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ORIGINAL ARTICLE *Clinical haemophilia*

Target plasma factor levels for personalized treatment in haemophilia: a Delphi consensus statement

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Background: Prophylactic replacement with factor concentrate is the optimal treatment for persons with severe haemophilia to avoid or minimize bleeding. This ultimately prevents or reduces joint disease and improves life expectancy and quality of life towards values matching those in the normal population. However, uncertainty still exists around the optimal regimens to be prescribed for prophylaxis. An increasing number of treating physicians and patients are showing interest in patient-tailored approaches to prophylaxis, which aim to harmonize the prophylaxis regimen with the patients' bleeding phenotype, levels of physical activity and a variety of other variables. **Methods:** A modified Delphi technique was adopted to generate consensus. The expert panel met in person to set the objectives, be trained on the Delphi technique and agree on the desired level of consensus. Three iterations were used to identify the targets, the scenarios and their combinations. **Results:** Twenty-eight scenarios and eight target levels were identified and used to issue recommendations. The panel reached the desired level of consensus on positive or negative recommendations. Areas where consensus was not reached were identified and proposed as areas for future research. Prospective assessment of the validity of most of the proposed targets is recommended. **Conclusions:** We have generated, by expert consensus, target plasma levels of factor concentrate to be used to tailor treatment for persons with haemophilia.

Keywords: haemophilia, individualization, personalized, prophylaxis, tailoring

Introduction

Prophylactic treatment, either as long-term regular administration of factor concentrates or time-limited situational prophylaxis, has been unequivocally demonstrated as the optimal care for persons with haemophilia [1–5]. Full-dose prophylaxis regimens are intended to maintain factor VIII or factor IX levels above 0.01 U·mL^{-1} (1%) [6], and have been shown to reduce the frequency of bleeding by 90% in comparison to on-demand treatment [1–5]. The importance of a 1% trough level was recently confirmed by Collins and colleagues who showed that for every hour spent with a FVIII level <1%, the annual bleed rate increased by 2.2% in children (ages: 1–6 years), and by 1.4% in adolescents and adults (ages: 10–65) [7]. However, not all bleeds occur at factor levels below 0.01 U·mL^{-1} and there is mounting evidence that the same prophylaxis

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regimen is not optimal in all persons with severe haemophilia. Moreover, not only are trough levels important, but also the time the patient spends above certain levels, or, in other words, what factor level he presents with during certain physical sport or work activities [8]. Indeed, due to patient heterogeneity, standard prophylaxis may for some patients be more than they need, whereas for others, it may still not be completely adequate to protect them from bleeds [8]. The sources of this heterogeneity, just to mention some include: individual pharmacokinetic responses to infused clotting factor concentrates; other pro- and anticoagulant factors; levels of physical activity; and musculoskeletal structure and function.

The mounting evidence for inter-individual variability has prompted a challenge of the basic concept that tailored prophylaxis should fundamentally adjust the dosing regimen to best target a trough level of 0.01 $U{\cdot}mL^{-1}$. More recently, the focus has switched to tailoring treatment to the individual need by targeting the appropriate levels as the critical component.

Unfortunately, there is poor evidence based on clinical trials and non-interventional cohort studies to direct choice of treatment regimens, providing support for a consensus guidance document. The scope of this project was to use structured expert opinion to define a range of target factor levels for use in different clinical situations.

Methods

A modified three-round Delphi approach was used for this study [9–11]. An initial consensus conference was held in Frankfurt, Germany, in January 2015, to address whether different plasma factor VIII/IX target levels could be identified for specific subgroups of patients or specific situations (physical activity, bleeds, surgery). The consensus perspective was to account for responsible utilization of resources but without specifically addressing the high constraints of developing countries. The goal of this meeting was to discuss these topics in the form of a consensus conference, and to plan a consensus process using the Delphi method, with a leaderless approach where all responses were equally weighted. The discussion panel decided to focus on haemophilia A and B patients and on specific plasma FVIII and FIX levels, and then evaluate which group of patients and/or what situations merit use of predetermined factor levels.

