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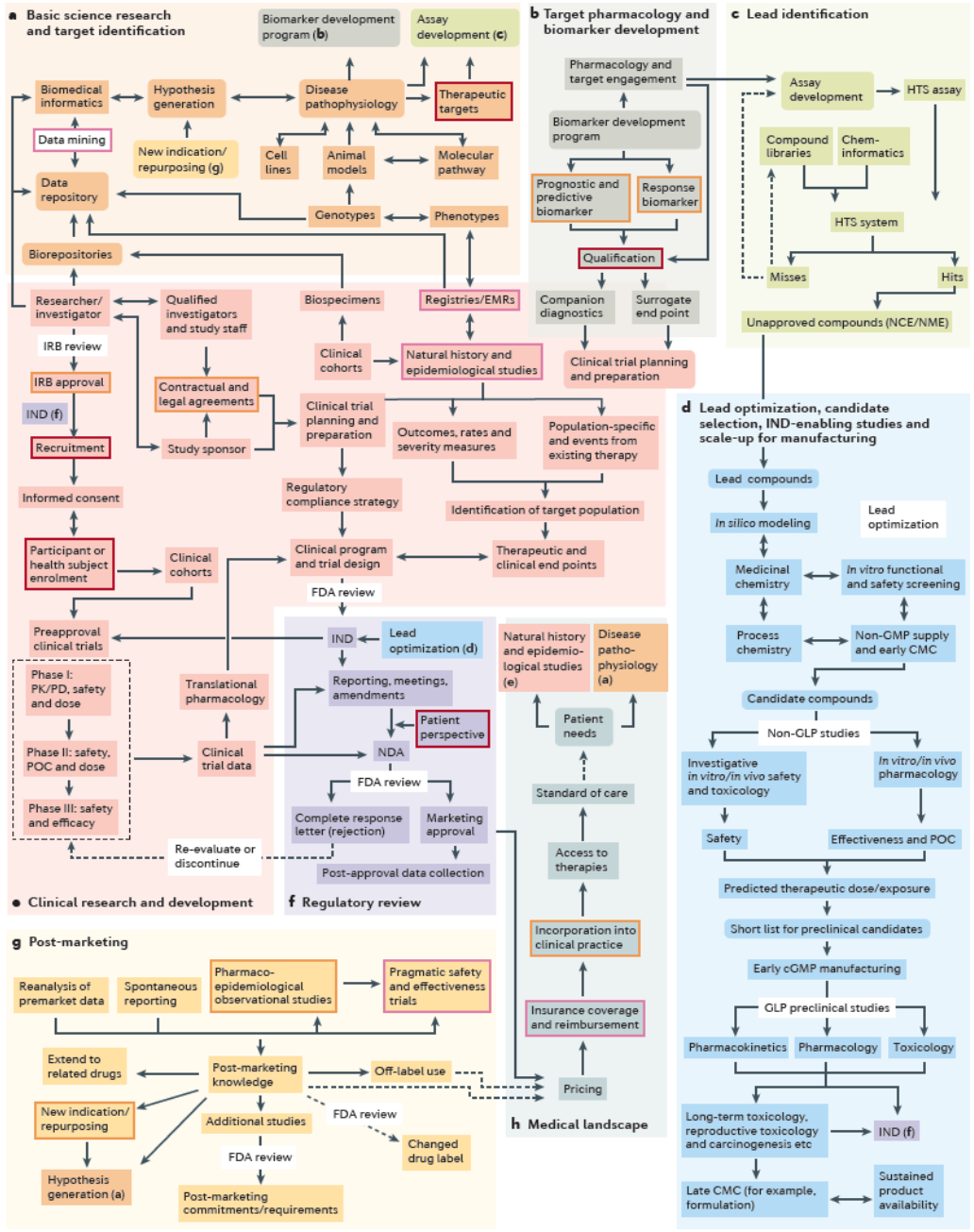
LF Data & Analytics Collaboration

