

Definitions for haemophilia prophylaxis and its outcomes: The Canadian Consensus Study

S. OTA,** M. MCLIMONT,** M. D. CARCAO,*§** V. S. BLANCHETTE,*§** N. GRAHAM,††
E. PARADIS‡‡ and B. M. FELDMAN*†‡¶**

*Departments of Pediatrics, †Health Policy Management and Evaluation, and ‡Public Health Sciences, University of Toronto; §Divisions of Hematology/Oncology and ¶Rheumatology, and **Research program in Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada; ††Canadian Physiotherapists in Hemophilia Care; and ‡‡Canadian Association of Nurses in Hemophilia Care, Canada

Summary. The creation of acceptable standard definitions for terms used in the care and assessment of haemophilia patients has become increasingly important, as a growing number of international clinical studies have been initiated. The Delphi approach has been used in health research to reach consensus in large groups and can be used to develop definitions by using several iterations of surveys eliciting opinions from specialists in the field. Three consecutive surveys were designed based on the Delphi approach and distributed to specialist physicians, nurses and physiotherapists in order to develop definitions for seven haemophilia terms: 'primary prophylaxis', 'secondary prophylaxis', 'target joint', 'joint bleed', 'significant soft-tissue bleed', 'superficial soft-tissue bleed' and 'mucosal bleed'. Suggestions were solicited, compiled into a subsequent survey

and fed back to the group to rank-order the importance of each suggested component of the definition. Final definitions were created using the top-ranked suggestions and sent back to the experts for approval. Five of the seven terms were highly endorsed with greater than 90% agreement. Some differences in agreement were found when analysed by profession. Haemophilia terms were successfully defined using the Delphi approach. Further refinement from members of the international haemophilia community will ensure that comprehensive standard definitions can be used in multicentre studies in the future.

Keywords: bleed types, definitions, Delphi Approach, haemophilia, survey

Introduction

The World Federation of Haemophilia estimates that 400 000 people worldwide have haemophilia. Prophylaxis is being practiced more widely to prevent recurrent joint bleeding in individuals with severe haemophilia which often leads to painful and disabling arthritis; however, the optimal dose and frequency of factor infusions remain unknown and several prospective multicentre studies are addressing this question. It may however be difficult to directly compare these studies as they use different definitions for haemophilia outcomes. Standard definitions of

clinical endpoints and types of bleeds in haemophilia do not currently exist. The development of standard definitions will be important for evaluating the effectiveness of therapies across centres. For example, the Canadian Haemophilia Prophylaxis Study research team recognized the need during study development to define the terms 'primary prophylaxis', 'target joint' and different types of bleeding episodes [1].

The goal of our project was to develop Canadian consensus definitions for clinical endpoints and bleed types in the haemophilia population. Our chosen consensus method was the Delphi approach which has been applied extensively to medical, health, social and nursing research studies [2–6]. This method seeks to achieve consensus in a large group setting using successive iterations of questionnaires with controlled feedback; it has been used successfully to develop clinical practice guidelines [7],

Correspondence: Brian Feldman MD, MSc, FRCPC, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada.

Tel.: 416 813 5828; fax: 416 813 4989;
e-mail: brian.feldman@sickkids.ca

Accepted after revision 18 October 2006

disease severity indicators [2], assessment forms [8] and clinical criteria [9].

The specific aim of this study was to develop consensus definitions for: 'target joint', 'primary prophylaxis', 'secondary prophylaxis', 'joint bleed', 'superficial bleed', 'mucosal bleed' and 'significant soft-tissue bleed' using the Delphi technique.

Methods

The study was approved by the Research Ethics Board at The Hospital for Sick Children.

Study population

Members of the Association of Haemophilia Clinic Directors of Canada (AHCDC), the Canadian Association of Nurses in Haemophilia Care (CANHC) and the Canadian Physiotherapists in Hemophilia Care (CPHC) were chosen to participate owing to their expertise and involvement in comprehensive care haemophilia clinics nation-wide. The study was formulated during an annual meeting and all members agreed to participate.

Questionnaires

The Delphi approach is a systematic process used to generate ideas and arrive at consensus in a large group. The first step in our study involved soliciting proposed definitions using an open-ended questionnaire. These definitions were collated and categorized and a second questionnaire was created with the intent of identifying the most widely accepted suggestions. Using these highly endorsed selections, penultimate definitions were created and sent out in a third questionnaire for final approval (Fig. 1).