The first round was used to complete the scoping phase, generate consensus on the target levels and propose relevant scenarios, to be rated in later rounds to achieve consensus. For example, for the target plasma factor level lower than 0.01 $IU{\cdot}mL^{-1}$ (<1%), a proposed generated scenario was 'any child before the first bleed'. The two subsequent rounds narrowed the scope of the scenarios and looked for consensus on wording of the recommendations.

Participants

The Delphi panel consisted of 11 members, selected based on long-lasting expertise in the field of assessment and care of persons with haemophilia, geographical location and willingness to participate in the Delphi process. Four additional people constituted a core technical group to support the process; these individuals did not take part as voting members (Appendix 1). Panel members were reimbursed for participating in the meeting held at Frankfurt, but did not receive any other personal financial support to participate in the process and or the final preparation of the consensus statements.

Definitions

The following definitions were adopted in the process. We defined '*target level*' as a plasma factor level of interest. A target plasma factor level can sometimes indicate a trough level (the minimum acceptable level); other times, it can indicate a level to be reached for a limited and well-defined period of time (a desirable level). For example, a target can be 0.01 $IU{\cdot}mL^{-1}$ (e.g. 1%). We defined '*scenario*' as a specific combination of clinical and social elements defining a condition for which a specific target level can be considered. As an example, a child on primary prophylaxis or an adolescent performing intense physical activity are two scenarios. We defined '*modifier*' as a specific condition or event triggering the need for a change in management based on the specific scenario. As an example, considering a specific number of bleeds over a given time period was a modifier. Finally, we defined '*recommendation*' as the suggestion to adopt a specific *target factor level* for a specific *scenario* as a default, or until/after the occurrence of a specific *modifier*.

Questionnaire

All rounds of the survey were developed by AI, AG, KS and reviewed for clarity of language by EI. The survey was implemented with the in-house Delphi software program created by the Health Information Research Unit (HIRU) at McMaster University (plus.mcmaster.ca/Delphi!). Panel members were invited and reminded to participate in the different rounds of the survey using specific personal and anonymous links automatically sent via email by the software. All responses were kept anonymous.

Delphi survey implementation

Round 1: selecting the target levels and defining candidate scenarios. In this round, all participants considered each of eight target levels proposed at the

consensus conference, and for each level, were asked to: (i) indicate whether each target factor level should be included in the consensus recommendation; (ii) list all *scenarios* for which they would consider that target factor level appropriate; and (iii) list all *modifiers* for their proposed scenarios. Target levels agreed upon by 50% or more of the panellists were retained. The core team condensed and combined similar scenario proposed by different panellists to create a list of suggested scenarios for Round 2.

Round 2: selecting scenarios. Participants were asked to *consider the target factor levels* selected in Round 1 one at a time. Panellists were shown all the *scenarios* proposed in Round 1 for each *target factor level*, with the total number of panellists (but not their names) proposing each scenario in Round 1, and with a brief description of the scenario and the proposed modifiers; panellists were asked to indicate whether the *scenario* should be retained (yes/no) or modified (panellists could ask for wording changes or propose brand new scenarios). Depending on votes received in round 2, *scenarios* moved onto round 3, or were either dropped, merged or split based on suggestions from panellists.

Round 3: defining recommendations. The core team drafted at least three alternative *recommendations* for each scenario consented upon in Round 2, taking into account the feedback from the prior rounds and the initial meeting minutes. Panellists were then requested to review each scenario (each presented indicating the original number of proponents in Round 1 and supporters in Round 2), and asked to cast a final vote for its inclusion/exclusion, and which of the alternative recommendations they preferred. Panellists were invited to propose wording changes or new statements if they wished to do so.

Analysis

Consensus level was set at 60% for either inclusion (60% in favour) or exclusion (40% in favour); tie votes (between 40% and 60%) were defined as absence of consensus. All analyses were done with the in-house HIRU Delphi software and Microsoft Office Excel.

Results

Round 1: selecting the target levels and defining candidate scenarios

All 11 panellists completed the first round of questions. The majority of the participants accepted all the *target factor levels* proposed at the in-person meeting (Table 1). The panellists suggested 141 total scenarios, which were condensed and combined by the core team into 48 scenarios. For example, for a factor level of <1%, nine panellists suggested the scenarios 'newborns before the first bleed' and 'children up to age 2 years before the first bleed'. Those suggestions were combined together to make one scenario, 'children below the age of 2 years and before the first bleed'.

