The Liver Forum:

Addressing Challenges & Opportunities

Paris NASH 2023

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Director FCR

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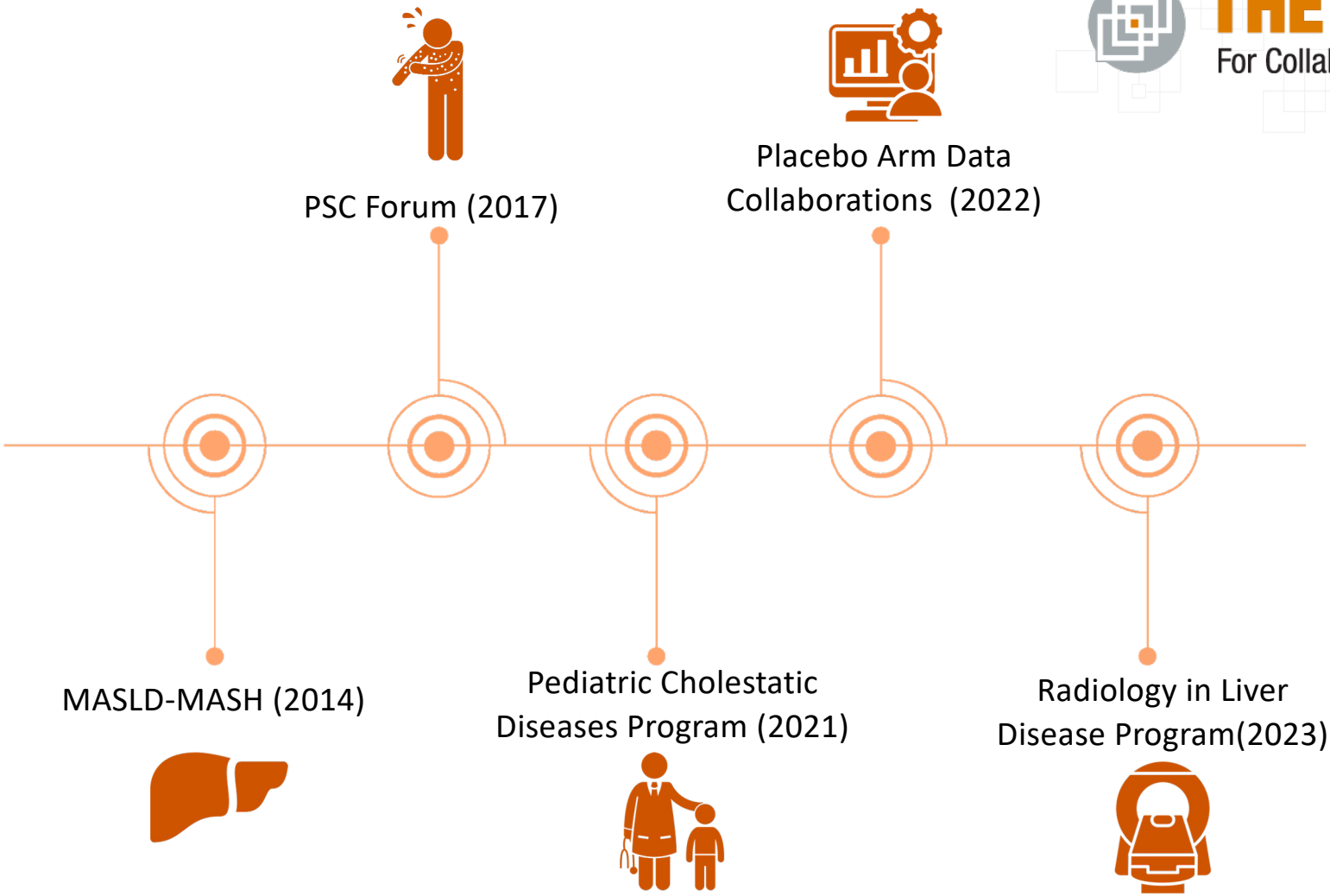

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PSC Forum (2017)

Placebo Arm Data Collaborations (2022)

Facilitate Drug Development through Collaboration

MASLD-MASH (2014)

Pediatric Cholestatic Diseases Program (2021)

Radiology in Liver Disease Program(2023)

Congratulations!
Féliciations!
Bravo!

nature medicine

Article

https://doi.org/10.1038/s41591-023-02539-6

Diagnostic performance of circulating biomarkers for non-alcoholic steatohepatitis