Liver Forum Meeting 12

Veronica Miller, PhD, Director

The Forum for Collaborative Research

Berkeley Public Health



Drug development is not for the faint of heart

A dynamic map for learning, communicating, navigating and improving therapeutic development

John Wagner, Andrew M. Dahlem, Lynn D. Hudson, Sharon F. Terry, Russ B. Altman, C. Taylor Gilliland, Christopher DeFeo and Christopher P. Austin

Nature Review Drug Discovery 2017

Understanding Failure (phase 3)

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- Some causes
  - Weak clinical link between phase 2 biomarker evidence and registrational endpoint
  - Overenthusiastic interpretation of data
  - Multifactorial chronic disease – reliance on biomarkers for specific pathways
  - Inadequate understanding of pathophysiology
  - Inappropriate patient selection
  - Absence of validated biomarkers of target engagement
  - etc

Galson et al. Failure to fail smartly. Nat Rev Drug Disc 2021

Importance & Value of Data Sharing

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- Develop better tools to stratify patient populations/assess treatment benefits
- Promote development of biomarkers, simulation tools to improve clinical trial design; improve likelihood of success
- Reduce risk/increase confidence
- Reduce time, size and cost of phase 3 trials through optimization

Galson et al. *Failure to fail smartly*. Nat Rev Drug Disc 2021
Thompson & Parekh. *Value of data sharing to advance drug development: a regulatory perspective*. TIRS 2021

Liver Space – Data & Analytics Collaborations

- LITMUS
- NIMBLE
- Target NASH
- NASH CRN

- Complementary
- Fit-for-purpose
  - Different “purposes”
- Opportunity for exploring innovation in analytics

Liver Forum Contribution

- Neutral venue for cross-study collaboration
- Explore application of analytic approaches
- “Workshop” opportunities for exploratory, hypothesis generating, confirmatory type of analysis

Liver Forum Placebo Arm DB Project

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- An integrated patient-level database from completed phase 2 and phase 3 NASH studies
- Natural history cohort representing patients eligible for RCT's
  - Natural history across the spectrum of NASH stages in clinical trials
    - Identify predictors of "placebo response" vs. disease progression
    - Reduce placebo-arm burden in future phase 3 (phase 4) trials
    - Increase specificity of patient selection
- Collaborative database serving the Liver Forum community
  - Sponsors and regulators

Database Security & Infrastructure

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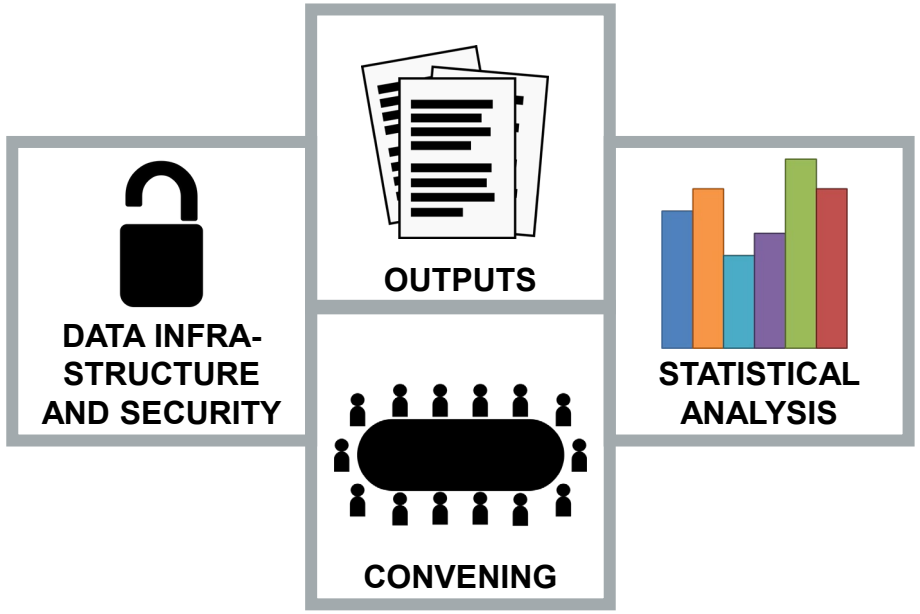
- Data will be housed in a secure research data and compute (SRDC) platform developed at Berkeley for researchers working with highly sensitive (P4 level) data.

