



PARIS MASH MEETING

11th edition

Organized by
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September 11 & 12, 2025
Institut Pasteur, Paris





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SESSION 6: CLINICAL TRIALS

Design of trials in real-world setting to establish value of MASH therapies

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Motivation for Real-World Setting Trials

Patients

Healthcare
providers

Regulators

Payers

Industry

- Reduced burden of visits and procedure and broader patient access
- Accelerated enrolment and increased efficiency
- Results generalizability and focus on patient-relevant outcomes
- Patient-centric longitudinal data collection
- Evidence reflecting more inclusive and diverse population
- Evidence reflecting clinical practice
- Maintained randomization

Focus on Randomized Pragmatic Trials

Continuum of designs

Confirmatory
Trials

Pragmatic trials

Observational
Evidence

Eligibility - Recruitment - Setting - Organization - Flexibility in delivery/adherence - Follow-up - Primary outcome/analysis

Augmented
RCT

RCT with
decentralized
elements

Embedded
RCT

Registry-
based RCT*

Decentralized
RCT

*Registry-based study ≠ Patient registry

**Robust causal inference
conclusion on treatment effect**



**External validity to be
applicable to clinical practice**

Pragmatic Confirmatory Trials

Considerations for Decentralized studies

- Identify and manage bias
 - Assessment to be specified by protocol
- Increased variability
 - Standardization of procedures
- Samples size determination
 - Adaptive designs
- Non-inferiority margin determination

Applications for Pragmatic studies

- Approved drugs studied for new indications, populations, routes of administration, doses
- Safety and other post-market studies
- Comparative effectiveness studies
- Unapproved drugs with well-characterised safety
- Complement evidence generation for regulatory submission

Ford I et al. Pragmatic Trials. NEJM, 2016., PRECIS-2; <https://www.fda.gov/media/152503/download>; <https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica>; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrating-randomized-controlled-trials-drug-and-biological-products-routine-clinical-practice>; https://health.ec.europa.eu/document/download/2ccc46bf-2739-4b9a-ab6b-6f425db78c61_en?filename=mp_decentralised-elements_clinical-trials_rec_en.pdf; <https://www.ema.europa.eu/en/guideline-registry-based-studies-scientific-guideline>; <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/accelerating-clinical-trials-eu-act-eu>
FDA Draft Guidance "Conducting Clinical Trials With Decentralized Elements" Sept 2024

Considerations limiting generalizability

Confirmatory trials

- Strict inclusion / exclusion criteria
 - Exclude comorbidities
 - Restrict enrolment
- Treatment under experimental conditions
 - Endpoint
 - Comparator selection
 - Permitted concomitant medications
 - Combinations of treatments
 - Full information in available

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MASH trials'

- Heterogeneity and overlapping diseases
- Liver biopsy to confirm diagnosis
- Long follow up for clinical endpoints
- Histopathological endpoints

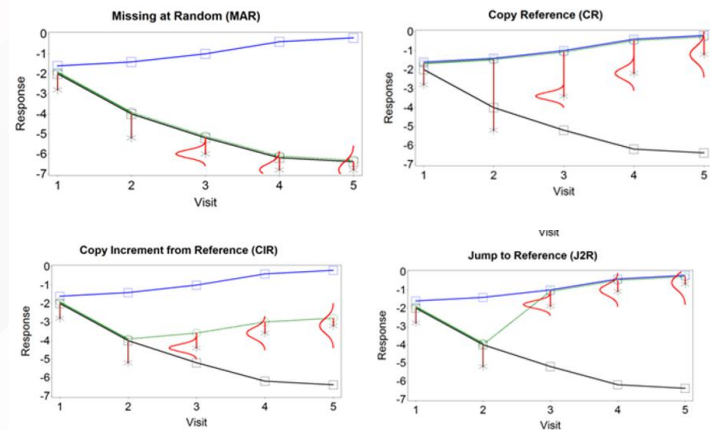
FDA accepts proposal for reasonably likely surrogate endpoint for 'MASH' all-cause mortality or liver-related events

