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EXECUTIVE SUMMARY

METHODS
coreHEM was initiated by the National Hemophilia Foundation in partnership with the Center for Medical Technology Policy and McMaster University. The aim of the project was to determine a core set of outcomes to evaluate efficacy, safety, comparative effectiveness, and value for hemophilia gene therapy.

coreHEM utilized a multi-stakeholder collaborative process that included patients and patient advocates, clinicians, hemophilia researchers, US and international payers and HTA groups, representatives from government organizations, and life science companies with hemophilia gene therapy in development. A core technical group and a steering committee were appointed. coreHEM used a modified Delphi consensus process that was adapted from the COMET Initiative approach. A literature review and key informant interviews were used to create an initial list of outcomes, organized based on the COMET Initiative naming schematic for domains. A rating scale from 1 (not important to include in the core set) to 9 (critical to include) was used. Participants could suggest new outcomes to include or recover after deletion. Outcomes were eliminated if <70% of voters rated the outcome 7-9. But, if the patient stakeholder group average score was 7 or higher, the outcome was re-proposed for voting in subsequent rounds (a mechanism implemented to ensure that the “patient important” outcomes were not overturned by other stakeholder groups early in the process without the opportunity for additional discussion.) Project principal investigators were not part of the voting panel for the Delphi.

RESULTS
coreHEM was conducted between May and November 2017, and the data analysis completed on December 20th, 2017. The project included three online survey rounds and one in-person meeting. The initial list of candidate outcomes included 48 outcomes, from which six core outcomes were identified as crucial for evaluating the effectiveness of gene therapy: frequency of bleeds, factor activity level, duration of expression, chronic pain, mental health status, utilization of the healthcare system (direct costs). During the process, the group agreed to separately list core outcomes and relevant adverse events, as the latter would be required for regulatory purposes. The adverse events that were voted as important by the group were liver toxicity, short-term immune response to FVIII/FIX, immune response to gene therapy (cytotoxic), and thrombosis in the short-term adverse events domain, development of other disorders, vector integration into the host genome, and duration of vector neutralizing response in the long-term adverse events domain, and cause of death in the mortality domain. During a breakout session at the in-person meeting, participants outlined parameters for the types of measurements/instruments that would ideally be used to measure the core set.

IMPACT
coreHEM recruited an international multi-stakeholder panel with participants from over 40 organizations from nine countries. The project had sponsorship and participation by seven companies in the hemophilia gene therapy space. coreHEM achieved consensus on a core outcome set in less than 1 year, and initiated work on outlining parameters for the types of measurements and instruments that should be used to measure and report the core set.

Participating organizations took part in the coreHEM project with the goal of identifying a core set of outcomes for use in future clinical studies of gene therapy in hemophilia. Collectively, they believe this
recommended core outcome set, developed with multi-stakeholder input, will be useful in future assessments of gene therapies for hemophilia. They encourage product developers and other researchers to consider this recommended core outcomes set when developing study protocols for future clinical trials, registries and other studies.

**FUNDING**

coreHEM was funded by a grant from the National Hemophilia Foundation and with participation fees from the following life science industry companies and academic gene therapy groups: Bayer AG, BioMarin Pharmaceutical Inc, Pfizer Inc, Shire Plc, Spark Therapeutics, St. Jude Children’s Research Hospital, and uniQure B.V.

Alnylam Pharmaceuticals, Novo Nordisk, and Roche Genentech participated in the in-person meeting as observers, and contributed a meeting attendance fee. Observers did not vote in the Delphi.

Project participants did not receive an honorarium for participating in the Delphi or attendance at the meeting. The Steering Committee served as voting panelists and additionally provided project guidance and oversight without compensation. Grants, participation and attendance fees supported all project-related expenses, including salaries for CMTP project staff, in-person consensus meeting expenses and travel costs.

**coreHEM WRITING AND EDITING TEAM**

**Principal Investigators**

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**CMTP (Center for Medical Technology Policy)**

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**ACKNOWLEDGEMENTS**

Appendix 1 lists the coreHEM Steering Committee, Delphi voters, in-person consensus meeting observers, and key informants who provided interviews.
INTRODUCTION
BACKGROUND
Hemophilia is a genetic bleeding disorder caused by a deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B) in the blood clotting pathway. Hemophilia A occurs in 1 in 10,000 live births and hemophilia B occurs in about 1 in 50,000; it is considered a rare disease with an estimated 20,000 and 400,000 people living with the disease in the US and worldwide, respectively. Persons living with hemophilia experience various degrees of bleeding, depending on residual coagulation factor levels. Bleeding occurs most commonly in joints, soft tissue, and muscles, causing short-term symptoms (acute bleeding, acute pain) and long-term complications (chronic pain, hemophilia arthropathy, or disability). Acute and chronic complications may dramatically reduce health-related quality of life (HRQoL) of persons living with hemophilia (PWH).

Hemophilia is managed either by maintaining a routine of prophylactic infusions of the missing clotting factor (Factor VIII, FVIII or Factor IX, FIX), or treatment with on-demand infusions at the time of a bleed. The goal of disease management is to control the frequency and severity of bleeds and prevent joint damage and other complications associated with bleeding episodes. Recent gene therapy trials in hemophilia have reported promising results, demonstrating that gene therapy could yield a long-term functional “cure” by changing or replacing the missing and abnormal genes. A “cure” may come in the form of a permanent correction of the underlying genetic defect or through prevention of all complications of living with hemophilia; a functional cure eliminates the day-to-day burden, though the underlying genetic disease remains. This would allow the body to produce the previously-missing clotting factor without the need for, or with a much-reduced need for, factor replacement therapy. Gene therapy would be life-changing for patients, relieving them of many of the daily burdens and limitations they currently endure. Phase 3 trials of gene therapy are beginning. This new treatment technology has the potential to change the landscape of hemophilia management. Therefore, we are at an opportune time to establish the standards for collecting and reporting on relevant, well-specified outcomes that are important to patients. Outcomes associated with a functional “cure” may be different than the outcomes used to assess the current standard of care.

RATIONALE
A core outcome set is a minimum set of outcomes that should be measured and reported in all clinical trials for a specific condition. Currently, there are no guidelines on which outcomes should be included in the hemophilia gene therapy trials, and each trial may choose to include certain outcomes based on factors such as time, availability of clinical and laboratory resources, interest to the investigators, funding, or whether a specific outcome will highlight a benefit of a specific product. Heterogeneity in the outcomes measured and reported across clinical trials on the same disease or of the same intervention make it difficult to compare the studies with each other and can lead to uncertainty about which treatment is best for patients. Even worse, in the field of rare diseases an inability to pool results across studies may prevent attainment of the critical evidence body mass needed to support adoption of a new treatment modality. Hemophilia clinical trials that collect the same outcome may report the results differently. For example, one study may report a mean level of circulating FVIII/FIX and another study may instead report the percentage of participants who have reached a certain (and sometimes arbitrary) threshold of FVIII/FIX. In systematic reviews, data from certain studies may not be included in meta-analyses if the outcome definition, timing of outcome collection, or measurement instrument was not consistent with other trials, or if the outcome was not collected on or reported at all. The lack of relevant or comparable outcomes in clinical research studies for a given condition undermines efforts across the healthcare sector to make evidence-based health policy decisions and improvements to...
health care delivery. The use of core outcome sets, agreed-upon minimum sets of outcomes that should be measured and reported in all clinical studies for related evaluations of a specific condition, can offer a potential solution. The development of a core outcome set can help to address some of the problems associated with heterogeneity of outcome collection and reporting.\textsuperscript{12,13}

Core outcome sets are developed with robust input of relevant stakeholders who agree on a minimum set of outcomes through a structured consensus process. Defining and uniformly implementing a core set of outcomes for inclusion across trials and gene therapy products would enhance the predictability and consistency of the assessment and appraisal of these treatments by payers and Health Technology Assessment (HTA) organizations when making coverage and reimbursement decisions.\textsuperscript{a} From the payer perspective, core outcomes have the additional advantage of facilitating comparison of results from different trials and potentially reducing the risk of selective outcome reporting. Patient involvement and support by patient organizations should ensure that the outcomes are meaningful to, and their measurement acceptable by, patients enrolled in trials, and adoption of the technology in clinical practice foreseeable. Overall, multi-stakeholder input on core outcomes sets helps to assure alignment across the basic evidence needs of regulatory authorities, payers, and patients, and can therefore smooth the regulatory review and market access process for companies using these core outcomes.

**METHODS**

The goal of coreHEM was to develop a core outcome set for use in hemophilia gene therapy clinical trials. The project used a modified Delphi consensus process that included three online surveys and one in-person meeting. The objective of the project was to develop a set that, when used, will help evaluate efficacy, safety, comparative effectiveness and value of gene therapy for hemophilia. The methods recommended by the Core Outcomes Measures in Effectiveness Trials (COMET) Initiative were consulted and adapted for rapid turn-around given the plans for near-term initiation of several pivotal trials. The study was registered in COMET’s database of core outcome set projects. Standard definitions, adapted from COMET, were used throughout the project (Table 1). Although we used a modified Delphi on an accelerated timeline, each of the 11 quality standards recommended by COMET as part of the Core Outcome Set-STAndards for Development (COS-STAD) recommendations were fulfilled.\textsuperscript{14} The coreHEM protocol underwent ethical review by Chesapeake IRB (Reference Pro00023013) and determined to be exempt from IRB oversight.

Table 1. coreHEM Definitions

<table>
<thead>
<tr>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core outcome set</strong></td>
<td>An agreed set of outcomes which should be measured and reported, as a minimum, in all trials of a specific clinical area or of a specific condition.(^9)</td>
</tr>
<tr>
<td><strong>Domain</strong></td>
<td>A broad category, an element of a person’s overall health and life in relation to their treatment.</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Contained within each domain, “what” we want to measure.</td>
</tr>
<tr>
<td><strong>Measurements or Instruments</strong></td>
<td>“How” something is measured; measurement/instrument is a tool to measure an outcome. The tool can be a single question, a questionnaire with a composite score, a score obtained through physical examination, laboratory measurement, or observation of an image</td>
</tr>
</tbody>
</table>

PARTICIPANT RECRUITMENT
The consensus project involved stakeholders from all aspects of the product lifecycle, including patients, clinicians, life science industry representatives, academic researchers, regulators, and post-regulatory decision-makers such as payers and HTA groups (full participant list in Appendix 1). Participant recruitment began in April 2017 and continued through early September 2017 when all stakeholder groups were sufficiently represented and at which time the Delphi began. Participants were invited to an introductory webinar that provided more detail on the methods and goals of the project. The coreHEM team worked to ensure a balance between the stakeholder groups, based on pre-defined categories, including approximately equal numbers of patients or patient advocates; clinicians; US and international payers and HTA groups; research funders; and regulators. Two representatives from each participating life science company with a gene therapy product for hemophilia in phase 1 or later clinical trials were invited, with the total number of participants from the life sciences industry not exceeding the total number of non-industry participants. One academic gene therapy group also participated and was allowed two representatives. The stakeholder groups included some individuals who were not specifically trained in hemophilia and blood disorders but who otherwise had extensive knowledge of outcomes research, methods research, or systematic review experience, and provided insight on selecting well-specified outcomes that can measure value in a new treatment such as gene therapy. Forty-nine individuals representing the various stakeholder groups participated in the Delphi. A steering committee of six participants was selected, and included one patient, one clinician, one US payer, one international payer, and two representatives from the life science industry (one each from a company working on a gene therapy product for hemophilia A and hemophilia B).

DEVELOPING AN OUTCOME LIST FOR VOTING
A non-structured literature review was used to generate a starting list of potential outcomes for the core outcome set. From the literature review, a list of outcomes already in use in hemophilia trials was compiled. We abstracted outcomes from Cochrane review on hemophilia, records on interventions for
hemophilia on clinicaltrials.gov, and from reports in the journal *Haemophilia*. The search terms and data abstraction rules are described in Appendix 2. The references that were reviewed and from which outcomes were abstracted are listed in Appendix 3. Because our core set was focused on gene therapy, a number of studies describing gene therapy in other fields were references. They are listed separately in Appendix 3.

Interviews with participants were conducted to complement the literature search. To ensure that our initial list was not missing any relevant outcomes, we asked questions that reflected each interviewee’s personal knowledge about and experience with hemophilia. This also served as an opportunity to suggest novel outcomes that have not been used before but were potentially relevant for gene therapy trials. Individual interviews were held with coreHEM participants in-person at the International Society on Thrombosis and Hemostasis XXVIth Congress (July 2017) to understand various stakeholder perspectives and priorities regarding the most important outcomes to measure. Interviewees were invited to suggest novel outcomes for the hemophilia gene therapy space that may not yet be in the literature. Patient/patient advocate interviews which included a balance of US / international perspectives were held by teleconference or during the National Hemophilia Foundation’s Annual Meeting (August 2017). A list of participants and patients interviewed is available in Appendix 4. The structured list of questions used for the interviews is available in Appendix 5.

**Grouping Outcomes into Domains**

The coreHEM project team and Steering Committee developed and reviewed the comprehensive list of outcomes generated from the literature review and interviews grouped across 10 domains. Domain names and groupings were based on the outcome naming taxonomy proposed by COMET, with some modifications recommended by the coreHEM Steering Committee to better reflect the hemophilia landscape. The initial list of coreHEM outcomes and domains for voting mapped to the COMET domains is provided in Appendix 6.

**DELPHI**

A modified Delphi process was used to arrive at consensus on a core outcome set, with a special focus on patient-important and patient-reported outcomes. The coreHEM Delphi process included a total of three surveys (Round 1-Round 3, with an extra round of deliberations at the in-person meeting [Advisory Vote for Round 3]) plus one sub-survey to confirm results (Round 1A) (Figure 1). SurveyMonkey® software was used for the online voting. The survey was pilot-tested by non-participants with an interest in the project; suggestions from pilot testers were reviewed and incorporated.

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b Adapted from Iorio A, Skinner MW, Clearfield E, et al.; for the coreHEM panel. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. *Haemophilia*. 2018;00:1–6. https://doi.org/10.1111/hae.13504
Delphi Voting
Voters rated each outcome on a scale from 1 (not important to include in a core set) to 9 (critical to include) indicating the importance of including each outcome in clinical trials of gene therapy for hemophilia; three categories of importance were assigned (Table 2). Participants could review outcome definitions via circulated reference documents and through links in the online survey (Appendix 7). The response period lasted approximately 10 days for each Delphi round; participants received email reminders to complete the survey. Participants could suggest new outcomes to include or recover after deletion. Project Principal Investigators were not part of the voting panel for the Delphi.
Delphi Analysis
The outcome list was condensed and prioritized using the definitions of consensus shown in Table 3. Using the rating scale from 1-9, outcomes were eliminated if <70% of voters rated the outcome 7-9. But, if the patient stakeholder group average score was 7 or higher, the outcome was re-proposed for voting in subsequent rounds (a mechanism implemented to ensure that the “patient important” outcomes were not overwhelmed by other stakeholder groups early in the process without the opportunity for additional discussion. For the final voting round (Round 3), the “patient-important” retention category was dropped and outcomes needed to reach high consensus to be included in the core set.

Upon completion of voting for each round, mean ratings by stakeholder group were graphed for each outcome, along with a histogram showing the number of people who selected each rating and a scatterplot showing the scope of the votes for that outcome on the 1-9 scale, broken down into seven stakeholder categories (Appendix 8 for Delphi Round 1 Results, Appendix 9 for Delphi Round 2 Results). Voters received personalized feedback on a summary table that contained the overall mean rating for each outcome and the mean rating by stakeholder group, color-coded to show whether their selection was higher or lower than the mean rating for their stakeholder group (Appendix 10).

Round 1A Sub-survey
In order for participants to see the effect of the consensus criteria on the outcome list and to confirm agreement with the group decisions, a sub-survey (Round 1A) was developed. Participants could confirm, by voting agree or disagree, their agreement with the results. New outcome suggestions from the free-text comments were also assessed in Round 1A. Results from Round 1A informed the development of Round 2.

IN-PERSON CONSENSUS MEETING
The in-person consensus meeting was held on November 14-15, 2017 in Baltimore, Maryland. The meeting was attended by 41 voters (84% of voters), and 8 observers. An evening reception on November 14th included three level-setting presentations on hemophilia, gene therapy, and core outcome sets. The agenda for the full day meeting on the 15th included a multi-stakeholder panel and plenary sessions. Attendees were assigned to breakout sessions ensuring a balanced stakeholder mix for each subgroup; during the breakout sessions, participants discussed one or more of the outcomes retained in the process until then, each one bringing the specific perspective of their stakeholder group.

### Table 2. Levels of Importance (on a scale of 1-9)

| 1-3 | The outcome is **not important** to include in the core outcome set |
| 4-6 | The outcome is **important but not critical** to include in the core outcome set |
| 7-9 | The outcome is **critical** to include in the core outcome set |

### Table 3. coreHEM Consensus Definitions

| Consensus to Select (high consensus) | An outcome in which ≥70% of all voters rated the outcome with a score of 7, 8, or 9 (“critical importance”) |
| Consensus to Select (patient-important) | An outcome in which <70% of all voters rated the outcome 7, 8 or 9, but the stakeholders in the Patient group gave the outcome an average rating of ≥7 |
| Consensus to Eliminate | An outcome in which <70% of voters rated the outcome 7, 8, or 9, AND the Patient group average rating was <7 |
An Advisory Vote for Round 3 was held in real time and included three questions about combining remaining outcomes.