PROTECTION LEVEL 4
• Protected Health Information (PHI) / patient records
• Research information classified as Protection Level 4 (P4) by an IRB or otherwise required to be stored or processed in a high-security environment.
• Sensitive Identifiable Human Subject Research data - including certain types of individually identifiable genetic information

SRDC Features

- High performance computing
- Protected storage large enough to store imaging

THE FORUM DATA & ANALYSIS CENTER



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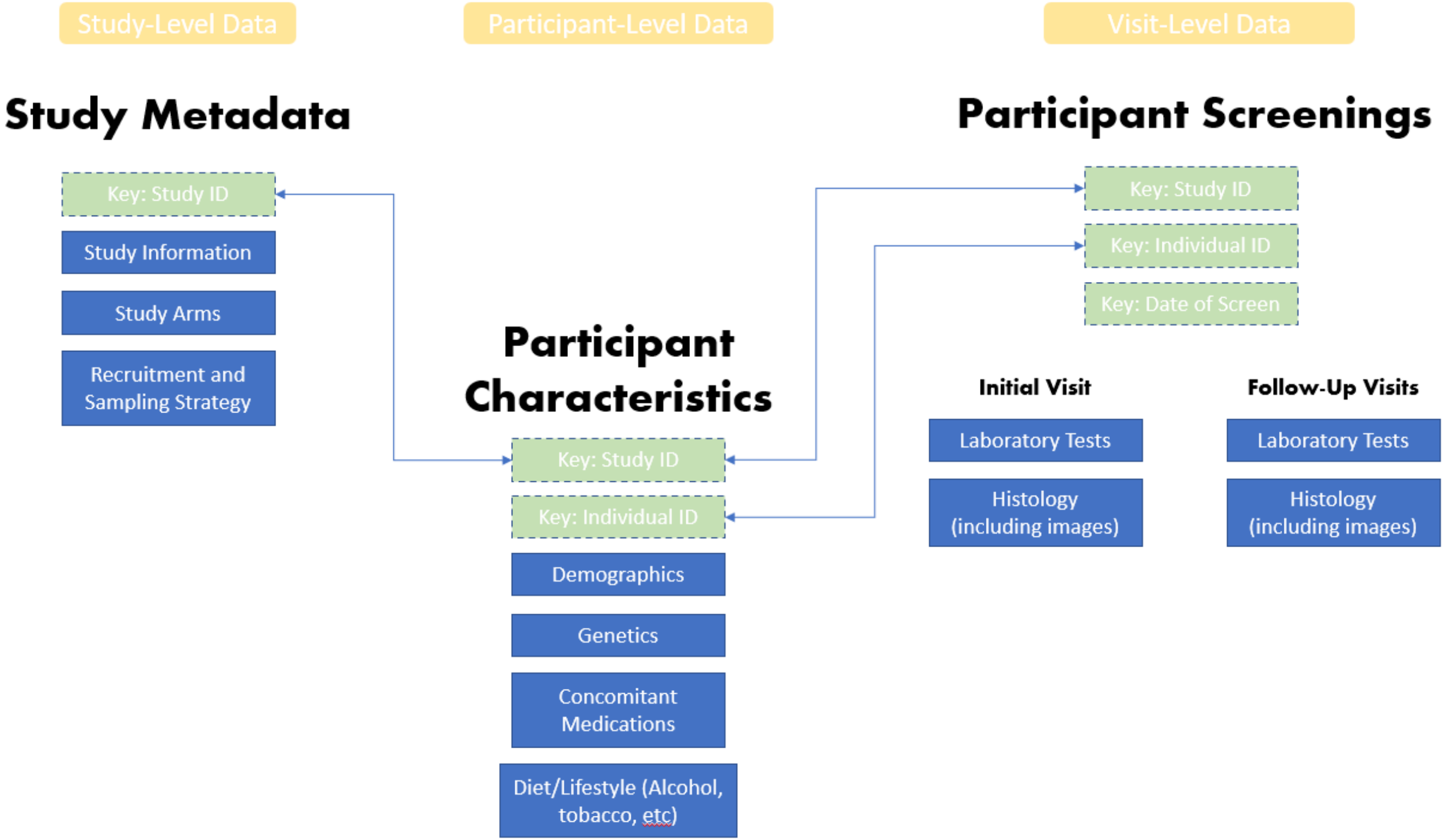
Study-Level Data
Participant-Level Data
Visit-Level Data
Study Metadata
Key: Study ID
Study Information
Study Arms
Recruitment and Sampling Strategy
Participant Characteristics
Key: Study ID
Key: Individual ID
Demographics
Genetics
Concomitant Medications
Diet/Lifestyle (Alcohol, tobacco, etc)
Participant Screenings
Key: Study ID
Key: Individual ID
Key: Date of Screen
Initial Visit
Laboratory Tests
Histology (including images)
Follow-Up Visits
Laboratory Tests
Histology (including images)

