phuse·hybrid

Single Day Event

Master Protocols – A Quick View

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Definition

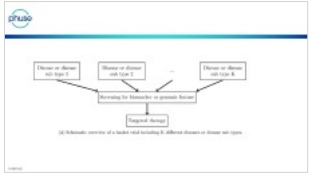
A master protocol is defined as a protocol designed with multiple sub-studies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure.

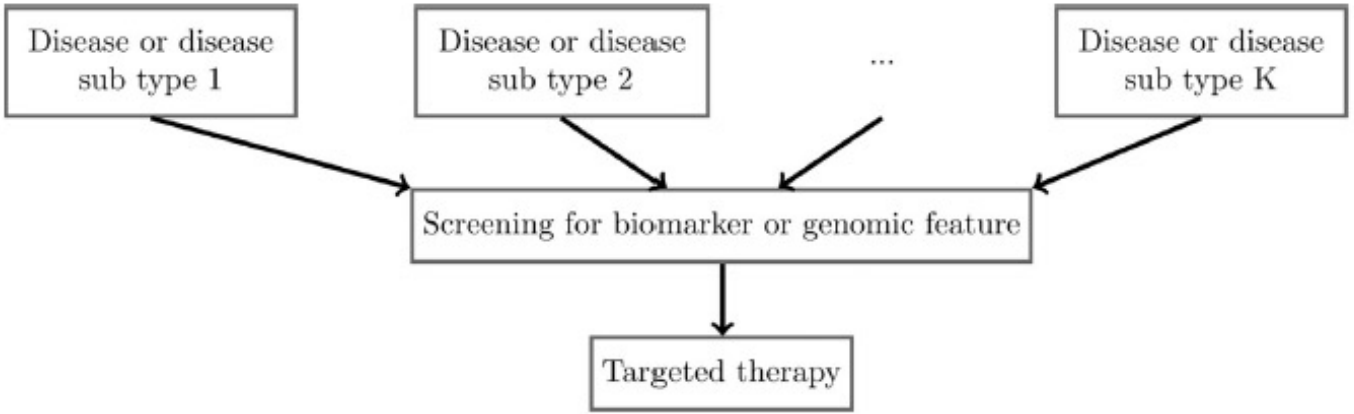
Types

- Basket Trial Design
- Umbrella Trial Design
- Platform Trial Design

Basket Trial

- A single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics
- Generally, investigate the safety/efficacy/effect of an Investigational Medicinal Products or combination of IMPs across a variety of populations
- A strong response signal seen in a sub-study may allow for expansion of the sub-study
- Each sub-study should include a detailed Statistical Analysis Plan (SAP)

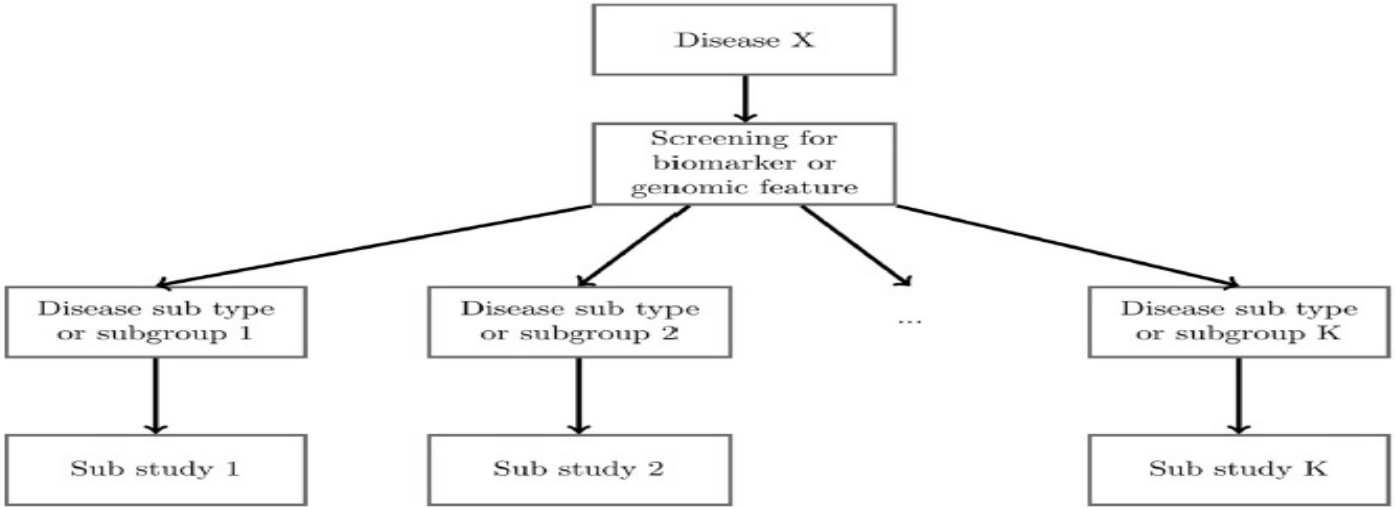




(A) Schematic overview of a basket trial including K different diseases or disease sub types.

