Update:
MASH Placebo Database Working Group

Bethesda

Liver Forum 16, Session III

March 22, 2024

Chris Hoffman, *PhD*

Veronica Miller, *PhD*

The Forum for Collaborative Research

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Berkeley Public Health

Agenda - Last night's WG dinner

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- Introductions
- MASH Placebo Database (PDB) Project Overview
- Data update
- Research use case
- Next steps and how to get involved

MASH Placebo Database Project Overview

Placebo Cohort: Unique NH Study

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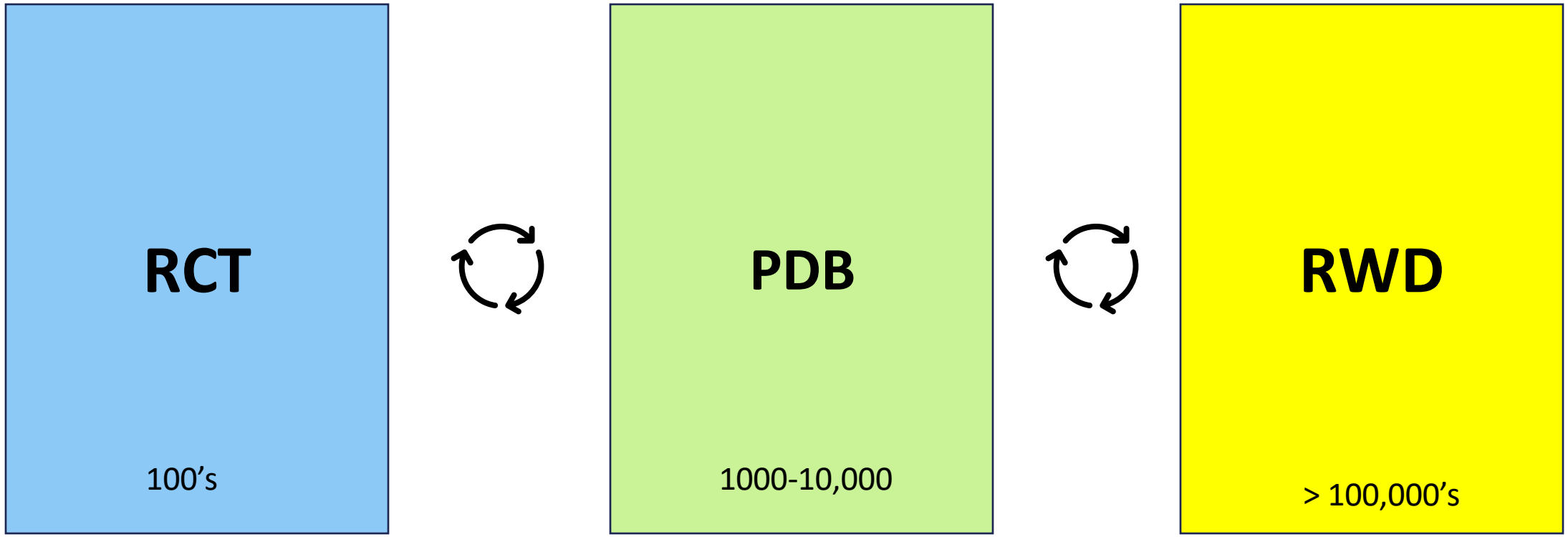

Advantages

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- Patients selected/experienced RCT
- Patients more diverse than in any individual trial
- Time zero defined
- Benchmark RCT to RWD
- Data collection and monitoring more rigorous than RWD, defined data formats and structure
- Patient-level data available to regulatory agencies

Research Questions

... as identified by our Working Group last year and earlier

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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
- Others?

