Recommendations for Multi-Arm Umbrella Trials and Platform Trials

Daniel Rubin

Food and Drug Administration (FDA/CDER/OTS/OB/DBIV)

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Disclaimer

- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.
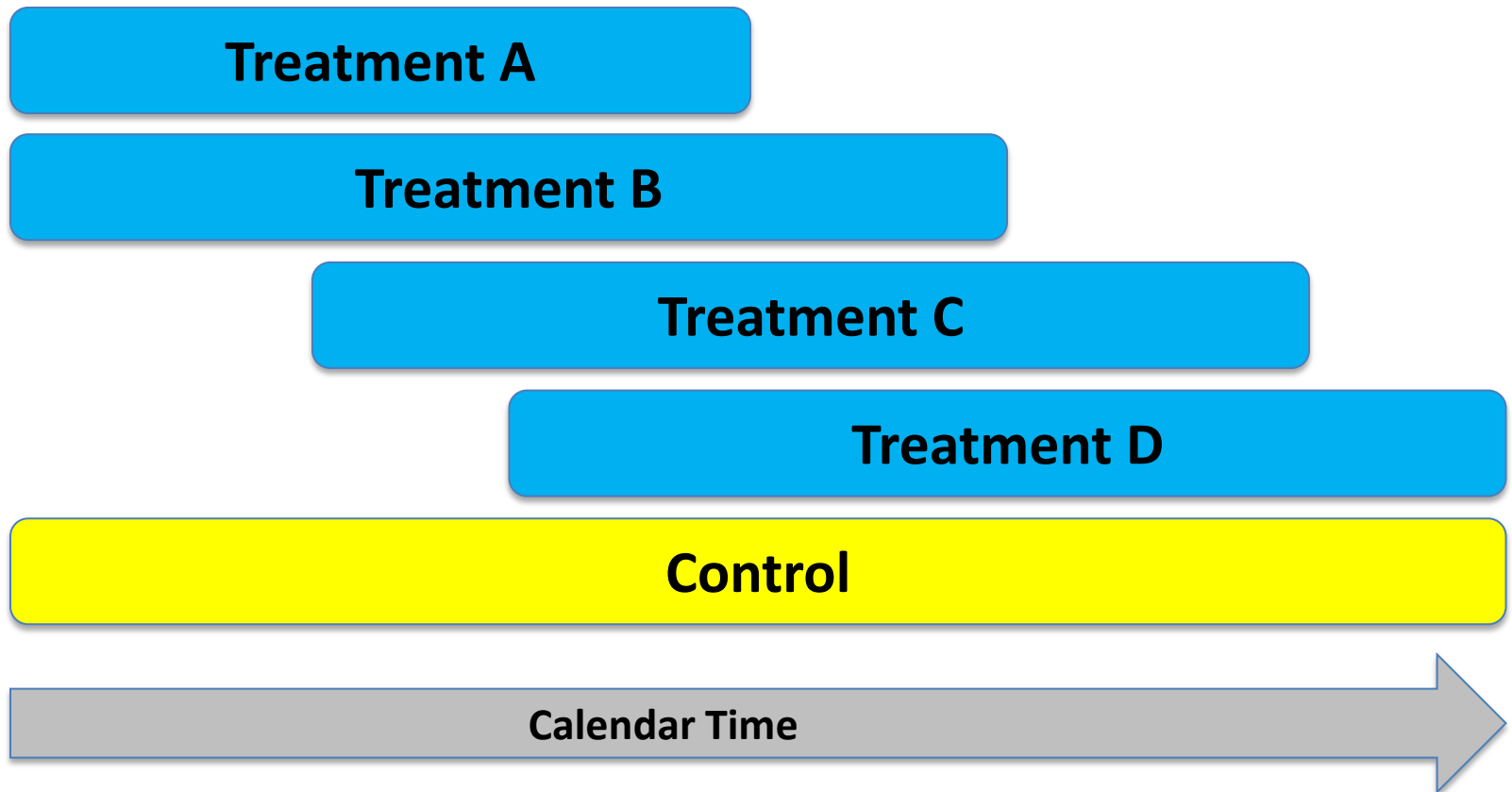
Outline