Round 2: selecting scenarios

Ten out of 11 panellists completed round 2. Of the 48 scenarios identified in Round 1, 36 were included in Round 3 (Table 2).

Round 3: defining recommendations

The panellists were asked to vote again on whether each scenario would be included, with the result that 28 of 36 scenarios were included by majority vote. For each scenario, the panellists voted to indicate which of the 3–4 proposed alternatives for the recommendations they preferred, with the possibility to reword the recommendation or propose a new wording. Since no new recommendation was proposed, and minor non-substantial changes were suggested to the wording, it was not necessary to proceed to a second iteration in Round 3, and the final recommendations were selected based on those receiving most of the votes in the single iteration. Nine panellists scored all of the surveys, while one additional panellist completed only the first four levels (<1% through 15%).

Table 3 reports the final list of recommendations with supporting votes across all phases of the process. Final agreed recommendations are listed here:

A Plasma factor level lower than 0.01 IU·mL^{-1} (1%)

A.1 The authors recommend considering delaying the start of treatment in children below the

Table 1. Round 1 – Initial set of trough levels to be included and used to propose clinical scenarios.

	Yes	No	Unsure	Total # of suggestions for scenarios
Plasma factor level lower than 0.01 IU·mL^{-1} (<1%)	11	0	0	25
Plasma factor level between 0.01 and 0.03 IU·mL^{-1} (1–3%)	11	0	0	18
Plasma factor levels between 0.03 and 0.05 IU·mL^{-1} (3–5%)	10	1	0	20
Plasma factor level between 0.05 and 0.15 IU·mL^{-1} (5–15%)	11	0	0	19
Plasma factor level between 0.15 and 0.30 IU·mL^{-1} (15–30%)	10	1	0	10
Plasma factor level between 0.30 and 0.50 IU·mL^{-1} (30–50%)	9	1	1	13
Plasma factor level between 0.50 and 0.80 IU·mL^{-1} (50–80%)	10	1	0	19
Plasma factor level above 0.80 IU·mL^{-1} (80–100%)	9	1	1	17

age of 2 years in the absence of bleeding, in order to limit the need to position a central venous access device to facilitate treatment.

A.2 The authors recommend considering on-demand treatment for *informed adult patients* unwilling to practice prophylaxis, refusing prophylactic infusions for difficult vein access, reporting poor compliance or documented poor adherence. The choice of recommending on-demand treatment must always follow a thorough discussion with the patient, where a maximum number of bleeds or progression of arthropathy has to be agreed on between the doctor and the patient on a case-by-case basis.

A.3 The authors recommend considering continuing treatment regimens not producing a measurable threshold (i.e. <0.01 IU·mL^{-1}) at all times (e.g. weekly or less frequent infusions of standard half-life concentrates) in *adult patients* already on such regimens and not experiencing bleeding events. This suggestion includes considering this option for adult patients on regular prophylaxis, not experiencing bleeding events, and willing to reduce their treatment frequency. The authors suggest that in such cases, the doctor and the patient identify and agree upon a reasonable number of bleeds to be used to return to a regular prophylaxis regimen (as low as one, depending on patient preference and joint health status).

B Plasma factor level between 0.01 and 0.03 IU·mL^{-1} (1–3%)

B.1 The authors recommend considering this as the *acceptable* target trough factor level range in *most patients on prophylaxis* without additional comorbidities increasing the risk of bleeding and irrespective of their current joint status and their physical activity level, and in the absence of spontaneous bleeding requiring treatment with factor concentrates.

B.2 The authors recommend this as an *appropriate* target factor level range in *patients on prophylaxis*, experiencing no or a limited number of spontaneous bleeding events requiring treatment with factor concentrates. To qualify for this target factor trough level, the patient has to present one or more of the following characteristics:

i. No repeated bleeding in the same joint.
ii. A moderate or mild degree of joint arthropathy.
iii. Absence of comorbidities associated with an increased risk of bleeding.
iv. Low level of physical activity (particularly at the end of the prophylaxis interval).

