

Innovative Adaptive Trial Designs

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Fixed Sample Designs

- Patient population, disease assessments, treatment, sample size, hypothesis to be tested, primary outcome measure - all fixed
- No change in the design features during the study

Adaptive Designs

- A study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (interim data) from subjects in the study

Bayesian Designs

- In the Bayesian paradigm, the parameter measuring treatment effect is regarded as a random variable
- Bayesian inference is based on the posterior distribution (Bayes' Rule – updated based on observed data)
 - Outcome adaptive
- By definition adaptive design

Adaptive Designs (Frequentist or Bayesian)

- Allows for planned design modifications
- Modifications based on data accrued in the trial up to the interim time
- Unblinded or blinded interim results
- Control probability of false positive rate for multiple options
- Control operational bias
- Assumes independent increments of information

Enrichment Designs – Prognostic or Predictive

- **Untargeted or All comers design:**
 - post-hoc enrichment, prospective-retrospective designs
 - Marker evaluation after randomization (example: KRAS in cetuximab mCRC trials)
- **Marker stratified design**
 - Marker evaluation before randomization, all patients randomized
 - Stratify by marker (example: Histology in pametrexed NSCLC trials)
- **Marker strategy design**
 - Randomization to two strategies (marker based and not marker based). In marker based strategy assign marker positives to new product and negatives to SOC

Enrichment Designs – Prognostic or Predictive

- Enrichment design
 - Marker evaluation before randomization, only marker positive patients randomized (example: BRAF mutation in vemurafenib melanoma trials)
- Adaptive Enrichment design
 - All patients randomized, marker evaluation before the interim analysis
 - Based on interim results stop accruing marker negative patients if found futile or unsafe to treat patients with the new product

More Complex Designs

- Multiple markers
- Multiple Treatments
- Combination of enrichment and marker strategy design
- Adaptive designs - Modifications based on data accrued in the trial up to the interim time