Received: 18 January 2023

Accepted: 8 August 2023

Published online: 07 September 2023

Check for updates

Arun J. Sanyal[1,16], Sudha S. Shankar[2,16], Katheri
James Bolognese[4], Erika Daly[4], Clayton A. Dehn[5], I
Kris Kowdley[7], Raj Vuppalanchi[8], Cynthia Behlin
Anthony Samir[10], Claude Sirlin[11], Sarah P. Sher
Helen Heymann[13], Tania N. Kamphaus[13], Rohit Loo
& Roberto A. Calle[15,17]

NIMBLE
NASH CRN

Global PBC Study Group

September 7, 2023

CYMABAY THERAPEUTICS

CymaBay's Seladelpar Achieves High Statistical Significance for the Primary and Key Secondary Endpoints in the Phase 3 RESPONSE Trial in Primary Biliary Cholangitis

Primary composite endpoint at 12 months of serum alkaline phosphatase and bilirubin was met by 61.7% of patients treated with seladelpar 10 mg vs. 20.0% of placebo treated patients ($p<0.0001$)

Normalization of alkaline phosphatase at 12 months was achieved by 25.0% of patients treated with seladelpar vs. 0% on placebo ($p<0.0001$)

In patients having moderate-to-severe itch at baseline, the seladelpar treated group improved their pruritus at 6 months compared to those in the placebo group ($p<0.005$)

Value of collaboration
Complementarity of RWD and RCT
In for the long haul!

Liver Forum Highlights

Working Groups

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1. Evidence for NITs
2. AI/ML assisted histology
3. Placebo database
4. Rational approaches for combination treatment
5. Bridging between trials in F3 and F4
6. Trials for Met-ALD patients
7. Radiology in liver diseases
8. Pediatric trials

AI/ML Histology

Collaborators

- BioCellvia
- HistoIndex
- PathAI
- PharmaNest

Working Group Chairs:

- David Kleiner, Arun Sanyal

Address

- Common issues
- Integration of digital path to assess fibrosis in clinical trials and liver research

Collaborate

- Joint studies

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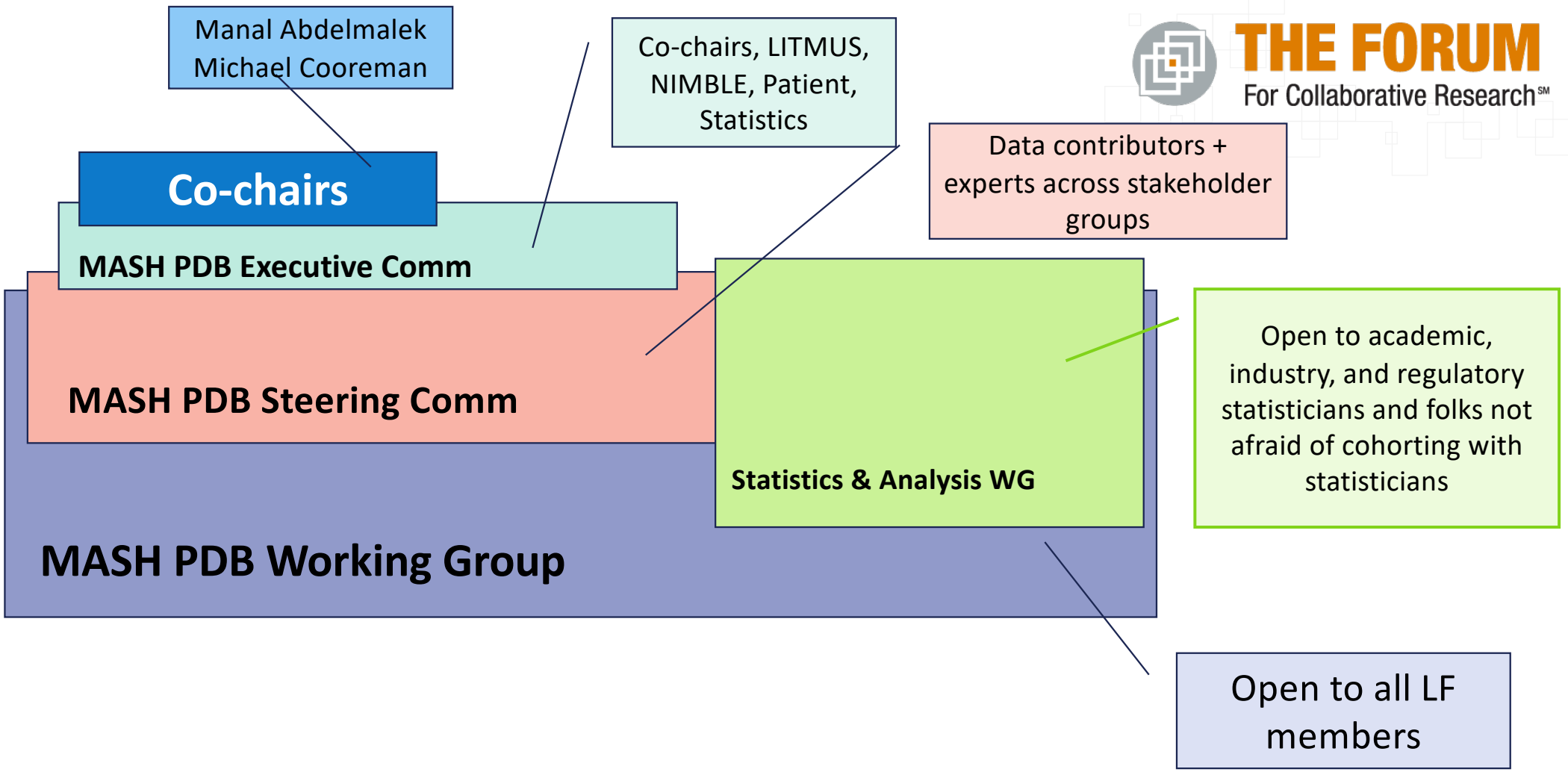
PDB Working Group