Umbrella Trial

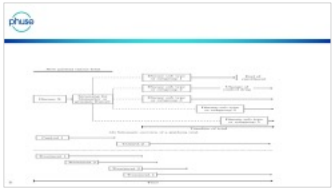
- A master protocol designed to evaluate multiple investigational drugs administered as single drugs or as drug combinations in a single disease population
- Investigate the safety/efficacy/effects of several IMPs in a single population
- Eligible patients were assigned to sub-studies based on their biomarkers or to a nonmatch therapy sub-study for patients not eligible for the biomarker-specific sub-studies

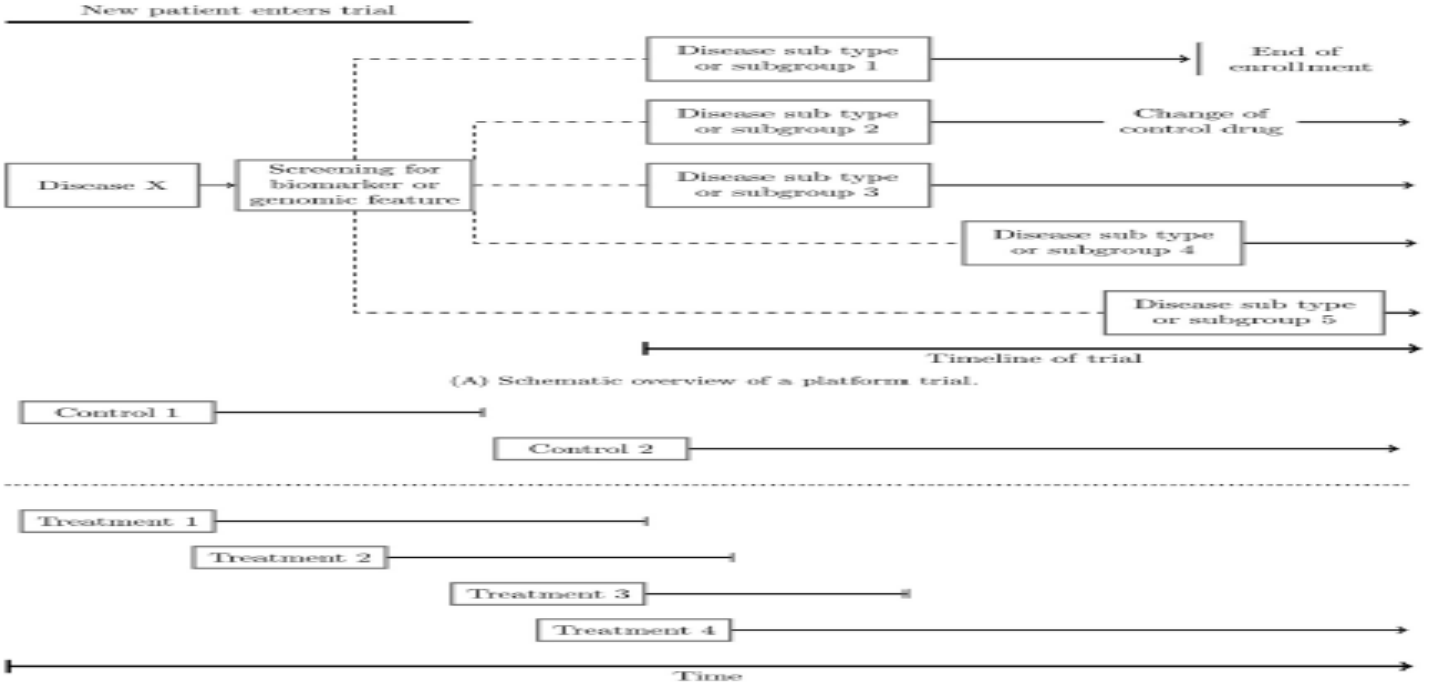


(B) Schematic overview of an umbrella trial including K different sub studies.

Platform Trial

- Incorporate design features common to both *basket* and *umbrella* trials
- May evaluate multiple investigational drugs and/or drug combination regimens across multiple tumor types
- Highly dynamic in design
- New arms can be added or dropped based on pre-defined algorithms





(A) Schematic overview of a platform trial.

