Health Technology Assessment for Gene Therapies: Are Our Methods Fit for Purpose? — A Patient Perspective

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## Disclosures for: Mark W. Skinner

<table>
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<tr>
<th>CONFLICT</th>
<th>DISCLOSURES (If potential for conflict of interest exists)</th>
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<tbody>
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<td>Institution received research support for the PROBE study, an independent investigator-initiated research project</td>
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<td><strong>DIRECTOR, OFFICER, EMPLOYEE</strong></td>
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<tr>
<td><strong>CONSULTANT</strong></td>
<td>NHF</td>
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“The safest and most effective drug that no one can afford, is not available or arrives too late is of no benefit to a patient.”

Real world evidence (RWE) is transforming the process through which health care payers make coverage and formulary decisions⁠¹

Standards for prospective RWE analyses ... to ensure evidence generated is both rigorous and fully informed by what matters most to patients⁠¹

Defining and measuring health outcomes with greater direct patient engagement is vital for assessing value of novel technologies⁠²

Improved patient involvement can drive the development of innovative medicines that deliver more relevant and impactful patient outcomes⁠²

• Historically, outcomes measurement has focused on clinical status and left out functional status

• Survival and “objective” outcomes that are readily captured by laboratory tests

• What matters to patients are outcomes that encompass the whole cycle of care

• Survival, functional status, quality of life
“One reason ICER and some drug companies disagree on a drug’s fair price is the difficulty in capturing the drug’s social benefits, such as a patient’s increased work productivity, or family members who don’t have to be full-time caregivers anymore.”¹

“In assessing the value of treatments for hemophilia, payers should be aware of important benefits and contextual considerations that are not typically captured in cost-effectiveness analyses.”²

¹Xconomy Boston 4/23/19 Can We Afford to Be Cured? A Conversation With ICER's Steve Pearson
²ICER report reviewing clinical effectiveness and value of emicizumab for patients with hemophilia A and inhibitors to factor VIII – April 2018
Robust Patient-Centered Evidence Essential

Consistent collection and timely reporting of relevant well-specified Patient Reported Outcomes

**Aims**
- Timely collection and reporting of relevant outcomes

**Uses**
- Market Authorization
- Product Registration
- Advocacy
- Insurance Coverage
- Ministry of Health

Increases predictability and consistency of payer and Health Technology Assessment decisions

Longitudinal data collection on outcomes meaningful to the quality of life and functioning of patients

Shared Decision Making
Clinical Applications
Benchmarking Progress
Promoting Health Equity
Reporting outcomes patients deem relevant

- Pain - chronic/acute, interference, occurrence
- Independence - limitations, impact on activities of daily living
- Education - attainment, attendance
- Employment - duration, underemployment, attendance
- Family life - marriage, children
- Mobility - assistance required, impairment
- Current health status (EQ-5D-5L and VAS)

VAS, EuroQol visual analog scale
A “core outcome set” to measure, demonstrate and differentiate the effectiveness and value of gene therapy

<table>
<thead>
<tr>
<th>Domain</th>
<th>Outcome</th>
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<tr>
<td>Physiological/Clinical</td>
<td>• Frequency of bleeds</td>
</tr>
<tr>
<td></td>
<td>• Factor activity level</td>
</tr>
<tr>
<td></td>
<td>• Duration of expression</td>
</tr>
<tr>
<td>Pain/Discomfort</td>
<td>• Chronic pain</td>
</tr>
<tr>
<td>Resource Use</td>
<td>• Utilization of healthcare system (direct costs)</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>• Mental health</td>
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| Additional Outcomes  | Duration/frequency/type of physical activity/sport/play                 |
|                      | Physical health/general health perception                                |

| Adverse Events       | Short-Term, Long-Term, Mortality                                         |

Visit Poster Code PCR45 - Development of a Patient-reported Outcome Measure (PROM) to Fully Report a Proposed Core Outcome Set

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
Is the World Ready for Gene Therapy?

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Contents

SUPPLEMENT ARTICLES

5 Is the world ready for gene therapy?
L. P. Garrison and D. Kleinerman

9 A preliminary application of a haemophilia value framework to emerging therapies in haemophilia

19 Health technology assessment for gene therapies in haemophilia
J. O'Hara and P. J. Neumann on behalf of the International Haemophilia Access Strategy Council

27 Alternative payment models for durable and potentially curative therapies: The case of gene therapy for haemophilia A
C. Goodman, E. Berntorp and O. Wong on behalf of the International Haemophilia Access Strategy Council

35 Preparing for tomorrow: Defining a future agenda
B. O'Mahony, O. Wong, H. Eichler, P. Neumann, K. Sten Carlson and D. Noone

Is the World Ready for Gene Therapy?

