencies and advocates around the world. These are trustworthy, reliable, evidence-informed, and expert-driven recommendations that should inform and empower medical professionals, patients and their caregivers so that they can be better informed and active participants in shared decision-making guiding hemophilia treatment and management plans.

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SUPPORTING INFORMATION

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

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