Hybrid Models

Matrix

- A study that is both an umbrella and basket design
- Includes analyses in multiple disease subtypes
- No initial fixed duration or sample size

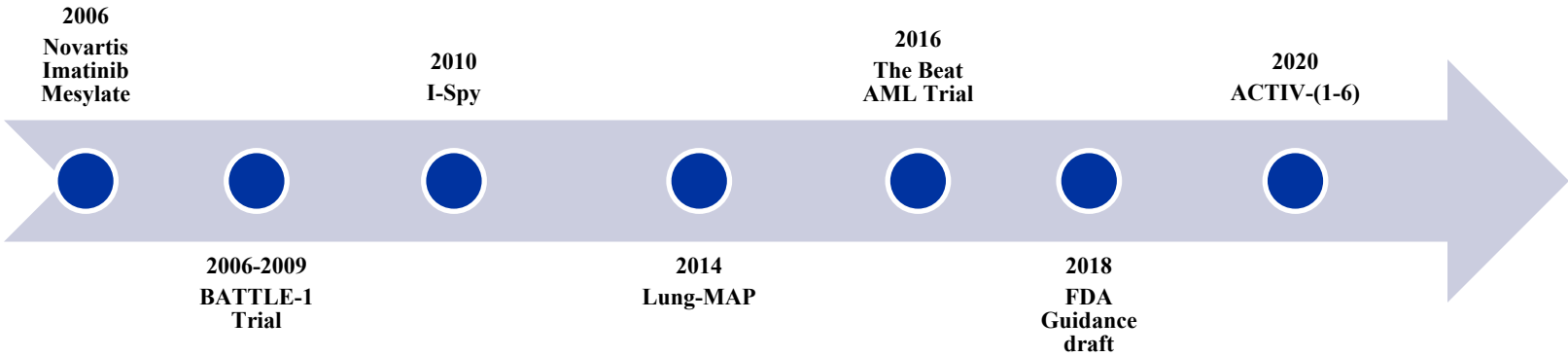
Multi-Arm Multi-Stage (MAMS)

- Framework used in combination with umbrella or platform designs
- Controls Type I Error
- Advantageous for response adaptive randomization, sub-group analysis and longitudinal modelling

POTENTIAL OPPORTUNITIES AND CHALLENGES

- Big leap in the area of precision medicine or personalized medicine
- Flexibility and efficiency in drug development
- An opportunity to incorporate efficient approaches, such as a shared control arm and/or the use of centralized data capture systems to enhance efficiency
- Difficulty in attribution of adverse events to one or more investigational drugs
- Assessing the safety profile of any given investigational drug is difficult
- The presence of multiple study groups allows potential overinterpretation of findings

EVOLUTION


2006
Novartis Imatinib Mesylate
2006-2009
BATTLE-1 Trial
2010
I-Spy
2014
Lung-MAP
2016
The Beat AML Trial
2018
FDA Guidance draft
2020
ACTIV-(1-6)

Master Protocols & COVID 19

- FDA came up with guidance IN May2021,“COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention Guidance for Industry”
- ACTIV studies – a coordinated effort to bring efficiencies in Covid 19 treatments/preventions
- ACTIV public-private partnership
- Uses mainly Umbrella and Platform designs

Master Protocols & Personalized Medicine

- I-Spy Trial Platform Design is an example
- Uses genetic profiles to highlight ‘biomarker’ differences among patients and to match drugs to patients with biomarkers that predict benefits
- Patient with same disease indication may get different therapies based on their biomarker profile in same clinical trial

Overview of Indications using Master Protocol

Indication	Basket	Umbrella	Platform
Alzheimer disease			2
Autoinflammatory disease		1	
Ebola			2
Influenza			1
Oncology	15	8	6
Ophthalmology	1		
Pneumonia			1

- Table is replicated from the article “The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review” published in Clinical Therapeutics/Volume 42, Number 7, 2020

Regulatory Guidance

- "Master Protocols: Efficient Clinical Trial Design Strategies To Expedite Development of Oncology Drugs and Biologics" by FDA in Oct 2018
- "Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials" by Clinical Trials Facilitation and Co-Ordination Group (CTFG) in Feb2019
- "COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention" by FDA issued in May 2021

For more information

- ACTIV: https://www.nih.gov/research-training/medical-research-initiatives/activ
- I-SPY: https://clinicaltrials.gov/ct2/show/NCT04488081
- BATTLE: https://clinicaltrials.gov/ct2/show/NCT00409968
- LUNG- MAP: https://www.cancer.gov/types/lung/research/lung-map
- BEAT AML: https://clinicaltrials.gov/ct2/show/NCT03013998