The authors recommend this is *not an appropriate* target factor level range if the patient experiences more than 1–2 'spontaneous' joint bleeds within a limited time period when factor VIII trough levels are maintained in the 1–3% range (the authors are cognizant that 'limited time' might be interpreted very differently by different health care professionals).

B.3 The authors recommend this as an appropriate target level range in *children and adult patients on prophylaxis with a sedentary lifestyle* and without additional comorbidities increasing the risk of bleeding, in the absence of spontaneous bleeding requiring treatment with factor concentrates.

B.4 The authors discussed the option of adopting a 1–3% trough factor level as a universal target for standard primary prophylaxis, but they did not reach consensus, and felt more appropriate to articulate the recommendation as under B.1–B.3.

B.5 The authors recommend this is not an appropriate trough level range for all patients with *moderate haemophilia*. It might apply to moderate patients with factor levels around 1–2% presenting spontaneous bleeding, which requires treatment with factor concentrates.

C Plasma factor levels between 0.03 and 0.05 IU·mL^{-1} (3–5%)

C.1 Three recommendations were made for this scenario.

i. The authors preferences were equally divided between the following two statements:
   a. The authors recommend considering this factor level as the trough during *mild physical activity*, provided the patient does not present activity-related bleeds. This recommendation applies independently of the patient being on continuous or situational prophylaxis. In patients with pre-existing joint damage, a minimum number of bleeds might be acceptable; the doctor and patient should agree on a case-by-case basis on the number of bleeds to use as a decision threshold, and the level of intensity, duration and type of exercise that is planned.
   b. The authors recommend considering this factor level as the trough during *mild physical activity*, provided the

Table 2. Scenarios proposed in Round 1 and agreed upon in Round 2.

Trough level	Scenario	Round 1: # of proponents	Round 2: votes for inclusion
Plasma factor level lower than 0.01 IU·mL^{-1} (<1%)	Children before the first bleed	9	9
	Any patient treated on demand	6	9
	Patients of any ages on prophylaxis w/o bleeds, not very active	7	7
	Any patient before any limb, organ or life-threatening bleed, e.g. overt gastrointestinal haemorrhage requiring hospitalization/RBC transfusion	1	0
	Any patient before the first radiologically confirmed intracranial haemorrhage	1	0
Plasma factor level between 0.01 and 0.03 IU·mL^{-1} (1–3%)	Trough levels for most patients on prophylaxis	6	9
	Patients on prophylaxis with low bleeding phenotype or no bleeds	5	7
	Children and adults on prophylaxis with a sedentary lifestyle, if no or low bleeding rate	4	6
	Patients on prophylaxis with target joint bleeding defined as three or more 'spontaneous' bleeds into a single joint within a consecutive 6-month period	1	2
	Children on prophylaxis up to 2 years before the first bleed	1	5
	Moderate haemophilia	1	3
Plasma factor levels between 0.03 and 0.05 IU·mL^{-1} (3–5%)	Trough levels for active patients	6	10
	Patients with target joints/arthropathy	5	10
	Patients still bleeding despite prophylaxis at lower threshold	4	9
	Patients on prophylaxis 2–3 times a week (*merged with*)	1	2
	Moderate haemophilia	1	2
	On concomitant anti-platelet therapy	1	3
	Prophylaxis for previous life-threatening bleed	1	6
	Young children to safely prevent joint bleed and subsequent joint damage (* merged with *)	1	2
Plasma factor level between 0.05 and 0.15 IU·mL^{-1} (5–15%)	Levels for children and adults with high-risk activity	6	9
	Levels when patients are performing moderate activities	3	3
	Trough level for patients with target joints and severe arthropathy	3	6
	Trough level for patients with high bleeding rate/still bleeding at lower levels	3	7
	Anti-Platelet therapy/and antithrombotic treatments	2	4
	Severe comorbidities increasing the risk of bleeding	1	4
	Moderate and mild haemophilia A	1	1
Plasma factor level between 0.15 and 0.30 IU·mL^{-1} (15–30%)	Trough levels in the late postsurgery period	4	8
	Trough level for minor invasive procedures	3	7
	Levels when intensive sport activity is carried out	2	4
	Trough level sufficient to prevent spontaneous + traumatic in patients with and without target joints	1	1
Plasma factor level between 0.30 and 0.50 IU·mL^{-1} (30–50%)	Trough levels to maintain after major surgery, when the risk of re-bleeding is considered minor (after 5th–7th postoperative day)	6	10
	Levels to maintain during moderate to high-risk activities	3	3
	Trough levels to achieve in patients with target joints/chronic synovitis	2	3
	Level to achieve to treat mild moderate bleeds	2	3
	Trough level for the first 4 weeks following intracranial haemorrhage	1	4
	For minor surgery	1	3
Plasma factor level between 0.50 and 0.80 IU·mL^{-1} (50–80%)	Levels to maintain during minor to moderate surgery	6	9
	Trough levels after major surgery/post major trauma	6	9
	Major bleeds	4	7
	Levels to maintain in patients with very high impact physical activity	2	4
	None. No troughs have to be this high	1	1
	Recovery values after routine FVIII substitution	1	2
Plasma factor level above 0.80 IU·mL^{-1} (>80%)	Trough levels for high-risk surgery and post major trauma or surgery	9	9
	Life- and limb-threatening bleed	6	9
	None	1	0
	Preoperative (arthroscopy)	1	0