**Measurements and Instruments**

A final session of the in-person meeting was dedicated to explore how to measure outcomes that would be part of the core set. Each breakout group was assigned to discuss certain outcomes already included or which were candidates for inclusion in the core set. Discussion questions were based on the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines. COSMIN has developed methodological standards for the studies measurement properties, with the goal of improving the selection of measurements/instruments. Table facilitators directed the conversation to define parameters of an ideal instrument or measurement and build upon the collective knowledge of the group to identify measurements/instruments already being used in hemophilia or that they were aware of from other therapeutic fields that may apply to the novel outcomes in the coreHEM set. The full worksheet is provided in Appendix 11. A summary of parameters that were to be considered was developed from the COSMIN and COMET Initiative guideline (Table 4). The breakout session ended with a report-back to the large group; additionally, each breakout group discussion was recorded and transcribed, and a narrative summary was provided to coreHEM participants following the conclusion of the Delphi and completion of data analysis.

<table>
<thead>
<tr>
<th>Table 4. Parameters to consider for measurements and instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
</tbody>
</table>
| Definition                      | • What does the item measure?  
• Does it only measure one thing, or do several results/ideas fit into the outcome? |
| How to measure?                | • What type of measurement/instrument is ideal to measure this outcome?  
(survey a patient fills out, clinical assessment a doctor performs, a laboratory test, etc.) |
| Feasibility                     | • How long should/does it take to measure this outcome?  
• How long is too long?  
• What is/should be the patient/clinician burden associated with this measure? |
| Generic vs disease-specific   | • Should this outcome be measured using a generic instrument/measurement, or a hemophilia-specific instrument/measure? |
| Timing and recall              | • When should the outcome be measured?  
• How often the outcome should be measured?  
• How often should the outcome be reported?  
• If using an instrument for a patient-reported outcome, how far back should the patient have to remember to answer the questions? |
| Current landscape              | • Are there instruments/measurements currently being used that could capture this outcome?  
• If so, would it be adequate/appropriate to use with gene therapy?  
• Do the existing instruments capture the difference between gene therapy and current standard of care (are they sensitive enough)? |
| Related measurements           | • Do other therapeutic areas also measure this outcome?  
• Which instruments do they use? |
RESULTS
The targeted literature search was performed in July and August 2017. Overall, we abstracted outcomes from 52 journal articles, 195 records on clinicaltrials.gov and nine Cochrane reviews. Individual interviews were held with 12 coreHEM participants (24% of the group) to gain perspective on how trial endpoints and related outcomes may change with gene therapy technology. Seven patients were interviewed; these interviews included a particular focus on living with hemophilia, outcomes that are important in day-to-day life, and outcomes that a patient could foresee affected by a treatment that potentially represents a functional cure. The outcome list that was developed for voting included 48 outcomes that had been identified from the literature review and/or interviews with coreHEM participants.

Forty-nine Delphi voters agreed to be part of coreHEM (Table 5). Participation rates were >90% for each Delphi round (Appendix 12). After Round 2, three outcomes with high consensus were included in the core set without further discussion or vote at the meeting (frequency of bleeds, factor activity level, and duration of expression). Seven outcomes, although not high consensus by the primary definition, met criteria as “patient-important” and were also included for discussion at the meeting: target joints, mental health (anxiety/depression/coping/worry), feeling of physical health/general health perception, transformational psychological or emotional impact of experiencing a cure (or that of having made an irreversible treatment decision whatever the outcome), risk aversion (including confidence to participate in physical activity/sports/play), burden of treatment regimen on patient/family, and chronic pain (frequency/intensity/duration/character). This ensured that patient-important outcomes would not be dismissed without careful consideration of the group. In addition, participants could request that an outcome previously eliminated be added back in for discussion at the in-person meeting by providing, in writing, a request and explanation for why the outcome required further discussion and another vote. One outcome was re-introduced into the discussion in this way (utilization of the healthcare system [direct costs]). In the final voting round, three more outcomes were selected to be part of the core set (chronic pain, utilization of the healthcare system [direct costs], and mental health status, an outcome that represents a combination of the mental health [anxiety/depression/coping/worry] outcome and the transformational psychological or emotional impact of experiencing a cure [or that have having made an irreversible treatment decision] outcome, which was suggested and voted on at the consensus meeting). The results of the final Delphi voting round are available in Appendix 13.

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Number of Voters</th>
<th>% of Total Voters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/Patient Advocates</td>
<td>5</td>
<td>10.2</td>
</tr>
<tr>
<td>Clinicians</td>
<td>5</td>
<td>10.2</td>
</tr>
<tr>
<td>Researchers</td>
<td>5</td>
<td>10.2</td>
</tr>
<tr>
<td>Regulators</td>
<td>4</td>
<td>8.1</td>
</tr>
<tr>
<td>Public Research Funding Agencies</td>
<td>3</td>
<td>6.1</td>
</tr>
<tr>
<td>HTA Organizations</td>
<td>6</td>
<td>12.2</td>
</tr>
<tr>
<td>Payers</td>
<td>9</td>
<td>18.4</td>
</tr>
<tr>
<td>Life Science</td>
<td>12</td>
<td>24.5</td>
</tr>
</tbody>
</table>

FINAL CORE OUTCOME SET
The coreHEM Delphi produced three categories of results (Figure 2):

1) The recommended core outcome set, including frequency of bleeds, factor activity level, duration of expression, chronic pain, utilization of the healthcare system (direct costs), and
mental health condition. Three of these achieved high consensus in Round 2 (frequency of bleeds, factor activity level, and duration of expression), while the other three (chronic pain, mental health status, and utilization of the healthcare system [direct costs]) achieved high consensus in the final voting round. The six outcomes are intended to be measured and reported in each clinical trial for hemophilia gene therapy.

2) Adverse events that were rated as critically important by the group and/or by patients. Following voting Round 2, a decision was made to omit adverse events from the outcome list presented for further voting, since adverse events are typically collected to meet regulatory requirements and for post-market surveillance. These were not included as part of the core outcome set, however, their importance to panelists warranted highlighting for consideration in trial planning and longitudinal data collection. The adverse event outcomes were categorized as three domains: short-term adverse events, long-term adverse events, and mortality.

3) Additional outcomes that did not reach the threshold for inclusion in the core set, but which were rated as highly important by the majority of the group but did not reach the inclusion threshold of 70% (i.e. 50-69% of participants voted the outcome as “critical to include” on the Delphi rating scale). These were: duration/frequency/type of physical activity/sport/play (65% of panel calling this a “critically important” outcome) and feeling of physical health/general health perception (52% of voters calling it critical). As these two are the only outcomes rated >50% from the Physical Functioning and Perceived Health Status domains (respectively), they are proposed as a complement to the core set and may be desirable to be considered for measurement in clinical trials when and where feasible. (As noted above, product developers using core outcomes may also use additional outcome measures relevant to the specific study purposes and design.)

Definitions for the core outcomes, additional outcomes and adverse events are provided in Appendix 14.

Figure 2. Three groups of outcomes selected by coreHEM Delphi voting.
MEASUREMENTS AND INSTRUMENTS

For the measurement and instrument breakout group discussions at the in-person meeting, one group was assigned all three of the clinical/physiological outcomes (frequency of bleeds, factor activity level, and duration of expression), and one group discussed chronic pain. Two groups each were assigned to discuss the two topics of mental health and utilization of healthcare system (direct costs). The summaries of these discussions are presented in Tables 4-7.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency of bleeds</th>
<th>Factor activity level</th>
<th>Duration of expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>The group did not reach consensus.</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>How to measure?</td>
<td>Patient reported; group debated whether ultrasound should be required to confirm a bleed</td>
<td>Validated factor activity assay; two are available: chromogenic and one-stage</td>
<td>Measuring factor activity level to determine if expression is durable is likely to become part of long-term follow-up within the comprehensive care setting for people who receive gene therapy. If it transitions to be measured at an annual clinic visit, feasibility is high.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Measurements are subjective, but easy to record. Imaging, if required to confirm, is not invasive, but it does add the burden of the patient going to clinic.</td>
<td>*Feasibility was not discussed</td>
<td>Measuring factor activity level to determine if expression is durable is likely to become part of long-term follow-up within the comprehensive care setting for people who receive gene therapy. If it transitions to be measured at an annual clinic visit, feasibility is high.</td>
</tr>
<tr>
<td>Generic vs disease-specific</td>
<td>Measuring bleeds is hemophilia-specific</td>
<td>Factor activity level is hemophilia-specific</td>
<td>Duration of expression is hemophilia-specific, in particular for those who receive gene therapy</td>
</tr>
<tr>
<td>Timing and recall</td>
<td>A bleed should be reported as it happens, but the bleed rate will be calculated and reported annually. It would be useful to obtain more information about the cause of the bleed (e.g. was it a traumatic injury). A short questionnaire could be filled out each time a bleed occurs.</td>
<td>During trial, measured frequently. After trial, ideally measured every 6 months. In the long term, if gene therapy allows a patient to be treated as having a mild hemophilia phenotype, this may only be measured once per year.</td>
<td>Pivotal trials will have mandated observation of 5 to 15 years during which factor activity level, and consequently duration of expression will be measured. Like factor activity level, it will be measured frequently during the trials and will likely transition to be measured once per year. Factor level might be validated as a surrogate for it in the long term.</td>
</tr>
</tbody>
</table>
Trials use different measurement tools for patients to report bleeds (apps or diaries). Within trials bleeding frequency may be reported as median annual bleeding rate, total joint bleeds, etc. Each trial may collect some but not the same data about a bleed. This should be standardized across trials.

There are two accepted standard factor activity assays: chromogenic and one-stage. They may not be interchangeable or produce the same results without additional interpretation.

Global coagulation assays (TGA, ETA, ROTEM) exist, but are not necessary.

Current landscape was not discussed

Related measures were not discussed

---

**Table 5. Parameters to measure chronic pain for gene therapy in hemophilia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>“A patient has chronic pain when they report pain for more than three months. Pain may be intermittent or continuous, and may be of variable intensity over this time. This is pain that is not associated with an acute bleeding episode.”</td>
</tr>
<tr>
<td>How to measure?</td>
<td>Two options to measure pain: pain itself (intensity and tolerability) or pain in the context of how it affects function. The group prefers the latter. Chronic pain is patient reported.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Pain questionnaires can be completed quickly and the burden on the patient and clinician is low.</td>
</tr>
<tr>
<td>Generic vs disease-specific</td>
<td>The group favors using generic pain instruments over hemophilia-specific instruments so that payers can compare treatment effects on chronic pain in hemophilia patients to treatment effects on chronic pain in patients with other conditions.</td>
</tr>
<tr>
<td>Timing and recall</td>
<td>Currently used instruments ask about pain over a variety of timelines (the current day only, the past week, since the last clinic visit, etc). The group believed that regulators will soon require an instrument that asks about pain for the past week, and supported an instrument that measured that timeframe.</td>
</tr>
<tr>
<td>Current landscape</td>
<td>The group noted the following generic instruments of interest:</td>
</tr>
<tr>
<td></td>
<td>• McGill Pain Questionnaire uses words to describe pain, but is qualitative rather than quantitative.</td>
</tr>
<tr>
<td></td>
<td>• The BPI only asks about the past 24 hours</td>
</tr>
<tr>
<td></td>
<td>• VAS (PAIN) is easy to fill out but only asks about the current day. The scale could be compromised if photocopied.</td>
</tr>
<tr>
<td></td>
<td>The group also noted a disease-specific instrument that may be useful to measure pain:</td>
</tr>
<tr>
<td></td>
<td>• WOMAC has five scales depending on situation (pain at night, pain in activity, pain at rest, etc.) and is used to evaluate patients who have osteoarthritis of</td>
</tr>
</tbody>
</table>
the knee and hip, including pain, stiffness, and physical functioning of the joints. *There are other instruments currently available which include pain domains, but were not put forward by the group. This cell notes only the instruments discussed by the breakout group at the in-person meeting.*

**Related measurements**

The group considered whether pain medication use could be a good proxy for chronic pain, but reporting may be inaccurate and the two do not always correlate. Pain instruments (other than WOMAC) specific to other therapeutic areas were not mentioned.

**Table 6. Parameters to measure mental health for gene therapy in hemophilia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>“The impact of the intervention on the emotional well-being of the recipient, including mental health.”</td>
</tr>
<tr>
<td>How to measure?</td>
<td>An instrument with a summary score that asks about the reasons for mental health status (rather than just the presence or absence of depression/anxiety) would be ideal.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>A concise questionnaire taking 10-15 minutes, would be feasible.</td>
</tr>
<tr>
<td>Generic vs disease-specific</td>
<td>Anxiety and depression are general, but things like coping (with a disease, or with effects of a cure) are disease-specific. A generic and a disease-specific instrument used simultaneously can help show the effect of gene therapy; a positive change in the disease-specific instrument without a similar change in a generic instrument could indicate improvement due to the therapy.</td>
</tr>
<tr>
<td>Timing and recall</td>
<td>The amount of time before a change in mental health status associated with gene therapy may be linked to a patient’s expectations about treatment and how quickly they should expect a change. The instrument should be administered at study enrollment and every 3-6 months during a trial.</td>
</tr>
<tr>
<td>Current landscape</td>
<td>For depression and anxiety, the group noted the Hospital Anxiety Depression Scale (HADS), HAM-A, GAD-7, the BDI and the clinically Useful Anxiety Outcome Scale (CUXOS). Quality of life questionnaires such as the EQ-5D have domains with questions about mental health status. The patient advocacy organization PatientsLikeMe has a quality of life instrument that could be tailored to hemophilia. The group was not aware of currently-existing instruments to measure the transformational aspect of being cured.</td>
</tr>
<tr>
<td>Related measurements</td>
<td>To capture the transformational changes to mental health, the group suggested the following fields that may have instruments that could be related: surgery, cancer survival, non-emergency bypass surgery, post-partum depression, and organ transplant literature. Ultimately, qualitative data may be required to capture how a cure affects mental health status.</td>
</tr>
</tbody>
</table>

**Table 7. Parameters to measure utilization of the healthcare system (direct costs) for gene therapy in hemophilia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>“Use of the healthcare systems physical products and services (adverse events requiring hospitalization, non-study-mandated clinic visits, factor use) whose costs are borne directly by standard payers.”</td>
</tr>
</tbody>
</table>
**How to measure?**

Annual report of the costs incurred within the healthcare system for a patient calculated either by 1) summing the actual cost each year, or 2) observing the number of units of something that is used and then applying a standard price to each unit.

**Feasibility**

These events and related resource utilization are typically already captured on a CRF by clinical research staff.

**Generic vs disease-specific**

Factor usage is a large cost that is hemophilia-specific. However, as this is a data point rather than an instrument, a discussion generic vs. disease-specific is not relevant.

**Timing and recall**

Since this would be collected from a CRF, data collection would coincide with clinic visits. Reporting forms or apps should be standardized, so that events that are part of the direct cost burden are captured similarly across all trials.

**Current landscape**

The information needed for direct costs is already measured; events in which a patient utilizes the healthcare system are all collected and reported on a case report form.

**Related measurements**

N/A

**DISCUSSION**

coreHEM is unique among core outcome set initiatives in that the voting group included a significant number of HTA and payer representatives (the combined number of HTA representatives and payers was equal to the combined number of patients/patient advocates, clinicians and researchers). Making up 12.2% and 18.4% of the voting panel, respectively, the number of these types of stakeholders is greater than in any core outcome set initiative that we are aware of. Initiating a conversation with HTA groups and payers before pivotal trials begin allows the life science companies to take multiple points of view into account in the protocol development stage. Because these therapies will be costly, it is important that the trial not only show safety and effectiveness for regulatory approval, but benefits for the patient experience that can compete to show the value of the product when decisions must be made about which product to recommend and reimburse. A core outcome set, if used as recommended, can ensure that outcomes from various trials are comparable. HTA and other decision-makers who are part of the conversation can advocate for outcomes that may make assessment more straightforward. Having representatives from HTA and payer groups as part of the voting group and in-person discussion also allows these stakeholders to meet with those who will use the product and hear real stories about why certain outcomes are important to these patients and clinicians.

Participating organizations took part in the coreHEM project with the goal of identifying a core set of outcomes for use in future clinical studies of gene therapy in hemophilia. Collectively, they believe this recommended core outcome set, developed with multi-stakeholder input, will be useful in future assessments of gene therapies for hemophilia. They encourage product developers and other researchers to consider this recommended core outcomes set when developing study protocols for future clinical trials, registries and other studies. Several of the participating payer and HTA organizations have approved specific language recognizing the core outcome set (Appendix 15).

The original Delphi method developed by RAND was designed to allow the participating experts to influence one another through the provisions of feedback, comments, and analyses from round to round. However, this feedback was anonymized (or semi-anonymized by the use of code names) and communications between the experts was mediated through the research group. This was done to prevent undue influence of particularly senior or distinguished participants, and also conversely to encourage the opinions and insights of more junior experts to be considered seriously. In addition to the aspect of anonymity, the Delphi method is considered a “structured communication” in which there
is feedback of individual contributions of information and knowledge, assessment of the group judgement or view, and opportunity for individuals to revise views. A later, “modified” version of the Delphi was developed by RAND which included an in-person meeting to eliminate this mediation and allow for direct interaction of the experts. These researchers concluded that effective meeting facilitation would be able to manage these interpersonal issues. This is the approach that we have also used. This approach is particularly warranted since the coreHEM group is multi-stakeholder in composition (multiple types of expertise are in the room, not a single group of people in the same field). Hence, while voting decisions are made individually, the in-person meeting provides opportunities for co-learning to inform the vote.

A potential limitation of this study was that we included only five patients/patient advocates in the voting group. However, this represents 10% of all voters, and was equal to the number of clinicians and researchers who took part in the project. Some core outcome set initiatives are now including a large number of patients in their Delphi; participation is offered to any patient presenting with the condition at specific medical centers involved with the core outcome set project. Due to the timing of the pivotal hemophilia gene therapy trials, coreHEM required a rapid turn-around in which large-scale invites of that nature were not possible. Instead, patients were selected and invited to be part of the project because they are well-versed and/or previously involved in other hemophilia trials, studies, or had roles in patient organizations and were aware of the changing hemophilia treatment field. The targeted literature review to develop the initial list of outcomes was supplemented by interviews with patients in order to ensure that outcomes of particular importance to patients that may or may not have been used previously in hemophilia trials were on our list for voting. We also included one of our patient/patient advocate representatives as part of our Steering Committee, who advised on team decisions from a patient perspective. Finally, our built-in rules to keep the patient-important outcomes in the list for discussion prior to the final Delphi round was included in our analysis rules so that the patient voice would not be overwhelmed by other stakeholder groups. Because of these measures, we feel confident that the patient perspective remained strong throughout the process and that other stakeholder groups intentionally sought out the patient point of view.