PDB – Oversight and Collaboration

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- PDB Working Group
  - LF members experts from all stakeholder groups
- PDB Oversight/Advisory Committee
  - Key expert representative from each stakeholder group
    - Academic, industry, regulatory, patient
    - Guide/advise overall process
    - Review analysis proposals
    - Guide publication policy and process

Access

- Berkeley security wall
  - Sponsors request study specific analyses specific to their drug development program
- Direct access for regulatory agencies
- LF community (PDB WG)
  - Propose analysis to benefit field

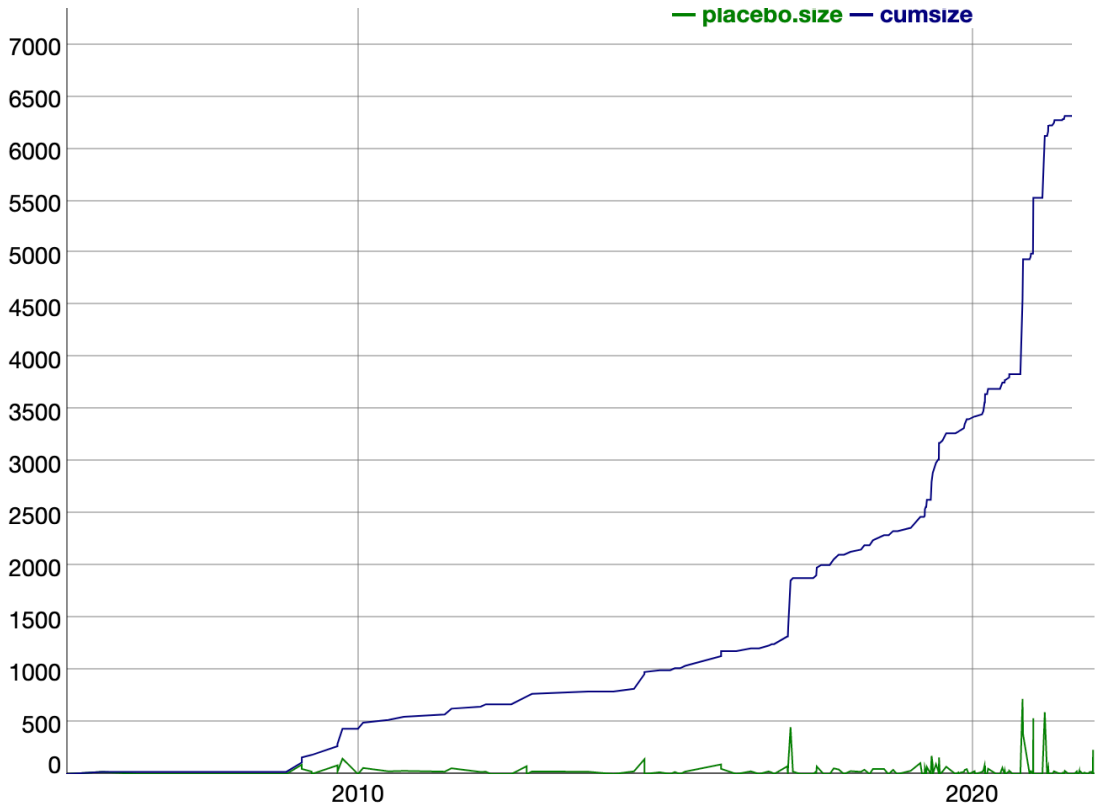
NASH-PDB

Method

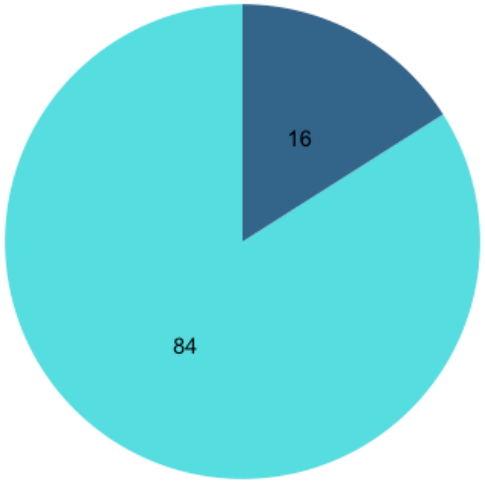
- Reviewed studies completed by December 2021
- Phase 2 and phase 3
- Placebo-controlled

Estimated Number of Placebo Participants

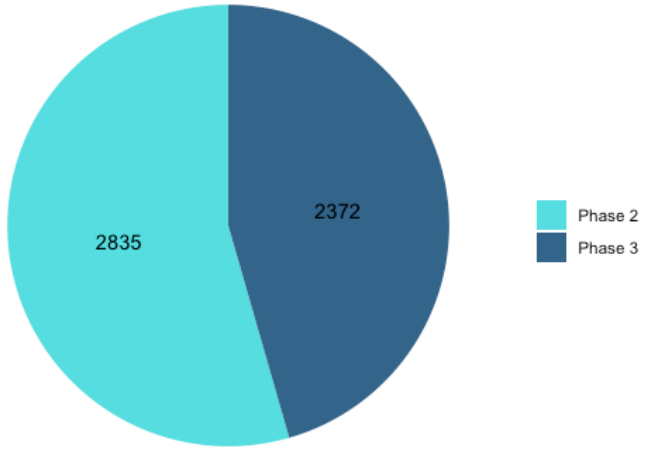
Placebo Size Increases Over Time (Interactive Chart)



