Strategic Selection of Clinical Trial Core Outcomes Customized to Disease and Drug Therapy

Examples Generated During coreVWD and coreHEM Initiatives

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Question

In clinical studies of rare bleeding disorders, what is the optimal set of outcomes to consistently report?

Objective

Multistakeholder consensus facilitates alignment and consistency in outcomes measured in trials for a given condition.

We aimed to develop and compare **2 core outcome sets**

coreHEM for gene therapy for hemophilia

coreVWD for prophylaxis and perioperative treatment for von Willebrand Disease (VWD).

Core Outcome Set (COS)

- Set of outcomes recommended to be measured/reported in every clinical trial
- Standardized outcomes, prioritized with input from multiple stakeholders
- Intended to ensure consistency in reporting relevant outcomes
- Research implications depends on how extensively it is adopted

Methods

For both initiatives, international multistakeholder panels (**Figure 1**) were invited to participate in a modified Delphi exercise to condense and prioritize a list of candidate outcomes that was compiled from a literature/evidence review.

- 88 participants on 2 panels (49, coreHEM; 39 coreVWD) rated each outcome on a scale from 1-9 (least important to critically important to include in a COS).
- Outcomes were retained or eliminated over voting rounds using pre-set criteria:
  if ≥70% rated the outcome 7-9, the outcome moved to the next round, otherwise it was dropped.
- Patient-important criteria were incorporated during Delphi Rounds 1 and 2 to elevate patient opinions. If the patient group average rating was ≥7, an outcome was retained until the next round.
- In the 3rd and final Delphi round, held after an in-person consensus meeting for each initiative, all outcomes had to reach ≥70% consensus from the full panel.

Each initiative had a post-meeting survey to agree on outcome combinations and additions that had been discussed at the consensus meeting.

Results

- **Final core outcome sets** were developed after 3 Delphi rounds (**Figure 2**).
- **Type of treatment** considered and **differences in bleeding experiences** for people with hemophilia compared with people with VWD drove ratings.
- Consequently, the COS for coreVWD had **multiple, diverse bleeding outcomes**, while coreHEM (for gene therapy trials) included only one.
- A subset of outcomes for prophylaxis treatment was included within coreVWD for Women, Girls and People with the Potential to Menstruate (**WGPPM**).

Conclusions

These initiatives demonstrate

- Outcomes in both final core sets reflect
  - Phenotypic experience of living with the condition
  - Treatment modality
- An optimal set of outcomes to consistently report balances different stakeholders' perspective on **outcomes-of-importance**.
- Greater opportunity when **COS process** is planned at outset of clinical research programs.