Manal Abdelmalek
Michael Cooreman
Co-chairs, LITMUS, NIMBLE, Patient, Statistics
Data contributors + experts across stakeholder groups
Co-chairs
MASH PDB Executive Comm
MASH PDB Steering Comm
Statistics & Analysis WG
MASH PDB Working Group
Open to academic, industry, and regulatory statisticians and folks not afraid of cohorting with statisticians
Open to all LF members

MASH PDB Progress

- Data Use Agreement
  - Distributed and under review
- CDISC standards
  - Potential collaboration for MASH standards
- Database infrastructure
  - Mapping data fields using CDISC and FDA technical standards for MASH

Themes/questions MASH PDB Project

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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
- Screen failures
- Application of AI/ML to paired biopsies
- Comparison of causal inference statistical methods
- Shared placebo arm in future trials
- Others?

... as identified by our Working Group

Data Sources & Data Availability

- Invited to participate:
  - All completed phase 2 and phase 3 studies
- Potential total # of placebo patients: ~5,500*
- Strong commitment: ~1,950
  - Verbal, “handshake”, reviewing DUA
- Negative: 0

* Azza Karrar LF14 Presentation

First Proposed Research Use Case
Analysis of Biomarker Fluctuation

- Over time/across studies
- Circulating
  - Clinical
  - Liver function
  - Fibrosis
  - Metabolic
- Imaging
- Specialized biomarkers (next phase)