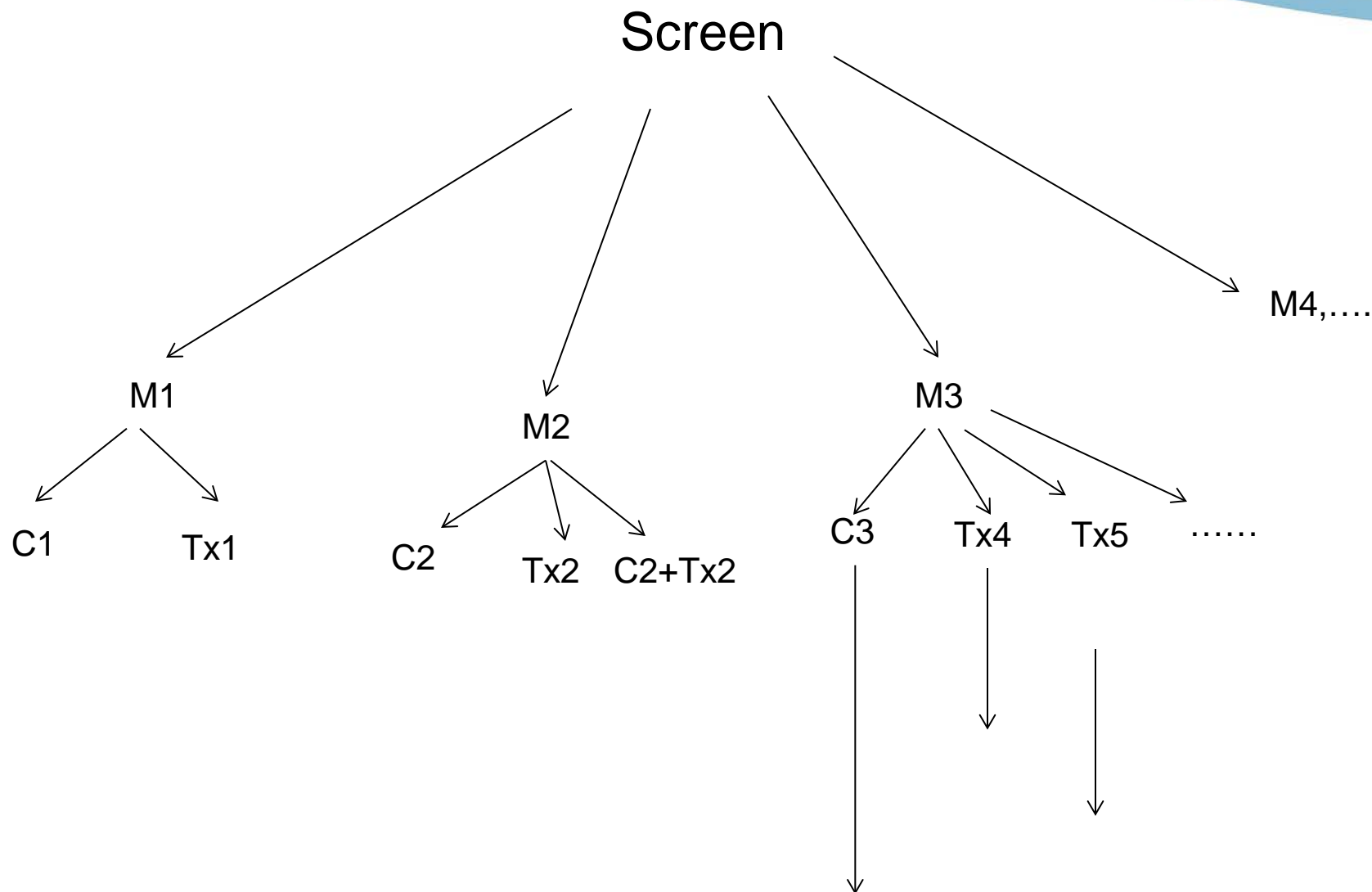
Master Protocols

- One overarching perpetual protocol that includes one or more of the following:
 - Multiple diseases
 - Multiple treatments
 - Multiple molecular markers
- Trial network – Common infrastructure
- Other names:
 - Platform Trials
 - Umbrella Trials
 - Cloud Trials
 - Basket Trials

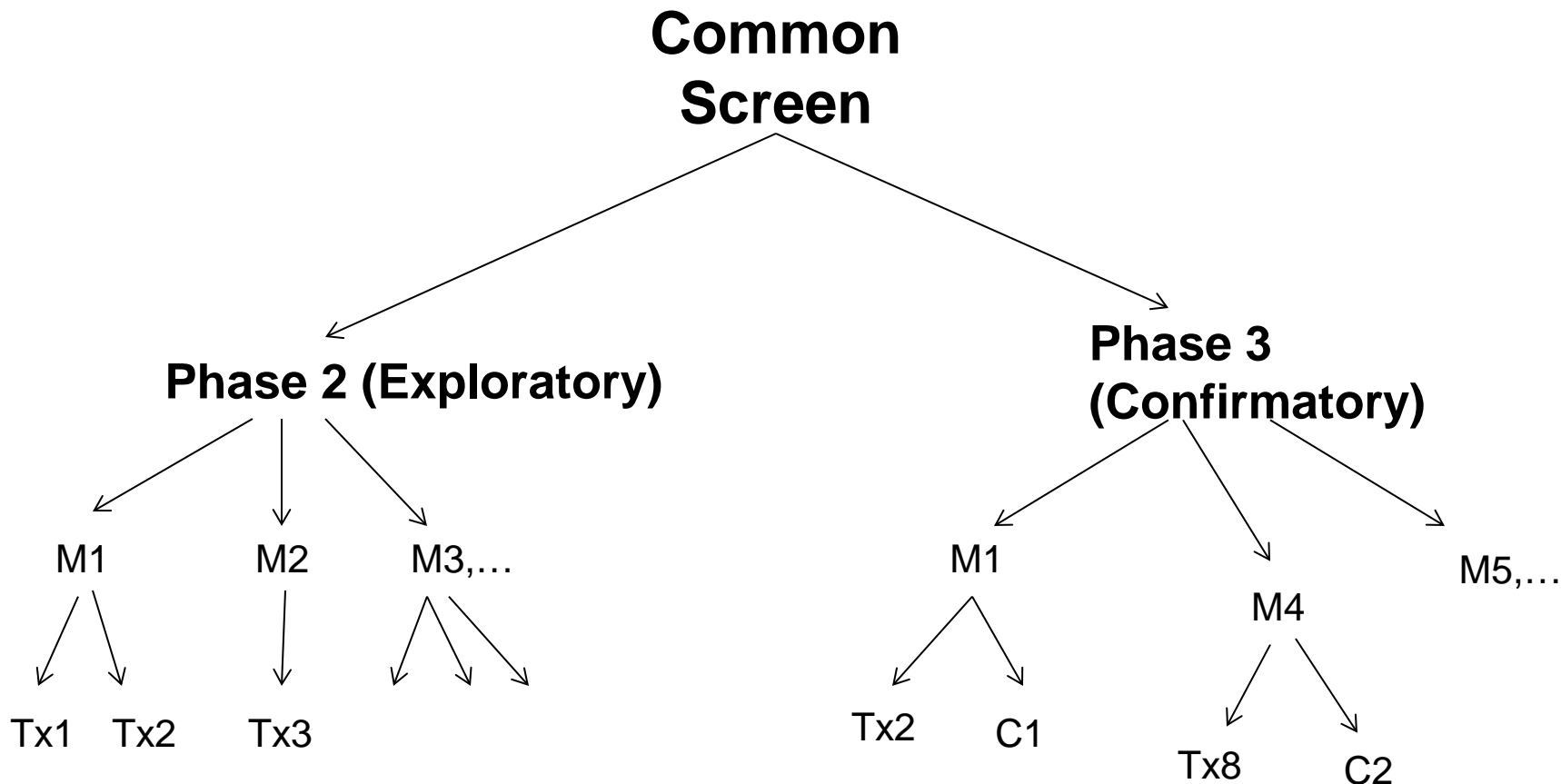
Characteristics of an Ideal Master Protocol