It is possible that there was a bias among the patients and patient advocates who agreed to participate in coreHEM; patients particularly invested in the future of gene therapy may have been more likely to agree to participate in the project or be interviewed during the background research stage. While our built-in rules ensured that the patient opinion was given weight among the opinions of other stakeholder groups, we cannot be sure that the opinion of the patients was coming from a broad-based representation. It is possible that with a different group of patients/patient advocates, the results would differ. However, we feel that by maintaining a balanced multi-stakeholder group we have developed a set of six outcomes that can show the effectiveness and value of gene therapy, while remaining acceptable, in general, to the patients who must endure the trials and the disease.

The six outcomes in the set are versatile and well-rounded. Two are outcomes measured within a clinical setting (factor activity level and duration of expression). Three are patient reported outcomes: frequency of bleeds (which is within the physiological / clinical domain), chronic pain, and mental health (reflecting a physical and emotional manifestation of hemophilia). The remaining outcome is an economic outcome utilizing data captured within a health system and reflecting the potential importance of cost impacts of these treatments. The list also reflects a set that can capture the novelty of gene therapy while providing a basis of comparison to existing therapies. For example:
Frequency of bleeds is a “legacy” outcome that has been used in past hemophilia trials. Including it in the core set enables some degree of comparisons of efficacy and effectiveness with existing treatments.

Factor activity level was used as an early measure in hemophilia treatment but had fallen out of favor as prophylactic treatment became standard. As gene therapy shows promise to achieve near-normal factor activity levels, measurement of factor level may reemerge as a relevant outcome for regulatory approval.

Duration of expression replaces pharmacokinetic measurements of previous treatments, and can represent the long-term value of an investment in gene therapy.

Chronic pain and mental health outcomes will capture the impact of gene therapy as a functional cure, and changes in these outcomes should reflect the transformational nature of gene therapy.

Measurement of direct costs of healthcare resource allows for a value-based approach (where value equals costs relative to outcomes) and may reflect the expected changes to a gene therapy patients’ medical needs, if factor use and hospitalizations are greatly reduced, considering the expected high prices of gene therapy.

Multi-stakeholder agreement on a core set of outcomes is an important achievement that can help to ground comparisons between gene therapies and traditional ones, and among the gene therapies themselves. However, the optimal value of the core set will only be achieved if agreement is also reached on common standards and instruments for measurement and reporting of each outcome. Guidance on how to measure and report the outcomes in the core set is therefore a necessary component.

As noted, participants discussed measurement instruments during the afternoon session of the in-person meeting. However, this discussion only sketched overall priorities the group might specify for a general framework. Specific instruments or approaches for measurement were not selected. Nevertheless, with the input from these discussions and analysis of the nature of the recommended outcomes, the project team can envision a pathway for selecting the appropriate measurement/instrument for each outcome in the coreHEM set, and planning for this work is underway.

Some of the outcomes in the core set have straightforward measurements that could be implemented presently or shortly following some further limited discussion to standardize definitions.

Frequency of bleeds is a patient-reported outcome recorded and followed clinically. Consistent rules of how and when a trial participant should report a bleed requiring factor use can help equalize data collection, and therefore reporting, of this outcome. It does not require an instrument but will require agreement on definition. It is typically reported annually. A standardized method to measure and report bleeds could be developed after agreement on details such as whether confirmatory imaging is needed, how bleeds should be reported, and associated questions about the bleed (e.g., mechanism for patient-reporting).

For factor level and duration of expression, scientific debate over which assay is preferred may be necessary. However, regulators may soon harmonize requirements which will likely become the standard. Duration of expression is an extension of factor activity level, and is measured over time, but may require post-approval studies to fully capture gene therapy’s effect on this outcome.

For utilization of the healthcare system (direct costs), the breakout group that discussed this outcome at the in-person meeting proposed three events which account for the majority of
direct costs associated with hemophilia: adverse events requiring hospitalization, non-study-mandated clinic visits, and factor use. These events are already collected and reported during trials, and the costs could be summed annually.

Chronic pain and mental health require instruments, and possibly qualitative data collection. To capture the transformational aspect of a functional cure and the related effects on pain and mental health, instruments that have been previously used to measure these outcomes may not be sufficient; alternative instruments may need to be identified or developed.

For chronic pain, the coreHEM participants supported a general rather than hemophilia-specific instrument, to allow for payers and other post-regulatory decision makers to make comparisons to treatments in other therapeutic areas. For mental health, until an appropriate instrument is identified to capture the transformation of a cure, we suggest using a general and a hemophilia-specific instrument in tandem to help delineate changes in mental health that are due to treatment from those unrelated to hemophilia or disease. Upcoming instruments on “life interference” may fulfill the need for a way to measure the transformational changes of a cure.

Further research on the benefits or drawbacks of the various instruments already available (in hemophilia or other therapeutic fields) for these outcomes is required. Follow-on work will be needed to answer the questions outlined above and develop a consensus particularly on measurement of chronic pain and mental health. The effort should be informed by guidance published jointly by the Core Outcome Measures in Effectiveness Trials (COMET) initiative and the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) initiative on selecting outcome measurement instruments. That said, based on the discussion above, a more streamlined and rapid process of selecting instruments is conceivable while still serving the needs of patients and all relevant stakeholders.
REFERENCES


APPENDIX ONE – THE coreHEM PARTICIPANTS

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Observers. Donna Coffin, MSc (World Federation of Hemophilia (WFH)); Katherine High, MD (Spark Therapeutics); John Ko, PharmD, MS (Alnylam Pharmaceuticals); Gallia Levy, MD, PhD (Genentech);
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**Pilot Testers. Donna Coffin**, MSc (World Federation of Hemophilia (WFH)); **Samantha Craigie**, MSc (McMaster University); **Declan Noone** (Irish Haemophilia Society); **Ian Saldanha**, MBBS, PhD (Johns Hopkins Bloomberg School of Public Health), **Victoria Zuk** (McMaster University).

**Interviews. Randall Curtis**, MBA (Factor VIII Computing); **Samantha Gouw**, MD, PhD (Academic Medical Center Amsterdam and Leiden University Medical Center); **Daniel Hart**, BSc, MBChB, FRCP, FRCPath, PhD (The Royal London Hospital Haemophilia Centre, Barts and the London School of Medicine and Dentistry, QMUL, UK); **Mohit Jain**, PhD, MBA (BioMarin); **James Jorgenson**, RPh, MS, FASHP (Visante, Inc. & Visante Limited); **Snejana Krassova**, MD, MMBS (Bayer); **Declan Noone**, MEng (Irish Haemophilia Society); **Jamie O’Hara**, MSc (HC Economics, Ltd and Haemophilia Society); **David Page** (Canadian Haemophilia Society); **Edmund Pezalla**, MD, MPH, PhD (enlightenment bioconsult, LLC); **Glenn F. Pierce**, MD, PhD (Third Rock Ventures); **Eileen Sawyer**, PhD (uniQure); **Clive Spiegler**, PhD (Spark Therapeutics); **Michelle Witkop**, DNP, FNP-BC (National Hemophilia Foundation).

**Technical Support. Janelle King** (Center for Medical Technology Policy); **Julie Simmons**, CMP (Center for Medical Technology Policy).
# APPENDIX TWO - LITERATURE SEARCH ABSTRACTION PLAN

<table>
<thead>
<tr>
<th>Source</th>
<th>Timeframe for Search</th>
<th>Search Term</th>
<th>Outcomes Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Reviews</td>
<td>All available</td>
<td>hemophilia</td>
<td>Primary and secondary outcomes reported in the Methods section</td>
</tr>
</tbody>
</table>
| **Haemophilia journal articles** | Previous 5 years of archives | N/A – all titles reviewed | 1. Outcomes reported in the Methods section  
2. Outcomes reported in the Results section (if required) |
| Clinicaltrials.gov      | Records first posted in the previous 5 years | hemophilia  | From the trial record:  
• Current Primary Outcome Measures  
• Current Secondary Outcome Measures  
• Current Other Outcome Measures |
APPENDIX THREE - TARGETED LITERATURE SEARCH REFERENCES

COCHRANE REVIEWS


JOURNAL ARTICLES


Nugent D, Kalnins W, Querol F, Gregory M, Pilgaard T, Cooper DL, Iorio A. Haemophilia Experiences, Results and Opportunities (HERO) study: treatment-related characteristics of the population. Haemophilia. 2015 Jan 1;21(1).


**CLINICALTRIALS.GOV REFERENCES**


NCT00108797. Trial of NovoSeven® in Haemophilia - Joint Bleeds. [https://clinicaltrials.gov/ct2/show/NCT00108797](https://clinicaltrials.gov/ct2/show/NCT00108797)

NCT00141843. Study to Establish Bioequivalence of ReFacto AF (BDDrFVIII) With Advate (FLrFVIII) in Hemophilia A. [https://clinicaltrials.gov/ct2/show/NCT00141843](https://clinicaltrials.gov/ct2/show/NCT00141843)


NCT001686309. The FEIBA NovoSeven Comparative Study. [https://clinicaltrials.gov/ct2/show/NCT001686309](https://clinicaltrials.gov/ct2/show/NCT001686309)


NCT00245245. Study of Recombinant Porcine Factor VIII (FVIII) in Hemophilia and Inhibitors to FVIII. [https://clinicaltrials.gov/ct2/show/NCT00245245](https://clinicaltrials.gov/ct2/show/NCT00245245)


NCT00581126. Study Evaluating BENEFIX in Previously Treated Patients With Hemophilia B. https://clinicaltrials.gov/ct2/show/NCT00581126


NCT00623480. Trial to Evaluate the Effect of Secondary Prophylaxis With rFVIII Therapy in Severe Hemophilia A Adult and/or Adolescent Subjects Compared to That of Episodic Treatment (SPINART). https://clinicaltrials.gov/ct2/show/NCT00623480

NCT00623727. BAY79-4980 Compared to rFVIII-FS in Previously Treated Patients With Severe Hemophilia A. https://clinicaltrials.gov/ct2/show/NCT00623727


NCT00765726. Study Evaluating The Safety Of Xyntha In Usual Care Settings. https://clinicaltrials.gov/ct2/show/NCT00765726

NCT00782470. Evaluation of the Reasons and Consequences of Bleeding in Late Teens and Early Adulthood Patients With Severe Hemophilia A. https://clinicaltrials.gov/ct2/show/NCT00782470


NCT00874926. EFFEKT - Efficacy and Safety of Long-term Treatment With KOGENATE Bayer/FS. https://clinicaltrials.gov/ct2/show/NCT00874926


NCT00950170. Study of Safety And Efficacy Of ReFacto AF In Previously Untreated Hemophilia A Patients In The Usual Care Setting. https://clinicaltrials.gov/ct2/show/NCT00950170


NCT00989196. Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of a Recombinant FVIII in Patients With Severe Hemophilia A. https://clinicaltrials.gov/ct2/show/NCT00989196


NCT01027364. Study of recombinant factor IX Fc fusion protien (rFIXFc) in participants with hemophilia B. https://clinicaltrials.gov/ct2/show/NCT01027364

NCT01027377. Study of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Subjects With Severe Hemophilia A. https://clinicaltrials.gov/ct2/show/NCT01027377


NCT01128881. IMMUNINE Pre-Treatment Study. https://clinicaltrials.gov/ct2/show/NCT01128881


NCT01181128. Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Previously Treated Subjects With Severe Hemophilia A. https://clinicaltrials.gov/ct2/show/NCT01181128


NCT01228669. Safety of NNC 0172-0000-2021 in Healthy Male Subjects and Subjects With Haemophilia A or B (Explorer 1). https://clinicaltrials.gov/ct2/show/NCT01228669


NCT01335061. Study To Compare On-Demand Treatment To A Prophylaxis Regimen Of BeneFIX In Subjects With Moderately Severe to Severe HemophiliaB. https://clinicaltrials.gov/ct2/show/NCT01335061

NCT01341912. Study to Investigate the Long-term Efficacy and Safety of Human-cl rhFVIII in Previously Treated Patients (PTPs). https://clinicaltrials.gov/ct2/show/NCT01341912


NCT01395810. Safety and Efficacy of NNC-0156-0000-0009 After Long-Term Exposure in Patients With Haemophilia B: An Extension to Trials NN7999-3747 and NN7999-3773 (paradigm™ 4). https://clinicaltrials.gov/ct2/show/NCT01395810

NCT01425723. Long-Term Safety and Efficacy of rFIXFc in the Prevention and Treatment of Bleeding Episodes in Previously Treated Participants With Hemophilia B (B-YOND). [https://clinicaltrials.gov/ct2/show/NCT01425723]

NCT01434511. Study of Modified Recombinant Factor VIII (OBI-1) in Subjects With Congenital Hemophilia A. [https://clinicaltrials.gov/ct2/show/NCT01434511]

NCT01454739. Long-Term Safety and Efficacy of rFVIIIFc in the Prevention and Treatment of Bleeding Episodes in Previously Treated Participants With Hemophilia A (ASPIRE). [https://clinicaltrials.gov/ct2/show/NCT01454739]


NCT01496274. A Safety and Efficacy Study of a Recombinant Fusion Protein Linking Coagulation Factor IX With Albumin (rIX-FP) in Patients With Hemophilia B. [https://clinicaltrials.gov/ct2/show/NCT01496274]

NCT01510418. Socialization of Adult Men With Congenital Hemophilia A or B (PWBCD). [https://clinicaltrials.gov/ct2/show/NCT01510418]

NCT01568580. Efficacy and Safety of Recombinant Factor VIII (GreenGene) in Patients With Hemophilia A. [https://clinicaltrials.gov/ct2/show/NCT01568580]


NCT01599819. BAX 855 dose-escalation safety study. [https://clinicaltrials.gov/ct2/show/NCT01599819]

NCT01619046. Safety, Efficacy and Pharmacokinetics of GreenGene™ F to Previously Treated Patients With Severe Hemophilia A. [https://clinicaltrials.gov/ct2/show/NCT01619046]


NCT01623960. Quality of Life in Adult Patients with Severe Hemophilia in Turkey (TurkHaemQoL). [https://clinicaltrials.gov/ct2/show/NCT01623960]

NCT01625390. A Phase 2/3 Trial to Evaluate the Efficacy and Safety of BAY86-6150. [https://clinicaltrials.gov/ct2/show/NCT01625390]


NCT01863758. Assess the Safety and Efficacy of Individually Tailored Prophylaxis With Human-cl rhFVIII in Patients With Severe Haemophilia A. [https://clinicaltrials.gov/ct2/show/NCT01863758](https://clinicaltrials.gov/ct2/show/NCT01863758)

NCT01921855. Study of FVIIa Variant BAY86-6150 (B0189) in Subjects With Moderate or Severe Hemophilia Types A or B With or Without Inhibitors (MATCHBOX). [https://clinicaltrials.gov/ct2/show/NCT01921855](https://clinicaltrials.gov/ct2/show/NCT01921855)


NCT01992549. Study to Investigate Immunogenicity, Efficacy and Safety of Treatment With Human-cl rhFVIII. [https://clinicaltrials.gov/ct2/show/NCT01992549](https://clinicaltrials.gov/ct2/show/NCT01992549)

NCT02020369. Phase III Study of Coagulation FVIIa (Recombinant) in Congenital Hemophilia A or B Patients With Inhibitors. [https://clinicaltrials.gov/ct2/show/NCT02020369](https://clinicaltrials.gov/ct2/show/NCT02020369)


NCT02234323. An Open Label Study to Determine the Safety and Efficacy of Replacement Factor VIII Protein (Known as rFVIIIFc) in Untreated Males With Severe Hemophilia A. [https://clinicaltrials.gov/ct2/show/NCT0223423](https://clinicaltrials.gov/ct2/show/NCT0223423).


NCT02484638. Study of Recombinant Factor VIIa Fusion Protein (rVIIa-FP, CSL689) for On-demand Treatment of Bleeding Episodes in Patients With Hemophilia A or B With Inhibitors. [https://clinicaltrials.gov/ct2/show/NCT02484638](https://clinicaltrials.gov/ct2/show/NCT02484638).


NCT02976753. Prospective, Non-interventional Study to Evaluate the Effectiveness of Elocta Compared to Conventional Factor Products. [https://clinicaltrials.gov/ct2/show/NCT02976753](https://clinicaltrials.gov/ct2/show/NCT02976753).