MASH Placebo Database Project

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Community-based project oversight ("governance") based on nearly 25 years of experience building trust with our stakeholders to make collective progress on global health challenges

Co-Chairs

MASH PDB Executive Comm

MASH PDB Steering Comm

Data contributors + experts across stakeholder groups

Statistics & Analysis WG

Open to academic, industry, and regulatory statisticians and folks not afraid of cohorting with statisticians

MASH PDB Working Group

Open to all LF members

The Data & Analysis Center Team

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Principal Investigator/Director Veronica Miller, PhD		Lead Data Scientist Margot Yann, PhD	
IT & Operations Director Chris Hoffman, PhD		Technical/Infrastructure Zach Rooney, MSCS	
Introducing Forum/DAC Advisor Richard Haubrich		**To be hired** Research Data Analyst Data Engineer (part-time)	

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DAC Advisors

Regulatory Science
Data Science
Statistics
Novel Analytics

FCR Data & Analysis Center (DAC)
DAC Team and Platform

DAC Project Portfolio

Liver Forum – MASH Placebo Database

Liver Forum – Digital Histology AI/ML

PSC Forum

Other Forums:
HBV
HIV
Ocular
TAVI

Disease Specific Annual Workshops

Data Science
RWD-RWE
ML-AI
Causal Inference
ETC

The DAC Platform

A safe place for data sharing and analysis

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- Data protection by design & by default
- Built on UC Berkeley's SRDC (Secure Research Data and Compute) system which is approved for ePHI and highly sensitive data
- Deep collaborations with experts in UC Berkeley's Privacy, Human Subjects, Information Security, and Vice Chancellor of Research Offices
- Virtual machines, HPC cluster, and parallel file system storage

Data & Analysis Center Progress

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- Data Use Agreement (authored with VC Research Office)
  - Under review by nearly 20 companies
- CDISC standards for data organization and exchange
- Data management to support provenance and reproducibility guided by regulatory processes
- Novel analytics to combine clinical trials and RWE to support regulatory approval of new treatments and therapies

Data Sources & Data Availability

As of 13-Mar-2024

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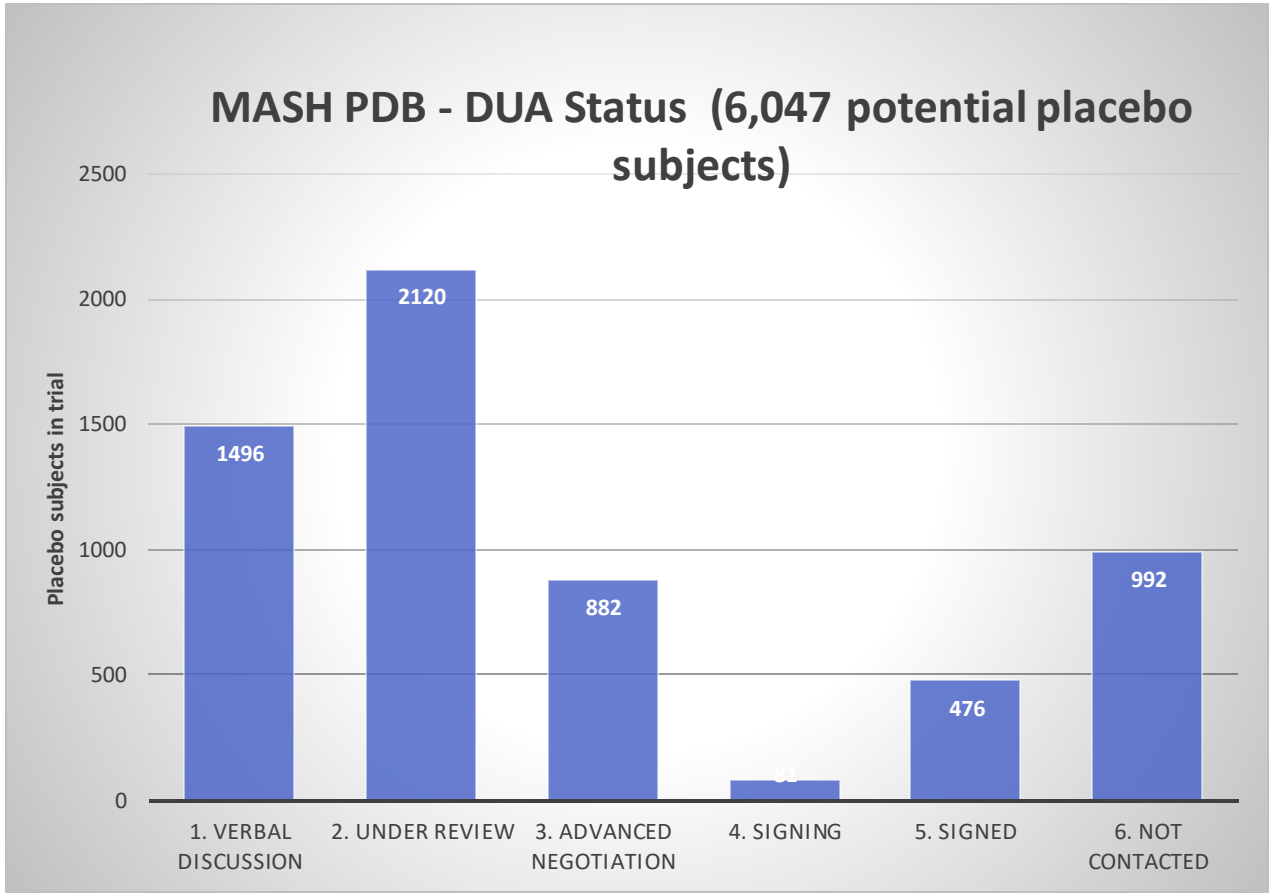
- Invited to participate
  - All completed phase 2 and phase 3 studies
- Potential # of placebo patients: >6K
  - Signed / data received: 476 (2 companies plus five clinical trials from NIH NIDDK)
  - Signing - 81 (1 company)
  - Advanced negotiations – 882 (3 companies)
  - Under review / strong commitment: 2,120 (8 companies)
  - Verbal discussion – 1,496 (7 companies)
  - Declined to share data: 0