Number of Studies - Phase



Placebo Size - Phase



Placebo-Arms Cohort Baseline Characteristics

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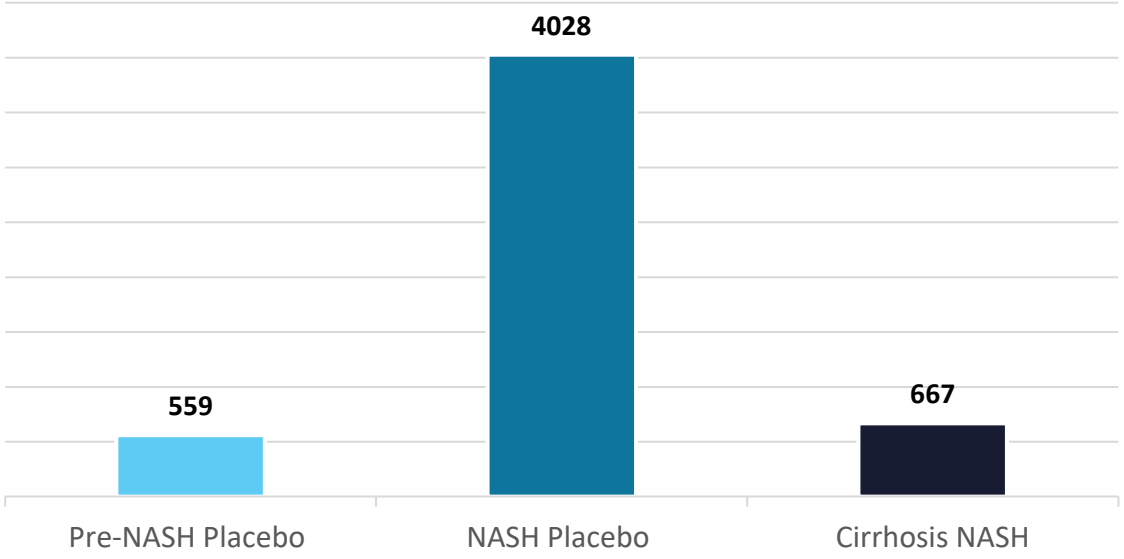
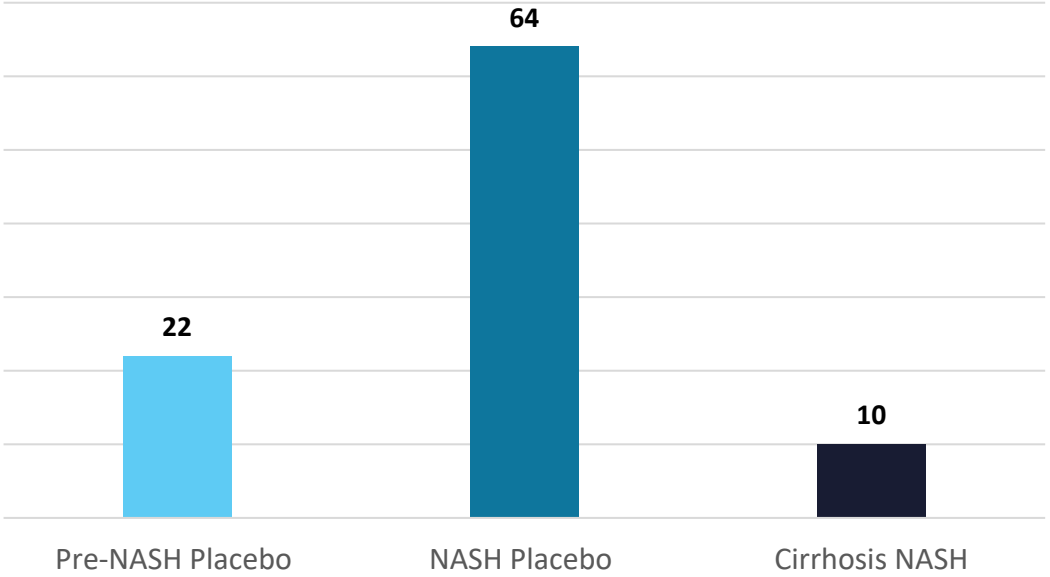
Estimate of Placebo Participants with Pre-NASH, NASH, and Cirrhotic NASH



Estimate of studies involving placebo participants per group



Berkeley Public Health

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Liver-specific annual workshops

- Lessons learned from different cohorts/collaborations
- Comparison of analytic approaches
  - Causal inference
- Cross-talk w RWD/E

NASH Placebo Arm Database Project Team

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- Veronica Miller – Director
- Brenda Rodriguez – Deputy Director
- Maggie Kuang – Graduate Student Researcher
- Tyler Mansfield – Graduate Student Researcher
- Nicholas Murdock – Research Associate
- Chelsey Campillo – Research Associate