GENE THERAPY LITERATURE


## APPENDIX FOUR – PARTICIPANT AND PATIENT INTERVIEWS

<table>
<thead>
<tr>
<th>Interviewee</th>
<th>Date of Interview</th>
<th>Location of Interview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randall Curtis, MBA</strong>&lt;br&gt;Member Board of Directors&lt;br&gt;Hemophilia Council of California&lt;br&gt;Co-Investigator&lt;br&gt;Patient Reported Outcomes, Burdens, and Experiences (PROBE) Study</td>
<td>August 24, 2017</td>
<td>NHF’s 69th Annual Meeting&lt;br&gt;Chicago, USA</td>
</tr>
<tr>
<td><strong>Samantha Gouw, MD, PhD</strong>&lt;br&gt;Pediatric Hematologist&lt;br&gt;Academic Medical Center Amsterdam&lt;br&gt;Clinical Epidemiologist&lt;br&gt;Leiden University Medical Center</td>
<td>July 12, 2017</td>
<td>ISTH XXVI Congress&lt;br&gt;Berlin, Germany</td>
</tr>
<tr>
<td><strong>Daniel Hart, MD, PhD</strong>&lt;br&gt;Senior Lecturer/Honorary Consultant&lt;br&gt;Haematologist&lt;br&gt;Barts and the London School of Medicine and Dentistry</td>
<td>July 10, 2017</td>
<td>ISTH XXVI Congress&lt;br&gt;Berlin, Germany</td>
</tr>
<tr>
<td><strong>Mohit Jain, PhD, MBA</strong>&lt;br&gt;Executive Director, Market Access EUMEA&lt;br&gt;BioMarin</td>
<td>July 11, 2017</td>
<td>ISTH XXVI Congress&lt;br&gt;Berlin, Germany</td>
</tr>
<tr>
<td><strong>James Jorgenson, RPh, MS, FASHP</strong>&lt;br&gt;Chief Executive Officer &amp; Chairman of the Board&lt;br&gt;Visante, Inc. &amp; Visante Limited</td>
<td>August 25, 2017</td>
<td>NHF’s 69th Annual Meeting,&lt;br&gt;Chicago, USA</td>
</tr>
<tr>
<td><strong>Snejana Krassova, MD, MMBS</strong>&lt;br&gt;VP, Head of Medical Affairs Therapeutic Area&lt;br&gt;Hematology&lt;br&gt;Bayer</td>
<td>July 11, 2017</td>
<td>ISTH XXVI Congress, Berlin, Germany</td>
</tr>
<tr>
<td><strong>Declan Noone, MEng, MSc</strong>&lt;br&gt;Project Coordinator, PARTNERS Programme&lt;br&gt;European Haemophilia Consortium&lt;br&gt;Health Economist&lt;br&gt;HCD Economics</td>
<td>August 24, 2017</td>
<td>NHF’s 69th Annual Meeting,&lt;br&gt;Chicago, USA</td>
</tr>
<tr>
<td><strong>Jamie O’Hara, MSc</strong>&lt;br&gt;Trustee&lt;br&gt;Haemophilia Society&lt;br&gt;Director&lt;br&gt;HCD Economics Ltd</td>
<td>August 25, 2017</td>
<td>NHF’s 69th Annual Meeting,&lt;br&gt;Chicago, USA</td>
</tr>
<tr>
<td><strong>Brian O’Mahony, FACSLM, FIBMS</strong>&lt;br&gt;Chief Executive&lt;br&gt;Irish Haemophilia Society, Ltd&lt;br&gt;President&lt;br&gt;European Haemophilia Consortium</td>
<td>August 2, 2017</td>
<td>Phone interview</td>
</tr>
<tr>
<td><strong>David Page</strong></td>
<td>August 29, 2017</td>
<td>Phone interview</td>
</tr>
<tr>
<td>National Executive Director</td>
<td>Canadian Hemophilia Society</td>
<td></td>
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<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Edmund Pezalla, MD, MPH, PhD</td>
<td>Subject Matter Expert</td>
<td>Formerly with Aetna</td>
</tr>
<tr>
<td>Glenn Pierce, MD, PhD</td>
<td>Entrepreneur in Residence</td>
<td>Third Rock Ventures</td>
</tr>
<tr>
<td>Eileen Sawyer, PhD</td>
<td>Director, Global Medical Affairs</td>
<td>uniQure</td>
</tr>
<tr>
<td>Clive Spiegler, PhD</td>
<td>Head of Portfolio &amp; New Product Planning</td>
<td>Spark Therapeutics</td>
</tr>
<tr>
<td>Michelle Witkop, DNP, FNP-BC</td>
<td>Head of Research</td>
<td>National Hemophilia Foundation (NHF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>August 25, 2017</td>
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<td>July 10, 2017</td>
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<td>August 25, 2017</td>
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<td>July 10, 2017</td>
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<td></td>
<td></td>
<td>August 25, 2017</td>
</tr>
</tbody>
</table>
APPENDIX FIVE – INTERVIEW QUESTIONS

• For patients: Are there any health indicators (outcomes) related to your hemophilia that you regularly keep track of for yourself that your doctor does not ask about?

• Thinking of your ideal core outcome set for gene therapy in hemophilia, what type of balance would you want to have between hemophilia-specific outcomes (such as circulating factor VIII or IX levels) and gene-therapy specific outcomes (such as immune system reactions)?

• What is the most important outcome to you when you hear about a trial of a new treatment for hemophilia? (What results do you look at first in a study report/what do you ask the doctor about first when he/she recommends a new treatment?)

• Do you think the thresholds of “treatment success” will be different for gene therapy compared with conventional treatment? (right now, the goal is trough levels of 1% - would you want higher?)
  ○ Related: Will “treatment success” be defined by a different measure in gene therapy than it has been before?

• How do you think outcomes that will be measured in gene therapy studies will differ from outcomes measured in other intervention trials?

• Will some outcomes that are measured today be no longer relevant in gene therapy trials?

• In what ways do you imagine that gene therapy might improve patient quality of life and function compared to current therapies?

• Why are some outcomes used more than others? What prevents certain outcomes from being more widely used? What needs to be done to promote greater use of a set of core outcomes across hemophilia trials?
## APPENDIX SIX - INITIAL OUTCOME LIST FOR VOTING MAPPED TO COMET TAXONOMY

<table>
<thead>
<tr>
<th>coreHEM Domains</th>
<th>COMET Categories (mapped list)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADVERSE EVENTS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Short Term</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion site reactions</td>
<td>Adverse events/effects</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>Adverse events/effects</td>
</tr>
<tr>
<td>Immune response to FVIII/FIX (inhibitor development)</td>
<td>Adverse events/effects OR Immune system outcomes</td>
</tr>
<tr>
<td>Immune response to gene therapy</td>
<td>Adverse events/effects OR Immune system outcomes</td>
</tr>
<tr>
<td>Germline transmission (vector shedding)</td>
<td>Adverse events/effects</td>
</tr>
<tr>
<td><strong>Long Term</strong></td>
<td></td>
</tr>
<tr>
<td>Vector integration into host genome</td>
<td>Adverse events/effects</td>
</tr>
<tr>
<td>Development of unusual disorders (auto-immune diseases/cancers/etc.)</td>
<td>Adverse events/effects</td>
</tr>
<tr>
<td>Immune response to FVIII/FIX (inhibitor development)</td>
<td>Adverse events/effects OR Immune system outcomes</td>
</tr>
<tr>
<td><strong>MORTALITY</strong></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td>Mortality/survival</td>
</tr>
<tr>
<td>Age of death</td>
<td>Mortality/survival</td>
</tr>
<tr>
<td><strong>PHYSIOLOGICAL/CLINICAL</strong></td>
<td></td>
</tr>
<tr>
<td>Frequency of bleeds</td>
<td>Physiological/clinical – Blood and lymphatic system outcomes</td>
</tr>
<tr>
<td>Severity of bleeds</td>
<td>Physiological/clinical – Blood and lymphatic system outcomes</td>
</tr>
<tr>
<td>Factor activity level</td>
<td>Physiological/clinical – Blood and lymphatic system outcomes</td>
</tr>
<tr>
<td>Duration of factor expression</td>
<td>Physiological/clinical – Blood and lymphatic system outcomes</td>
</tr>
<tr>
<td><strong>PHYSIOLOGICAL/CLINICAL: PAIN/DISCOMFORT</strong></td>
<td></td>
</tr>
<tr>
<td>Acute pain (including frequency/intensity/duration/character)</td>
<td>Physiological/clinical - Musculoskeletal and connective tissue outcomes</td>
</tr>
<tr>
<td>Interference of acute pain on daily life/activities of daily living (e.g. walking, lifting a full glass of water, sexual activity, etc)</td>
<td>Functioning – Physical functioning</td>
</tr>
<tr>
<td>Chronic pain (including frequency/intensity/duration/character)</td>
<td>Physiological/clinical - Musculoskeletal and connective tissue outcomes</td>
</tr>
</tbody>
</table>
Interference of chronic pain on daily life/activities of daily living (e.g. walking, lifting a full glass of water, sexual activity, etc) | Functioning – Physical functioning

### EMOTIONAL FUNCTIONING: WELL-BEING

<table>
<thead>
<tr>
<th>Description</th>
<th>Functioning – Emotional functioning/wellbeing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health (including anxiety/depression/coping/worry)</td>
<td></td>
</tr>
<tr>
<td>Vitality/tiredness/fatigue</td>
<td></td>
</tr>
<tr>
<td>Contentment/happiness/elation/exhilaration (mood)</td>
<td></td>
</tr>
</tbody>
</table>

### SOCIAL FUNCTIONING

<table>
<thead>
<tr>
<th>Description</th>
<th>Functioning – Social functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify as a person with hemophilia (including disclosure)</td>
<td>Perceived health status OR</td>
</tr>
<tr>
<td>Sense of belonging to a community</td>
<td>Functioning – Social functioning</td>
</tr>
<tr>
<td>Feeling of inequality compared to peers</td>
<td>Functioning – Social functioning</td>
</tr>
<tr>
<td>Sexual intimacy</td>
<td>Functioning – Social functioning</td>
</tr>
</tbody>
</table>

### PHYSICAL FUNCTIONING

<table>
<thead>
<tr>
<th>Description</th>
<th>Functioning – Physical functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, frequency, intensity of physical activity/sports/play</td>
<td></td>
</tr>
<tr>
<td>Sexual activity</td>
<td></td>
</tr>
<tr>
<td>Mobility (including use of mobility aids)</td>
<td></td>
</tr>
<tr>
<td>Target joints</td>
<td>Physiological/clinical - Musculoskeletal and connective tissue outcomes</td>
</tr>
<tr>
<td>Joint function</td>
<td>Physiological/clinical - Musculoskeletal and connective tissue outcomes</td>
</tr>
</tbody>
</table>

### ROLE FUNCTIONING

<table>
<thead>
<tr>
<th>Description</th>
<th>Functioning – Physical functioning AND Global quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independence</td>
<td></td>
</tr>
<tr>
<td><strong>Education (School)</strong></td>
<td></td>
</tr>
<tr>
<td>Education attainment/achievement (absenteeism, grades)</td>
<td>Functioning – Role functioning</td>
</tr>
<tr>
<td>Education choice (where to go to school, decisions regarding field of study)</td>
<td>Personal circumstance</td>
</tr>
<tr>
<td><strong>Employment (Work)</strong></td>
<td></td>
</tr>
<tr>
<td>Career choice (location, type of work, taking a job because it supplies insurance)</td>
<td>Personal circumstance</td>
</tr>
<tr>
<td>Work absenteeism</td>
<td>Functioning – Role functioning</td>
</tr>
<tr>
<td>Career choices for caregiver (location, type of work, taking a job because it supplies insurance)</td>
<td>Resource use – societal/carer burden</td>
</tr>
<tr>
<td>Caregiver absenteeism</td>
<td>Resource use – societal/carer burden</td>
</tr>
<tr>
<td><strong>Family Life</strong></td>
<td></td>
</tr>
<tr>
<td>Family decisions (moving near a hemophilia treatment center, paternity decisions)</td>
<td>Personal circumstance OR Functioning – Role functioning</td>
</tr>
<tr>
<td>Child care (ability to find and maintain)</td>
<td>Personal circumstance</td>
</tr>
<tr>
<td>Interaction with children (carry babies, run/play/attend events)</td>
<td>Functioning – Role functioning AND Functioning – Physical functioning</td>
</tr>
</tbody>
</table>

**PERCIEVED HEALTH STATUS**

| Feeling of normalcy | Functioning – Emotional functioning/wellbeing |
| Feeling of physical health/general health perception | Perceived health status |
| Perceived burden (treatment and disease) | Perceived health status |
| Risk aversion (including confidence to participate in physical activity/sports/play) | Perceived health status AND Functioning – Physical functioning |

**HEALTH SYSTEM COSTS/ECONOMICS**

| Utilization of health care system (days in hospital/hospital readmissions, emergency room visits, bleeds, inhibitors, bypass agent use, pain and other medications, home health/homecare services, mobility aids, orthopedic interventions, specialist consultations, professional caregiver) | Resource use – Hospital AND Resource use – Need for Intervention |
| Cost on patient/family (out of pocket costs, underemployment, caregiver burden, hemophilia community resources/grants for care) | Resource use – Economic AND Resource use – Societal/carer burden |
| Cost on society (missed days of work, days parents have to take off for caregiving) | Resource use – Societal/carer burden |
| Cost of treatment regimen (including frequency of infusions and complications of venous access) | Resource use – Need for intervention |
APPENDIX SEVEN – DELPHI VOTING REFERENCE DOCUMENT

DELPHI ROUND 1 REFERENCE DOCUMENT

BACKGROUND

PROJECT GOAL
Determine a set of clearly defined, “core set” of outcomes to measure, demonstrate and differentiate the effectiveness and value of gene therapy in hemophilia.

DEFINITIONS
These following definitions are adapted from the Core Outcome Measures in Effectiveness Trials (COMET) Initiative. The COMET Initiative brings together researchers interested in the development and application of core outcome sets.3

- **Core outcome set** – An agreed standardized collection of outcomes which should be measured and reported, as a minimum, in all trial for a specific clinical area or of a specific condition4

- **Domain** - A domain is a broad category, an element of a person’s overall health and life in relation to their treatment (for example, mobility/physical functioning)

- **Outcomes** - Each domain contains one or more outcomes, which are the “what” we want to measure. Within the mobility/physical functioning domain, an example of an outcome might be joint impairment.

- **Measurements or Instruments** - Each outcome can be measured using measurements or instruments – the “how” something is measured. A measurement/instrument is a tool to measure an outcome. The tool can be a single question, a questionnaire with a composite score, a score obtained through physical examination, laboratory measurement, or observation of an image.5 In our example, there are several measurements or instruments to assess joint impairment e.g. X-Ray Petterssen score, change in range of motion, Hemophilia Joint Health Score (HJHS).

PURPOSE
We are conducting the survey now because gene therapy represents a pivotal moment in therapeutics for hemophilia. For the first time, patients may have an opportunity not merely to manage their condition, but to cure it.

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3 http://www.comet-initiative.org/about/overview
5 http://www.comet-initiative.org/glossary/cos/
Historically, the clinical standards, measures, and concepts used in hemophilia clinical trials have been designed to assess disease management. These standards, measures, and concepts must now be updated to reflect a new generation of potentially curative therapies and the dramatic benefits they offer to patients over existing treatments. The Delphi exercise is therefore designed to survey experts and stakeholders in the hemophilia community on a CORE SET of outcomes that should be measured in gene therapy clinical trials for interventions in hemophilia.

Note that specifying a core set does not prevent study designers from adding measures, as appropriate; it “sets a floor, not a ceiling,” for outcomes. We will address the adequacy of measures/instruments for outcomes judged most important in a later stage of this exercise.

**INSTRUCTIONS FOR VOTING**

In the survey, we will ask you to rate the importance of DOMAINS and OUTCOMES as core outcomes in gene therapy clinical trials for hemophilia.

On each page, you will see a scale that ranges from 1 to 9. For this survey, a higher number is equal to higher importance to be included in a core outcome set.

The number you select should be based on how important you think each outcome is to be included in the core set:

- Numbers 1-3 should be selected if you feel that the outcome we are asking you about is not important to be included in the core set
- Numbers 4-6 indicate that the outcomes are important but not critical to include in a core set
- Numbers 7-9 indicate that the outcomes are critical to include in a core set

Your assessment of importance:

- should be based on what you believe will be the most valuable information for decision-makers: regulatory approval, care decisions by patients and providers, coverage and reimbursement decisions
- should consider new risks and benefits not previously seen in older generations of treatments
- should not consider whether adequate and well validated measures currently exist

This reference document provides further detail about the outcomes included in the coreHEM Delphi Round 1 survey. As you work through the survey, you may refer to this document for descriptions of the outcomes that are listed.
OVERVIEW OF THE DOCUMENT

The order of the outcomes here parallels the order of the outcomes presented in the online survey. You may refer to this document and use the information provided to assist in your rating of importance for each outcome.

ROUND 1 GUIDANCE

For the first round of the Delphi voting, we will only be asking about domains and outcomes. After the panel has voted on the outcomes, or “what” to measure, we will then ask about the measures/instruments, or “how” we will measure, in a later round. Think about the outcomes you think should be included in our core outcome set. We want to know if the outcomes are important regardless of whether there are already “good” measures or instruments to report on the outcome.

HOW THIS DOCUMENT IS STRUCTURED

For each outcome we will ask you about, we provide a brief description of what it is/what it measures.

Structure

<table>
<thead>
<tr>
<th>DOMAIN NAME:</th>
<th>The domain category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome name:</td>
<td>A brief description of the outcome.</td>
</tr>
</tbody>
</table>

Sample

<table>
<thead>
<tr>
<th>DOMAIN: PHYSICAL FUNCTIONING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint function:</td>
</tr>
</tbody>
</table>
DOMAIN: ADVERSE EVENTS

Adverse event outcomes are safety outcomes, or measures of how safe a certain treatment is. Adverse events are undesired health problems or experiences associated with the use of a medical product, in this scenario, gene therapy. Adverse events may occur quickly after treatment or may take many years to develop. We have divided the adverse events into those which happen within one year after gene therapy and those which happen beyond one year after gene therapy.

SHORT TERM (UP TO 12 MONTHS)

Infusion reactions: response to infusion of gene therapy product, including pain, swelling, or itching at the injection site

Liver toxicity: gene therapy products are targeted to enter liver cells; liver toxicity, measured by elevated liver enzymes, may occur

Immune response to FVIII/FIX (Inhibitor development): when the gene for the missing clotting factor (FVIII or FIX) is inserted into the cell, it is possible that the body may not recognize FVIII or the FIX that the cells are now producing and will initiate an immune response against it; if the body develops antibodies against the FVIII/FIX, it is called an inhibitor (patients with inhibitors may require special and expensive treatments for bleeds that can bypass the immune response against the needed clotting factor)

Immune response to gene therapy: when gene therapy is administered, the patient’s body may mount an immune response against elements of the product injected (antibodies against the viral vector, gene therapy vector capsid-specific T cells, etc.)