The Forum for Collaborative Research Award for Data Sharing

ENYO Pharma

Mirum Pharma

NIH NIDDK

National Institute of Diabetes and Digestive and Kidney Diseases

Group Discussion

Lessons learned and challenges being addressed

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- Privacy issues and informed consent
- Intellectual property and other legal issues
- Corporate culture/process and competing priorities
- Finding the right persons and committees to talk to
- Asking the right questions of the data
- Sharing what we've learned: We are authoring a series of articles on patient data sharing – challenges and solutions

Data Workflows

Data Management Flow

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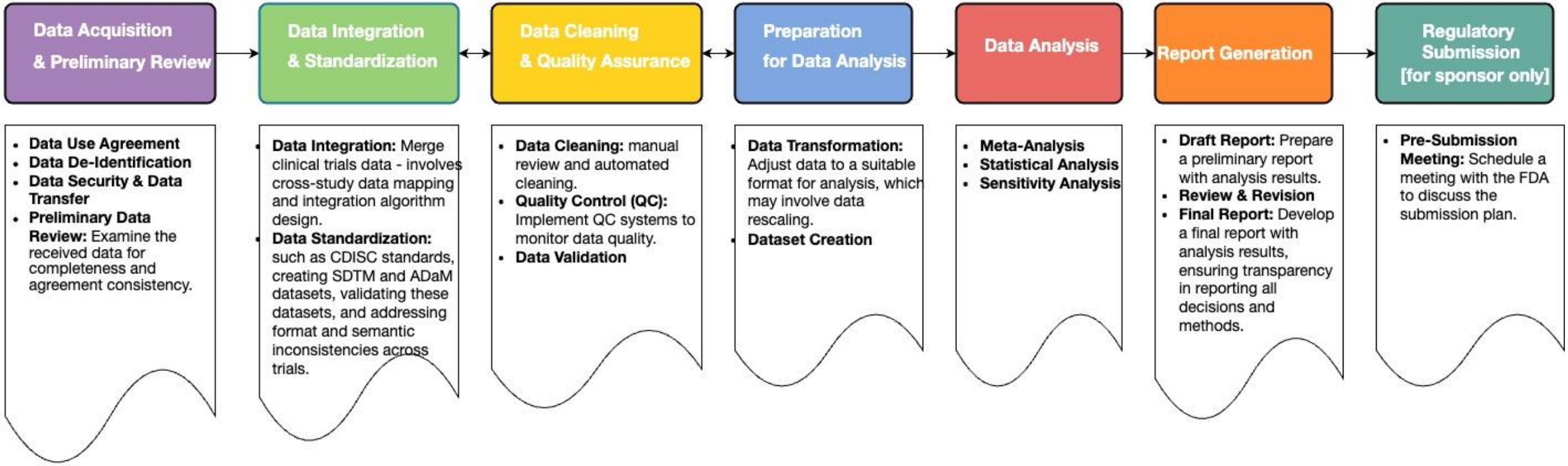