- Master protocols
- Control groups and randomization
- Blinding
- Multiplicity
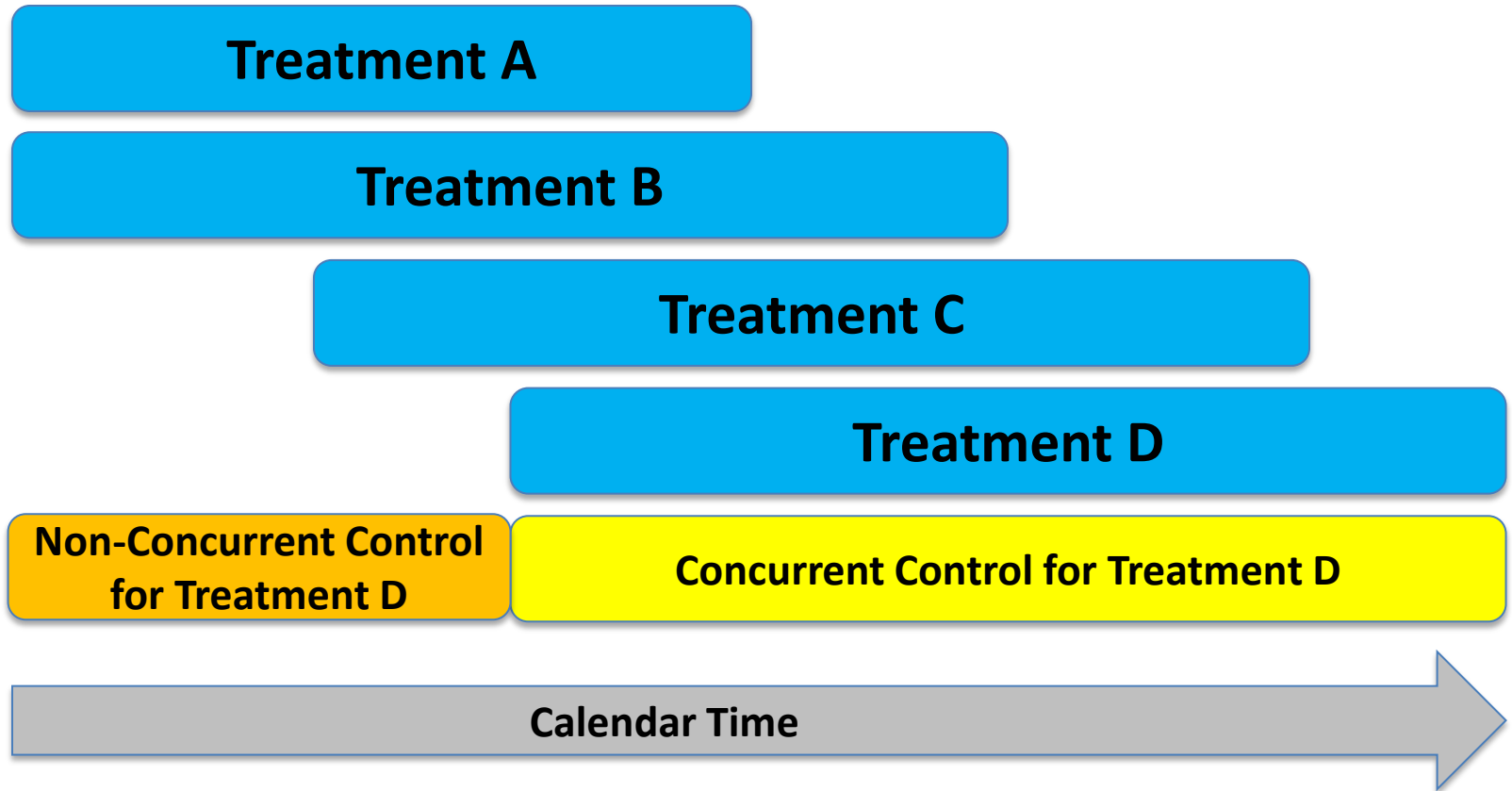- Disseminating results
- Summary