Germline transmission (vector shedding): the virus/vector spread within the body and excretion outside of the body (in blood, saliva, urine, stool, semen, nasal secretions, feces) could be a potential public health concern if there is human to human transmission

LONG TERM (BEYOND 12 MONTHS)

Vector integration into host genome: the DNA of the virus becomes integrated into the human cells, potentially altering the expression of the genes or causing other genes to become inactivated

Development of other disorders: development of serious medical problems associated with gene therapy such as auto-immune diseases or cancer

Immune response to FVIII/FIX (Inhibitor development): when the gene for the missing clotting factor (FVIII or FIX) is inserted into the cell, it is possible that the body may not recognize FVIII or the FIX that the cells are now producing and will initiate an immune response against it; if the body develops antibodies against the FVIII/FIX, it is called an inhibitor
**DOMAIN: MORTALITY (SURVIVAL)**

**Cause of death:** official determination of the reason for a patient’s death

**Age of death:** the age at which a person dies

**DOMAIN: PHYSIOLOGICAL/CLINICAL**

**Frequency of bleeds:** how often a person with hemophilia experiences a bleed (an example measure is the annualized bleed rate, ABR)

**Severity of bleeds:** the seriousness/intensity of a bleed (joint bleeds, muscle bleeds, intracranial hemorrhage, whether a bleed requires treatment with FVIII/FIX and how much)

**Factor activity level and duration of expression:** the amount of clotting factor in the blood, measured as a percentage, and how long after gene therapy that level lasts (normal clotting factor activity is described as 100 percent, though anywhere in the range of 50 to 150 percent is considered normal; for people with hemophilia A, the activity level of Factor VIII (FVIII) would be measured, and for people with hemophilia B, the activity level of Factor IX (FIX) would be measured)

**DOMAIN: PAIN/DISCOMFORT**

**Acute pain:** the presence of sharp but limited pain related with tissue damage including the frequency, intensity, duration and character of the pain

**Interference of acute pain on daily life/activities of daily living:** the influence of acute pain on a person’s ability to go throughout their day for example, walking, lifting a full glass of water, sexual activity, etc.

**Chronic pain:** the presence of persistent pain that can last for a long time including the frequency, intensity, duration and character of the pain

**Interference of chronic pain on daily life/activities of daily living:** the influence of chronic pain on a person’s ability to go throughout their day for example, walking, lifting a full glass of water, sexual activity, etc.
DOMAIN: EMOTIONAL FUNCTIONING: WELL-BEING

Emotional functioning assesses how gene therapy for hemophilia and having hemophilia impacts a person’s emotions and well-being. These outcomes measure a person’s satisfaction in life and how they feel about themselves and their disease.

Mental health (including anxiety/depression/coping/worry): a person’s psychological condition; whether a person feels anxiety or depression about having and living with hemophilia, how they cope with the disease and the psychological elements of having a lifelong illness, how much they worry about their condition

Vitality/tiredness/fatigue: how full of life a person feels, and enthusiasm for living; may be associated with level of tiredness and fatigue

Contentment/happiness/elation/exhilaration (mood): a person’s mood and attitudes toward their decision to receive gene therapy treatment

DOMAIN: SOCIAL FUNCTIONING

Social functioning assesses how gene therapy for hemophilia and having hemophilia impacts a person’s social health, such as their ability to have a social life, and companions, if desired, and their behavior and participation in social situations.

Identifying as a person with hemophilia (disclosure): the experience of revealing hemophilia status to others

Sense of belonging in a community: the feeling of being part of the hemophilia community, and having shared experiences with others who have hemophilia

Feeling of inequality compared to peers: envy or sadness about inability to do certain activities (for example, participate in an extreme sport) due to having hemophilia

Sexual intimacy: relating to romantic relationships, the confidence and level of comfort to get close to a person and pursue romantic/sexual relationships

DOMAIN: PHYSICAL FUNCTIONING

Physical functioning outcomes measure how well a person with hemophilia can perform the physical requirements throughout daily life.

Duration, frequency, intensity and type of physical activity/sports/play: characterization of the physical activity that a person can comfortably do, how long and how often they can do it and how much effort it requires (physical activity may include exercise, or general activities that have a physical element such as gardening, dancing, cleaning)
**Sexual activity:** a person’s ability to engage in the physical aspect of sex

**Mobility:** a person’s ability to move, including the use of mobility aids such as a wheelchair, a walker, canes and crutches

**Target joints:** joints that bleed often; this could be a measure of the presence of, the number of, or changes in target joints

**Joint function:** how well one can move, flex and bend (their range of motion), or any impairment, weakening or damage, including functional loss and pain to the points of the body where bones meet (for example, shoulders, knees and elbows)

**DOMAIN: ROLE FUNCTIONING**

Role functioning describes the impact of hemophilia on a person’s ability to fulfil the roles of their life, in their education and career, and to perform roles as a family member and a member of society.

**Independence:** including a person’s ability to go about their daily life and perform the activities of self-care without or with minimal assistance, a person’s confidence in being able to have financial and job security, and to know how to treat their hemophilia

**EDUCATION (SCHOOL)**

**Education attainment/achievement:** the ability to receive an education, including absenteeism from school, grades and academic achievement

**Education choice:** decisions about school including where to attend college/university (need to be close to a hemophilia treatment center?), regarding field of study (choosing to major in a field that has sedentary/non-physical jobs), etc.

**EMPLOYMENT (WORK)**

**Career choice:** for a person with hemophilia, decisions made about employment including choosing a career due to physical restrictions, or within a career field, and type of desk job over physical work, the location of the chosen career and taking a job because it provides health insurance (rather than starting a private business, for example)

**Work absenteeism:** missed days/time from work associated with aspects of having and/or treating hemophilia

**Career choice for caregiver:** employment decisions made by a caregiver such as taking a job for health insurance benefits for the family, choosing not working in order to be a primary caretaker for a person with hemophilia, choosing a job in a certain location or with flexible hours

**Caregiver absenteeism:** missed days/time from work of a parent or caregiver to take care of a person with hemophilia
FAMILY LIFE

Family decisions: choices made to accommodate a person with hemophilia that affect family life, such as moving to a certain area to be near a hemophilia treatment center and paternity decisions

Child care: ability to find and maintain care for a child with hemophilia

Interact with children: the ability for a parent with hemophilia to engage in interactions with children that involve movement and physical activity, such as carrying a baby, getting down to the floor to play with toys, or run and play outside

DOMAIN: PERCEIVED HEALTH STATUS

This domain includes outcomes that are associated with a person’s view on their disease and their opinions about their health status.

Feeling of normalcy: the feeling of being able to live a life that is perceived as “normal,” based on a person’s individual description of normal

Feeling of physical health/general health perception: how a person with hemophilia feels about their overall state of health

Perceived burden (treatment and disease): the feeling of the amount of work and effort a person with hemophilia must put into maintaining their treatment regimen and live with the disease

Risk aversion: decisions made by a person with hemophilia to pursue or avoid certain activities based on current health and expected requirements/results of participating in that activity (including confidence to participate in physical activity/sports/play)

DOMAIN: RESOURCE USE

Resource use refers to the costs associated with treatment and with living as a person with hemophilia. This can mean economic costs, the use of resources at a hospital or associated with medical treatment, and the burden on the patient, the patient’s family and on society.

Utilization of health care system: measures of uses and related costs incurred from the need of healthcare and treatment associated with hemophilia, including days in hospital, hospital readmissions, emergency room visits, bleeds, inhibitors, bypass agent use, pain and other medications, home health/homecare services, mobility aids, orthopedic interventions, specialist consultations, and professional caregivers

Cost on patient/family: out of pocket costs to the patient and the family that are not covered by health insurance or not included in healthcare costs such as paying for specialists beyond the allowed number of visits, paying for products that are needed due to complications of hemophilia (such as custom orthotics), underemployment (taking a lower-paying job because of flexible schedules or
type of insurance provided), caregiver burden, and access to hemophilia community resources/grants for care

**Cost on society**: the burden of costs to the community around the person with hemophilia, such as missed days of work/days parents have to take off for caregiving, productivity levels associated with missing work, costs of premiums of others in insurance pools

**Cost of treatment regimen**: costs of products needed to maintain health, including frequency of infusions and complications of venous access
APPENDIX EIGHT – DELPHI ROUND ONE RESULTS

coreHEM DELPHI ROUND 1 RESULTS
OCTOBER 9, 2017
## coreHEM Delphi Round 1 Results

### DOMAIN: Short Term Adverse Events (<12 months)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Scored 1-3 (%)</th>
<th>Scored 4-6 (%)</th>
<th>Scored 7-9 (%)</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion site reaction</td>
<td>35</td>
<td>45</td>
<td>18</td>
<td>4.4</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>0</td>
<td>6</td>
<td>92</td>
<td>8.6</td>
<td>Retain</td>
</tr>
<tr>
<td>Immune response to FVIII/FIX (inhibitor development)</td>
<td>0</td>
<td>8</td>
<td>90</td>
<td>9.0</td>
<td>Retain</td>
</tr>
<tr>
<td>Immune response to gene therapy</td>
<td>2</td>
<td>10</td>
<td>86</td>
<td>8.2</td>
<td>Retain</td>
</tr>
<tr>
<td>Germline transmission (vector shedding)</td>
<td>14</td>
<td>20</td>
<td>57</td>
<td>8.0</td>
<td>Retain (patient-important)</td>
</tr>
</tbody>
</table>

### DOMAIN: Long Term Adverse Events (beyond 12 months)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Scored 1-3 (%)</th>
<th>Scored 4-6 (%)</th>
<th>Scored 7-9 (%)</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector integration into host genome</td>
<td>4</td>
<td>18</td>
<td>71</td>
<td>8.0</td>
<td>Retain</td>
</tr>
<tr>
<td>Development of other disorders (auto-immune diseases/cancers/etc.)</td>
<td>4</td>
<td>8</td>
<td>86</td>
<td>8.2</td>
<td>Retain</td>
</tr>
<tr>
<td>Immune response to FVIII/FIX (inhibitor development)</td>
<td>0</td>
<td>12</td>
<td>86</td>
<td>9.0</td>
<td>Retain</td>
</tr>
</tbody>
</table>

### DOMAIN: Mortality

<table>
<thead>
<tr>
<th>Event</th>
<th>Scored 1-3 (%)</th>
<th>Scored 4-6 (%)</th>
<th>Scored 7-9 (%)</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
<td>8</td>
<td>6</td>
<td>84</td>
<td>7.4</td>
<td>Retain</td>
</tr>
<tr>
<td>Age of death</td>
<td>10</td>
<td>22</td>
<td>63</td>
<td>5.4</td>
<td>Eliminate</td>
</tr>
</tbody>
</table>

### DOMAIN: Physiological/Clinical

<table>
<thead>
<tr>
<th>Event</th>
<th>Scored 1-3 (%)</th>
<th>Scored 4-6 (%)</th>
<th>Scored 7-9 (%)</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of bleeds</td>
<td>0</td>
<td>8</td>
<td>92</td>
<td>7.6</td>
<td>Retain</td>
</tr>
<tr>
<td>Severity of bleeds</td>
<td>4</td>
<td>18</td>
<td>78</td>
<td>5.8</td>
<td>Retain</td>
</tr>
<tr>
<td>Factor activity level</td>
<td>2</td>
<td>14</td>
<td>84</td>
<td>8.8</td>
<td>Retain</td>
</tr>
<tr>
<td>Duration of expression</td>
<td>4</td>
<td>10</td>
<td>84</td>
<td>8.8</td>
<td>Retain</td>
</tr>
</tbody>
</table>

### DOMAIN: Pain/Discomfort

<table>
<thead>
<tr>
<th>Event</th>
<th>Scored 1-3 (%)</th>
<th>Scored 4-6 (%)</th>
<th>Scored 7-9 (%)</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pain (including frequency/intensity/duration/character)</td>
<td>8</td>
<td>41</td>
<td>49</td>
<td>7.0</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Interference of acute pain on daily life/activities of daily living</td>
<td>4</td>
<td>29</td>
<td>65</td>
<td>6.6</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Chronic pain (including frequency/intensity/duration/character)</td>
<td>6</td>
<td>33</td>
<td>59</td>
<td>7.6</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Interference of chronic pain on daily life/activities of daily living</td>
<td>2</td>
<td>22</td>
<td>74</td>
<td>7.2</td>
<td>Retain (patient-important)</td>
</tr>
</tbody>
</table>

### DOMAIN: Emotional Functioning

<table>
<thead>
<tr>
<th>Event</th>
<th>Scored 1-3 (%)</th>
<th>Scored 4-6 (%)</th>
<th>Scored 7-9 (%)</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health (e.g. anxiety/depression/coping/worry)</td>
<td>6</td>
<td>37</td>
<td>55</td>
<td>7.4</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Vitality/tiredness/fatigue</td>
<td>10</td>
<td>43</td>
<td>45</td>
<td>6.4</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Mood (e.g. contentment/happiness/elation/exhilaration)</td>
<td>14</td>
<td>49</td>
<td>35</td>
<td>6.4</td>
<td>Eliminate</td>
</tr>
</tbody>
</table>

### DOMAIN: Social Functioning

<table>
<thead>
<tr>
<th>Event</th>
<th>Scored 1-3 (%)</th>
<th>Scored 4-6 (%)</th>
<th>Scored 7-9 (%)</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifying as a person with hemophilia (disclosure)</td>
<td>29</td>
<td>51</td>
<td>14</td>
<td>4.0</td>
<td>Eliminate</td>
</tr>
</tbody>
</table>
### APPENDIX 8
Delphi Round 1 Results

<table>
<thead>
<tr>
<th>Sense of belonging to a community</th>
<th>37</th>
<th>49</th>
<th>8</th>
<th>4.2</th>
<th>Eliminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of inequality compared to peers</td>
<td>22</td>
<td>45</td>
<td>27</td>
<td>4.2</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Romantic relationships</td>
<td>27</td>
<td>37</td>
<td>35</td>
<td>4.2</td>
<td>Eliminate</td>
</tr>
</tbody>
</table>

**DOMAIN: Physical Functioning**

<table>
<thead>
<tr>
<th>Duration, frequency, intensity and type of physical activity/sports/play</th>
<th>4</th>
<th>31</th>
<th>63</th>
<th>6.4</th>
<th>Eliminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual activity</td>
<td>16</td>
<td>37</td>
<td>45</td>
<td>5.6</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Mobility (including use of mobility aids)</td>
<td>2</td>
<td>18</td>
<td>78</td>
<td>8.0</td>
<td>Retain</td>
</tr>
<tr>
<td>Target joints</td>
<td>4</td>
<td>31</td>
<td>61</td>
<td>8.0</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Joint function</td>
<td>4</td>
<td>20</td>
<td>74</td>
<td>7.8</td>
<td>Retain</td>
</tr>
</tbody>
</table>

**DOMAIN: Role Functioning**

<table>
<thead>
<tr>
<th>Independence</th>
<th>6</th>
<th>12</th>
<th>80</th>
<th>6.6</th>
<th>Retain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education attainment/achievement</td>
<td>20</td>
<td>33</td>
<td>43</td>
<td>5.2</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Education choice</td>
<td>33</td>
<td>41</td>
<td>22</td>
<td>5.0</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Career choice for patient (location/type of work/insurance)</td>
<td>20</td>
<td>35</td>
<td>41</td>
<td>5.2</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Patient work absenteeism</td>
<td>6</td>
<td>22</td>
<td>69</td>
<td>7.4</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Caregiver career choice (location, type of work, taking a job because it supplies insurance)</td>
<td>29</td>
<td>41</td>
<td>29</td>
<td>5.2</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Caregiver work absenteeism</td>
<td>14</td>
<td>31</td>
<td>53</td>
<td>7.0</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Family decisions (moving near a hemophilia treatment center, paternity decisions)</td>
<td>29</td>
<td>47</td>
<td>22</td>
<td>5.0</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Childcare (ability to find and maintain)</td>
<td>31</td>
<td>47</td>
<td>20</td>
<td>4.6</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Interaction with children (carry babies, run/play)</td>
<td>20</td>
<td>39</td>
<td>39</td>
<td>5.8</td>
<td>Eliminate</td>
</tr>
</tbody>
</table>

**DOMAIN: Perceived Health Status**

<table>
<thead>
<tr>
<th>Feeling of normalcy</th>
<th>8</th>
<th>37</th>
<th>53</th>
<th>7.0</th>
<th>Retain (patient-important)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of physical health/general health perception</td>
<td>6</td>
<td>27</td>
<td>65</td>
<td>6.8</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Perceived burden (treatment and disease)</td>
<td>6</td>
<td>37</td>
<td>55</td>
<td>6.6</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Risk aversion (including confidence to participate in physical activity/sports/play)</td>
<td>12</td>
<td>33</td>
<td>53</td>
<td>6.2</td>
<td>Eliminate</td>
</tr>
</tbody>
</table>

**DOMAIN: Resource Use**

<table>
<thead>
<tr>
<th>Utilization of health care system</th>
<th>0</th>
<th>29</th>
<th>71</th>
<th>8.0</th>
<th>Retain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost to patient/family</td>
<td>4</td>
<td>29</td>
<td>67</td>
<td>8.0</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Burden of treatment regimen on patient/family</td>
<td>2</td>
<td>18</td>
<td>80</td>
<td>8.4</td>
<td>Retain</td>
</tr>
<tr>
<td>Societal costs</td>
<td>6</td>
<td>31</td>
<td>63</td>
<td>7.0</td>
<td>Retain (patient-important)</td>
</tr>
</tbody>
</table>
SHORT TERM ADVERSE EVENTS - Infusion site reactions