There are many benefits for using this approach. The promise of participant anonymity reduces peer pressure often present in consensus conferences [10]. This process does not require all participants to meet as a group which enables responses from individuals who are far apart geographically [10]. The Delphi approach also serves to balance the effect of dominant personality types in the creation of the final consensus.

First questionnaire The terms for which we sought definitions were: primary prophylaxis, secondary prophylaxis, target joint, joint bleed, significant soft-tissue bleed, superficial soft-tissue bleed and mucosal bleed. The questionnaire format was open-ended and participants were asked to submit the

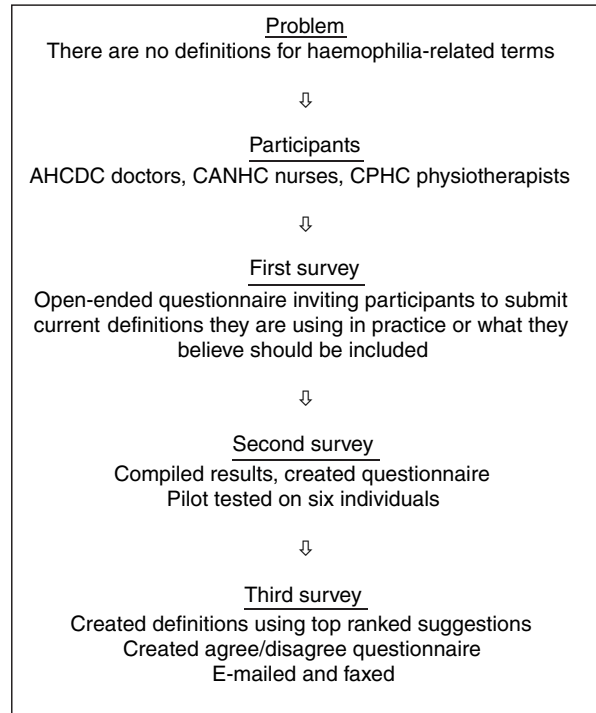


Fig. 1. Delphi technique for creating consensus definitions.

definitions they were currently using, or any phrases they felt would be useful in defining the terms.

Second questionnaire Investigators and research staff met and combined like items from questionnaire-1 responses. All resulting items were used to create a 13-page questionnaire in which suggestions for each term were separated into broad concepts, and each concept separated into smaller items (see Appendix). The questionnaire was pilot-tested in a sample of six respondents and modified for word clarity based on their feedback. A question regarding years of experience working with haemophilia was added in order to examine the amount of experience represented by the respondents. The resulting questionnaire was sent to all participants who were then asked to rank-order the suggestions.

Third questionnaire After completion of the second iteration of questionnaires, investigators met and analysed data for each term. Top-rated components were determined based on natural cut-offs and statistically significant differences between suggestions for each definition. Newly created definitions were sent to participants via electronic mail and fax, and respondents were asked to either 'agree' or 'disagree' with the new definitions. At the end of this step, the preliminary results of the survey were

presented to AHCDC members and associated nurses and physiotherapists at an investigators meeting for the Canadian Haemophilia Prophylaxis Study (Hamilton, Ontario, May 2005). Forty people in attendance made suggestions on how to clarify the wording of the definitions without materially changing their meaning.

Survey methods

The Tailored Design method [11] was used. This included a 'prenotice' which alerted respondents to the forthcoming questionnaire. An initial mail-out was sent soon thereafter via post mail and electronic mail with attachments in both Microsoft Word and Adobe Acrobat formats. A subsequent reminder postcard was sent 1 week later to all who did not respond. A second mail-out was sent again using post mail and electronic mail and all who did not respond after this were called by the research coordinator for follow-up.

The Tailored Design method is designed to achieve high response rates. Additional methods we used to increase response rate included personalized letters, envelopes with hand-written addresses, first-class mail stamps and self-addressed stamped return envelopes. Surveys were printed on off-white paper to make them stand out on crowded desks, and an additional 'special contact' by phone was made to all participants who did not respond by the due date.

The third step in the Delphi process was conducted by electronic mail in order to contain costs. Those who did not have a working e-mail address were contacted via fax and asked to participate.

Analysis

No analysis was needed for the first phase; all suggestions were included. Responses were grouped into more manageable categories for the subsequent questionnaire.

For the second step, a Microsoft Access database was created and all survey responses were double-

entered to ensure keying accuracy. Using Data Desk 6.1 statistical software, the most highly ranked suggestions were determined by examining their mean and median scores and their box plot distributions. The Kruskal-Wallis nonparametric analysis of variance was used to compare responses to determine whether the most highly ranked suggestion was indeed statistically significantly different from other suggestions.

