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MASH Placebo-Arm Database Project Update

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March 6, 2026

Berkeley Public Health

Outline

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- Data Source
- Data Harmonization Updates
- Analyses Updates- Placebo Response Rate

Data Sources

As of March 1, 2026

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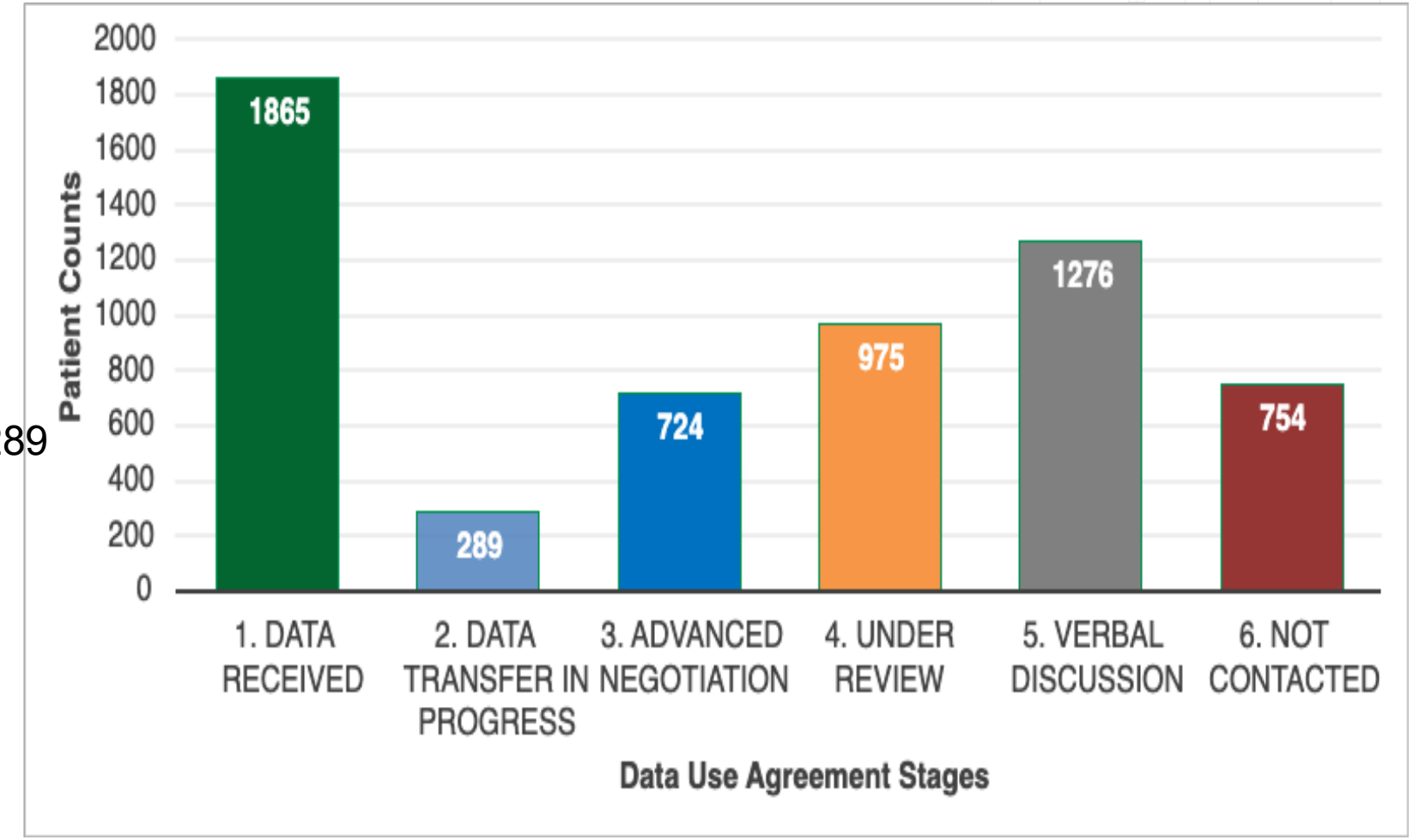
- Invited to participate
  - All completed phase 2 & phase 3 studies
- Potential # of patients: 5883
  1. Data Received: 1865
     5 companies & NIDDK
  2. Signed, data transfer in progress: 289
     2 companies
  3. Advanced negotiations: 724
     2 companies
  4. Under review: 975
  5. Verbal discussion: 1276
  6. Not contacted: 754