KEY POINTS OF CONSIDERATION

• It is important for HTA bodies to consider the limitations to conduct randomized controlled trials for gene therapy and to consider intra-patient data as evidence of comparative effectiveness.
• Given the uncertainties around the long-term gene therapy use, clinical trial data should be extrapolated ~10 years, using scenarios that consider different durations of effect.
• The major value drivers in a model, in addition to drug pricing itself, will be based on assumptions about duration of effect and savings/cost offsets from reduced use of replacement therapy.
• Assessment methodologies and modelling configurations need to evolve to fully capture the value of gene therapy, including patient meaningful outcomes, in a validated and quantitative fashion.
• Regardless of payment system archetype, the intersection between NGOs, the clinical community’s voice, HTA willingness to collaborate, and alignment with regulatory acceptance of benefit is critical.

Is the World Ready for Gene Therapy?

KEY POINTS OF CONSIDERATION

• With the emergence of high-cost, paradigm changing treatments across multiple areas of medicine, we, the haemophilia community, need to be equipped to meet the growing demands for more rigorous evidence-based value assessments using the tools expected by assessors.

• The traditional access toolbox needs to evolve to meet the paradigm shift in treatment options. Value can no longer be defined by annualized bleed rates alone. To realize the full impact of new therapies, we need to utilize tools, such as a value framework, to organize evidence, identify data gaps, and assess patient-defined, meaningful outcomes across a multi-faceted dimension.

• The haemophilia value framework is an effective tool for organizing the available evidence and identifying gaps in the evidence. This can be used for assessing the value of emerging therapies in haemophilia utilizing data generated through randomized clinical trials and real world evidence generation.

• This is a call for incorporating the Value Framework into official submissions to authorities, as it captures a broader range of outcomes, including patient meaningful outcomes, in ways that better assess the potential benefits of new therapies.
### Haemophilia Value Framework Integrated with coreHEM

<table>
<thead>
<tr>
<th>Tier 1: Health Status Achieved or Retained</th>
<th>Statistical life expectancy</th>
<th>Overall survival</th>
<th>Function/activity</th>
<th>Bleeding</th>
<th>Serious bleeds</th>
<th>Pain</th>
<th>Musculoskeletal complications</th>
<th>HRQOL</th>
<th>“Cure”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 2: Process of Recovery</td>
<td>Time to initial diagnosis</td>
<td>Time to onset of treatment</td>
<td>Time to recover from a bleeding episode</td>
<td>Time missed at education or employment for treatment</td>
<td>Development of inhibitors</td>
<td>Pathogen transmission</td>
<td>Orthopedic intervention</td>
<td>Infection</td>
<td>Long-term venous access</td>
</tr>
<tr>
<td>Tier 3: Sustainability of Health</td>
<td>Frequency of breakthrough bleeds</td>
<td>Joint preservation</td>
<td>Lifelong productivity</td>
<td>Sustained good health</td>
<td>Long-term disability of insufficient/inappropriate therapy</td>
<td>Age-related comorbidities &amp; complications</td>
<td></td>
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- **coreHEM outcomes** are related to multiple value framework outcomes
- Mapped data from the value framework literature review showed differentiating clinical data between GT and SOC for each coreHEM outcome
- Several mapped outcomes (dark gray) lacked accompanying clinical data representing areas that warrant additional research and timely publication

Beware of Panglossian* Thinking


Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes
G. F. Pierce1,2 | A. Iorio3

Haemophilia. 2020;00:1–3.

Gene therapy to cure haemophilia: Is robust scientific inquiry the missing factor?
Glenn F. Pierce1 | Radoslaw Kaczmarek2 | Declan Noone3 | Brian O'Mahony4 | David Page5 | Mark W. Skinner6

Molecular Therapy Vol. 29 No 12. December 2021

Eliminating Panglossian thinking in development of AAV therapeutics
Radoslaw Kaczmarek,1 Glenn F. Pierce,2 Declan Noone,3 Brian O'Mahony,4 David Page,5 and Mark W. Skinner6

*Characterized by or given to extreme optimism, especially in the face of unrelieved hardship or adversity.
Adapted from R Kaczmarek WFH World Congress 2022; May2022
Thank you.
Questions?

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