For the last questionnaire iteration, all responses were entered into a Microsoft Excel spreadsheet and responses for each definition were tallied. Accuracy was verified using a double-entry system. Per cent agreement was calculated per professional group and overall. We defined 'consensus' as agreement from 75% of respondents or more.

Results

All physicians, nurses and physiotherapists listed in the AHCDC were contacted (46 physicians, 27 nurses, 24 physiotherapists). The number of participants varied with each iteration because of changes in AHCDC, CANHC and CPHC membership (Table 1).

Iteration 1

Out of the 97 experts who were sent the questionnaire, 78 responded (80%). The response rate by profession was 78% of physicians, 85% of nurses and 79% of physiotherapists. Four responded that they would not be participating in this study (one physician, one nurse, two physiotherapists). Many suggestions were made and there were many duplicates.

Iteration 2

Eighty-one respondents out of a total of 100 mailed survey participants (81.0%) responded to the second questionnaire. Seventy-three per cent of physicians, 83% of nurses and 92% of physiotherapists responded. Twelve respondents indicated they would no

Table 1. Questionnaire response rates for all survey iterations.

	Mailed questionnaires (<i>n</i>)			Responses (<i>n</i>)				Response rates (%)		
	Doctor	Nurse	PT	Doctor	Nurse	PT	Unknown	Doctor	Nurse	PT
Round 1	46	27	24	36	23	19	0	78	85	79
Round 2	45	30	25	33	25	23	0	73	83	92
Round 3	44	25	20	33	20	17	2	75	80	85

PT, physiotherapist.

longer participate in this study: one physician, four nurses and seven physiotherapists.

For target joint, the most highly ranked concept out of the four choices was *recurrent bleeds over time* ($T = 68.891$, $P < 0.0001$) and the most highly ranked item within that category was ≥ 3 in 3 months ($T = 122.28$, $P < 0.0001$).

For primary prophylaxis the most highly ranked concept was *objective* ($T = 170.29$, $P < 0.0001$) and the most highly ranked item was *prevent joint bleeding* ($T = 124.58$, $P < 0.0001$). As this item alone would not provide a comprehensive definition, other highly ranked items were included in this definition. 'After 1st bleed', 'age 1 to 2 years' and 'before 3 bleeds into any single joint over 1 year' were all highly ranked ($T = 70.1538$, $P < 0.0001$) and were therefore included in the definition. This change was brought to a consensus conference where attendees voted that this alteration was acceptable.

For secondary prophylaxis, the most highly ranked concept was *objective* ($T = 143.17$, $P < 0.0001$) and the most highly ranked item in that category was *prevent recurrent bleeding* ($T = 48.372$, $P < 0.0001$). It was realized that this item alone would not differentiate secondary prophylaxis from primary prophylaxis so other highly ranked items were examined for inclusion and some items within the category of 'time of onset starts after' including 'a target joint', '3 bleeds in a 6-month period' and some items in the 'frequency' category 'regular schedule' and 'prior to activity (not regularly scheduled)' were added. This alteration was also brought to a consensus conference where attendees voted that it was acceptable.

For joint bleed, the most highly ranked concept was *signs and symptoms* ($T = 195.03$, $P < 0.0001$). The most highly ranked item was *pain* ($T = 166.45$, $P < 0.0001$).

For superficial bleed, the most highly ranked concept was *anatomy* ($T = 82.308$, $P < 0.0001$). The most highly ranked items were *subcutaneous* and *cutaneous* (overall $T = 267.01$, $P < 0.0001$, no significant difference between *subcutaneous* and *cutaneous*).

For mucosal bleed, the most highly ranked concept was *anatomy* ($T = 106.36$, $P < 0.0001$) and the most highly ranked item was *any mucosal site* ($T = 194.35$, $P < 0.0001$).

For significant soft-tissue bleed, the most highly ranked concept was *anatomy* ($T = 170.24$, $P < 0.0001$) and the most highly ranked items were *intracranial*, *spinal cord*, *confined space*, *oral/retropharyngeal*, *neck*, *iliopsoas* and *retroperitoneal*

(overall $T = 164.29$, $P < 0.0001$, no significant difference between these listed items).

The average number of years working with haemophilia was determined in this survey iteration as being 13.6 years, with a range from 8 months to 30 years. Given this broad range, it is quite possible that different levels of experience may affect the strength of opinions. The data was re-analysed twice, first by using only respondents in the longest fiftieth percentile of experiences, and second by using only respondents in the seventy-fifth percentile for length of experience; the top-ranked items were consistent with those found using the entire respondent pool.

