Recommendations and Considerations for Umbrella and Platform Trials

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Outline

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- Master Protocols during COVID-19
- Recommendations and Considerations
  - Randomization
  - Blinding
  - Control Group
  - Informed Consent
  - Multiplicity
  - Dissemination of Results
  - Adaptive Designs
- Conclusions

INTRODUCTION

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
- Focus today is on randomized umbrella and platform trials

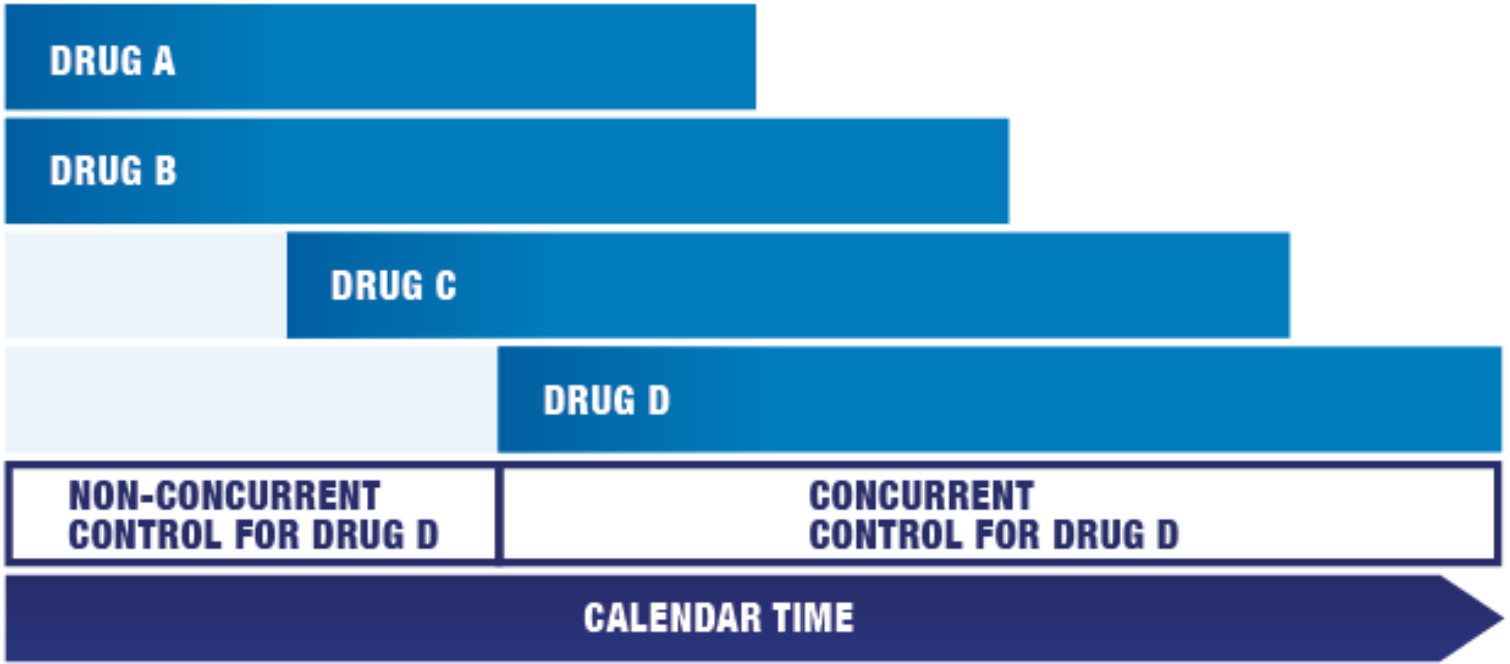
Additional Definitions

- A **substudy** contains the information and design features specific to evaluation of a single drug in a single disease or disease subtype under the master protocol
- A **master protocol sponsor** is the person or organization who takes responsibility for and initiates the master protocol
- An **individual drug sponsor** is the person or organization who takes responsibility for and initiates a clinical investigation of an individual drug
- A master protocol sponsor and an individual drug sponsor may or may not be the same entity.

