Master Protocols

Gregory Levin
FDA/CDER/OTS/OB

Clinical Investigator Training Course – December 8, 2021

Disclaimer

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

Learning Objectives

- Define different types of master protocols
- Describe the motivation for master protocols
- Discuss some potential issues with master protocols

Outline

- Definitions
- Motivation
- Examples
- A Few Issues
- Resources

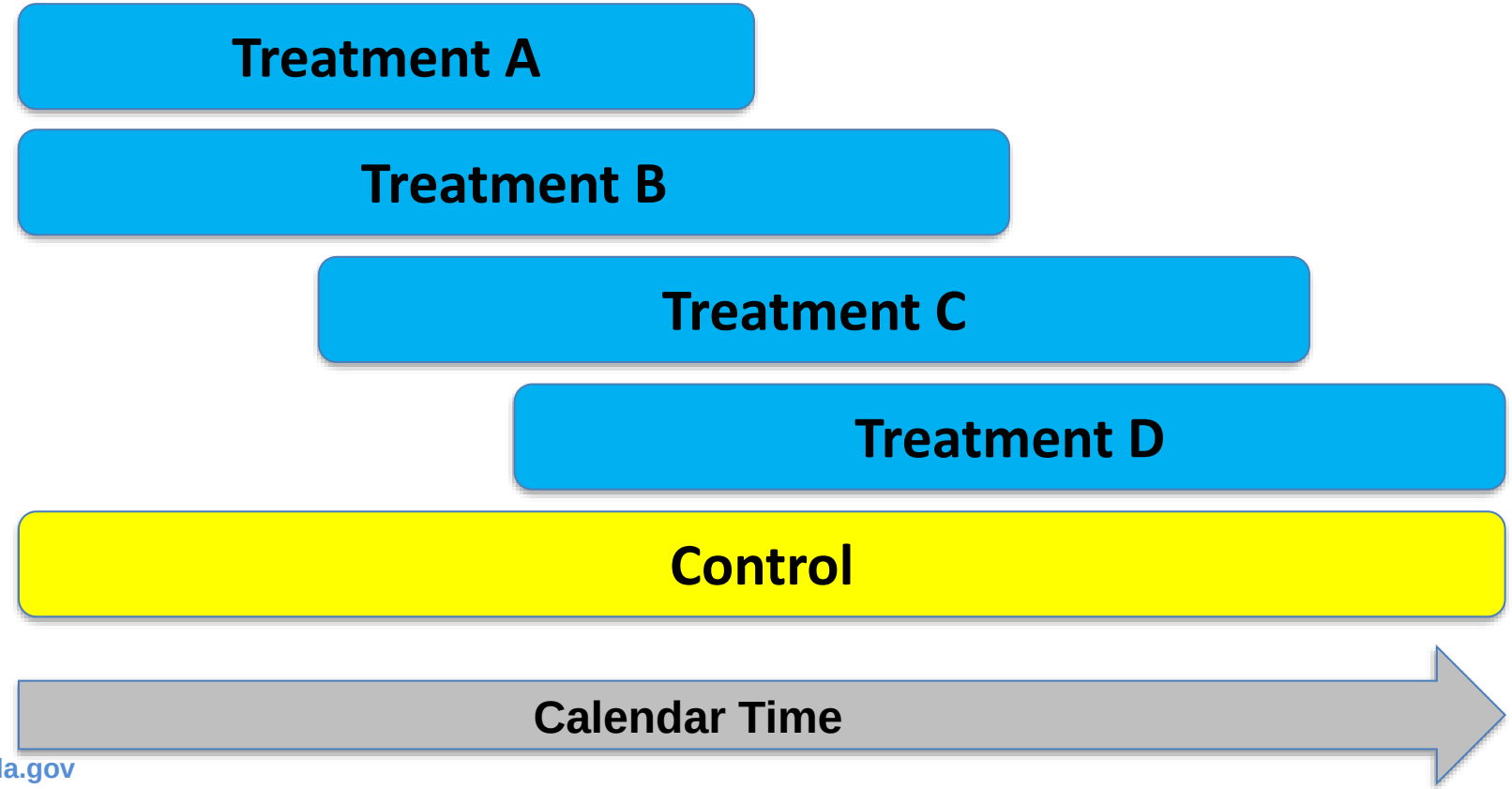
Definitions

- 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

Motivation

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

An Example Platform Trial



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.