Iteration 3

The final step in the Delphi process had a response rate of 81% (72 respondents out of 89 surveys mailed). Seventy-five per cent (33/44) of physicians, 80% of nurses (20/25) and 85% of physiotherapists (17/20) who were mailed a survey responded. Two additional surveys were returned without identifying information and one respondent no longer wished to participate. Percent agreement was high (greater than 90%) for five of the definitions; however the definitions for 'joint bleed' and 'significant soft-tissue bleed' had considerably lower agreement rates that were above – but close to – our predetermined 75% cut-off for agreement. Variation in agreement rates were seen when analysed by profession, particularly for definitions of 'joint bleed' and 'significant soft-tissue bleed'; there were lower approval rates from nurses (76% and 68%, respectively) and physiotherapists (50% and 70%) than doctors (93% and 86%) (Table 2).

The final consensus definitions which were approved in this step are in Table 3.

Discussion

We were able to use the Delphi approach successfully to create consensus definitions for clinical end points and bleed types in haemophilia. By conducting this study using e-mail and postal mail, we were able to obtain expertise from haemophilia experts who were far apart geographically and who were therefore representative of all Canadian haemophilia treaters.

There were high response rates to all three iterations of the study, and the majority of respondents who participated agreed with the definitions created in the process. As such, it suggests that there is some early endorsement for the adoption of these definitions. They may however require future fine-tuning as they are used in practical settings. Five out of the

Haemophilia term	Doctors (%)	Nurses (%)	Physiotherapists (%)	Overall (%)
Target joint	90.7	100	100	95.5
Primary prophylaxis	90.7	88.0	95.0	90.9
Secondary prophylaxis	93.0	88.0	95.0	92.0
Joint bleed	93.0	76.0	50.0	78.4
Superficial bleed	95.3	100	95.0	96.6
Mucosal bleed	100	100	95.0	98.9
Significant soft-tissue bleed	86.0	68.0	70.0	77.3

Table 2. Percent agreement of respondents by profession, Delphi 3.

Table 3. Final definitions of haemophilia prophylaxis and its consequences.

Haemophilia term	Definition
Target joint	Three or more bleeds into the same joint in a consecutive 3-month period
Primary prophylaxis	Factor infusions given to prevent bleeding and its consequences, usually starting in the first or second year of life, before the third but usually after a first bleed
Secondary prophylaxis	Factor infusions <i>in order to prevent</i> recurrent bleeding, beginning after target joint bleeding has developed or after three joint or significant soft-tissue bleeds have occurred and given regularly or prior to activities
Joint bleed	An episode characterized by pain, thought to represent intra-articular bleeding
Superficial bleed	A skin or subcutaneous bleed with minimal or no symptoms and with no functional problems
Mucosal bleed	A bleed into any area of mucosal tissue
Significant soft-tissue bleed	A bleed into a muscle or confined space which may include neural tissues

seven proposed definitions had particularly strong support, however two were not as solidly endorsed and may require substantial adjustments in order to be adopted for common use. In particular, the definitions for 'joint bleed' and 'significant soft-tissue bleed' were well supported by physicians who responded to the survey but not by nurses or physiotherapists. While this may have been a chance finding, it may also have been because of varied educational backgrounds and a different clinical focus. Continued efforts with input from these two professions may be beneficial in making these definitions more acceptable to the entire haemophilia professional community.

These definitions – as proposed – are perhaps not as precise as desired for the purposes of clinical studies. For example, the definition of secondary prophylaxis allows for many different ways of providing clotting factor (i.e. just before strenuous activities or on any regular schedule). The consensus methods that we used might not provide the 'best' definitions because compromises are often made in order to get wider agreement. Also, we have only used Canadian respondents in this study. As such, the definitions may reflect idiosyncrasies particular to the Canadian context. We are aware of efforts in Europe by the PedNet group to create precise definitions of some haemophilia terms including primary prophylaxis, secondary prophylaxis, target joint and re-bleed. For example, the PedNet group defined primary prophylaxis as regular, continuous treatment started before the age of 2 years or after the first joint bleed in their

1998 meeting report [12] and refined these definitions further in their 2003–2004 meeting report as either: (i) regular continuous treatment started after the first joint bleed and before the age of 2 years; or (ii) regular continuous treatment started before the age of 2 years without previous joint bleed [13]. Berntorp *et al.* developed definitions during an international conference where prophylaxis was defined as treatment by intravenous injection of factor concentrate in anticipation of and in order to prevent bleeding. Primary prophylaxis was defined as long-term continuous (≥ 46 weeks per year) treatment, determined by age (started before the age of 2 years and prior to any clinically evident joint bleeding) or determined by first bleed (started prior to the onset of joint damage, presumptively defined and having had no more than one joint bleed, irrespective of age) [14]. Our definition agrees with the two aforementioned definitions but explicitly includes the aim to prevent bleeding and its consequences.