MASH Data

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- Current Data Size:
  - NIDDK trials: 5
  - Industry phase 2-3 trials: 7
  - Incoming industry trials by 2026 June: 7
- Expected total trial count: 72
- Expected placebo patient count: 5883

Harmonization Updates

Data Flowchart

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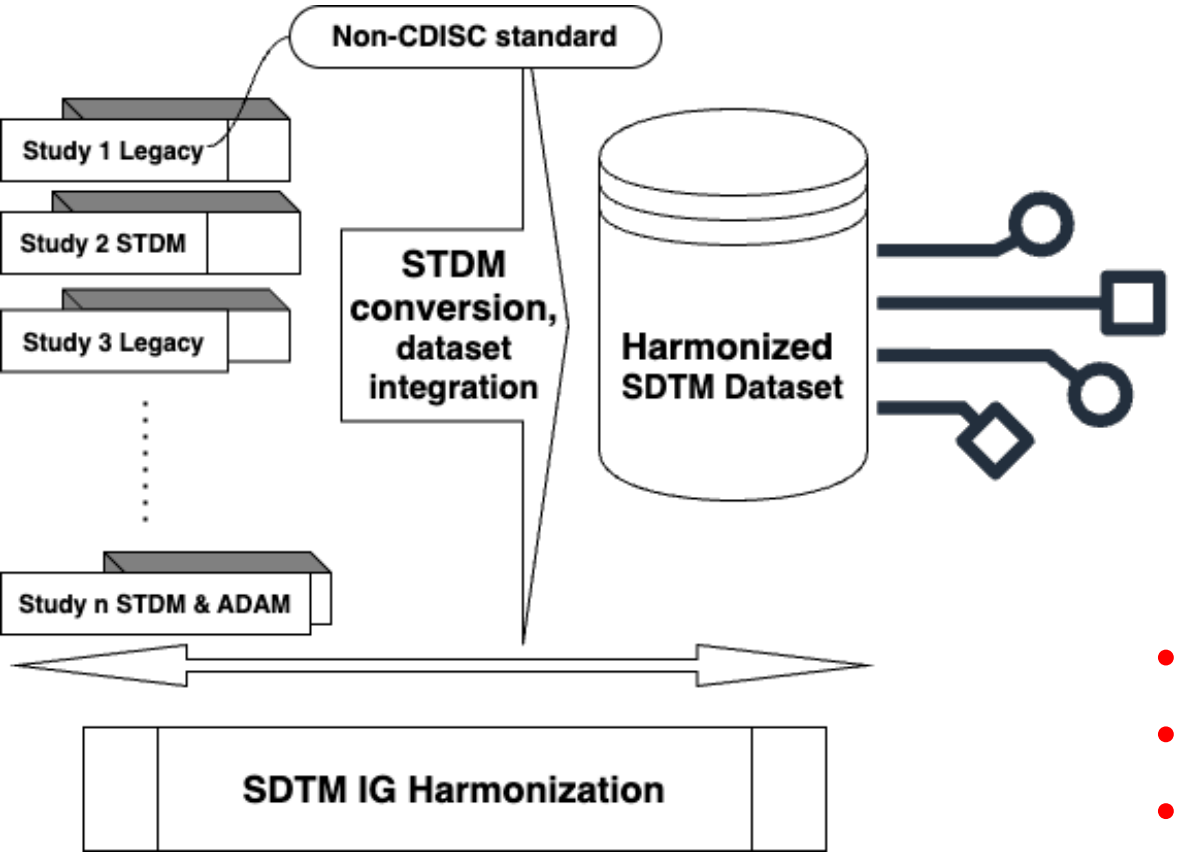
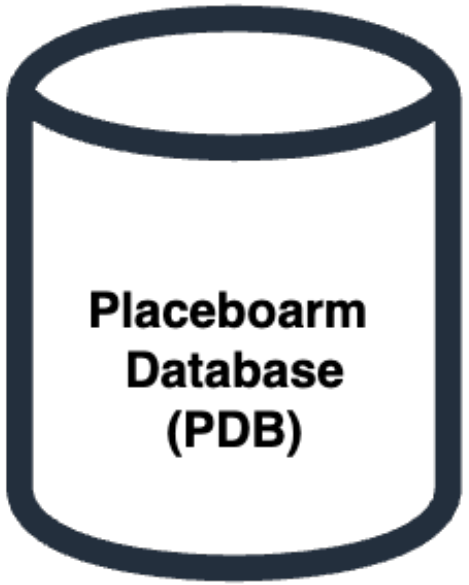


