A Digital Twin-Based Framework for Mitigating Missing Data in Clinical Trials: Application to Anti-Obesity Drug Development

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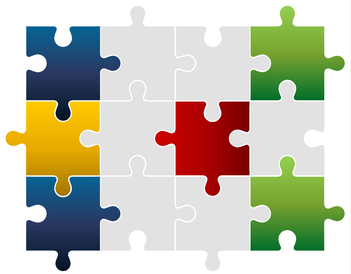
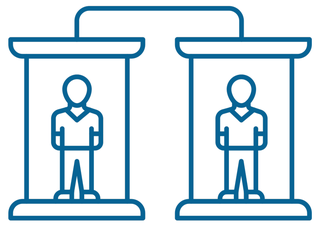
Missing Data in Clinical Trials

- Missing data are common across clinical trials and therapeutic areas
- Non-random missingness can bias treatment-effect estimation
- Incomplete data undermine interpretability and regulatory confidence



Digital Twins as an Emerging Solution

- Generate individualized, model-based outcome trajectories
- Enable inference when observed clinical data are incomplete
- Increasingly explored within model-informed drug development frameworks



Why Anti-Obesity Trials?

- High rates of non-random discontinuation across treatment arms
- Longitudinal endpoints sensitive to missing data
- Strong need for estimand-aligned, regulatory-relevant analyses

Objective

To establish and validate a digital twin–based imputation framework that generates individualized, model-based trajectories for key endpoints, enabling robust analysis of incomplete data consistent with ICH E9 estimand strategies.

Approach

1. Context of Use — Define estimands and limitations of conventional missing-data approaches
2. Model Development — Build and internally validate digital twin models using completed trial data
3. Imputation Framework — Implement estimand-aligned imputation with guidance-consistent sensitivity analyses
4. External Validation — Re-analyze independent completed trials to assess robustness and generalizability

Potential Impact

- Improved robustness and interpretability of treatment-effect estimates in the presence of non-random missing data
- A reuseable, estimand-aligned analytical framework applicable beyond obesity
- A foundation for evaluating alternative control strategies, including model-informed comparators

Next Steps

- Present the project concept to the Metabolic Disorders Steering Committee (MDSC) for consideration of formal Work Group formation
- Explore pathways for cross–Steering Committee collaboration within the Biomarkers Consortium
- Engage cross-sector stakeholders to further refine context of use and validation strategy
- Advance toward formal, collaborative evaluation using completed clinical trial datasets

Alignment with the Mission of the FNIH Biomarkers Consortium

This project is a precompetitive, methodological effort focused on advancing approaches to address persistent challenges in missing data and treatment-effect estimation. The proposed framework aligns with the Biomarkers Consortium mission to improve the quality, efficiency, and interpretability of biomedical research. While anti-obesity trials serve as the initial use case, the approach is designed for broader applicability across therapeutic areas, enabling opportunities for cross–Steering Committee collaboration and shared learning.

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