Communication Between Different Stakeholders

- Master protocol sponsor communicates with
  - regulatory agencies
  - individual drug sponsors
  - Data Monitoring Committee (DMC)
  - Investigators
- A communication plan for timely and effective communications
- Ensure rapid communication of serious safety issues

Example Platform Trial

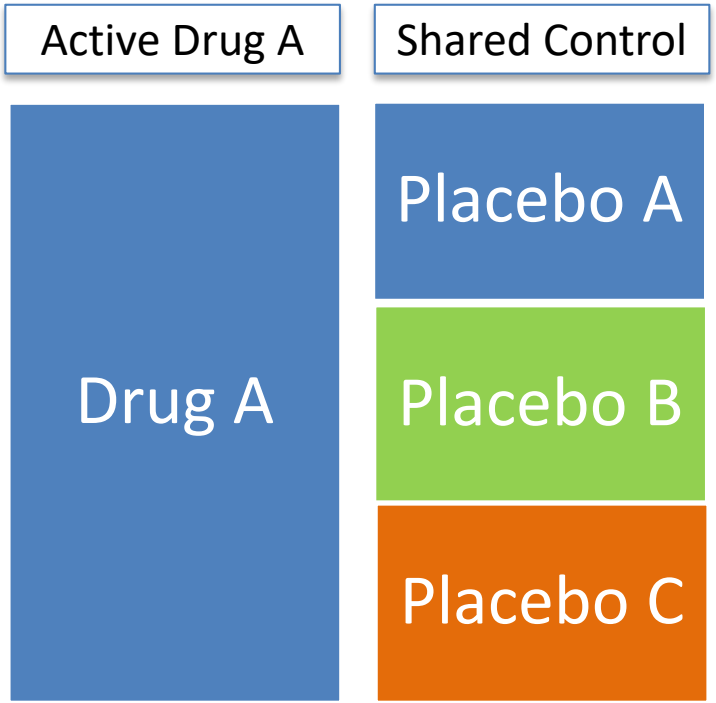


Potential Advantages of Umbrella/Platform Trials

- Shared control data
- Shared protocol elements
  - E.g., visit schedule, measurement procedures
- Shared infrastructure
  - E.g., network of clinical sites, central facilities, central randomization system, data management systems
- Shared oversight

Complexities of Umbrella/Platform Trials

- Start up time
- Implementation of blinding
- Alterations in conduct of one substudy may lead to challenges in the analysis if shared control arm used
  - e.g., selective data collection that is substudy-specific



MASTER PROTOCOLS DURING COVID-19

Master Protocols During 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.

Source: https://www.centerwatch.com/articles/24655-fda-commissioner-says-agency-wants-to-develop-master-protocol-trials-to-test-multiple-covid-19-drug-and-vaccine-candidates-at-once

COVID-19 Master Protocols Guidance

"…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

Source: https://www.fda.gov/news-events/press-announcements/fda-brief-fda-provides-guidance-master-protocols-evaluating-prevention-treatment-options-covid-19

Some Examples in COVID-19

- Adaptive COVID-19 Treatment Trial (ACTT)
- Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Trials
- COVID-19 Multiple Agents and Modulators Unified Industry Members (COMMUNITY) Trial
- Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial

COVID-19 Master Protocols

Varying attributes of COVID-19 master protocols

- Goals: screening vs. confirmatory
- Master protocol sponsor types: government, industry, academia
- Patient populations (disease severity): outpatient, hospitalized
- Approaches to inclusion of products: repurposed vs. novel products, drug class specific vs. multiple classes

Recommendations and Considerations

RANDOMIZATION

Randomization Recommendations

- Randomization is recommended to remove systematic imbalances between treatment arms in both measured and unmeasured prognostic factors and to ensure reliable inference
- May be necessary to utilize drug-specific eligibility criteria
  - Subjects should not be randomized to a drug substudy for which they are not eligible

Randomization Recommendations

- If randomization ratio to a drug and its control group changes, the analysis should account for time periods of different randomization ratios
- Consider allocating more subjects to the control arm than each individual drug arm
  - Reduces the chance of multiple correlated erroneous findings
  - Can lead to increased power