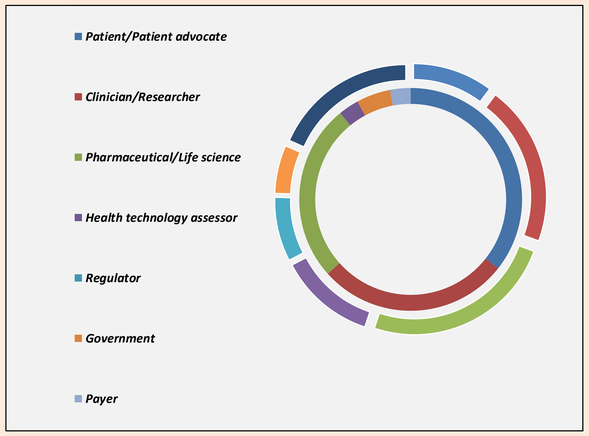

Figure 1. Panel Participants outer ring, coreHEM inner ring, coreVWD

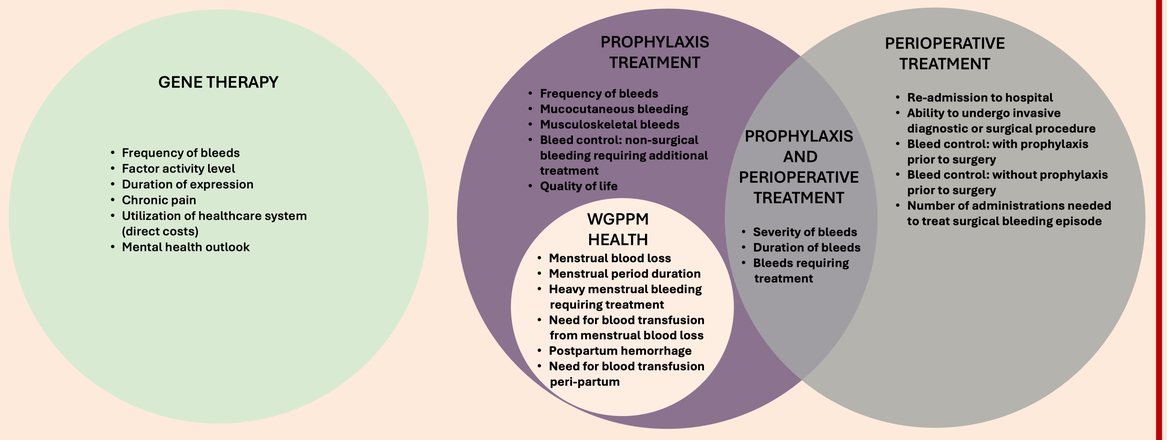

Figure 2. Final COS. Left: coreHEM, Gene therapy; Right: coreVWD, Factor and non-factor therapies

Table. Comparison of Features and Outcomes

	Hemophilia (coreHEM)	VWD (coreVWD)	Implications in Final COS
Bleeding experience	**Musculoskeletal** accounts for 80-90% of bleeds in hemophilia	Most bleeding at **mucocutaneous** sites: nose bleeds, oral cavity bleeds, joint bleeds, heavy menstrual periods	coreHEM included one bleeding outcome, i.e., the **frequency of bleeds**. coreVWD included multiple bleeding outcomes, e.g., **frequency**, **severity**, **duration** and categorized bleeding by site: **mucocutaneous** versus **musculoskeletal**. In a special subset within the prophylaxis branch, referred to as **WGPPM outcomes**, coreVWD highlighted outcomes associated with gynecologic and obstetric bleeding
Treatments being considered Rx	coreHEM was specifically developed for trials for **gene therapy**	coreVWD aimed to develop two COS branches for **prophylaxis** and **perioperative** treatments, both **factor** and **non-factor** options	coreHEM identified novel outcomes of importance associated with a durable treatment. Final set included **duration of (gene) expression** and **factor activity levels.** Both can be monitored to assess effects of gene therapy. As gene therapy may significantly reduce annualized bleeding rates, coreHEM included **quality of life** outcomes beyond bleeding, e.g., **chronic pain** and **mental health outlook**. In coreVWD, bleeding outcomes were the focus as a means of assessing effectiveness of **prophylaxis** regimens and **treatment** before, during, and after **surgeries**.
Resource use outcomes $	With focus on gene therapy, cost **comparisons to standard of care** is of interest	As prophylaxis treatment is more widely adopted, **hospital costs** (and a reduction in resource use) are important outcomes	coreVWD included resource use outcomes in perioperative branch: **hospital re-admission, number of administrations of treatment** needed to resolve a surgical bleeding episode. coreHEM included **utilization of the healthcare system (direct costs)** to measure how receiving gene therapy changed a person's average resource use.

References

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Acknowledgments

coreHEM sponsored by Bayer, BioMarin, Sanofi, Spark, Pfizer, and uniQure

coreVWD sponsored by Band Therapeutics, BioMarin, Roche, Star Therapeutics, and Takeda

Presented at American College of Clinical Pharmacology (ACCP) Annual Meeting, North Bethesda, MD, USA; Sep 8-10, 2024

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