Berntorp *et al.* [14] also defined secondary prophylaxis as prophylaxis started after the onset of joint damage or other significant bleeding. In contrast, the European Paediatric Network for Haemophilia Management (PedNet) defined secondary prophylaxis as either: (i) regular continuous (long-term) treatment, started at the age of >2 years or after two or more joint bleeds, or (ii) periodic treatment (short-term) owing to frequent bleeds [12]. In their revised definitions, the word 'periodic' was changed to 'intermittent' [13]. Our definition combines these two and includes a component that

addresses prophylaxis prior to activities. Separate definitions for short-term and longer-term secondary prophylaxis did not arise out of the consensus process however delineating these terms may make clinical sense, as the intent of these treatments are quite different. This may be a point to consider in future refinement of this definition.

The PedNet group recently decided to define the term 'target joint' as three or more bleeds in a period of 6 months in a particular joint. Such a joint is no longer considered a target joint where there has been no bleed in this same joint for 12 months [13]. The term 'target joint' has been previously defined as a joint in which recurrent bleeding has occurred on four or more occasions during the previous 6 months or one in which 20 life-time bleeding episodes have occurred [15]. Blanchette *et al.* [16] defined a target joint as one that has had two to four bleeds over a 3–6-month consecutive period, and Dunn *et al.* [17] defined it as a joint that bled three or more times within 6 months. The Universal Data Collection Program of the United States Center for Disease Control has defined a target joint as one in which recurrent bleeding has occurred on four or more occasions during the previous 6 months or one in which 20 life-time bleeding episodes have occurred [15]. It has also been defined by Kern *et al.* [18] as those that have frequent recurrent bleeding, with three or more bleeds into any one joint over a consecutive 3-month period. The definition created in our consensus approach corresponds with this last definition.

Significant bleeds have been defined in the past by Liesner *et al.* [19] as 'bleeding episodes that occurred spontaneously or after minimal trauma and caused pain and/or loss of function'. Our definition is somewhat different as it focuses on the location of the bleed and not on its effects or how it was caused. It is of interest that the definition we created using a consensus process did not include the concept of functional impairment, as the Liesner definition did.

The definitions will need to be refined in the future as more sensitive imaging techniques become available. In the Colorado Joint Outcomes Study (the data for which have recently been presented), the number of joint bleeds that are believed to have occurred do not necessarily correspond to magnetic resonance imaging (MRI) evidence of joint damage. Imaging may therefore indicate an otherwise unperceivable (subclinical) joint bleed. As more studies are conducted, definitions will need to be adjusted to reflect improvements in our technology and our understanding of the pathophysiology of haemophilic

arthropathy; our consensus definitions should be considered part of an evolving process.

These definitions were created using the Delphi method which is a well-established technique that is similar to a voting procedure. Although this was deemed a fair method to capture all opinions, the *strength* of opinions were not captured with a 'weighting' step that would ask respondents to apply a weight to each ranked item. This may have an impact on the results although it is impossible to predict how. This may be a point of consideration for future consensus studies.

Overall, definitions created in the Canadian context using a consensus approach were somewhat different than those created in other areas. These discrepancies reflect the differences that arise in different countries and communities. Expansion of these efforts by collaborating with international groups may yield definitions suitable for a broader international context.

In conclusion, we have developed seven definitions for terms that are often used in the care and study of patients with haemophilia, but have not been previously well defined. We would propose that further international consensus be sought to further clarify these and other terms that are important for the clinical study of patients with haemophilia.

Acknowledgements

This project was supported by a Canadian Haemophilia Society studentship. Dr. Feldman is supported by a Canada Research Chair. We wish to thank Afshandokht Amini and Gina Schwamborn for their help with questionnaire development and data management. In addition, we wish to thank the Association of Haemophilia Clinic Directors of Canada (AHCDC) and associated nurses and physiotherapists for their assistance in completing this project.

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Appendix

Joint Bleeds Definition Survey

If you do not wish to complete the survey please check one of the following and mail back the survey in the self-addressed envelope:

I do not wish to participate in this project

I am too busy to answer this questionnaire this time around, but I would like to participate in the next round of questionnaires

Instructions:

Each definition is given in quotations. Consider each definition separately.