**Infusion Site Reaction**

Mean Rating of Importance

- All voters
- Patients/Advocates
- Clinicians
- US Payers
- International Payers
- Life Science Industry
- Regulators/Funders
- Researchers

**Infusion Site Reaction**

Number of Votes vs Rating of Importance

Stakeholder Group:
- Patients/Advocates
- Clinicians
- US Payers
- International Payers
- Life Science Industry
- Regulators/Funders
- Researchers

**Infusion Site Reaction**

Rating of Importance vs Stakeholder Category

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers
SHORT TERM ADVERSE EVENTS - Liver toxicity
APPENDIX 8
Delphi Round 1 Results

SHORT TERM ADVERSE EVENTS - Immune response to FVIII/FIX (Inhibitor development)
**SHORT TERM ADVERSE EVENTS - Immune response to gene therapy**

**Mean Rating of Importance**

- **All voters**
- **Patients/Advocates**
- **Clinicians**
- **US Payers**
- **International Payers**
- **Life Science Industry**
- **Regulators/Funders**
- **Researchers**

**Number of Votes**

- **Rating of Importance**
  - **1**
  - **2**
  - **3**
  - **4**
  - **5**
  - **6**
  - **7**
  - **8**
  - **9**
  - **No Opinion**

**Stakeholder Category**

- **Patients**
- **Clinicians**
- **US Payers**
- **International Payers/HTA**
- **Life Science Industry**
- **Research Funders/Regulators**
- **Academic Researchers**
APPENDIX 8

Delphi Round 1 Results

SHORT TERM ADVERSE EVENTS - Germline transmission/vector shedding
LONG TERM ADVERSE EVENTS - Vector integration into host genome

Vector Integration Into Host Genome

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Mean Rating of Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All voters</td>
<td>8</td>
</tr>
<tr>
<td>Patient/Advocates</td>
<td>7</td>
</tr>
<tr>
<td>Clinicians</td>
<td>6</td>
</tr>
<tr>
<td>US Payers</td>
<td>5</td>
</tr>
<tr>
<td>International Payers</td>
<td>4</td>
</tr>
<tr>
<td>Life Science Industry</td>
<td>3</td>
</tr>
<tr>
<td>Regulator/Funders</td>
<td>2</td>
</tr>
<tr>
<td>Researchers</td>
<td>1</td>
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</tbody>
</table>

Number of Votes

Rating of Importance

Vector Integration into Host Genome

Stakeholder Category

<table>
<thead>
<tr>
<th>Stakeholder Category</th>
<th>Rating of Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Life Science Industry</td>
</tr>
<tr>
<td>Clinicians</td>
<td>Life Science Industry</td>
</tr>
<tr>
<td>US Payers</td>
<td>Life Science Industry</td>
</tr>
<tr>
<td>International Payers</td>
<td>Life Science Industry</td>
</tr>
<tr>
<td>HTA</td>
<td>Life Science Industry</td>
</tr>
<tr>
<td>Life Science Industry</td>
<td>Life Science Industry</td>
</tr>
<tr>
<td>Regulator/Funders</td>
<td>Life Science Industry</td>
</tr>
<tr>
<td>Researchers</td>
<td>Life Science Industry</td>
</tr>
</tbody>
</table>

APPENDIX 8
Delphi Round 1 Results
LONG TERM ADVERSE EVENTS - Development of other disorders

Development of Other Disorders (auto-immune diseases/cancers/etc.)

Mean Rating of Importance

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>All voters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Patients/Advocates</td>
<td></td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>9</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Clinicians</td>
<td>3</td>
<td>5</td>
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<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Payers</td>
<td>4</td>
<td>7</td>
<td>9</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>International Payers</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life Science/Industry</td>
<td></td>
<td></td>
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<tr>
<td>Regulators/Funders</td>
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<tr>
<td>Researchers</td>
<td></td>
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</tbody>
</table>

Number of Votes

Rating of Importance

Stakeholder Category

LONG TERM ADVERSE EVENTS - Immune response to FVIII/FIX (Inhibitor development)
MORTALITY - Cause of death

Cause of Death

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Cause of Death</th>
<th>Mean Rating of Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All voters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients/Advocates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinicians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Payers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Payers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life Science Industry</td>
<td></td>
<td></td>
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Number of Votes vs Rating of Importance

Stakeholder Category

APPENDIX 8
Delphi Round 1 Results
MORTALITY - Age of death

### Age of Death

#### Stakeholder Group

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#### Stakeholder Category

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Researchers
- Funders/Regulators
- Academic Researchers

### Delphi Round 1 Results

#### Age of Death

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#### Stakeholder Category

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Researchers
- Funders/Regulators
- Academic Researchers
PHYSIOLOGICAL/CLINICAL - Frequency of bleeds

APPENDIX 8
Delphi Round 1 Results
PHYSIOLOGICAL/CLINICAL - Severity of bleeds

Severity of Bleeds

Mean Rating of Importance

Stakeholder Group

Severity of Bleeds

Number of Votes

Rating of Importance

Severity of Bleeds

Rating of Importance

Stakeholder Category

APPENDIX 8
Delphi Round 1 Results
PHYSIOLOGICAL/CLINICAL - Factor activity level

APPENDIX 8
Delphi Round 1 Results
APPENDIX 8
Delphi Round 1 Results

PHYSIOLOGICAL/CLINICAL – Duration of factor expression

Duration of Factor Expression

Number of Votes

Rating of Importance

No Opinion

Rating of Importance

Duration of Factor Expression

Stakeholder Category

Duration of Factor Expression

Mean Rating of Importance

Stakeholder Group

Duration of Factor Expression

Patients
Clinicians
US Payers
International Payers
Life Science Industry
Regulator/Funders
Researchers

All voters
Patients/Advocates
Clinicians
US Payers
International Payers
Life Science Industry
Regulator/Funders
Researchers

No Opinion

Rating of Importance

Stakeholder Category

Duration of Factor Expression

Patients
Clinicians
US Payers
International Payers/HTA
Life Science Industry
Research Funders/Regulators
Academic Researchers

Rating of Importance

Stakeholder Group

Duration of Factor Expression

Patients/Advocates
Clinicians
US Payers
International Payers
Life Science Industry
Regulator/Funders
Researchers

Mean Rating of Importance
PAIN/DISCOMFORT - Acute pain
PAIN/DISCOMFORT - Interference of acute pain on daily life/activities of daily living

Interference of acute pain on daily life

Mean Rating of Importance

Number of Votes

Rating of Importance

Interference of acute pain on daily life

Rating of Importance

Stakeholder Category

Stakeholder Group
PAIN/DISCOMFORT - Chronic pain

**Mean Rating of Importance**

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**Stakeholder Category**

- Patients
- Clinicians
- US Payers
- International Payers
- Life Science Industry
- Regulator/Funders
- Researchers
PAIN/DISCOMFORT - Interference of chronic pain on daily life/activities of daily living

### Interference of Chronic Pain on Daily Life

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### Stakeholder Category

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Regulators/Funders
- Researchers
- Life Science Industry Funders/Regulators
- Regulatory
- Academic Researchers

---

APPENDIX 8
Delphi Round 1 Results
EMOTIONAL FUNCTIONING - Mental health (including anxiety/depression/coping/worry)

**Mean Rating of Importance**

- All voters: 9
- Patients/Advocates: 9
- Clinicians: 7
- US Payers: 9
- International Payers: 5
- Life Science Industry: 7
- Regulators/Funders: 5
- Researchers: 9

**Number of Votes**

- Rating of Importance: 0, 2, 4, 6, 8, 10, 12

**Stakeholder Group**

- Patients/Advocates
- Clinicians
- US Payers
- International Payers
- Life Science Industry
- Regulators/Funders
- Researchers

**Rating of Importance**

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers
- No Opinion
EMOTIONAL FUNCTIONING - Vitality/tiredness/fatigue

APPENDIX 8
Delphi Round 1 Results
**EMOTIONAL FUNCTIONING - Contentment/happiness/elation/exhilaration (mood)**

![Graph showing mean rating of importance for emotional functioning across different stakeholder groups.](image1)

![Bar chart showing number of votes and rating of importance for emotional functioning across different stakeholder groups.](image2)

![Scatter plot showing emotional functioning ratings across different stakeholder categories.](image3)
SOCIAL FUNCTIONING - Identifying as a person with hemophilia (disclosure)
SOCIAL FUNCTIONING - Sense of belonging in a community

Mean Rating of Importance

Stakeholder Group

- All voters
- Patients/Advocates
- Clinicians
- US Payers
- International Payers
- Life Science Industry
- Regulatory/Funders
- Researchers

Number of Votes

Rating of Importance

Stakeholder Category

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers

APPENDIX 8
Delphi Round 1 Results
SOCIAL FUNCTIONING - Feeling of inequality compared to peers

Mean Rating of Importance

Rating of Importance

Number of Votes

Stakeholder Group

Stakeholder Category

Mean Rating of Importance

Rating of Importance

Number of Votes

Stakeholder Category
SOCIAL FUNCTIONING - Romantic relationships

![Graph showing mean rating of importance for Romantic Relationships across different stakeholder groups.](image)

![Graph showing number of votes by rating of importance for Romantic Relationships.](image)

![Scatter plot graph showing rating of importance by stakeholder category.](image)
PHYSICAL FUNCTIONING - Duration, frequency, intensity, and type of physical activity/sports/play

[Charts and graphs showing data on physical activity preferences and ratings by different stakeholder groups.]
PHYSICAL FUNCTIONING - Sexual activity

![Graph showing mean rating of importance for sexual activity by stakeholder group]

![Bar chart showing number of votes for rating of importance]

![Scatter plot showing rating of importance by stakeholder category]

APPENDIX 8
Delphi Round 1 Results
APPENDIX 8
Delphi Round 1 Results

PHYSICAL FUNCTIONING - Mobility

Mean Rating of Importance

Rating of Importance

Stakeholder Category

Stakeholder Group
PHYSICAL FUNCTIONING - Target Joints

Target Joints

Mean Rating of Importance

Number of Votes

Rating of Importance

Target Joints

Stakeholder Group

Number of Votes

Rating of Importance

Stakeholder Category

Stakeholder Category

APPENDIX 8
Delphi Round 1 Results
**PHYSICAL FUNCTIONING - Joint function**

![Graph](image1)

**APPENDIX 8**

Delphi Round 1 Results
ROLE FUNCTIONING- Independence

![Mean Rating of Importance](image1)

![Number of Votes](image2)

![Rating of Importance](image3)
ROLE FUNCTIONING - Education attainment/achievement

Educational Attainment/Achievement

![Graph showing educational attainment and achievement across different stakeholder groups.](image1)

Educational Attainment/Achievement

![Bar chart showing the number of votes and rating of importance for educational attainment/achievement across different stakeholder groups.](image2)

Educational Attainment/Achievement

![Scatter plot showing the rating of importance for educational attainment/achievement across different stakeholder categories.](image3)
ROLE FUNCTIONING - Education choice

Education Choice

Stakeholder Group

Mean Rating of Importance

Education Choice

Rating of Importance

Number of Votes

Stakeholder Category

Education Choice

Stakeholder Category

Rating of Importance
## Role Functioning: Career Choice

### Delphi Round 1 Results

#### Career Choice for Patient

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#### Stakeholder Category

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers
ROLE FUNCTIONING - Work absenteeism

Patient Work Absenteeism

Rating of Importance

Mean Rating of Importance

Stakeholder Group

Patient Work Absenteeism

Number of Votes

Rating of Importance

Stakeholder Category

Patient Work Absenteeism

Rating of Importance

Stakeholder Category
ROLE FUNCTIONING - Career choice for caregiver
ROLE FUNCTIONING - Caregiver absenteeism

**Caregiver Work Absenteeism**

- **Mean Rating of Importance**
  - All voters
  - Patients/Advocates
  - Clinicians
  - US Payers
  - International Payers
  - Regulators/Funders
  - Researchers

- **Number of Votes**
  - Rating of Importance

**Caregiver Work Absenteeism**

- **Rating of Importance**
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - No Opinion

**Stakeholder Category**

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers

**APPENDIX 8**

Delphi Round 1 Results
ROLE FUNCTIONING - Family decisions
## ROLE FUNCTIONING - Childcare

### Stakeholder Group

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### Graphs

- **Graph 1:** Mean Rating of Importance for Childcare (ability to find and maintain).
- **Graph 2:** Number of Votes and Rating of Importance for Childcare (ability to find and maintain).
- **Graph 3:** Scatter plot showing the Rating of Importance for Childcare (ability to find and maintain) across different stakeholder categories.
**ROLE FUNCTIONING - Interaction with children**

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**Number of Votes**

- Rating of Importance: 1, 2, 3, 4, 5, 6, 7, 8, 9, No Opinion

**Stakeholder Category**

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers

**APPENDIX 8**

Delphi Round 1 Results
PERCEIVED HEALTH STATUS - **Feeling of normalcy**

**Feeling of Normalcy**

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<td>2</td>
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<td>8</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>No Opinion</td>
</tr>
</tbody>
</table>
PERCEIVED HEALTH STATUS - Feeling of physical health/general health perception
PERCEIVED HEALTH STATUS - Perceived burden (treatment and disease)
PERCEIVED HEALTH STATUS - Risk aversion

[Graph showing mean rating of importance for risk aversion across different stakeholder groups.]
RESOURCE USE - Utilization of health care system

Utilization of Health Care System

Mean Rating of Importance

Stakeholder Group

Utilization of Health Care System

Number of Votes

Rating of Importance

Utilization of Health Care System

Rating of Importance

Stakeholder Category
RESOURCE USE - Cost on patient/family

Cost to Patient/Family

- Mean Rating of Importance
- Number of Votes
- Rating of Importance

Stakeholder Group:
- All voters
- Patients/Advocates
- Clinicians
- US Payers
- International Payers
- Life Science Industry
- Regulator/Funders
- Researchers

Cost to Patient/Family

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers
RESOURCE USE – Societal Costs

Delphi Round 1 Results

Societal Costs

Mean Rating of Importance

Rating of Importance

Number of Votes

Stakeholder Category

Societal Costs

Rating of Importance

Stakeholder Category

Societal Costs

Rating of Importance

Stakeholder Category
RESOURCES USE - Cost of treatment regimen

Burden of Treatment Regimen on Patient/Family

Rating of Importance

Number of Votes

Burden of Treatment Regimen on Patient/Family

Rating of Importance

Stakeholder Group

Burden of Treatment Regimen Patient/Family

Rating of Importance

Stakeholder Category

APPENDIX 8
Delphi Round 1 Results
coreHEM DELPHI ROUND 2 RESULTS

NOVEMBER 8, 2017
## coreHEM Delphi Round 2 Results

### Percentage of Participants Scoring in Each Category

<table>
<thead>
<tr>
<th>Domain</th>
<th>1-3</th>
<th>4-6</th>
<th>7-9</th>
<th>Patient Average</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological/Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Frequency of bleeds</td>
<td>2.1</td>
<td>4.2</td>
<td>93.8</td>
<td>7.80</td>
<td>Retain</td>
</tr>
<tr>
<td>Factor activity level</td>
<td>6.3</td>
<td>14.6</td>
<td>79.2</td>
<td>8.40</td>
<td>Retain</td>
</tr>
<tr>
<td>Duration of expression</td>
<td>6.3</td>
<td>10.4</td>
<td>83.3</td>
<td>8.60</td>
<td>Retain</td>
</tr>
<tr>
<td><strong>Pain/Discomfort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference of acute pain</td>
<td>10.4</td>
<td>54.2</td>
<td>36.2</td>
<td>5.80</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Interference of chronic pain</td>
<td>2.1</td>
<td>39.6</td>
<td>58.3</td>
<td>6.80</td>
<td>Eliminate</td>
</tr>
<tr>
<td><strong>Emotional Functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
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<td>41.7</td>
<td>50.0</td>
<td>7.60</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Transformational psychological</td>
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<td>37.5</td>
<td>39.6</td>
<td>7.00</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td><strong>Physical Functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, frequency</td>
<td>12.5</td>
<td>47.9</td>
<td>39.6</td>
<td>6.60</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Target joints</td>
<td>4.2</td>
<td>35.4</td>
<td>60.4</td>
<td>8.20</td>
<td>Retain (patient-important)</td>
</tr>
<tr>
<td>Joint function</td>
<td>2.1</td>
<td>45.8</td>
<td>52.1</td>
<td>6.20</td>
<td>Eliminate</td>
</tr>
<tr>
<td><strong>Role Functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Independence</td>
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<td>37.5</td>
<td>50.0</td>
<td>5.60</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Career choice for patient</td>
<td>29.2</td>
<td>43.8</td>
<td>27.1</td>
<td>5.80</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Patient work absenteeism</td>
<td>18.8</td>
<td>27.1</td>
<td>54.2</td>
<td>6.00</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Caregiver career choice</td>
<td>35.4</td>
<td>41.7</td>
<td>22.9</td>
<td>5.40</td>
<td>Eliminate</td>
</tr>
<tr>
<td><strong>Perceived Health Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of normalcy</td>
<td>20.8</td>
<td>47.9</td>
<td>31.3</td>
<td>6.00</td>
<td>Eliminate</td>
</tr>
<tr>
<td>Feeling of physical health</td>
<td>16.7</td>
<td>37.5</td>
<td>45.8</td>
<td>7.00</td>
<td>Retain (patient-important)</td>
</tr>
</tbody>
</table>

APPENDIX 9
Delphi Round 2 Results
### Perceived burden (treatment and disease)

<table>
<thead>
<tr>
<th></th>
<th>16.7</th>
<th>41.7</th>
<th>41.7</th>
<th>6.60</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Risk aversion (including confidence to participate in physical activity/sports/play)