IG: Implementation Guide



Core feature
- Database Schema Design: CDSIC-compliance
- Data Version Control
- Security: encryption, full HIPPA & FDA compliance with detailed audit trails
- Backup & disaster recovery plan

- **Traceability**
- **Consistency**
- **Regulatory Compliance**

The Automation Strategy

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Pain Points

- Human Error Risk
- Inefficiency, repetitive programming
- Limited scalability
- "More trials = more headcount"

Strategic Goal

Refactor harmonization processes from hardcoded SAS programs to a metadata-driven framework to improve:

- Standardization
- Maintainability
- Scalability
- Governance & auditability

The Vision - The 80/20 Rule

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Shifting from "Coder" to "Architect"

Goal: Trial-Agnostic harmonization framework

80% Automation:

- A core engine reads from a central mapping spreadsheet
- Logic validated once, reused across all trials

20% Expert Tweaks:

- Programmers write "Delta Code" for study-specific anomalies (i.e. unique lab tests)
- Domain experts review flagged exceptions

Key Shift: Validation moves from checking code -> reviewing metadata mappings

Human-in-the-Loop: Continuous Learning

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- Review Phase:

Domain experts (Clinical/Data Scientists) review flagged reports

- Decision Making:

Provide "Trial-Specific" logic for edge cases

- Feedback Loop:

- expert decisions saved back into Metadata
- engine becomes smarter with each trial

This creates a self-improving harmonization system.

The Impact

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- What 80% Less Manual Effort Looks Like
  - Reduced programming time
  - Reduced error risk
  - Faster onboarding of new trials
  - Centralized mapping governance
  - Validation logic reused across studies
  - Scalable without linear headcount growth
- Bottom Line:

We validate logic once -> reuse across every trial.

- Problems solved:
  - ~~Duplicate transformation logic~~
  - ~~Study-specific custom code~~
  - ~~High change effort~~
  - ~~Risk of inconsistency across outputs~~

Analyses Updates

PDB Analysis 1

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1. Characterizing Placebo Response Rates in PDB

- Objective: Establish benchmark placebo response rates using harmonized PDB data
- FDA-defined endpoints:
  - Histologic resolution of MASH without worsening of fibrosis
  - Improvement in fibrosis without worsening of MASH
  - Associated non-invasive test (NIT) markers
- Rationale:
  - Published Randomized Clinical Trials report placebo response rates between 10–30% or more
  - Quantifying this will allow robust cross-trial comparisons & inform trial design

Primary Objective & Endpoint

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- Primary Objective:
  - Determine **the placebo response rate** observed **between two liver biopsies** obtained at least 16 weeks apart
- Primary Endpoint:
  - a **>= 1 stage improvement** in fibrosis **without worsening of steatohepatitis** in paired biopsies
  - Endpoint type: categorical (yes/no)
  - Potential variables to evaluate for association of a placebo response:
    - Age, race, sex, weight, BMI, comorbidities
    - Histologic fibrosis stage and NAS steatohepatitis score
    - LSM, ELF score, Fib 4, AST/ ALT
    - Concomitant medications

Key Concerns - When Pooling Placebo Arms (Questions + How We'll Address)

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Domain 1: Trial-Level Design Differences

- Lifestyle counselling intensity
  - metabolic management
- Visit frequency
  - weight loss
- Background standard-of-care
- Geographic region
- Study era
- Pathology reading method
  - histological interpretation

Domain 2: Population Case-Mix Differences: (even after harmonization)

- Baseline disease severity
  - F2 vs F3; NAS; ALT/AST
- Metabolic Risk Profile
  - BMI / T2DM / Lipid/ Insulin resistance
- Weight Change Susceptibility
- Prior Therapy Exposure
  - GLP-1 / SGLT2 inhibitors

Domain 3: Endpoint & Missing Data Handling

- Histologic Endpoint Variability
- Biopsy Timing & Windowing
  - Early discontinuation before biopsy
- Missing data patterns
- Intercurrent event definitions
  - GLP-1
  - Bariatric Surgery

Key Concerns - Cont.