Each definition is followed by a list containing (on the left) *concepts*, and (on the right) specific *items*. The specific items are related to the concept that they follow.

Step 1: for each list of *items* rank the most important to the least important (where 1 is the **most important**).

Step 2: after you have rated the items, look at the concepts listed. Consider each definition separately. Rank the concepts from A to Z (where A is the **most important**).

FOR EXAMPLE - you might fill in the target joint section like this...

Rank	Concept (A is most important)	Rank	Item (1 is most important)
A "Target joint" is a joint with...			
A	Recurrent bleeds (no time)	3	Recurrent (number not specified)
		2	> 2
		1	> 3
		4	> 4
B	Recurrent bleeds over time	3	≥ 3 in 1 month
		4	≥ 2 in 3 months
		7	≥ 3 in 3 months
		5	≥ 2 in 6 months
		2	≥ 3 in 6 months
		1	≥ 4 in 12 months
		6	≥ 5 in 12 months

Appendix Continued

Start Here



Rank	Concept (A is most important)	Rank	Item (1 is most important)
A "Target joint" is a joint with...			
<input type="checkbox"/>	Recurrent bleeds (no time)	<input type="checkbox"/>	Recurrent (number not specified)
		<input type="checkbox"/>	> 2
		<input type="checkbox"/>	> 3
		<input type="checkbox"/>	> 4
<input type="checkbox"/>	Recurrent bleeds over time	<input type="checkbox"/>	≥ 3 in 1 month
		<input type="checkbox"/>	≥ 2 in 3 months
		<input type="checkbox"/>	≥ 3 in 3 months
		<input type="checkbox"/>	≥ 2 in 6 months
		<input type="checkbox"/>	≥ 3 in 6 months
		<input type="checkbox"/>	≥ 4 in 12 months
		<input type="checkbox"/>	≥ 5 in 12 months
<input type="checkbox"/>	Sequelae	<input type="checkbox"/>	Disability
		<input type="checkbox"/>	Chronic arthropathy
		<input type="checkbox"/>	Chronic damage
		<input type="checkbox"/>	Xray changes
<input type="checkbox"/>	Joint Signs/Symptoms	<input type="checkbox"/>	Synovitis
		<input type="checkbox"/>	Chronic Synovitis
		<input type="checkbox"/>	Pain

Appendix Continued

Rank	Concept (A is most important)	Rank	Item (1 is most important)
<i>"Primary prophylaxis" is defined by its...</i>			
<input type="checkbox"/>	<u>Objective</u>	<input type="checkbox"/>	Prevent joint bleeding
		<input type="checkbox"/>	Prevent bleeding
		<input type="checkbox"/>	Prevent spontaneous bleeding
		<input type="checkbox"/>	Prevent bleed complications
		<input type="checkbox"/>	Prevent arthropathy
		<input type="checkbox"/>	Prevent intracranial bleeding
		<input type="checkbox"/>	Allow participation in normal activities and acceptable sports
		<input type="checkbox"/>	Maintain FVIII/FIX level >1%
<input type="checkbox"/>	<u>Frequency</u>	<input type="checkbox"/>	Regular
		<input type="checkbox"/>	2-3 times weekly
		<input type="checkbox"/>	> 1 time weekly
		<input type="checkbox"/>	Adjusted to bleeding frequency
<input type="checkbox"/>	<u>Time of onset</u>	<input type="checkbox"/>	Newly diagnosed previously untreated (PUP)
		<input type="checkbox"/>	After 1 st bleed
		<input type="checkbox"/>	After 2-3 bleeds
		<input type="checkbox"/>	Before 3 bleeds into any single joint over 1 year
		<input type="checkbox"/>	Age 1 to 2 years
		<input type="checkbox"/>	Age 3 to 5 years
<input type="checkbox"/>	<u>Time course</u>	<input type="checkbox"/>	Forever
		<input type="checkbox"/>	Over 15 years
		<input type="checkbox"/>	Over a long time
<input type="checkbox"/>	<u>Dose</u>	<input type="checkbox"/>	Keep trough Factor level >1%
		<input type="checkbox"/>	Keep trough Factor level > 0.1% units
		<input type="checkbox"/>	25-40 U/kg
		<input type="checkbox"/>	Minimum dose adjusted to prevent bleeds
		<input type="checkbox"/>	Dose adjusted to activity levels
<i>"Secondary prophylaxis" is defined by its...</i>			
<input type="checkbox"/>	<u>Objective</u>	<input type="checkbox"/>	Prevent recurrent bleeding
		<input type="checkbox"/>	Prevent complications
<input type="checkbox"/>	<u>Frequency</u>	<input type="checkbox"/>	2-3 times weekly
		<input type="checkbox"/>	Regular schedule
		<input type="checkbox"/>	Prior to activity (not regularly scheduled)
<input type="checkbox"/>	<u>Time of onset starts after</u>	<input type="checkbox"/>	Several bleeds
		<input type="checkbox"/>	≥ 1 bleed
		<input type="checkbox"/>	≥ 2 bleeds
		<input type="checkbox"/>	Age 2
		<input type="checkbox"/>	A muscle bleed
		<input type="checkbox"/>	A target joint
		<input type="checkbox"/>	Joint damage
		<input type="checkbox"/>	A life-threatening bleed
		<input type="checkbox"/>	Joint surgery
		<input type="checkbox"/>	2 bleeds into the same joint within 3 months
		<input type="checkbox"/>	3 bleeds in a 6 month period
<input type="checkbox"/>	<u>Dose sufficient to keep trough Factor level > 1%</u>		
<input type="checkbox"/>	<u>Time course</u>	<input type="checkbox"/>	Long term
		<input type="checkbox"/>	Short term
		<input type="checkbox"/>	Sufficient to settle down the index bleed and allow healing
		<input type="checkbox"/>	2 weeks to 2 months
		<input type="checkbox"/>	2 to 3 months
		<input type="checkbox"/>	3 to 12 months
		<input type="checkbox"/>	Periodic