- One Protocol
- Central governance structure
- Central IRB
- Central DMC
- Central Independent review committee
- Central repository of data and specimens
- Study multiple drugs
 - Targeting more than one marker
 - More than one drug for one marker
- Study multiple markers
 - Overlapping expression of markers
- Leverage common control group(s)
- Flexibility to add/remove agents (Adaptive)

Example of a Schema for Master Protocol



Hypothetical Master Protocol



Example: Tx8 activity assessed outside of the Phase 2 portion of the master protocol

Master Protocols

Examples of Exploratory trials with Bayesian Designs – tumor response adaptive:

- BATTLE, BATTLE 2, I-SPY2

Examples of Exploratory trials with other adaptive Designs:

- NCI M-PACT Next Generation Trial in refractory solid tumors
- NCI-MATCH: Molecular Analysis for Therapy choice

Example of Confirmatory trial with adaptive features:

- SWOG1400: Biomarker-driven master protocol for second/third line therapy of squamous cell lung cancer
- NIH International Ebola trial (Bayesian Design): Master protocol – all investigational products with common control

Examples of approved products for “Rare” diseases

- The Imatinib Target Exploration Consortium Study (Study B2225) evaluated for the treatment of 40 different malignancies all sharing a common molecular driver BCR-ABL translocation – often referred as a basket trial. The following indications were approved based on durable response rates:
 - Dermatofibrosarcoma protuberans (incidence of 0.8-5/million/year)
 - Aggressive systemic mastocytosis (incidence 2/300,000/year – UK)
 - Hypereosinophilic syndrome/chronic eosinophilic leukemia(50 cases between 1971 to 1982 (NIH);
 - Relapsed/refractory pediatric PH+ ALL (ALL: 3-4/100,000)

Note: Incidences reported are approximate and what are available on the web

Examples of approved products for “Rare” diseases

- Siltuximab for the treatment of Multicentric Castleman’s disease - approval based on a randomized placebo controlled trial
 - **Total Sample size = 79; 2:1 randomization (53 vs. 26)**
 - Primary endpoint: durable tumor and symptomatic response
 - Prevalence < 1/100,000
 - Small randomized trials are adequate to demonstrate big treatment effect (34% vs. 0% response)

Note: Prevalence reported is approximate and what are available on the web

Examples of approved products for “Rare” diseases

- Ibrutinib for the treatment of Waldenstrom's Macroglobulinemia - approval based on a single arm trial
 - Total Sample size = 63
 - Primary endpoint: durable tumor response
 - Prevalence < 1/100,000
 - Unprecedented response rate (62%)

Note: Prevalence reported is approximate and what are available on the web

Other approved products for “Rare” diseases

- Bexarotene, Denileukin Difitox, Vorinostat, Romidepsin: Cutaneous T-cell lymphoma (6.4/million/year) – based on single arm trials
- *Eculizumab*: Paroxysmal Nocturnal Hemoglobinuria (incidence of 0.13/100,000/year – UK) – based on randomized clinical trial (N=87, 1:1 randomization)
- *Bortezomib*: Mantle cell lymphoma (1/100,000/year) based on single arm trial
- Everolimus: Subependymal giant cell astrocytoma (prevalence of 0.1 in 10,000 to 30,000) – based on randomized clinical trial in pediatric and adult patients (N = 117, 2:1 randomization)

Note: Incidences reported are approximate and what are available on the web

Challenges in Rare Disease

- Natural history of the disease unknown
- Incidence/prevalence unknown
- Short term vs. Long term disease
- Relationship between endpoints unknown
- Feasibility?

Key Considerations

- Objective: Assess activity *vs.* confirm efficacy
- Disease defined by molecular signature only *vs.* site of disease, histology and molecular signature
- Prevalence of each sub-population
- Knowledge of natural history of the disease in each of the sub-populations
- Available data from Phase 1 and Phase 2 studies: appropriate dose and preliminary information on activity
- Known targets?
- Feasibility of execution of the study – global trials adds even more complexity

Summary

- Trial networks with established infrastructure and use of a common protocol can address many of the challenges
 - Optimize trial design and conduct to realize efficiencies and improve data quality through centralization of processes, systems, and training
- Innovative trial designs could be considered, given the network infrastructure and resources available to implement such designs
 - Adaptive trial designs with stopping/adding treatment arms and/or new molecular subgroups; change of control arm – perpetually open trials?
 - Repository of data useful in designing future trials
- Overall objective is to serve the patients by reducing time and cost of developing promising drugs and bringing beneficial drugs to market expeditiously