Pragmatic trials to inform clinical practice

The goal is not to replicate RCT findings

Different Estimand

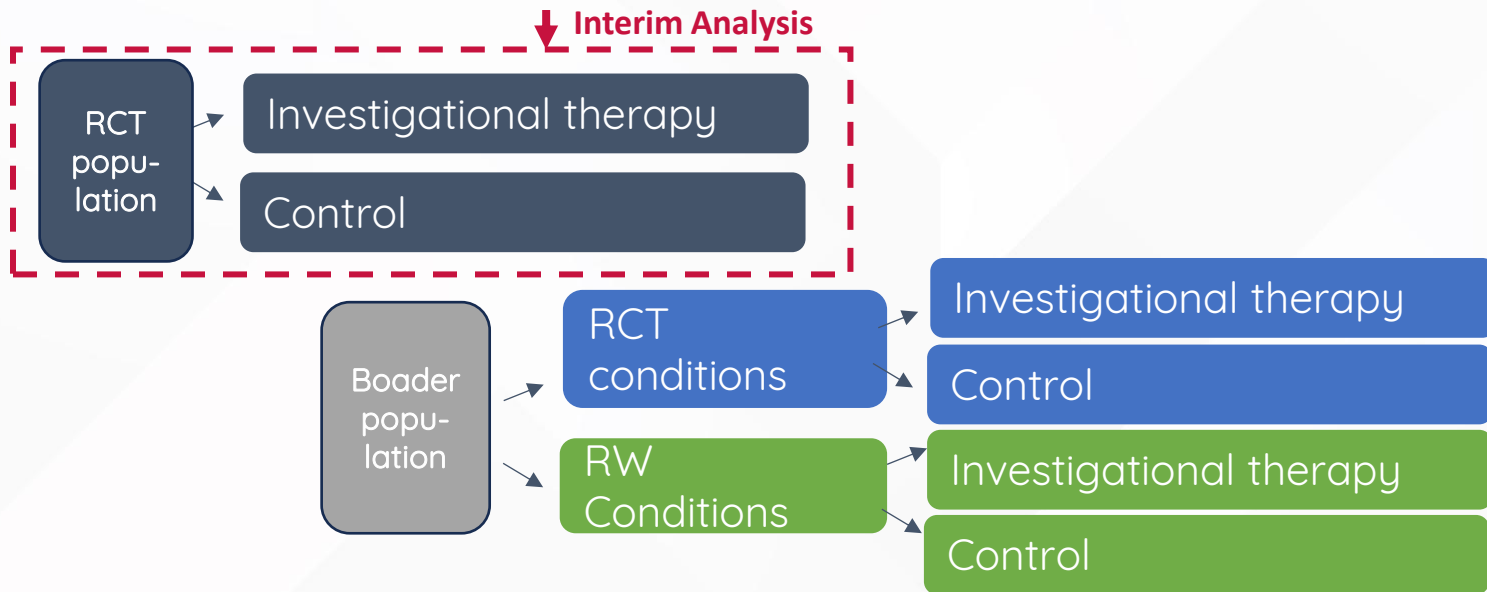
- The treatment condition of interest
- The population of patients targeted by the clinical question
- The variable (endpoint) at patient-level
- Intercurrent Events
- Population-level summary for the variable



Augmented Trials: FACTIVE design

FACTIVE = Flexible Augmented Clinical Trial for Improved evidence gEneration

Nested structure facilitates rigorous statistical analysis for causal effects of interest



Dunger-Baldauf C et al. Generating the Right Evidence at the Right Time: Principles of a New Class of Flexible Augmented Clinical Trial Designs. Clin pharmacol. ther. 2023



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Augmented Trials: Borrowing

- Designed to inform key secondary clinical endpoints
 - Composite primary endpoint -> mortality
 - Surrogate endpoint - > clinical endpoint
- “Conventional” approach to the primary analyses
- Bayesian borrowing from external control for a clinical endpoint