Randomization ratio with optimal power

- Consider an umbrella trial with a fixed total sample size
- Assume treatment effect is the same for each drug, outcomes for all groups have the same variance
- $\sqrt{k}:1$ allocation for pooled control arm to a given drug has optimal power
  - k = number of drugs for which a subject is eligible to be randomized
- Gives a larger sample size for each drug vs. pooled control comparison
- Probability that a subject will be assigned to control is less than in a typical two-arm controlled trial with 1:1 randomization

Example

- Total sample size for the umbrella trial is fixed at 600 subjects
- 4 drugs and 1 shared control group.
- $\sqrt{k}$: 1 ratio
  - 200 subjects allocated to the shared control group
  - 100 subjects allocated to each drug group
  - 300 subjects for the comparison of a given drug to the control group.
- 1:1 ratio
  - 120 subjects allocated to the shared control group
  - 120 subjects allocated to each drug group
  - 240 subjects for the comparison of a given drug to the control group

Recommendations and Considerations

BLINDING

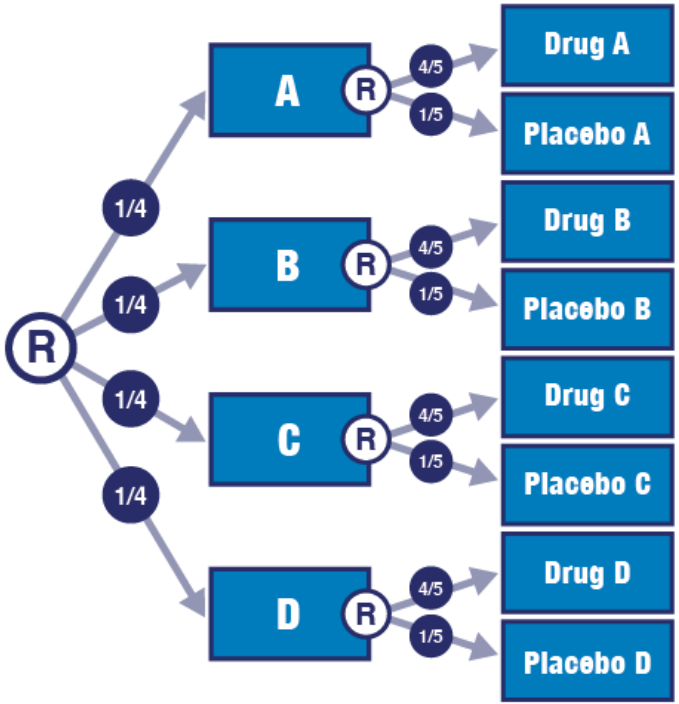
Blinding

- **Complete blinding –** blinded to both the drug-specific substudy and to drug vs. control
  - Multiple dummies
  - May become infeasible as number of drugs increases
- **Partial blinding -** knowledge of assigned drug-specific substudy but blinded to drug vs. matched control
  - Primary analysis could use shared control group
  - Sensitivity analysis can compare each drug to only those subjects receiving the matched control
    - Randomized, completely blinded, though likely underpowered

Considerations for Partial Blinding

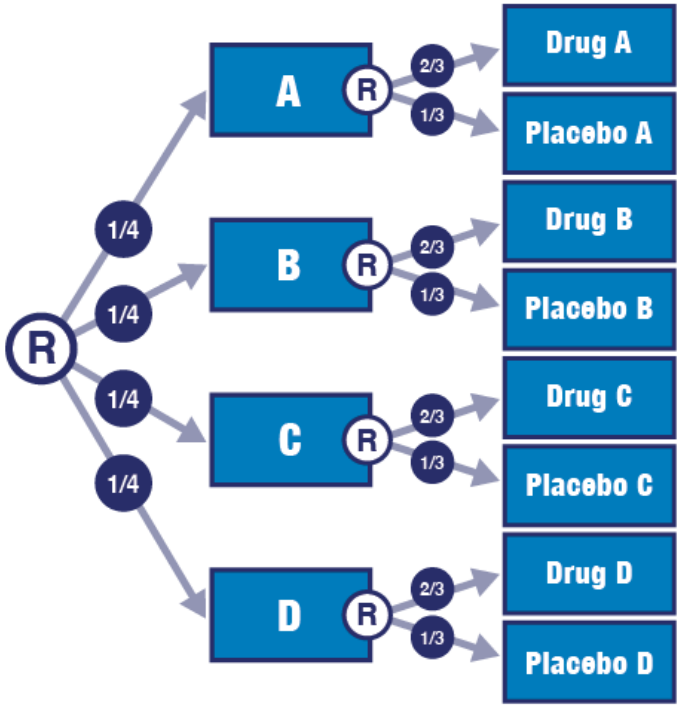
- Consider whether this strategy adequately addresses sources of potential bias
- Are main outcomes of interest likely to be affected by
  - knowledge of the assigned drug-specific substudy, or
  - different routes and/or schedules of administration of drugs in the master protocol?
- If so, complete blinding is recommended