Green background indicates a scenario carried forward to Round 3, a red background indicates a scenario dropped by the pan during round 2.

patient does not present activity-related bleeds.

ii. The authors recommend considering that the occurrence of spontaneous bleedings outside the *periods of mild activity* may usually affect the dosage indicated for the activity.

iii. The authors recommend considering this trough factor level when patients are *advised or invited to be more physically active* to limit a number of other comorbid complications (obesity, osteoporosis, psychosocial deterioration) *as a healthy lifestyle measure*.

C.2 The authors' preferences were equally divided between the following two statements:

i. The authors recommend considering this trough factor level for *patients presenting with one or more target joints, or severe or progressive haemophilic arthropathy*. In

Table 3. Final scenarios and recommendations, with scores received.

Target level	Scenario	# of votes to include (round 2)	# of votes to include (round 3)	# of votes supporting recommendation wording
A) Plasma factor level lower than 0.01 IU·mL^{-1} (1%; no prophylactic treatment)	A.1. Any child before the first bleed	9	10	5
	A.2. Any patient treated on demand	9	10	6
	A.3. Adult patients on prophylaxis with a sedentary lifestyle not presenting bleeding	7	9	5
B) Plasma factor level between 0.01 and 0.03 IU·mL^{-1} (1–3%)	B.1. Any patients on prophylaxis not presenting bleeding	9	10	5
	B.2. Patients with mild bleeding phenotype	7	9	5
	B.3. Adult and paediatric patients with a sedentary lifestyle	6	9	5
	B.4. Any child up to 2 years or until the first bleed	5	7	4
	B.5. Patients with moderate haemophilia	3	5	6
C) Plasma factor levels between 0.03 and 0.05 IU·mL^{-1} (3–5%)	C.1. Patients performing mild physical activity (three recommendations)	10	10	#1–4/4* #2–4 #3–8
	C.2. Patients with target joints or severe progressive haemophilic arthropathy	10	10	5/5*
	3. Patients presenting bleeding despite prophylaxis at a lower target threshold	9	10	6
	C.4. Children on primary prophylaxis	2	6	7
	C.5. Patients with previous life-threatening bleeding events	6	10	9
D) Plasma factor level between 0.05 and 0.15 IU·mL^{-1} (5–15%)	D.1. Children and adults performing high-risk activity (three recommendations)	9	9	#1–4 #2–7 #3–6
	D.2. Patients presenting bleeding despite prophylaxis at a lower target threshold	7	9	5
	D.3. Patients with target joints or severe arthropathy presenting bleeding despite prophylaxis at a lower target threshold	6	9	5
	D.4. Patients with severe comorbidities	4	5	8
E) Plasma factor level between 0.15 and 0.30 IU·mL^{-1} (15–30%)	E.1. Patients who had surgery, in the late postsurgery period	8	9	6
	E.2. Patient undergoing minor invasive procedures	7	9	6
	E.3. Patients performing intensive sport activity	4	6	6
F) Plasma factor level between 0.30 and 0.50 IU·mL^{-1} (30–50%)	F.1. Patients who had major surgery after the initial period of higher dose treatment	10	9	8
	F.2. Patients who had an intracranial haemorrhage, for the first 4 weeks following the event	4	5	8
G) Plasma factor level between 0.50 and 0.80 IU·mL^{-1} (50–80%)	G.1. Patients undergoing minor surgery	9	9	5
	G.2. Patients who had major surgery or a major trauma	9	9	4
	G.3. Patients presenting with a major bleeding	7	9	4
	G.4. Patients performing very high impact physical activity	4	5	6
H) Plasma factor level above 0.80 IU·mL^{-1} (>80%)	H.1. Patients undergoing high-risk surgery, or who had a major trauma or major surgery	9	9	5
	H.2. Patients presenting life and limb or organ-threatening bleed	9	9	5