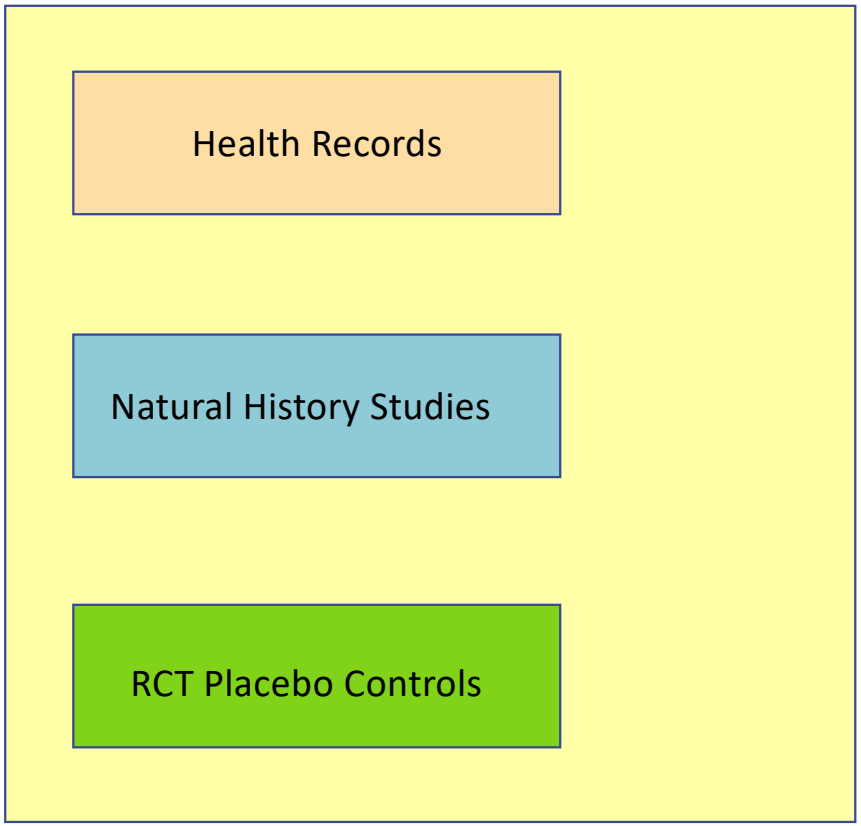
Next Steps

- Discuss proposal with SC and full WG
- Write data analysis plan
- Publication plans
- Develop next questions!

Placebo "Controlled"

- Diminishing scientific validity?
  - The smaller the patient population
    - Heterogenous patient populations
  - The longer the time of follow-up
    - Attrition
      - Survivor effect
    - Intercurrent events over 5-10 years
    - Functional unblinding

“Untreated” Patient Data



Working Together:
Explore potential for shared placebo arms based on “placebo cohort” as an intermediate to traditional master protocol trial design

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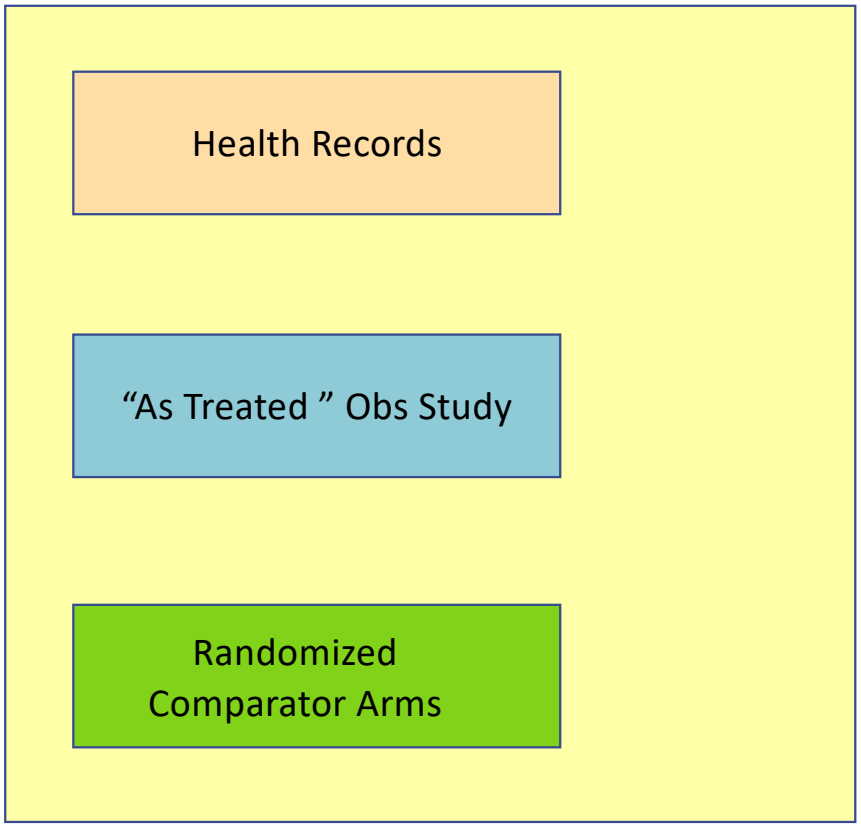
“SOC” Patient Data



Working Together:
Explore causal inference methodologies to strengthen scientific study outcomes

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Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler[1,2,*], Francesco Pignatti[1], Brigitte Schwarzer-Daum[2,3], Ana Hidalgo-Simon[1], Irmgard Eichler[1], Peter Arlett[1,4], Anthony Humphreys[1], Spiros Vamvakas[1], Nikolai Brun[5] and Guido Rasi[1,6]

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CONCLUSION

The nature of new drugs coming to market and the conundrum of demonstrating moderate effects in very small populations dictates new ways of generating decision-quality evidence. Nostalgia for the "magic" of large RCTs and prolonging the debate about "RCTs vs. RWE" are unhelpful. Whereas fully acknowledging the need to improve the feasibility of RCTs,[1] we need to embrace the inevitable change and explore sound, explicit methods of synthesizing randomized and nonrandomized data, including the time after market introduction.