Appendix Continued

Rank	Concept (A is most important)	Rank	Item (1 is most important)
<i>A "joint bleed" is defined by the...</i>			
<input type="checkbox"/>	<u>Anatomy</u>	<input type="checkbox"/>	Intra-articular
		<input type="checkbox"/>	Distends the joint capsule
		<input type="checkbox"/>	Hinge joint
<input type="checkbox"/>	<u>Signs and symptoms</u>	<input type="checkbox"/>	Pain
		<input type="checkbox"/>	Effusion
		<input type="checkbox"/>	Loss of range of motion
		<input type="checkbox"/>	Warmth
		<input type="checkbox"/>	Tingling
		<input type="checkbox"/>	Bubbling
		<input type="checkbox"/>	Prickling
		<input type="checkbox"/>	Stiffness
		<input type="checkbox"/>	Loss of function
		<input type="checkbox"/>	Decreased ability to bear weight
<input type="checkbox"/>	<u>Pathology</u>	<input type="checkbox"/>	Tear in the synovium
		<input type="checkbox"/>	Tear in a blood vessel
<input type="checkbox"/>	<u>Imaging signs of blood in the joint</u>		
<input type="checkbox"/>	<u>Time to resolve</u>	<input type="checkbox"/>	4 to 6 weeks
		<input type="checkbox"/>	Significant amount of time
<i>A "superficial bleed" is defined by the...</i>			
<input type="checkbox"/>	<u>Anatomy</u>	<input type="checkbox"/>	Subcutaneous
		<input type="checkbox"/>	Cutaneous
		<input type="checkbox"/>	Mucous membrane
		<input type="checkbox"/>	Not involving muscle
		<input type="checkbox"/>	Gastrointestinal
		<input type="checkbox"/>	Nostril
		<input type="checkbox"/>	Small muscle bleed
		<input type="checkbox"/>	Not in a confined space
<input type="checkbox"/>	<u>Extent</u>	<input type="checkbox"/>	Superficial spread
		<input type="checkbox"/>	Bruise
		<input type="checkbox"/>	≤ 4 cm. diameter
<input type="checkbox"/>	<u>Symptoms</u>	<input type="checkbox"/>	Minimal or asymptomatic
		<input type="checkbox"/>	No pain
<input type="checkbox"/>	<u>Prognosis</u>	<input type="checkbox"/>	No threat to surrounding organs
		<input type="checkbox"/>	No permanent limitations
<input type="checkbox"/>	<u>Treatment</u>	<input type="checkbox"/>	Local compression only
		<input type="checkbox"/>	No need for analgesics
		<input type="checkbox"/>	No need for Factor replacement
		<input type="checkbox"/>	Rest, Ice, Compression, Elevation (RICE) only
<input type="checkbox"/>	<u>Signs</u>	<input type="checkbox"/>	Superficial tenderness
		<input type="checkbox"/>	No functional problems
		<input type="checkbox"/>	No affect on range of motion
		<input type="checkbox"/>	Visible
		<input type="checkbox"/>	Palpable
		<input type="checkbox"/>	Blue colour
		<input type="checkbox"/>	No swelling