*Tie vote.

patients with pre-existing joint damage, a minimum number of bleeds might be acceptable; the doctor and patient should agree on a case-by-case basis on the number of bleeds to use as a decision threshold.

ii. The authors recommend considering this trough factor level for *patients presenting with one or more target joints, or severe or progressive haemophilic arthropathy*.

C.3 The authors recommend considering stepping up to this trough factor level for those *patients presenting more than the expected number of bleeds on a lower intensity regimen*.

C.4 The authors recommend considering this trough factor level for *primary prophylaxis in children* only after failure of less intensive regimens, considering that less intensive treatment might be more appropriate, more acceptable and less demanding for the patient and family.

C.5 The authors discussed this regimen as a possible prophylaxis trough factor level to treat

patients following a life-threatening bleed, but were unable to reach consensus. The appropriateness and duration of this target factor level has to be assessed on a case-by-case basis.

D Plasma factor level between 0.05 and 0.15 IU·mL^{-1} (5–15%)
- D.1 The authors made three recommendations for this scenario:
  - i. The authors recommend considering these plasma factor levels for *patients during high-risk physical activity*, provided they do not present bleeds related to high-risk physical activity while on this regimen.
  - ii. The authors recommend carefully considering the type of *high-risk physical activity* to be performed, the expected level of intensity and duration against the severity and the clinical phenotype of the individual patient. If the activity in question is considered inappropriate for the specific patient, a careful discussion with the patient is recommended and the doctor has to consider not providing an indication if the level of risk is perceived as excessive.
  - iii. The authors recommend to consider that the occurrence of spontaneous bleeding outside the periods of *high-risk physical activity* may or may not affect the dosage indicated for the activity, but may require considering starting regular prophylaxis to prevent spontaneous bleeding outside of high-risk physical activity.
- D.2 The authors suggest considering stepping up to this trough factor level those patients presenting *more than the expected number of bleeds on a lower intensity regimen*.
- D.3 The authors suggest considering stepping up to this trough factor level those patients with target joints or severe arthropathy presenting *more than the expected number of bleeds on a lower intensity regimen*.
- D.4 The authors discussed this trough factor level for all patients on prophylaxis with comorbidities, but were *unable to reach consensus*. The authors felt that the variability in possible combinations of comorbidities and related treatment is too wide and the experience too scanty to provide any advice. Decisions have to be made on a case by case basis

E Plasma factor level between 0.15 and 0.30 IU·mL^{-1} (15–30%)
- E.1 The authors recommend considering a trough factor level of 15–30% for *late postsurgical prophylaxis* (usually after the 15th postoperative day), which can be indicated for surgeries complicated by bleeding, for high-risk surgery or for patients with history of previous postsurgical bleeding.
- E.2 The authors suggest considering targeting a trough factor level of 15–30% to prevent bleeding in patients undergoing *minor invasive procedures* such as uncomplicated dental extractions or endoscopies, in the absence of previous bleeding for similar procedures.
- E.3 The authors discussed this trough factor level for patients during high intensity sport activities, but were *unable to reach consensus*. The authors felt that the difficulties in defining the intensity of sports activities and the relevance of the previous bleeding history of individual patients require making decisions on a case-by-case basis.