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- In MASH trials, placebo response is not "noise" — it is biologically and behaviorally driven.
- Therefore, pooling requires explicit modeling of metabolic and histologic heterogeneity. Quantifying this will allow robust cross-trial comparisons & inform trial design

How we address these concerns?

- Modelling + Sensitivity Analysis

Plans: Evaluating Trial Effects Before Defining the Estimand

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Stage 1: Quantify Between-Trial Variability

Objective: Understand the magnitude of trial effects across all (12) MASH placebo arms.

- Estimate between-trial heterogeneity (τ^2)
- Quantify signal-to-noise ratio (I^2) across trials
- Assess whether the pooled marginal placebo rate (β_0) reflects a common underlying rate or varies meaningfully by trial

Key Question:

Is a single pooled benchmark appropriate, or is variability driven by structural trial differences?

Step 2: Sensitivity & Influence Diagnostics

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Leave-One-Out (LOO) Sensitivity Analysis:

- Re-run the model 12 times, excluding one trial each time.
- Evaluate shifts in:
  - pooled placebo estimate rate (β_0)
  - Between-trial variance / heterogeneity (τ^2)
- Identify potentially influential or protocol-specific trials

Subset Analyses (if needed)

- Modern trials only
- Aligned eligibility criteria
- Similar geographic regions

Step 3: Standardization

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To obtain a transportable marginal estimate:

- Fit a covariate-adjusted model
- Standardize placebo response to a target population distribution using G-computation
- Report adjusted marginal placebo benchmark

Goal:
Estimate a robust, population-aligned placebo response rate suitable for trial design.

Intended Use

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We are using the PDB for two distinct purposes:

- Understand the historical placebo experience
- Inform future trial design and external control arms

These are related — but not identical scientific questions.

If we use only one estimand:

- It may describe history well
- But not be transportable to a future protocol

Or:

- It may be tailored to a future protocol
- But not reflect overall historical variability

Therefore, we define two complementary estimands.

Estimand 1: Historical PDB Benchmark (Phase 1)

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Purpose: Describe historical variability and baseline expectation

Definition: The marginal probability of achieving ≥1 stage fibrosis improvement without worsening of steatohepatitis at the harmonized follow-up biopsy under placebo, in the pooled placebo **population from the all harmonized MASH trials**, with pre-specified handling of intercurrent events and between-trial heterogeneity quantified, within harmonized time window (e.g.16 weeks)

Intercurrent Events
Missing biopsy -> non-responder.
Other metabolic changes -> as observed.

Summary Measure

- Represents historical average experience
- Report τ^2 and prediction interval
- Conditional on included trials

This answers: "What has placebo response looked like in completed MASH trials?"

Estimand 2: Target-Trial (Transported) Benchmark (Phase 2)

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Purpose: Inform future trial design and potential external control arm.

Definition: The marginal probability of achieving ≥1 stage fibrosis improvement without worsening of steatohepatitis under placebo, standardized to the covariate distribution of the intended future trial population, accounting for between-trial heterogeneity and prespecified intercurrent event handling.

Population

- future protocol-aligned MASH population

Method: Covariant adjustment + standardization (G Computation, AIPW (Augmented Inverse Probability Weighting)

Output:

- Transported marginal placebo probability for the triage design & external control

This answers:

- "What placebo rate should we expect in our planned trial population?"

Conceptual Bridge

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The historical estimand tells us:

- What variability exists
- How large trial effects are

The transported estimand tells us:

- What placebo rate is relevant for decision-making

The PDB-wide estimand characterizes heterogeneity across trial environments; the transported estimand aligns the placebo benchmark with a defined target population for inference and planning.

Both are necessary.

MASH PDB – Potential Research Questions

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- Natural history of MASH in untreated trial patients
- Comparability of RCT patients to "real world" patients
- Predictors of disease improvement, stability, worsening
- Fluctuation in safety parameters in untreated patients
- Analysis and prediction of screen failures
- Application of AI/ML to paired biopsies
- Comparison of causal inference and other analytical methods
- Shared placebo arm for future trials
- Evaluate 'placebo effect' for diverse participants
- Explore subject simulation strategies
- Others?

Thank you !

PDB Leadership:

- Manal Abdelmalek
- Michael Cooreman
- Quentin Anstee
- Bettina Hansen
- Veronica Miller
- Arun Sanyal
- Henry Chang

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