Data about Data - Example

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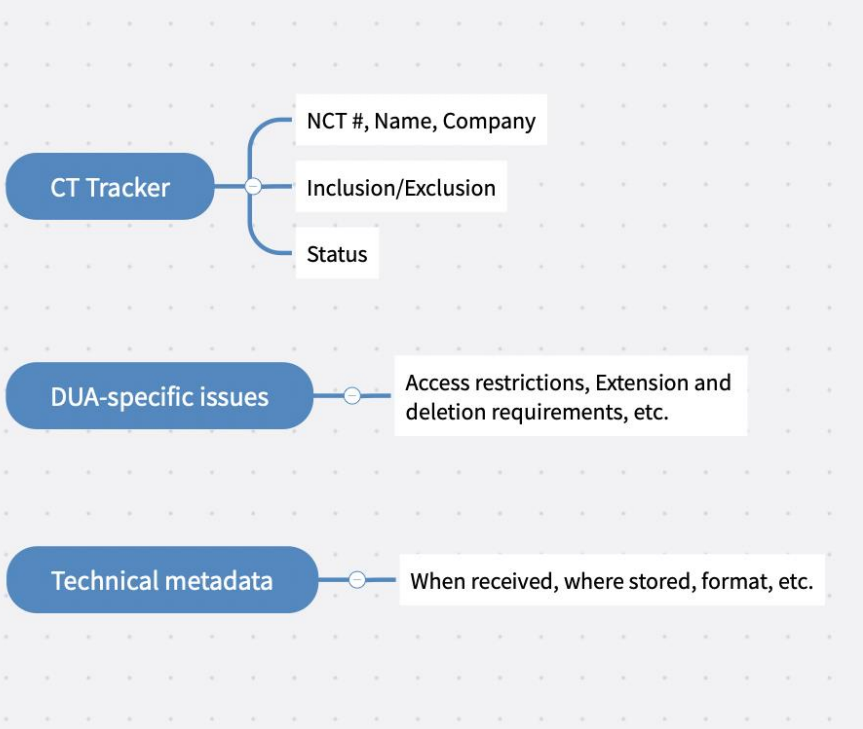