Example of Randomization Strategies for Partially-Blinded, Placebo-Controlled Studies



- 2-step randomization to target a 1:1 ratio for the pooled placebo arm relative to a given drug
  1. Randomize with equal probability (1:1:1:1) to one of the drug substudies for which the subject is eligible
  2. Randomize to the drug or matching placebo with allocation k:1, where k is the number of drugs for which the subject is eligible
- 1/5 probability receiving any placebo
- 4/5 probability receiving any drug
- Alternative randomization strategies also target a 1:1 ratio

Example of Randomization Strategies for Partially-Blinded, Placebo-Controlled Studies



- 2-step randomization to target a $\sqrt{k}:1$ ratio for the pooled placebo arm relative to a given drug, where k is the number of drugs for which the subject is eligible
  1. Randomize with equal probability (1:1:1:1) to one of the drug substudies for which the subject is eligible
  2. Randomize to the drug or matching placebo with allocation $\sqrt{k}:1$
- 1/3 probability receiving any placebo
- 2/3 probability receiving any drug

Recommendations and Considerations

CONTROL GROUP

Use of Concurrent Control

- Primary analysis generally should include only concurrently randomized subjects (i.e., a concurrent control)
- Comparison for given drug should be against only those control subjects who were eligible for and could have been randomized to drug
- Preserves the integrity of randomized comparisons
- Avoids systematic differences between groups with respect to both known and unknown factors that are prognostic of the key outcomes

Leveraging Non-Concurrent Control Data

- May be reasonable in settings with different bias-variance tradeoffs
  - e.g., early-phase trials and trials in very rare diseases with feasibility constraints
- Justification for use of non-concurrent control should address the
  - feasibility of relying on only concurrent control data
  - likelihood of temporal changes that could affect the comparison
  - amount of non-concurrent control data to be utilized
  - expected separation in calendar time between non-concurrent control subjects and initiation of randomization to the drug of interest
  - statistical methods intended to account for potential temporal changes and their underlying assumptions

Leveraging Non-Concurrent Control Data

- Use of non-concurrent data should be specified prior to the start of the trial
  - Avoids a scenario where the proposal may be motivated by seeing desirable results (e.g., a poorly performing control arm)
- Primary analysis should incorporate approaches to mitigate potential confounding due to changes in prognostic factors over time
  - Underlying assumptions of the analysis should be described
- Sensitivity analyses should be planned and conducted to understand the effect of the use of non-concurrent control data on the evaluation of the treatment effect

