

## **Comparing Outcomes Across Clinical Trials: Core Outcome Set for Hemophilia Gene Therapy as a Model for Other Diseases**

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Recent successes in gene therapy trials hold great promise for people living with hemophilia. Unlike other treatments, gene therapy can replace or repair the missing and abnormal genes, potentially curing the disease; if licensed, these therapies could be life-changing. As phase 3 efficacy trials are set to begin, we are at a pivotal time to consider whether outcomes collected in these studies can be selected to more fully capture the effects of a gene therapy that are most important to patients.

There is an urgent need to reassess the outcomes that have been used for clinical trials in hemophilia to determine if they are suitable for future evaluations of potentially curative technologies such as gene therapy. In response, CoreHEM, a joint initiative of the Green Park Collaborative (a program of the Center for Medical Technology Policy [CMTP]), the National Hemophilia Foundation (NHF), and McMaster University, will bring together experts and stakeholders to seek consensus on a “core set of outcomes” for evaluation of hemophilia gene therapies; i.e., a minimum set of outcomes that should be measured and reported in all clinical trials of a specific condition.

Hemophilia is an inherited bleeding disorder, caused by a deficiency of coagulation factor VIII (hemophilia A) and IX (hemophilia B). People living with hemophilia may have bleeding into the joints, soft tissue and muscles. This bleeding can cause short-term problems, such as intense pain usually and severely limiting activity, and long-term complications such as chronic pain, joint destruction, and eventually disability. Currently, the gold standard of treatment is lifelong recurrent intravenous injection of the missing protein, either to prevent or treat bleeds, which is burdensome and heavily impacts a patient’s life. For people with severe hemophilia, keeping up with the treatment regimen and avoiding bleeding episodes dominates daily routines and decisions for work and school schedules, travel, selection of recreational activities, and other issues of everyday life. Existing therapies control the disorder, but they are far from ideal. The disorder, and treating it, continues to impose a heavy toll on quality of life.

CoreHEM aims to identify which additional or alternative outcomes should be measured to properly compare these novel therapies with currently available treatments and each other. For example, in protein replacement therapy, a widely-adopted outcome measure is the annualized bleeding rate (ABR), reflecting how many times per year a patient had a significant bleed (events associated with the trough periods of intermittent protein replacement). Since ABR is already close to zero with current treatment,

changes in the ABR would no longer be as significant as they once were and thus not sensitive enough to serve as a single endpoint measure. Gene therapy has the potential to maintain clotting factor production at higher and near normal levels, an unprecedented result in this field, possibly increasing the capacity of people living with hemophilia to function at the same level as individuals without hemophilia. How will this be captured? How should the value added for patients be measured? Will new outcomes be needed to assess novel side effects or other aspects of gene therapy? Another aspect to consider is the fact that gene therapy involves altering a part of the patients' genetics, and while it configures a definitive cure, it is also an irreversible choice. The consequences on the psychological and social functioning of patients undergoing this treatment are still unknown.

CoreHEM seeks to address these questions through a multi-stakeholder consensus process, with the goal of agreeing on a standard approach to consistent collection and reporting of relevant and well-specified outcomes, with an emphasis on outcomes deemed most important by the hemophilia community.

Seeking a core outcome set (as opposed to more generic recommendations for outcomes) is important because disparities in outcome utilization are increasingly recognized as a challenge in clinical research. Lacking a harmonized set of outcomes to include when drafting clinical study protocols, clinical researchers are more likely to collect and report a wide variety of outcomes that may or may not reflect the most important benefits and risks to patients. Their choices may be based on several factors such as funding, time, availability of clinical and laboratory resources, interest to the investigators, or a desire to highlight a particular benefit of the intervention. Even studies that appear to collect the same outcome measures may report the results differently. For example, one study may report a mean level of a blood protein while another reports the percentage of participants who have reached a certain (perhaps arbitrary) threshold of that blood protein. Though the authors of both studies may state they had the same primary outcome, comparing or combining results would be difficult. In hemophilia research, the ability to combine data could be crucial in reaching the critical mass needed to effectively compare gene therapy to current treatment modalities.

These types of outcome mismatches contribute to one form of "research waste" in which data from certain studies cannot be included in meta-analyses of systematic reviews because the outcome definition, timing of outcome collection, or measurement instrument was not consistent with other trials, or because the outcome was not collected or reported at all. Designers of trials may not consider implications for systematic reviews, health technology assessment, clinical guidelines and other forms of research synthesis when designing individual trials. This variability of outcomes across clinical trials for the same disease or of the same intervention makes it difficult to compare or combine results across studies, and can lead to uncertainty about which treatment is best for patients. Development of a core outcome set is therefore an important step to help address challenges associated with heterogeneity of outcome collection and reporting.

To develop a core outcome set for gene therapy incorporating the values and priorities of the hemophilia community and other stakeholders, CoreHEM will be guided by the methods promulgated by the Core Outcomes Measures in Effectiveness in Trials (COMET) Initiative and similar methods used to develop core outcome sets. The project team will review literature to identify outcomes and related measurement instruments currently used in hemophilia and gene therapy research. Key informant interviews will provide insight on novel outcomes of interest for hemophilia gene therapy treatment.

From these sources, the team will compile a candidate list of outcomes to be assessed and prioritized using a modified Delphi method, an iterative, survey-based approach to consensus-building. Two rounds of online Delphi voting will be used to condense and prioritize the outcome list and facilitate agreement in the measurement and reporting of each selected outcome. The process will then culminate in an in-person consensus meeting, which will include a final round of Delphi voting to confirm the recommended core outcome set.

The CoreHEM team has assembled a diverse stakeholder group to participate in the Delphi. The voting panel will be composed of a balanced mix of patients, clinicians, hemophilia researchers, US and international payers and HTA groups, and government organizations. The initiative also has the support and participation of companies currently developing gene therapies for hemophilia space.

Through these efforts, CoreHEM participants have the opportunity to shape the future of hemophilia research in a way that prioritizes patient-relevant outcomes. A key constituency in CoreHEM, patients are well represented as voting members of the Delphi panel. They will provide insight as to which outcomes are meaningful to them, and within an outcome, what level of change or improvement would affect their lives as patients living with hemophilia. Patients' priorities and insights on the risks, benefits, and value of an intervention are likely to differ in important ways from those of other stakeholders, and have historically been accorded too little weight in the selection of outcomes in clinical research. While many reasons exist for why clinical trial outcomes fail to translate into benefits for patients, including the patient voice in CoreHEM will carry through to future clinical trials that adopt the final consensus core set.

In addition, this initiative may serve as a model for developing core outcomes sets for gene therapies in other diseases. Hemophilia is pioneering the field, but is likely to be followed by many other diseases. Breakthrough successes in multiple therapeutic areas with gene therapy will present new opportunities for redefining new sets of outcomes reflecting possible superiority over conventional therapies in clinical benefits, reduced harms, and improved quality of life. The added value for patients of curing disease, rather than simply managing it, must be defined in measurable ways. The CoreHEM team expects this to be true for hemophilia and for many other conditions in the future.

With a new era in hemophilia research, it is time to develop a core outcome set reflecting the priorities of the hemophilia community, thus serving as a relevant guide to future clinical research in hemophilia gene therapy, and allowing for more effective and patient relevant comparisons across trials, to learn more efficiently, and avoid research waste.

*References available upon request.*

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