<table>
<thead>
<tr>
<th></th>
<th>20.8</th>
<th>41.7</th>
<th>37.5</th>
<th>7.40</th>
<th>Retain (patient-important)</th>
</tr>
</thead>
</table>

### DOMAIN: Resource Use

<table>
<thead>
<tr>
<th></th>
<th>8.3</th>
<th>31.3</th>
<th>60.4</th>
<th>6.60</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Utilization of health care system

<table>
<thead>
<tr>
<th></th>
<th>8.3</th>
<th>37.5</th>
<th>54.2</th>
<th>7.00</th>
<th>Retain (patient-important)</th>
</tr>
</thead>
</table>

### DOMAIN: Short Term Adverse Events (<12 months)

<table>
<thead>
<tr>
<th></th>
<th>2.1</th>
<th>16.7</th>
<th>81.3</th>
<th>8.20</th>
<th>Retain</th>
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</thead>
</table>

### Liver toxicity

<table>
<thead>
<tr>
<th></th>
<th>16.7</th>
<th>33.3</th>
<th>50.0</th>
<th>6.20</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Germline transmission

<table>
<thead>
<tr>
<th></th>
<th>18.8</th>
<th>47.9</th>
<th>33.3</th>
<th>6.00</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Vector shedding

<table>
<thead>
<tr>
<th></th>
<th>2.1</th>
<th>25.0</th>
<th>72.9</th>
<th>8.40</th>
<th>Retain</th>
</tr>
</thead>
</table>

### Immune response to FVIII/FIX (inhibitor development)

<table>
<thead>
<tr>
<th></th>
<th>0.0</th>
<th>20.8</th>
<th>79.2</th>
<th>8.00</th>
<th>Retain</th>
</tr>
</thead>
</table>

### Immune response to gene therapy

<table>
<thead>
<tr>
<th></th>
<th>10.4</th>
<th>25.0</th>
<th>64.6</th>
<th>5.40</th>
<th>Eliminate</th>
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</thead>
</table>

### Anaphylactic response to treatment

<table>
<thead>
<tr>
<th></th>
<th>2.1</th>
<th>27.1</th>
<th>70.8</th>
<th>6.80</th>
<th>Retain</th>
</tr>
</thead>
</table>

### Thrombosis (blood clots)

<table>
<thead>
<tr>
<th></th>
<th>14.6</th>
<th>50.0</th>
<th>35.4</th>
<th>5.60</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Heart function (cardiac enzymes, ECG, Echo)

### DOMAIN: Long Term Adverse Events (beyond 12 months)

<table>
<thead>
<tr>
<th></th>
<th>8.3</th>
<th>39.6</th>
<th>52.1</th>
<th>7.40</th>
<th>Retain (patient-important)</th>
</tr>
</thead>
</table>

### Vector integration into host genome

<table>
<thead>
<tr>
<th></th>
<th>2.1</th>
<th>25.0</th>
<th>72.9</th>
<th>7.80</th>
<th>Retain</th>
</tr>
</thead>
</table>

### Development of other disorders (auto-immune diseases/cancers/etc.)

<table>
<thead>
<tr>
<th></th>
<th>8.3</th>
<th>25.0</th>
<th>66.7</th>
<th>5.80</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Immune response to FVIII/FIX (inhibitor development)

<table>
<thead>
<tr>
<th></th>
<th>22.9</th>
<th>22.9</th>
<th>54.2</th>
<th>5.80</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Birth defects/childhood malignancy of offspring

<table>
<thead>
<tr>
<th></th>
<th>6.3</th>
<th>35.4</th>
<th>58.3</th>
<th>7.80</th>
<th>Retain (patient-important)</th>
</tr>
</thead>
</table>

### Duration of vector-neutralizing immune response which affects ability to re-administer vector

### DOMAIN: Mortality

<table>
<thead>
<tr>
<th></th>
<th>10.4</th>
<th>18.8</th>
<th>70.8</th>
<th>7.40</th>
<th>Retain</th>
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</thead>
</table>

### Cause of death

<table>
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<tr>
<th></th>
<th>22.9</th>
<th>39.6</th>
<th>37.5</th>
<th>5.60</th>
<th>Eliminate</th>
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</thead>
</table>

### Age of death

<table>
<thead>
<tr>
<th></th>
<th>10.4</th>
<th>31.3</th>
<th>58.3</th>
<th>6.20</th>
<th>Eliminate</th>
</tr>
</thead>
</table>

### Survival time from gene therapy treatment to death
ADVERSE EVENTS AND MORTALITY OUTCOMES

RETAINED

Liver toxicity
Short-term immune response to FVIII/FIX (inhibitor)
Immune response to gene therapy
Thrombosis (blood clots)
Vector integration into host genome
Development of other disorders (auto-immune disease/cancers)
Duration of vector-neutralizing response
Cause of death

ELIMINATED

Germline transmission
Vector shedding
Anaphylactic response to treatment
Heart function (cardiac enzymes, ECG, Echo)
Long-term immune response to FVIII/FIX (inhibitor)
Birth defect/childhood malignancy of offspring
Age of death
Survival time from gene therapy treatment to death
RETAINED
SHORT-TERM ADVERSE EVENTS - Liver toxicity
RETAINED

SHORT-TERM ADVERSE EVENTS - Immune response to FVIII/FIX (Inhibitor development)

Mean Rating of Importance

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Patients/Advocates</th>
<th>Clinicians</th>
<th>US Payers</th>
<th>International Payers</th>
<th>Life Science Industry</th>
<th>Regulators/Funders</th>
<th>Researchers</th>
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<tbody>
<tr>
<td>Mean Rating of Importance</td>
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<td>6</td>
<td>5</td>
<td>8</td>
<td>6</td>
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Number of Votes

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<tr>
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<th>International Payers</th>
<th>Life Science Industry</th>
<th>Regulators/Funders</th>
<th>Researchers</th>
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Rating of Importance

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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Payers</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Regulators/Funders</td>
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APPENDIX 9
Delphi Round 2 Results
RETIRED
SHORT-TERM ADVERSE EVENTS - Immune response to gene therapy
RETAINED
SHORT-TERM ADVERSE EVENTS – Thrombosis (blood clots)
RETAINED
LONG-TERM ADVERSE EVENTS - Vector integration into host genome

Vector Integration into Host Genome

Mean Rating of Importance

Rating of Importance

Number of Votes

Stakeholder Category

APPENDIX 9
Delphi Round 2 Results
RETIRED
LONG-TERM ADVERSE EVENTS - Development of other disorders (auto-immune disease/cancers)
**RETAINED**

**LONG-TERM ADVERSE EVENTS** - *Duration of vector-neutralizing immune response which affects ability to re-administer vector*

---

![Graph showing duration of vector-neutralizing response](image1)

**Mean Rating of Importance**

- Patients/Advocates: 5
- Clinicians: 7
- US Payers: 6
- International Payers: 4
- Regulators/Funders: 2
- Researchers: 1

**Number of Votes**

- Rating of Importance: 1 to 9

---

![Graph showing duration of vector-neutralizing response](image2)

**Stakeholder Category**

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Regulators/Funders
- Academic Researchers

---

![Graph showing duration of vector-neutralizing response](image3)
RETAINED
MORTALITY - Cause of death

APPENDIX 9
Delphi Round 2 Results
ELIMINATED
SHORT-TERM ADVERSE EVENTS – Germline Transmission

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>All voters</th>
<th>Patients/Advocates</th>
<th>Clinicians</th>
<th>US Payers</th>
<th>International Payers</th>
<th>Life Science Industry</th>
<th>Regulators/Funders</th>
<th>Researchers</th>
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<td>6.0</td>
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<table>
<thead>
<tr>
<th>Rating of Importance</th>
<th>Patients</th>
<th>Clinicians</th>
<th>US Payers</th>
<th>International Payers</th>
<th>Life Science Industry</th>
<th>Regulators/Funders</th>
<th>Researchers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Votes</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stakeholder Category</th>
<th>Patients</th>
<th>Clinicians</th>
<th>US Payers</th>
<th>International Payers</th>
<th>Life Science Industry</th>
<th>Regulators/Funders</th>
<th>Researchers</th>
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<tbody>
<tr>
<td>Rating of Importance</td>
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<td>7.0</td>
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<td>7.0</td>
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</tbody>
</table>

APPENDIX 9
Delphi Round 2 Results
ELIMINATED
SHORT-TERM ADVERSE EVENTS – Vector Shedding

APPENDIX 9
Delphi Round 2 Results
ELIMINATED
SHORT-TERM ADVERSE EVENTS – Anaphylactic response to treatment

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Mean Rating of Importance</th>
<th>Number of Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All voters</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Patients/Advocates</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Clinicians</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>US Payers</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>International Payers</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Life Science Industry</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Regulators/Funders</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Researchers</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**Stakeholder Category**
- **Patients**
- **Clinicians**
- **US Payers**
- **International Payers/HTA**
- **Life Science Industry**
- **Research Funders/Regulators**
- **Academic Researchers**

**Rating of Importance**
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9

**APPENDIX 9**
Delphi Round 2 Results
ELIMINATED
SHORT-TERM ADVERSE EVENTS – Heart function (cardiac enzymes, ECG, Echo)
ELIMINATED
LONG-TERM ADVERSE EVENTS – Long-term immune response to FVIII/FIX (Inhibitor development)
ELIMINATED
LONG-TERM ADVERSE EVENTS – Birth defects/childhood malignancy of offspring

APPENDIX 9
Delphi Round 2 Results
ELIMINATED
MORTALITY – Age of death

**Stakeholder Group**

- All rosters
- Patients/Advocates
- Clinicians
- US Payers
- International Payers
- Life Science Industry
- Regulators/Funders
- Researchers

**Stakeholder Category**

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science Industry
- Research Funders/Regulators
- Academic Researchers

**Age of Death**

- Mean Rating of Importance
- Number of Votes

**Rating of Importance**

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9

**APPENDIX 9**
Delphi Round 2 Results
ELIMINATED
MORTALITY – Survival time from gene therapy to death

Survival time from gene therapy treatment to death

Survival time from gene therapy treatment to death

Survival time from gene therapy treatment to death

APPENDIX 9
Delphi Round 2 Results
## OTHER OUTCOMES

### RETAINED
- Frequency of bleeds
- Factor activity level
- Duration of expression
- Chronic pain (frequency/intensity/duration/character)
- Mental health (e.g. anxiety/depression/coping/worry)
- Transformational psychological or emotional impact of a cure
- Feeling of physical health/general health perception
- Risk aversion
- Burden of treatment regimen on patient/family

### ELIMINATED
- Interference of acute pain on daily life/activities of daily living
- Interference of chronic pain on daily life/activities of daily living
- Duration, frequency, intensity, type of physical activity/sports/play
- Joint function
- Independence
- Career choice for patient
- Patient work absenteeism
- Caregiver career choice
- Feeling of normalcy
- Perceived burden (of treatment and disease)
- Utilization of health care system
**RETAINED**

**PHYSIOLOGICAL/CLINICAL - Frequency of bleeds**

![Bar chart showing mean rating of importance for frequency of bleeds across different stakeholder groups.](chart1)

![Line graph showing number of votes for different rating levels of frequency of bleeds.](chart2)

![Scatter plot showing rating of importance against frequency of bleeds across different stakeholder categories.](chart3)
RETAINED
PHYSIOLOGICAL/CLINICAL - Factor activity level

APPENDIX 9
Delphi Round 2 Results
**RETAINED**

**PHYSIOLOGICAL/CLINICAL – Duration of factor expression**

[Graph showing mean rating of importance for different stakeholder groups (patients, advocates, clinicians, US payers, international payers, life science industry, regulatory/funders, researchers).]

[Bar chart showing number of votes by rating of importance for duration of factor expression across different stakeholder groups.]
**RETAINED**

**PAIN/DISCOMFORT - Chronic pain (frequency/intensity/duration/character)**

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Chronic Pain (frequency/intensity/duration/character)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Voters</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
<tr>
<td>Patients/Advocates</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
<tr>
<td>Clinicians</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
<tr>
<td>US Payers</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
<tr>
<td>International Payers</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
<tr>
<td>Life Science/Industry</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
<tr>
<td>Regulators/Funders</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
<tr>
<td>Researchers</td>
<td>9, 7, 5, 3, 1, 9, 7, 5, 3, 1</td>
</tr>
</tbody>
</table>

**Mean Rating of Importance**

**Stakeholder Category**

- Patients
- Clinicians
- US Payers
- International Payers
- Life Science/Industry
- Regulators/Funders
- Researchers

**Number of Votes**

**Rating of Importance**

- Patients
- Clinicians
- US Payers
- International Payers/HTA
- Life Science/Industry
- Research Funders/Regulators
- Academic Researchers

**APPENDIX 9**

Delphi Round 2 Results
RETIRED

EMOTIONAL FUNCTIONING - Mental health (including anxiety/depression/coping/worry)
RETAINED
EMOTIONAL FUNCTIONING - Transformational psychological or emotional impact of experiencing a cure, or that of having made an irreversible treatment decision whatever the outcome.
RETAINED

PHYSICAL FUNCTIONING - Target Joints

Target Joints

Mean Rating of Importance

Stakeholder Group

Number of Votes

Rating of Importance

Target Joints

Rating of Importance

Stakeholder Category

APPENDIX 9
Delphi Round 2 Results
**RETAINED**

**PERCEIVED HEALTH STATUS - Feeling of physical health/general health perception**

![Graph showing the mean rating of importance for Feeling of physical health/general health perception across different stakeholder groups.](image)

![Graph showing the number of votes for each rating of importance for Feeling of physical health/general health perception.](image)

![Graph showing a scatter plot for the rating of importance for Feeling of physical health/general health perception across different stakeholder categories.](image)

**APPENDIX 9**

Delphi Round 2 Results
RETAINED

PERCEIVED HEALTH STATUS - Risk aversion (including confidence to participate in physical activity/sports/play)
RETAINED

RESOURCE USE – Burden of treatment regimen on patient/family

Mean Rating of Importance

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Rating of Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/Advocates</td>
<td>8</td>
</tr>
<tr>
<td>Clinicians</td>
<td>6</td>
</tr>
<tr>
<td>US Payers</td>
<td>7</td>
</tr>
<tr>
<td>International Payers</td>
<td>4</td>
</tr>
<tr>
<td>Life Science Industry</td>
<td>2</td>
</tr>
<tr>
<td>Regulator/Funders</td>
<td>5</td>
</tr>
<tr>
<td>Researchers</td>
<td>9</td>
</tr>
</tbody>
</table>

Number of Votes

Rating of Importance

Stakeholder Category


APPENDIX 9
Delphi Round 2 Results
ELIMINATED
PAIN/DISCOMFORT – Interference of acute pain on daily life/activities of daily living

Interference of Acute Pain on Daily Life/Activities of Daily Living

<table>
<thead>
<tr>
<th>Mean Rating of Importance</th>
<th>Stakeholder Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>All voters</td>
</tr>
<tr>
<td>8</td>
<td>Patients/Advocates</td>
</tr>
<tr>
<td>7</td>
<td>Clinicians</td>
</tr>
<tr>
<td>6</td>
<td>US Payers</td>
</tr>
<tr>
<td>5</td>
<td>International Payers</td>
</tr>
<tr>
<td>4</td>
<td>Life-Science Industry</td>
</tr>
<tr>
<td>3</td>
<td>Regulators/Funders</td>
</tr>
<tr>
<td>2</td>
<td>Researchers</td>
</tr>
</tbody>
</table>

Number of Votes

Rating of Importance

Interference of Acute Pain on Daily Life/Activities of Daily Living

Rating of Importance

Stakeholder Category

Patients
Clinicians
US Payers
International Payers/HTA
Life Science Industry
Research Funders/Regulators
Academic Researchers
ELIMINATED
PAIN/DISCOMFORT – Interference of chronic pain on daily life/activities of daily living

Interference of Chronic Pain on Daily Life/Activities of Daily Living

Mean Rating of Importance

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Rating of Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All voters</td>
<td>7</td>
</tr>
<tr>
<td>Patients/Advocates</td>
<td>8</td>
</tr>
<tr>
<td>Clinicians</td>
<td>6</td>
</tr>
<tr>
<td>US Payers</td>
<td>5</td>
</tr>
<tr>
<td>International Payers</td>
<td>4</td>
</tr>
<tr>
<td>Life Science Industry</td>
<td>3</td>
</tr>
<tr>
<td>Regulators/Funders</td>
<td>2</td>
</tr>
<tr>
<td>Researchers</td>
<td>1</td>
</tr>
</tbody>
</table>

Number of Votes

Rating of Importance

Interference of Chronic Pain on Daily Life/Activities of Daily Living

Patients
Clinicians
US Payers
International Payers/HTA
Life Science Industry
Research Funders/Regulators
Academic Researchers

APPENDIX 9
Delphi Round 2 Results
ELIMINATED

PHYSICAL FUNCTIONING – Duration, frequency, intensity, type of physical activity/sports/play
ELIMINATED

PHYSICAL FUNCTIONING – Joint Function
ELIMINATED
ROLE FUNCTIONING – Independence

Stakeholder Group

Mean Rating of Importance

Stakeholder Category

Rating of Importance

Number of Votes

Stakeholder Category

Rating of Importance
ELIMINATED

ROLE FUNCTIONING – Career choice for patient (location, type of work, taking a job because it supplies insurance)
ELIMINATED
ROLE FUNCTIONING – Patient work absenteeism
**ELIMINATED**

**ROLE FUNCTIONING** – Caregiver career choice (location, type of work, taking a job because it supplies insurance)
ELIMINATED

PERCEIVED HEALTH STATUS – Feeling of normalcy

![Mean Rating of Importance for Stakeholder Groups](chart1)

![Number of Votes and Rating of Importance](chart2)

![Rating of Importance by Stakeholder Category](chart3)
ELIMINATED

PERCEIVED HEALTH STATUS – Perceived burden (of treatment and disease)

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Perceived burden (treatment and disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/Advocates</td>
<td>1</td>
</tr>
<tr>
<td>Clinicians</td>
<td>2</td>
</tr>
<tr>
<td>US Payers</td>
<td>3</td>
</tr>
<tr>
<td>International Payers</td>
<td>4</td>
</tr>
<tr>
<td>Life Science Industry</td>
<td>5</td>
</tr>
<tr>
<td>Regulators/Funders</td>
<td>6</td>
</tr>
<tr>
<td>Researchers</td>
<td>7</td>
</tr>
</tbody>
</table>

Mean Rating of Importance

<table>
<thead>
<tr>
<th>Rating of Importance</th>
<th>Number of Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
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<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
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<td>5</td>
<td>0</td>
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<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

APPENDIX 9
Delphi Round 2 Results
**ELIMINATED**

**RESOURCE USE—Utilization of healthcare system**

![Utilization of healthcare system](image1)

![Utilization of healthcare system](image2)

![Utilization of healthcare system](image3)
APPENDIX TEN - EXAMPLE PERSONALIZED FEEDBACK

PARTICIPANT NAME: ------------------------
The first column shows your rating for each outcome. A **green** background indicates that your rating was lower than the average rating for your stakeholder category, while a **red** background indicates that your rating was higher than the average rating for your stakeholder group.