Recommendations and Considerations

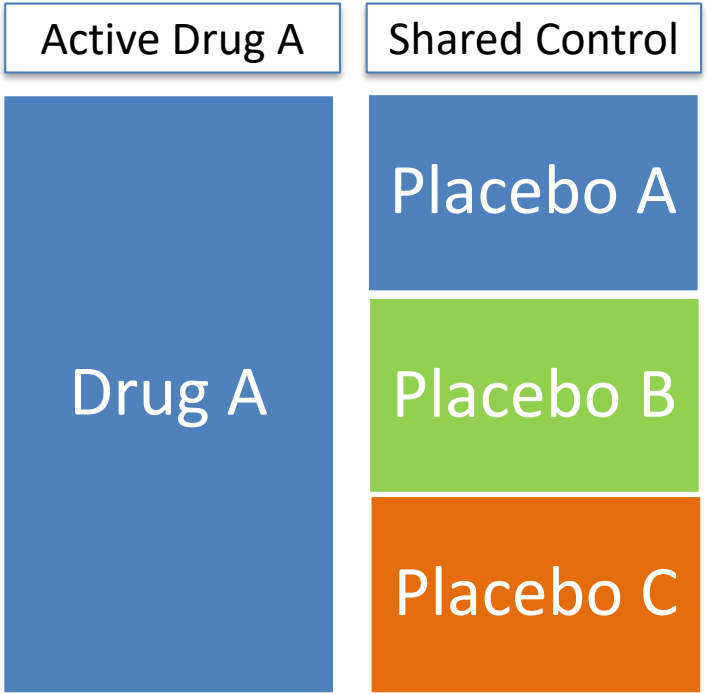
INFORMED CONSENT

Informed Consent Process

- Should occur prior to a subject's randomization and cover all treatment arms in the trial to which the subject could be randomized
- Informed consent document can be modified over time to reflect the drugs currently under evaluation in a platform trial
- Any part of a consent process that occurs after randomization raises concern about the comparability of the randomized treatment groups

Informed Consent

- Example process that is not recommended
  - Subjects consent to enter the trial
  - Randomized to one of the drug-specific substudies
  - Consent to the assigned substudy
  - Randomized to the drug or its matched control
- Comparing Drug A to the shared control arm may result in noncomparable groups
- Subjects who would consent the Drug A substudy may differ from subjects who would consent to the other drug substudies



Recommendations and Considerations

MULTIPLICITY

Multiplicity

- Do not need multiplicity adjustments to strongly control the probability of making at least one type I error across the multiple comparisons of different drugs to the control
- May be special circumstances with different considerations
  - closely related products, e.g., multiple doses, administrations, or formulations of the same drug
  - combination products

Rationale for 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
- 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

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

Additional Multiplicity Considerations

- Considerations related to Type I error rate control for other sources of multiplicity (e.g., multiple endpoints, doses) same as in other trials
- 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

Recommendations and Considerations

DISSEMINATION OF RESULTS

Dissemination of Results in Ongoing Trial

- Dissemination of results for one drug can lead to inadvertent dissemination of information about other drugs under ongoing evaluation
- Such knowledge can negatively affect trial conduct and integrity, e.g., through effects on recruitment, adherence, retention

Dissemination Example

- Event-driven trial where Drugs A, B, and C enter at same time
- Analysis after 100 recoveries (across specific drug + shared control)
- Trial reports Drug A is found to be superior to control
- Disseminated information implies that Drug B and Drug C have fewer recoveries than Drug A (given shared control, <100 recoveries)
- Inadvertent information leakage about Drugs B and C could impact trial conduct and integrity

Another Dissemination Example

- Safety reporting provides pooled mortality results (i.e., drug + shared control) for each drug-specific substudy
- If drugs entered trial around same time, these data could be used to compare mortality rates between drugs
- This information could negatively impact trial conduct and integrity

Dissemination Considerations

- DMC and study team should carefully consider information access, 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

Recommendations and Considerations

ADAPTIVE DESIGNS

Adaptive Designs

- Use of adaptive design elements requires careful consideration
- Important principles discussed in FDA guidance for industry, *Adaptive Designs for Clinical Trials of Drugs and Biologics* are generally applicable to adaptive designs for master protocols
- May be unique challenges in umbrella and platform trials

Example of additional complexity

- Consider umbrella or platform trial with interim analysis based on pooled blinded data to re-estimate sample size
  - Conducting and reporting (e.g., to drug sponsor) separate analyses for each drug-specific subprotocol may result in dissemination of information about comparative efficacy of drugs
  - Conducting the analysis based on pooled data across all the drug arms and the control arm may provide less accurate estimates of the sample size needed to ensure adequate power for the evaluation each drug

CONCLUSIONS

Conclusions

- Umbrella and platform trials can efficiently evaluate multiple drugs
  - May be particularly useful during public health emergencies
- Additional complexities with trial design and analysis
  - Preserving the integrity of randomized comparisons requires additional forethought on design and analysis choices
- Communication between stakeholders is essential

Acknowledgments

- Office of Biostatistics Master Protocols Working Group
  - Particularly Greg Levin and Dan Rubin

References

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