Definitions

- A *master protocol* is an overarching protocol with multiple substudies to evaluate one or more therapies in one or more disease subtypes
  - A *basket trial* evaluates a single therapy in multiple diseases or disease subtypes
  - An *umbrella trial* evaluates multiple therapies simultaneously for a single disease
  - A *platform trial* evaluates multiple therapies for a single disease in a perpetual manner, with therapies allowed to enter or leave the platform over time

An Example Platform Trial

Treatment A

Treatment B

Treatment C

Treatment D

Control

Calendar Time →

An Example Platform Trial

Treatment A

Treatment B

Treatment C

Treatment D

Non-Concurrent Control for Treatment D

Concurrent Control for Treatment D

Calendar Time

Motivation for umbrella and platform trials

- Increased efficiency through shared design components and operational aspects
  - Shared protocol elements, such as visit schedule, measurement procedures, control arm
  - Shared infrastructure, such as network of clinical sites, single system for data management, central randomization system
- Direct comparisons between treatment options

Master Protocols and COVID-19

FDA Commissioner Says Agency Wants to Develop Master Protocol Trials to Test Multiple COVID-19 Drug and Vaccine Candidates at Once

April 20, 2020

To get COVID-19 vaccine and therapeutics candidates through the pipeline faster, FDA Commissioner Stephen Hahn said yesterday that the agency is interested in developing master protocols, possibly in conjunction with regulatory agencies in other countries.

In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, master protocols use a single infrastructure, trial design and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple substudies, allowing for efficient and accelerated drug development. The drug candidates are each compared to the control group but not to one another.

"It's a very efficient way of looking at multiple different therapeutics, vaccines," said Hahn in a public presentation.

Master Protocols and COVID-19

"…Today, we're providing industry guidance for creating master protocols (an overarching protocol designed to answer multiple questions) when evaluating drugs for the treatment or prevention of COVID-19… Master protocols that are well designed and executed can accelerate drug development by maximizing the amount of information obtained from the research effort. These trials can be updated to incorporate new scientific information, as medical science advances. Master protocols also reduce administrative costs and time associated with starting up new trial sites for each investigational drug. They can also increase data quality and efficiency through shared and reusable infrastructure. These advantages are of particular importance during a public health emergency such as the current SARS-CoV-2 pandemic, where there is a critical need for efficient drug development. The FDA expects master protocols to continue to play an important role in addressing the public health needs created by the pandemic and in generating clinical evidence in general."

- Janet Woodcock, May 17, 2021

Selected Examples in COVID-19

- RECOVERY Trial
- ACTT Trials
- ACTIV Trials
- I-SPY COVID-19 Trial
- COMMUNITY Trial
- PANORAMIC Trial
- REMAP-CAP Trial
- TOGETHER Trial
- WHO Solidarity Trial

Concurrently Controlled Comparisons

- Use of only concurrently randomized control patients is usually recommended

- This avoids potential systematic differences between drug and non-concurrent control due to changes over time in patient characteristics, trial conduct, or standards of care