Appendix Continued

Rank	Concept (A is most important)	Rank	Item (1 is most important)
A "mucosal bleed" is defined by the...			
<input type="checkbox"/>	Anatomy	<input type="checkbox"/>	Any mucosal sites
		<input type="checkbox"/>	Gastrointestinal
		<input type="checkbox"/>	Uterine (menorrhagia)
		<input type="checkbox"/>	Urinary
<input type="checkbox"/>	Extent / Severity	<input type="checkbox"/>	Nose bleeds (please rank nose bleed options)
		<input type="checkbox"/>	Nose bleeds ≥ 3 times weekly
		<input type="checkbox"/>	Nose bleeds lasting ≥ 10 minutes
		<input type="checkbox"/>	Nose bleeds lasting ≥ 15 minutes
		<input type="checkbox"/>	Nose bleeds lasting ≥ 20 minutes
			Menorrhagia (please rank menorrhagia options)
		<input type="checkbox"/>	Menorrhagia requiring double protection
		<input type="checkbox"/>	Menorrhagia requiring changes every 2 hours
		<input type="checkbox"/>	Menorrhagia lasting > 5 days
		<input type="checkbox"/>	Severe enough to cause low ferritin
		<input type="checkbox"/>	Lasting ≥ 30 minutes
		<input type="checkbox"/>	Recurrent
		<input type="checkbox"/>	Presistent
		<input type="checkbox"/>	Requiring medical attention
<input type="checkbox"/>	Treatment	<input type="checkbox"/>	Needs fibrinolytics
		<input type="checkbox"/>	Local measures such as ice, pressure, soft diet
		<input type="checkbox"/>	Needs Factor replacement

Appendix Continued

Rank	Concept (A is most important)	Rank	Item (1 is most important)
A "significant soft tissue" bleed is defined by the ...			
<input type="checkbox"/>	Anatomy	<input type="checkbox"/>	Muscle
		<input type="checkbox"/>	Confined space
		<input type="checkbox"/>	Between muscles
		<input type="checkbox"/>	Associated with a ligament tear
		<input type="checkbox"/>	Peritoneal
		<input type="checkbox"/>	Oral / retropharyngeal
		<input type="checkbox"/>	Eye
		<input type="checkbox"/>	Intracranial
		<input type="checkbox"/>	Tongue
		<input type="checkbox"/>	Neck
		<input type="checkbox"/>	Spinal cord
		<input type="checkbox"/>	Bowel
		<input type="checkbox"/>	Calf
		<input type="checkbox"/>	Renal / urinary tract
		<input type="checkbox"/>	Retroperitoneal
		<input type="checkbox"/>	Iliopsoas
<input type="checkbox"/>	Prognosis	<input type="checkbox"/>	Life or limb threatening
		<input type="checkbox"/>	Compartment syndrome
		<input type="checkbox"/>	Nerve damage
		<input type="checkbox"/>	Scarring
		<input type="checkbox"/>	Muscle contracture
		<input type="checkbox"/>	Pseudotumour formation
<input type="checkbox"/>	Treatment	<input type="checkbox"/>	Needs fibrinolytics
		<input type="checkbox"/>	Local measures such as ice, pressure, soft diet
		<input type="checkbox"/>	Needs Factor replacement
<input type="checkbox"/>	Functional Impairment		
<input type="checkbox"/>	Signs	<input type="checkbox"/>	Hematuria
		<input type="checkbox"/>	Swelling
		<input type="checkbox"/>	Tenderness
		<input type="checkbox"/>	Warmth
		<input type="checkbox"/>	Decreased range of motion
		<input type="checkbox"/>	Delayed bruising
		<input type="checkbox"/>	Cyanosis
		<input type="checkbox"/>	Rapidly spreading
<input type="checkbox"/>	Symptoms	<input type="checkbox"/>	Severe pain
		<input type="checkbox"/>	Long-lasting pain
<input type="checkbox"/>	Confirmation by ultrasound		
<input type="checkbox"/>	Blood loss	<input type="checkbox"/>	Significant blood loss
		<input type="checkbox"/>	Hemoglobin lowered by ≥ 20 gm.
		<input type="checkbox"/>	Need for transfusion
<input type="checkbox"/>	Length of time		Lasts 3 to 4 weeks
<input type="checkbox"/>	Treatment	<input type="checkbox"/>	Requires Factor replacement
		<input type="checkbox"/>	Required analgestics

 We are interested in everyone's opinions regardless of how long you have been involved in hemophilia care and research. However, we would like to know:
 How long have you been working with hemophilia?