<table>
<thead>
<tr>
<th>Your rating</th>
<th>All Voters</th>
<th>Patients/ Patient Advocates</th>
<th>Clinicians</th>
<th>US Payers</th>
<th>International Payers</th>
<th>Life Science Industry</th>
<th>Regulators and Research Funders</th>
<th>Researchers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHORT TERM ADVERSE EVENTS (UP TO 12 MONTHS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>9</td>
<td>4.60</td>
<td>4.40</td>
<td>5.00</td>
<td>5.50</td>
<td>4.00</td>
<td>4.75</td>
<td>4.57</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>9</td>
<td>8.23</td>
<td>8.60</td>
<td>8.80</td>
<td>8.13</td>
<td>7.83</td>
<td>8.17</td>
<td>8.29</td>
</tr>
<tr>
<td>Immune response to FVIII/FIX (inhibitor development)</td>
<td>9</td>
<td>8.33</td>
<td>9.00</td>
<td>9.00</td>
<td>8.50</td>
<td>7.33</td>
<td>8.33</td>
<td>8.14</td>
</tr>
<tr>
<td>Immune response to gene therapy</td>
<td>9</td>
<td>7.96</td>
<td>8.20</td>
<td>8.40</td>
<td>8.25</td>
<td>7.83</td>
<td>7.92</td>
<td>7.43</td>
</tr>
<tr>
<td>Germline transmission (vector shedding)</td>
<td>9</td>
<td>6.87</td>
<td>8.00</td>
<td>6.80</td>
<td>7.13</td>
<td>6.00</td>
<td>6.67</td>
<td>7.50</td>
</tr>
<tr>
<td><strong>LONG TERM ADVERSE EVENTS (BEYOND 12 MONTHS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vector integration into host genome</td>
<td>3</td>
<td>7.37</td>
<td>8.00</td>
<td>6.80</td>
<td>8.00</td>
<td>6.80</td>
<td>6.75</td>
<td>7.50</td>
</tr>
<tr>
<td>Development of other disorders (auto-immune diseases/cancers/etc.)</td>
<td>6</td>
<td>8.08</td>
<td>8.20</td>
<td>7.60</td>
<td>9.00</td>
<td>8.33</td>
<td>8.17</td>
<td>7.14</td>
</tr>
<tr>
<td>Immune response to FVIII/FIX (inhibitor development)</td>
<td>6</td>
<td>8.17</td>
<td>9.00</td>
<td>8.60</td>
<td>8.50</td>
<td>7.33</td>
<td>7.92</td>
<td>7.86</td>
</tr>
<tr>
<td><strong>MORTALITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td>9</td>
<td>8.13</td>
<td>7.40</td>
<td>9.00</td>
<td>8.63</td>
<td>8.00</td>
<td>7.45</td>
<td>8.00</td>
</tr>
<tr>
<td>Age of death</td>
<td>9</td>
<td>6.74</td>
<td>5.40</td>
<td>6.60</td>
<td>7.50</td>
<td>7.17</td>
<td>6.00</td>
<td>6.86</td>
</tr>
<tr>
<td><strong>PHYSIOLOGICAL/CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of bleeds</td>
<td>9</td>
<td>8.27</td>
<td>7.60</td>
<td>8.00</td>
<td>9.00</td>
<td>7.86</td>
<td>8.25</td>
<td>8.57</td>
</tr>
<tr>
<td>Severity of bleeds</td>
<td>5</td>
<td>7.55</td>
<td>5.80</td>
<td>7.00</td>
<td>8.88</td>
<td>8.14</td>
<td>6.83</td>
<td>8.00</td>
</tr>
<tr>
<td>Factor activity level</td>
<td>9</td>
<td>7.96</td>
<td>8.80</td>
<td>9.00</td>
<td>8.13</td>
<td>6.29</td>
<td>8.33</td>
<td>7.86</td>
</tr>
<tr>
<td>Duration of expression</td>
<td>9</td>
<td>8.13</td>
<td>8.80</td>
<td>9.00</td>
<td>8.25</td>
<td>7.17</td>
<td>8.33</td>
<td>7.86</td>
</tr>
<tr>
<td><strong>PAIN/DISCOMFORT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pain (including frequency/intensity/duration/character)</td>
<td>5</td>
<td>6.31</td>
<td>7.00</td>
<td>6.80</td>
<td>6.00</td>
<td>6.83</td>
<td>5.42</td>
<td>6.57</td>
</tr>
<tr>
<td>Interference of acute pain on daily life/activities of daily living</td>
<td>8</td>
<td>6.83</td>
<td>6.60</td>
<td>7.00</td>
<td>6.63</td>
<td>7.67</td>
<td>6.50</td>
<td>6.86</td>
</tr>
<tr>
<td>Chronic pain (including frequency/intensity/duration/character)</td>
<td>5</td>
<td>6.67</td>
<td>7.60</td>
<td>6.80</td>
<td>6.63</td>
<td>6.83</td>
<td>5.75</td>
<td>6.57</td>
</tr>
</tbody>
</table>
APPENDIX ELEVEN – WORKSHEET USED AT IN-PERSON MEETING FOR DISCUSSION ON MEASUREMENTS/INSTRUMENTS

Table number: ____________________

Outcome discussed: ____________________

With your group, discuss the following parameters related to your outcome:

1. What is your group’s definition of the outcome (e.g. what is this outcome trying to measure, and does it measure only one thing, or are there several results/ideas that fit into this outcome)?

2. What type of measurement/instrument would be ideal to measure this outcome (for example, a survey a patient fills out, a clinical assessment a doctor performs, a laboratory test, etc., or a combination of some of these)?

3. Feasibility:
   a. How long should/does it take to measure this outcome? How long is too long?
   b. What is/should be the patient/clinician burden associated with this measure?

4. Should this outcome be measured using a generic instrument/measure, or a hemophilia-specific instrument/measure? Why?

5. What are some of the measurement metrics that your group have discussed (such as when should the outcome be measured, how often it should be measured, how it should be reported?)
**Instruments/Measurements Currently Being Used**

1. Are there any instruments/measurements currently being used that could capture this outcome?

   a. If instruments exist, are they adequate/appropriate for use with gene therapy? If applicable, consider whether existing instruments capture the difference between gene therapy and current standard of care (are they sensitive enough?).

   b. If instruments DO NOT exist, what would a novel measure be? How would it fit the ideal instrument described in #2 above?

2. What are the pros and cons of the instruments/measurements listed above?

3. Do any of the instruments/measurements above capture the outcome in the way the group has been discussing? How? If not, could things about the instrument/measurement be altered to match what has been discussed above?

---

**Instruments/Measurements in Other Therapeutic Fields**

1. What other therapeutic areas may also measure this outcome?
2. **Name any specific instruments/measurements in other therapeutic areas that you are aware of that may capture the same idea/outcome we are trying to assess with this measure?**
### APPENDIX TWELVE- DELPHI TIMELINE AND PARTICIPATION RATES

<table>
<thead>
<tr>
<th>coreHEM Delphi Timeline and Participation Rates</th>
<th>Date Sent</th>
<th>Cut-off Date for Response</th>
<th>Type of Voting on Outcomes</th>
<th>Additional Tasks</th>
<th>Free text comments</th>
<th># Voters Completed (Participation Rate)</th>
<th># Outcomes to Rate</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Round 1</strong></td>
<td>September 8th</td>
<td>September 22nd</td>
<td>Rate importance on scale from 1-9</td>
<td>Rank domains</td>
<td>✓</td>
<td>49 (100%)</td>
<td>48</td>
<td>-11 new outcomes were proposed by participants</td>
</tr>
<tr>
<td><strong>Round 1A (Sub-Survey)</strong></td>
<td>October 11th</td>
<td>October 18th</td>
<td>Agree/Disagree with outcomes for “Retention” and “Elimination”</td>
<td>Vote to include or not include new outcomes</td>
<td>✓</td>
<td>36 (73%)</td>
<td>59</td>
<td>-Re-vote on 48 from Round 1 plus 11 new outcomes</td>
</tr>
<tr>
<td><strong>Round 2</strong></td>
<td>October 24th</td>
<td>November 5th</td>
<td>Rate importance on scale from 1-9</td>
<td>List top 5 outcomes and top 5 adverse events</td>
<td></td>
<td>48 (98%)</td>
<td>37</td>
<td>-3 outcomes reached high consensus and were directly included in the core set; -Adverse events separated and 8 adverse events with high consensus were moved to the coreHEM list of important adverse events</td>
</tr>
<tr>
<td><strong>Advisory Vote for Round 3 (at meeting)</strong></td>
<td>November 15th</td>
<td>November 19th</td>
<td>Rate importance on scale from 1-9</td>
<td>Vote to combine selected outcome based on deliberations at meeting</td>
<td></td>
<td>42 (86%)</td>
<td>9</td>
<td>-3 questions about combining outcomes; one combination was accepted</td>
</tr>
<tr>
<td><strong>Round 3</strong></td>
<td>November 20th</td>
<td>December 2nd</td>
<td>Rate importance on scale 1-9; confirm or change vote from Advisory Vote at the in-person meeting</td>
<td>--</td>
<td></td>
<td>48 (98%)</td>
<td>8</td>
<td>-3 additional outcomes included in the core set</td>
</tr>
</tbody>
</table>
## APPENDIX THIRTEEN – DELPHI ROUND THREE RESULTS

<table>
<thead>
<tr>
<th>coreHEM Delphi Final Round Results</th>
<th>Percentage of Participants Scoring in Each Category</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-3</td>
<td>4-6</td>
</tr>
<tr>
<td><strong>DOMAIN: Pain/Discomfort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pain (including frequency/intensity/duration/character)</td>
<td>0.0</td>
<td>20.8</td>
</tr>
<tr>
<td><strong>DOMAIN: Emotional Functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Health Condition (<strong>new combined outcome</strong>)</td>
<td>6.25</td>
<td>22.9</td>
</tr>
<tr>
<td><strong>DOMAIN: Physical Functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, frequency, intensity and type of physical activity/sports/play</td>
<td>4.7</td>
<td>31.3</td>
</tr>
<tr>
<td>Target joints</td>
<td>10.4</td>
<td>47.9</td>
</tr>
<tr>
<td><strong>DOMAIN: Perceived Health Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of physical health/general health perception</td>
<td>10.4</td>
<td>37.5</td>
</tr>
<tr>
<td>Risk aversion (including confidence to participate in physical activity/sports/play)</td>
<td>31.3</td>
<td>47.9</td>
</tr>
<tr>
<td><strong>DOMAIN: Resource Use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utilization of health care system (direct costs)</td>
<td>6.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Burden of treatment regimen on patient/family (indirect costs)</td>
<td>8.3</td>
<td>54.2</td>
</tr>
</tbody>
</table>
## APPENDIX FOURTEEN – CORE OUTCOME SET DEFINITIONS

<table>
<thead>
<tr>
<th>coreHEM Outcomes</th>
<th>Outcome</th>
<th>Domain</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Outcome Set</td>
<td>Frequency of bleeds</td>
<td>Physiological/Clinical</td>
<td>How often a person with hemophilia experiences a bleed (e.g. the annualized bleeding rate)</td>
</tr>
<tr>
<td></td>
<td>Factor activity level</td>
<td>Physiological/Clinical</td>
<td>The amount of factor VIII (Hemophilia A) or factor IX (Hemophilia B) activity measured in the blood.</td>
</tr>
<tr>
<td></td>
<td>Duration of expression</td>
<td>Physiological/Clinical</td>
<td>How long after the gene therapy treatment the expression of FVIII or FIX lasts; the length of time that the heightened factor activity level is maintained.</td>
</tr>
<tr>
<td></td>
<td>Chronic pain</td>
<td>Pain/Discomfort</td>
<td>The presence of persistent pain that can last for a long time, such as over months or longer, including the frequency, intensity, duration and character of the pain.</td>
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<tr>
<td></td>
<td>Utilization of healthcare system (direct costs)</td>
<td>Resource Use</td>
<td>Measures of uses and related costs incurred from the need for healthcare and treatment associated with hemophilia, including days in hospital, hospital readmissions, emergency room visits, bleeds, inhibitors, factor VIII/IX infusion, bypass agent use, pain and other medications, home health/homecare services, specialist consultations, and professional caregivers</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
<td>Emotional Functioning</td>
<td>A person’s psychological status; whether a person has positive feelings (joy, excitement, ease of living, new outlook on life) or negative feelings (anxiety, depression, fear, uncertainty) associated with having hemophilia or the treatment of hemophilia. Can be related to the act of making an irreversible treatment decision or the effect of the gene therapy in curing one's hemophilia.</td>
</tr>
<tr>
<td>Important Adverse Events</td>
<td>Liver toxicity</td>
<td>Short-term Adverse Events</td>
<td>Measured by elevated levels of liver enzymes in the blood (a possible response to the gene therapy targeted at the liver cells, as the liver is where clotting factor is produced).</td>
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<td></td>
<td>Short-term immune response to FVIII/FIX (inhibitor development)</td>
<td>Short-term Adverse Events</td>
<td>After the gene for the missing clotting factor (FVIII or FIX) is inserted into the cell and starts producing the missing protein, the body may initiate an immune response (inhibitors) against FVIII or FIX, (patients with inhibitors may stop responding to factor VIII and IX and require special and expensive treatments for bleeds).</td>
</tr>
<tr>
<td></td>
<td>Immune response to gene therapy (cytotoxic)</td>
<td>Short-term Adverse Events</td>
<td>When gene therapy is administered, the patient’s body may mount an immune response against elements of the product injected (antibodies against the viral vector, gene therapy vector capsid-specific T cells, etc.).</td>
</tr>
<tr>
<td></td>
<td>Thrombosis</td>
<td>Short-term Adverse Events</td>
<td>The formation of a blood clot, which can obstruct the flow in a blood vessel.</td>
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<tr>
<td></td>
<td>Development of other disorders</td>
<td>Long-term Adverse Events</td>
<td>Development of serious medical problems associated with gene therapy such as cancer.</td>
</tr>
<tr>
<td></td>
<td>Vector integration into host genome</td>
<td>Long-term Adverse Events</td>
<td>An adverse form of vector integration, such as the DNA of the virus vector used to deliver the gene therapy to the cells becomes integrated into the human cells, potentially altering the expression, and potentially the function, of the genes or causing other genes to become inactivated.</td>
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<tr>
<td></td>
<td>Duration of vector-neutralizing response</td>
<td>Long-term Adverse Events</td>
<td>The length of time a patient’s body maintains an immune response to the viral vector. Gene therapy uses a viral vector to deliver the necessary clotting factor DNA to the cells. The body develops an immune response against the viral vector, therefore preventing any re-administration of gene therapy using the same viral vector because the immune system would attack the gene therapy.</td>
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<tr>
<td></td>
<td>Cause of death</td>
<td>Mortality</td>
<td>The determination of the reason for a patient’s death.</td>
</tr>
<tr>
<td>Additional Outcomes</td>
<td>Duration/frequency/type of physical activity/sport/play</td>
<td>Physical Functioning</td>
<td>Characterization of the physical activity that a person can comfortably do, how long and how often it can be done, and how much effort it requires (physical activity may include exercise, or general activities that have a physical element such as gardening, dancing, cleaning)</td>
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<tr>
<td></td>
<td>Feeling of physical health/general health perception</td>
<td>Perceived Health Status</td>
<td>How a person with hemophilia feels about their overall state of health.</td>
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</table>
APPENDIX FIFTEEN – RECOGNITION OF THE CORE OUTCOME SET

The Institute for Clinical and Economic Review (ICER), the Swedish Agency for Health Technology Assessment and Assessment of Social Service (SBU), the Canadian Agency for Drugs and Technologies in Health (CADTH), Blue Cross Blue Shield Association (BCBSA), and SharpRx Pharmaceutical Consultation Services have recognized the coreHEM core outcome set as follows:

- Our organization participated in the coreHEM project, with the goal of identifying a core set of outcomes for use in future clinical studies of gene therapy in hemophilia.
- We will consider this recommended core outcomes set, along with other relevant outcomes, in future assessments of gene therapies for hemophilia.
- The choice of outcomes in clinical studies is one of many factors that are considered in assessments done by our organization.

The Institute for Clinical and Economic Review (ICER), the Swedish Agency for Health Technology Assessment and Assessment of Social Service (SBU), Blue Cross Blue Shield Association (BCBSA), and SharpRx Pharmaceutical Consultation Services additionally agree:

- We would encourage product developers and other researchers to consider this recommended core outcomes set when developing study protocols for future clinical trials, registries and other studies.