F Plasma factor level between 0.30 and 0.50 IU·mL^{-1} (30–50%)
- F.1 The authors recommend considering targeting a trough factor level of 30–50% when the *risk of bleeding* after major surgery *has reached low values* (e.g. when the risk of rebleeding is considered minor, usually after 5th–7th postoperative day). High-risk surgeries like brain surgery or patients with history of previous postsurgical bleeding while on treatment might require a higher trough.
- F.2 The authors discussed this possible target factor level for bleed treatment, but were *unable to reach consensus*. The authors felt that the variability in possible presentations and the range of severity of the bleeding event make it unlikely to provide any useful general advice. Decisions have to be made on a case-by-case basis.

G Plasma factor level between 0.50 and 0.80 IU·mL^{-1} (50–80%)
- G.1 The authors recommend considering targeting a trough factor level of 50–80% to *prevent bleeding during surgery and minor to moderate risk of bleeding* in patients without previous history of surgical bleeding or additional risk factors for bleeding (e.g. thrombocytopenia).
- G.2 The authors recommend considering targeting a trough factor level of 50–80% to reduce the risk of *bleeding after major surgery* (usually until the 5th–7th postoperative day). High-risk surgeries like brain surgery or patients with history of previous postsurgical bleeding while on treatment might require a higher trough.
- G.3 The authors suggest considering peak factor levels of 50–80% for the *acute treatment of major acute bleeds*. The recommended treatment frequency is usually every 12 h until symptoms disappear.

G.4 The authors discussed this target factor level for high-risk activities, but were *unable to reach consensus*. The authors recommend carefully considering the type of high-risk activity to be performed, and the expected level of intensity and duration, against the severity and the clinical phenotype of the individual patient. If the activity is considered inappropriate for the specific patient, a careful discussion with the patient is recommended, and the doctor has to consider not providing an indication if the level of risk is perceived as excessive.

H Plasma factor level above 0.80 IU·mL^{-1} (>80%)

H.1 The authors recommend considering targeting a trough factor level of >80% to prevent surgical bleeding *during high-risk surgery* and post major trauma or major surgery.

H.2 The authors suggest considering trough factor levels of >80% for the acute treatment of *life and limb- or organ-threatening bleeds*.

Discussion

As a result of a rigorous consensus process based on the Delphi technique, a group of 11 international experts has defined a proposal for *target* factor *levels* to be adopted for optimal prevention of bleeding in haemophilia. Typical *scenarios* have been defined for each *target factor level*, and exceptions (*modifiers*) listed and described as needed. The choice of a specific *target factor level* is a critical component of implementing a personalized medicine regimen for different types of patients, like children or the elderly, those who are more or less active and those who are severe vs. non-severe bleeders.

Indeed, the concept that individualization can be done according to the observed bleeding patterns, with patients who bleed less receiving less intense prophylaxis, and those who bleed more receiving more intense prophylaxis is not new. This tailoring of prophylaxis based on the bleeding phenotype has been explored by a number of groups, and more formally in a Canadian dose escalation study led by Feldman and Blanchette [12–14]. In that study, young boys with severe haemophilia commenced once weekly infusions with FVIII; subsequently, only those who experienced unacceptable bleeding were escalated to twice/week prophylaxis, and finally those who continued to bleed despite twice/week prophylaxis were further escalated to every other day prophylaxis. The study showed that unfortunately this approach led to haemophilic arthropathy in an undesirable high percentage of children [13]. An alternative tailoring approach is to de-escalate therapy in those patients who are doing well on more intense regimens (e.g. from every other day to every third day prophylaxis). Similarly, the clinical value of alternative prophylaxis regimens (e.g. low- and intermediate-dose prophylaxis) has been recognized, and many countries that cannot afford standard prophylaxis have embarked on supporting less intense prophylaxis regimens, with considerable success in reducing bleeds and preserving joint health, or at least slowing the deterioration of joint health [15].

An obvious and relatively easy way of overcoming patient heterogeneity in the need for prophylaxis would be to increase the intensity (frequency and dose) of prophylaxis for everyone. This would, however, unacceptably increase the burden of care to both patients and society. Individualization is not just about the doctor's desire to prescribe the most effective regimen to reduce bleeds but instead involves selecting a regimen that is most suitable and acceptable to the individual patient, within the options affordable in the health care system in which they live [16]. Ultimately, some patients, depending on their lifestyle, might prefer to reduce the number of infusions as much as possible, accepting a higher risk when their target level would be lower, while others might prefer to maximize their target levels, even accepting, if that was the only way to accomplish the higher trough, more frequent infusions. In order to achieve the desired levels, the new extended half-life products might provide an attractive option if their overall cost is affordable.