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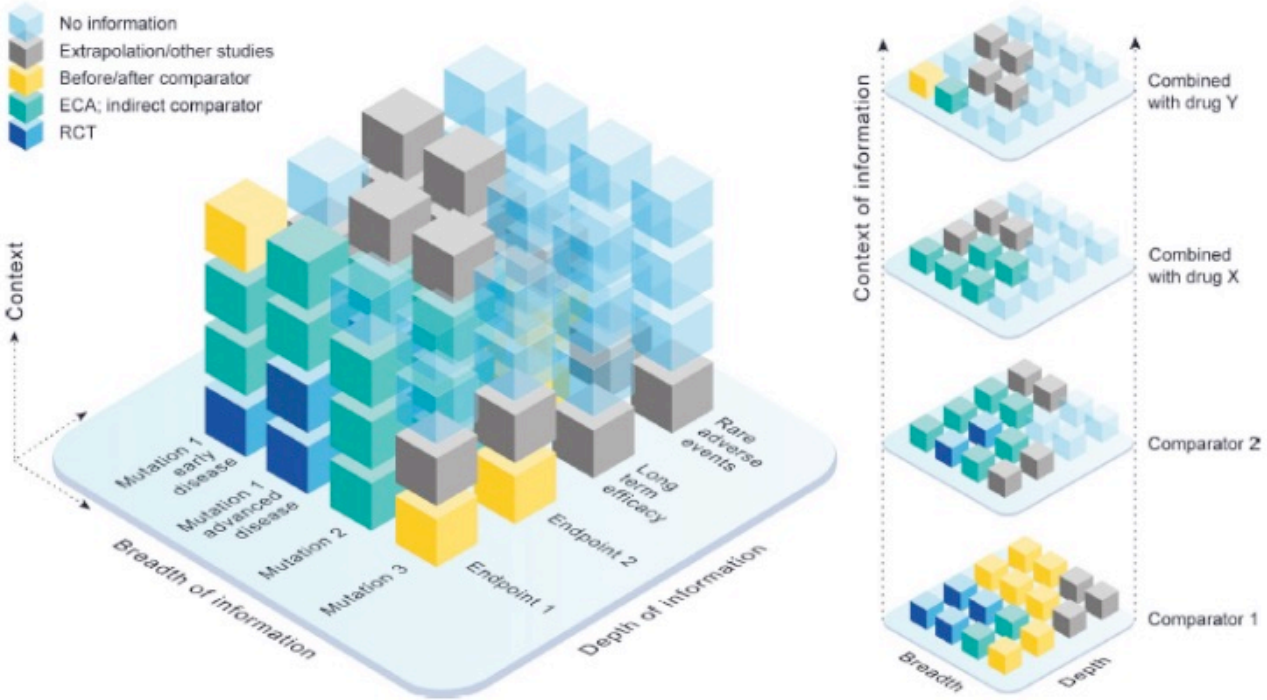

Figure 1 The complex matrix of research questions and methods. The graphic conceptualizes the complexities of research questions associated with a hypothetical drug treatment intended for a disease condition caused by different mutations in individual patients. Complexity is defined along three axes: the x-axis depicts breadth of information (i.e., different patient subgroups, based on mutation, phenotype, or disease stage), the z-axis depicts depth of information (i.e., different types of efficacy or safety end points of interest), and the y-axis depicts context of information (i.e., different comparators or treatment combinations). Each cell in the three-dimensional matrix represents an item of information that may be relevant for a particular decision maker and/or patient subgroup. Different study types (symbolized by different colors) will be required to generate the information, given the appropriateness of methods for different research questions as well as practical constraints on evidence generation. Note that for some research questions, there will be no data and information available at all, at least at the time of market launch. See main text for real-life examples that fit the schematic. ECA, external control arm; RCT, randomized controlled trial.

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Thank You
Liver Forum 16
March 22-23
Washington DC

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