Utilizing Concurrent Control Data

External
control

Non-concurrent
randomization

Concurrent
randomization

Reliability
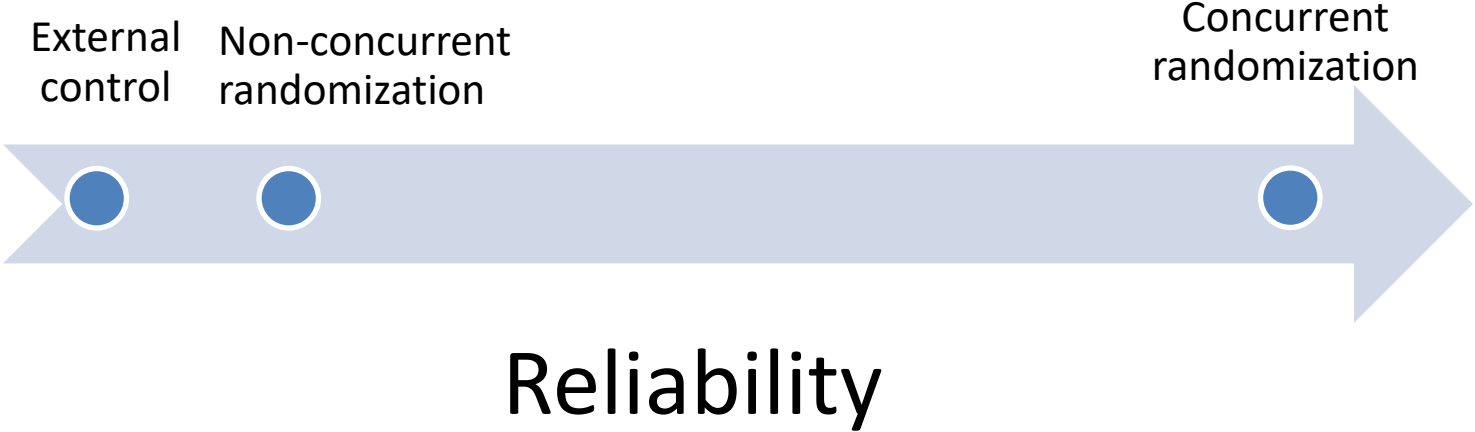
Preserving the Integrity of Randomization

- Comparison for given drug should (typically) be against only those control patients who were eligible for and could have been randomized to drug

- Example: issues with two-stage consent process
  - Impact of knowledge of specific drug/subprotocol on consent may result in lack of comparability between drug and shared control
  - Alternative to avoid issue: single informed consent covering all active drugs prior to randomization

- Example: scenario with fixed randomization scheme resulting in changes in ratio between given drug and control over time
(e.g., randomization ratio of sqrt(k):1:…:1 with k active drugs)
  - Analyses comparing drug to control should account for time periods with different randomization ratios, such as by stratifying by time periods defined by changes in number of active drugs

Leveraging Non-Concurrent Control Data

- Likely most reasonable in settings with different bias-variance tradeoffs such as trials in rare diseases and early-phase trials

- Rationale to leverage non-concurrent control data should include:
  - Likelihood of changes over time in prognostic factors
  - Feasibility of utilizing only concurrent control data
  - Extent of non-concurrent control data expected to be utilized
  - Ability and underlying assumptions of primary analysis methods to mitigate confounding and plan for sensitivity analyses to evaluate varying assumptions (e.g., less weighting of non-concurrent data)

Blinding

- If blinding to treatment assignment is considered critical, different strategies may be considered

- Multiple-dummy design (complete blinding)
  - Becomes impractical as number of different administrations increases

- Distinct placebo for each drug (partial blinding)
  - Patients first randomized to drug-specific subprotocol (among those they are eligible for) and then to that drug or matched placebo
  - Statistical comparisons for given drug include patients eligible for drug but randomized to placebo groups for other drugs
  - Bias possible if knowledge of subprotocol affects outcomes (but potential for bias mitigated relative to fully open-label design)