Whatever approach one might prefer to accomplish tailoring of treatment modalities to patient needs, one unavoidable step in the process will be defining the target factor levels to be considered desirable for each specific patient and/or activity. This is exactly the space where our contribution is positioned. In particular, the target levels we are suggesting can be used for addressing both long- and short-term prophylaxis. For the latter, relevant recommendations are: C5, D1, E1, E2, F1, F2, G1, G2, H1, H2.

The strengths of our work are in the expertise of the panel members, all experienced treating persons with haemophilia in real-world settings, and in the rigour of the Delphi method that was utilized in generating the recommendations presented in this report. An initial in-person meeting allowed the group to define the logical framework, discuss the approach and learn about the scope of the leaderless Delphi consensus technique. The anonymous iterations were adopted to define the target factor levels of interest and the most common clinical scenarios, and subsequently to match the former with the latter. This allowed the group to reach a significant level of consensus, and avoid any undue or inappropriate weight of individual opinions.

Limitations of this paper are that, though we are presenting state-of-the art *recommendations* from experts, the *target factor levels* we suggest have not been empirically tested, and might as a consequence

be too high or too low. We suggest that anyone who is going to adopt one of the *recommended target factor levels* consider prospectively recording bleeding events over time. In this way, they will verify the appropriateness to the individual and generate data useful to validating the *target factor levels* themselves. Also, in defining the *target factor levels*, the experts were invited to consider typical patients treated with conventional factor concentrates; however, we do not foresee any specific reasons why the proposed targets would not apply to extended half-life concentrates.

For some specific situations we have proposed a step up or step down approach. It has to be considered that every tailoring approach (escalation or de-escalation) involves causing patients to experience bleeds in order to demonstrate the appropriateness of the target factor level selected. Although some patients (particularly adults) may tolerate some bleeds without these contributing to long-term joint damage, other patients (particularly younger patients) are much more susceptible, and in these patients even a small number of bleeds might contribute to long-term joint damage. For this reason, we recommend careful discussion of the benefits and risks of choosing specific target factor levels with each individual patient, and where appropriate their families, by adopting a shared decision-making framework. Finally, this consensus took the perspective of a responsible utilization of resources but without specifically addressing the higher resource constraints of developing countries.

One might wonder how to warrant the desired factor level, once the decision to adopt a specific target factor level has been made. Indeed, patients clear factor VIII/IX differently depending on a multitude of variables; for FVIII, these include age, body mass, blood group, von Willebrand factor (VWF) levels and likely others yet unknown. In general, young children, those who are blood type O and those with lower VWF levels all have faster FVIII clearance than older patients, non-blood type O patients and those with higher VWF levels. Less is known about what influences patient FIX pharmacokinetic (PK). In the past, conducting a PK evaluation involved having a patient abstain from factor (washout) for an extended period of time (72 h for FVIII and 96–120 h for FIX), then infusing a specific dose of factor (usually, approximately 50 $IU \cdot kg^{-1}$) followed by frequent factor level measurements over 48 (for FVIII) or 72 h (for FIX). Due to the need for frequent venipunctures, this was difficult for most patients, particularly young children. Today, population PK modelling using Bayesian analysis has been developed and this has resulted in less or no need for long washout periods, and has led to fewer samples required to estimate a person's FVIII/FIX PK profile [17,18]. Therefore, once a specific target factor level – either trough or peak – has been selected for a patient, performing an individualized population PK assessment might allow a quicker identification of the required dose rooted on a more solid base than a fully empirical approach. Specific tools to facilitate adoption of population PK-based approaches to prophylaxis are becoming more and more available [19–21].

In conclusion, we have generated, by expert consensus, target plasma levels of factor VIII/IX to be used to tailor treatment for haemophilia patients. Prospective controlled assessment of their value in the real-world setting is warranted.

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Appendix 1

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- Michael Spannagl
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