Checklist	URL	Description
FLINT Data Dictionary	Data Dictionary	
FLINT Case Report Form (CRF)	Forms	Flint CRF (Case Report Form) records all protocol-required information on each subject.
FLINT Study Protocol	Protocol	
Statistical Analysis Plan	SAP	
FLINT Dataset Specification		
FLINT Dataset (Collected Data)		**Variable Count**
ad.sas7bdat	AD – Alcohol Use Disorders Identification Test (AUDIT)	**16**
bg.sas7bdat	BG - Baseline History	**301**
cg.sas7bdat	CG - Genetic Consent and Blood Collection Documentation	**7**
cr.sas7bdat	CR- Central Histology Review	**40**
cv.sas7bdat	CV- Cardiovascular Risk Factors	**60**
dr.sas7bdat	DR- Death Report	**18**
hi.sas7bdat	HI- Follow Up Medical History	**299**
ld.sas7bdat	LD- Lifetime Drinking History (Skinner)	**186**
lr.sas7bdat	LR- Laboratory Results - Tests Done at Screening and Followup Visits	**60**
ls.sas7bdat	LS- Laboratory Results - Tests Done only During Screening	**45**
pe.sas7bdat	PE- Physical Examination	**46**
pf.sas7bdat	PF- Focused Physical Examination	**17**
qf.sas7bdat	QF - SF–36v2 Health Survey	**41**
rd.sas7bdat	RD-Study Drug Dispensing and Return	**20**
rg.sas7bdat	RG-Registration	**34**
tx.sas7bdat	TX - Treatment Group	**2**
Total		**1192**

Data Workflows – Ingest

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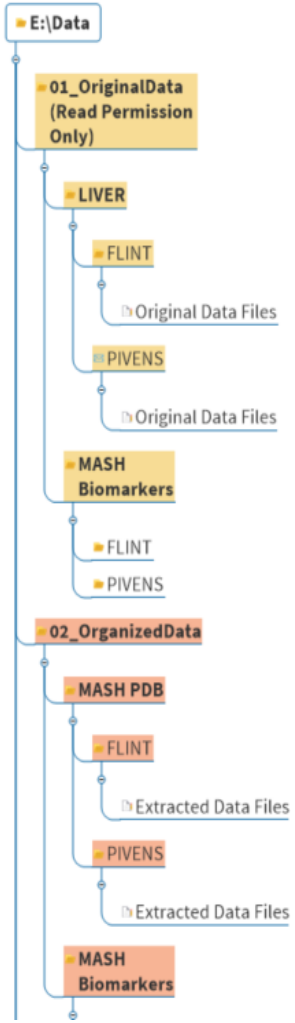