Example of Randomization and Partial Blinding Scheme

1. Randomize with equal probability (1:1:…:1) to one of drugs patients is eligible to receive

2. Randomize to drug or matching placebo with probability k:1 where k is number of drugs patient is eligible to receive
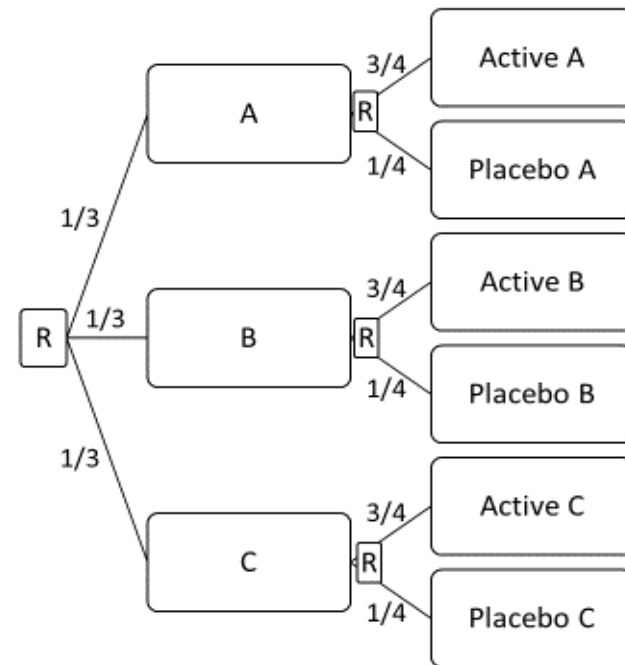
Example when there are 3 active agents that a patient is eligible to receive

Multiplicity Recommendation

- We generally do not recommend multiplicity adjustments to control the probability of at least one Type I error across the multiple comparisons of different drugs to the control group

Rationale for Multiplicity Recommendation

- Comparisons of different drugs to control aligned with distinct objectives typically evaluated in independent trials without multiplicity control across trials

- Relative to separate independent trials of each drug, an umbrella or platform trial with a shared control arm has:*
  - Equivalent expected total number of Type I errors
  - Lower probability of at least one Type I error
  - Greater probability of multiple Type I errors

- Strategies to control probability of at least one Type I error not aligned with strength of evidence
  - Correlation ↓ Collective evidence ↑ Adjusted significance level ↓

* See, e.g., Proschan and Follmann and Howard et al.

Additional Notes on Multiplicity

- There may be different considerations in special circumstances, such as closely related products or combination products

- Considerations related to Type I error rate control are similar to those in non-platform trials for other sources of multiplicity, such as multiple endpoints or multiple doses

- Should consider probability distribution for number of Type I errors and potential for multiple correlated erroneous findings
  - e.g., consider greater-than-equal allocation to control arm

- Additional factors beyond p-value important to evidence evaluation
  - Meaningfulness of effect; quality of design and conduct; results for other endpoints; robustness to assumption violations; substantiation in independent study; relevant external information; results for other master protocol drugs

Disseminating results

- Inadvertent dissemination of information from an ongoing trial conducted under a master protocol may pose a risk to trial integrity

- Example 1:
    - The primary endpoint is time to death
    - Multiple drugs enter the platform trial at approximately the same time
    - Event-driven sample sizes for each (drug versus control) comparison
    - If target number of events is reached for one (drug versus control) comparison and the drug is superior, strongly suggests that other drugs still under evaluation are also superior as they have had even fewer deaths

- Example 2:
    - Unblinded results reported for first drug while second drug still under evaluation
    - Knowledge of comparative results for (first drug vs control) in addition to blinded pooled results for (second drug + control) may lead to partial unblinding of comparative results for (second drug versus control)

Dissemination Considerations

- DMC and study team should carefully consider information access and communication plans and how to protect trial integrity

- Potential ways to avoid specific issues
  - Scheduling interim and final analyses at common calendar times for drugs entering trial at same time
  - Maintenance of confidentiality of pooled outcome data

Summary

- Master protocols can offer important advantages by leveraging a shared control group and other shared protocol elements

- Can add certain elements of complexity

- Master protocols involving multiple stakeholders can require increased coordination

A Few References

- FDA Guidance *COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention*

- FDA Guidance *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics*

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Acknowledgments

- FDA/CDER/OTS/OB Master Protocols Working Group (Chair: Greg Levin)