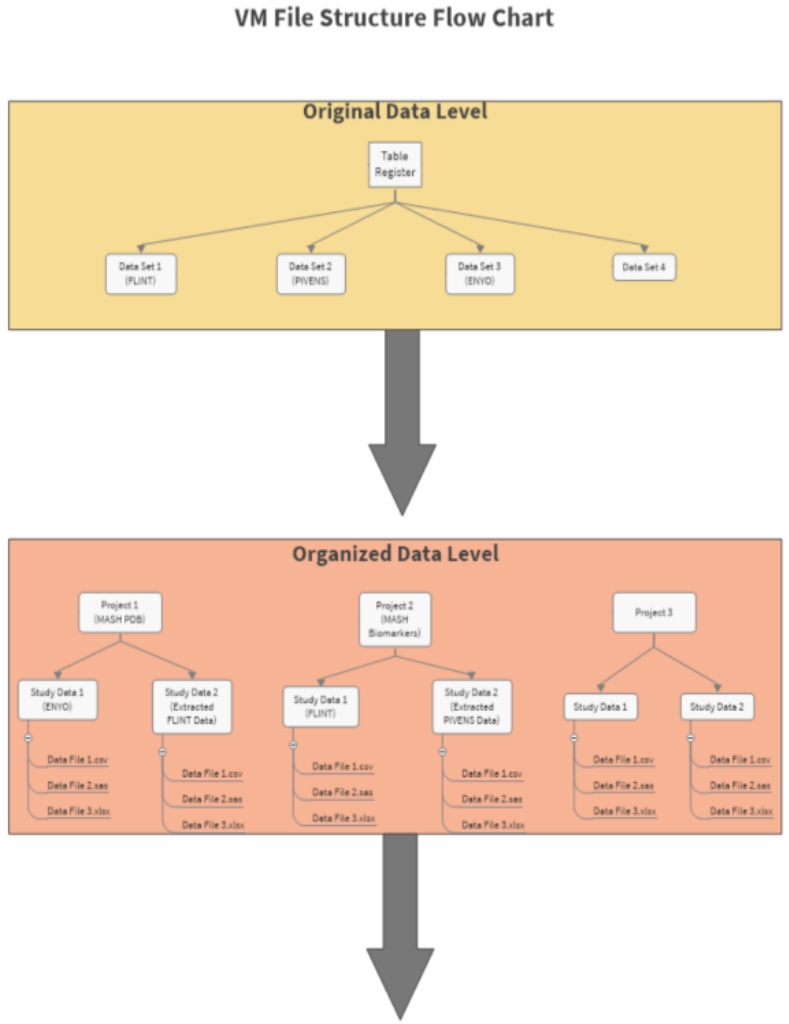

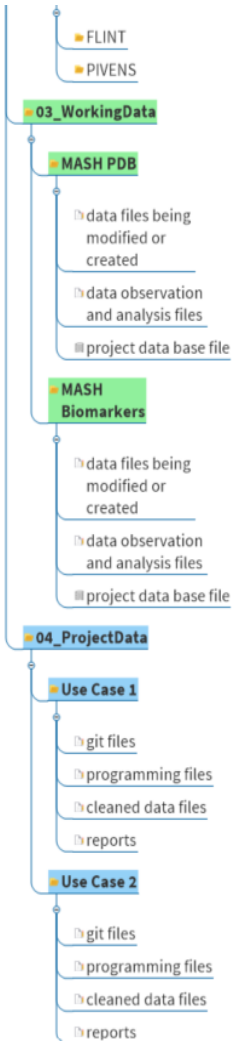

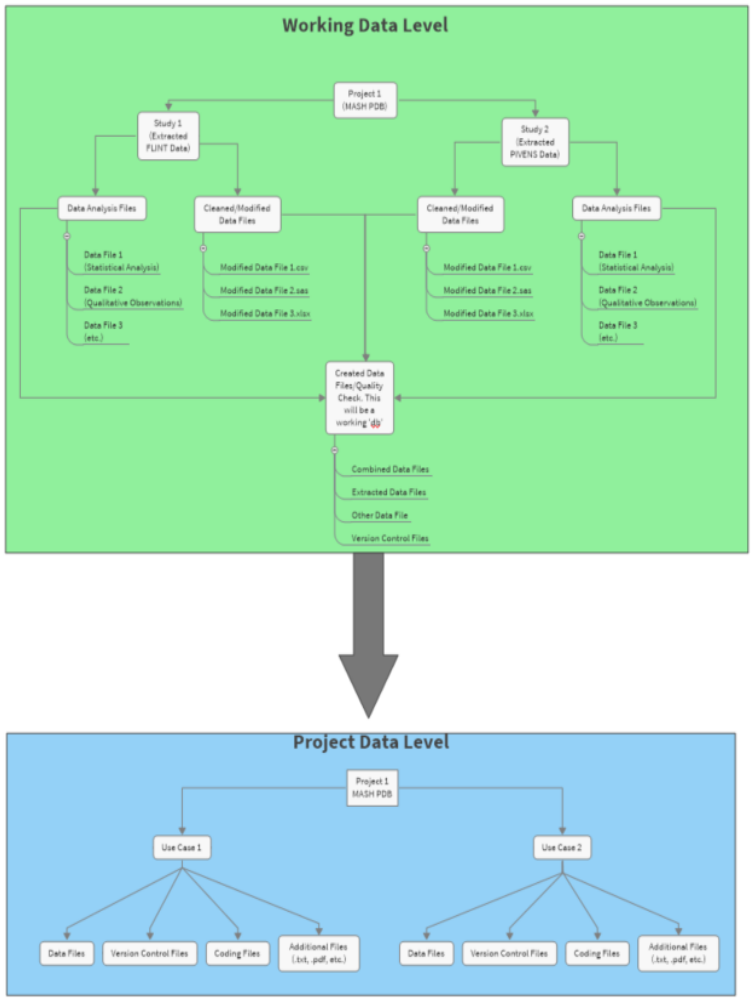

Specific Research Use Case:

...in response to requests from some companies for a specific research question

Specific Objectives

From a November discussion at the project's Executive Committee

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- Replicate the analysis presented in "Cirrhosis Regression is Associated with Improved Clinical Outcomes in Patients with Nonalcoholic Steatohepatitis" by Sanyal et al 2022.
- Primary Objective
  - Define the predictors of liver-related clinical disease progression
  - Considering factors at baseline (time of study entry) and change from baseline in predictors
  - With primary endpoints defined
- Expected Outcomes
  - Confirm the Sanyal et al 2022 analysis using MASH placebo data
  - Produce a broader biomarker analysis which allows for development of additional NIT combinations that might better predict liver-related clinical outcomes

Sanyal AJ, Anstee QM, Trauner M, et al. Cirrhosis regression is associated with improved clinical outcomes in patients with nonalcoholic steatohepatitis. *Hepatology*. 2022;75(5):1235-1246. doi:10.1002/hep.32204

Broader Objectives

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Goal: In addition to confirming associations between biomarkers and clinical liver-related outcomes, we aim to develop a machine learning model capable of identifying core biomarkers that best predict liver-related events in MASH patients.

a. Risk factors

b. Clinical biomarkers:
   - Liver Safety Markers
     - Alanine aminotransferase (ALT)
     - Aspartate aminotransferase (AST)
     - Bilirubin levels
   - Liver Function Markers
     - Albumin
     - Prothrombin time
     - International Normalized Ratio (INR)

c. Fibrosis Markers: Hyaluronic acid, Laminin, Pro-C3

d. Metabolic Markers:
   - Insulin resistance (HOMA-IR)
   - Cytokines: such as, Adiponectin, Leptin
   - Chemokines
   - Lipid profile

e. Imaging biomarkers: (next phase)
   - MRI - PDFF (Proton Density Fat Fraction)
   - MRE (Magnetic Resonance Elastography)
   - Ultrasound
   - CT Scan

f. Specialized biomarkers (next phase)
   - Proteomics
   - Genomics
   - Immunomics
   - Metabolomics

Data Analysis

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Statistics Approach in Sanyal's paper:

- Univariant association:
  - Fisher's exact and Wilcoxon rank sum tests for baseline parameters, and Analysis of covariance (ANCOVA) for parameters of change, adjusting for baseline.
- Kaplan-Meier and Cox proportional hazards regression analyses will be used to evaluate time to clinical disease progression

Additional Machine Learning Approach:

- Supervised learning
  - e.g., predict disease progression based on input features such as lab results and histology findings
- Unsupervised Learning
  - e.g., discover patterns or groupings in the data, identifying patients groups with similar profiles
- Deep Neural Networks: require substantial large datasets and computational resources
- Data Visualization
- Time series Analysis
  - e.g., Tracking disease progression over time

Group Discussion

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- Accelerated approval for Rezdiffra: Much has changed!
- The need for longer term clinical outcome data remains a challenge
  - Predicting clinical liver-related events less feasible given 1-2 yr study duration and low event rates

Urgency and Opportunity

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- Ethical and practical challenges to continuing and new trials
- How will approval of first MASH treatment impact ongoing and future studies?
  - Companies need to hear compelling questions in the 1-2 year timeframe
- Understanding the untreated (placebo) rates of fibrosis/ NAS progression and regression is critical
  - Define predictors and populations with low placebo progression/ regression rates (e.g., sex, age, post menopause)
  - Define variation in biomarkers in untreated populations
- Potential value for early phase studies, to improve patient selection (define homogenous populations), is high
- Potential to digitalize biopsy or radiology data, aligning with AI/ML Histology and Radiology WG's, is high
- Potential of connecting to EMR/ registries to obtain longer term data in registries is high (e.g., tokenize to identify patients and data from EMR to obtain longer term outcomes)

Next steps,
How to get involved

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Thank You

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