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

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

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

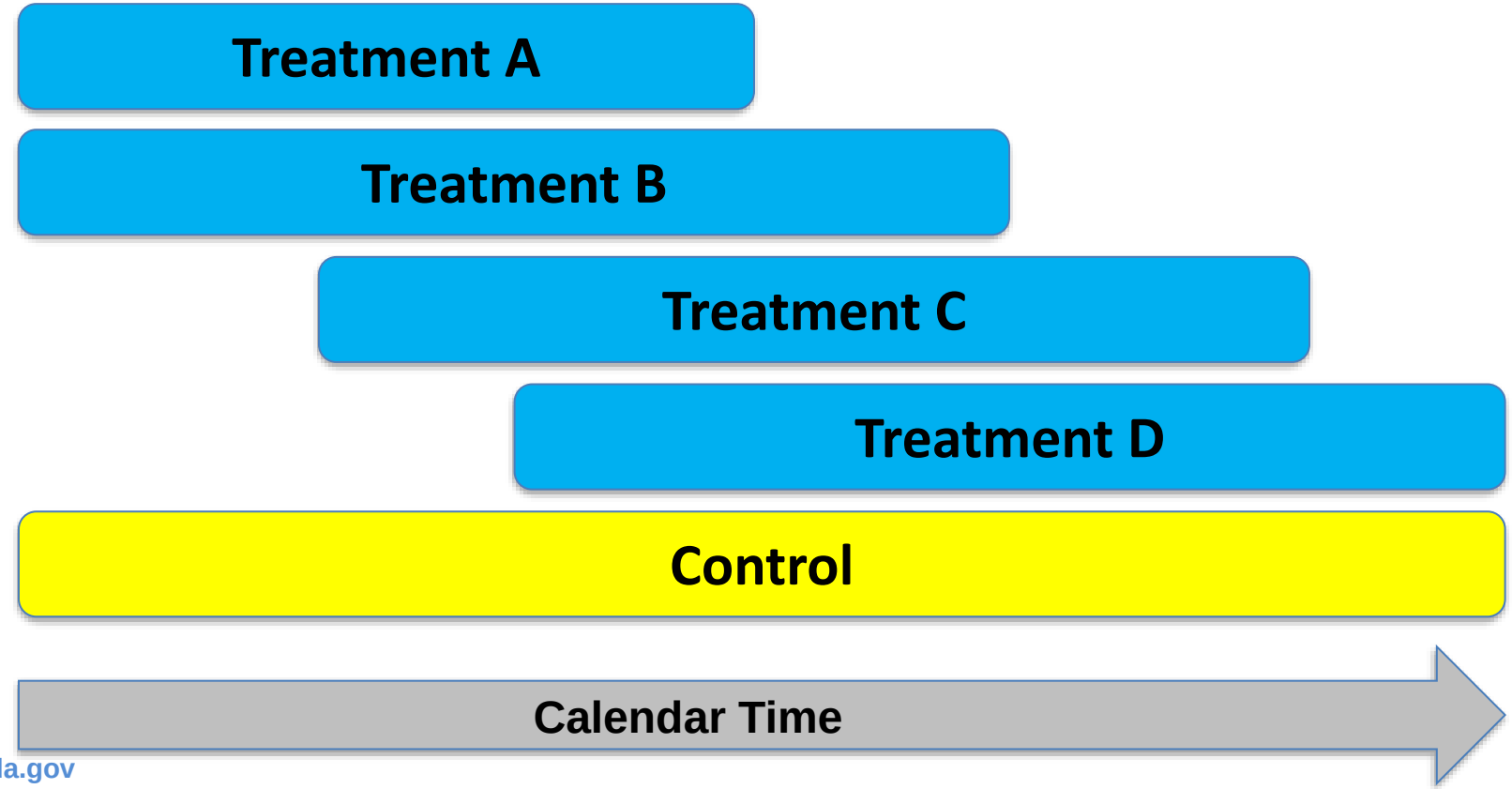
- Adaptive COVID-19 Treatment Trial (ACTT)
- Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Trial
- RECOVERY Trial
- I-SPY COVID-19 Trial
- COMMUNITY Trial
- REMAP-CAP Trial
- WHO Solidarity Trials

A Few Issues

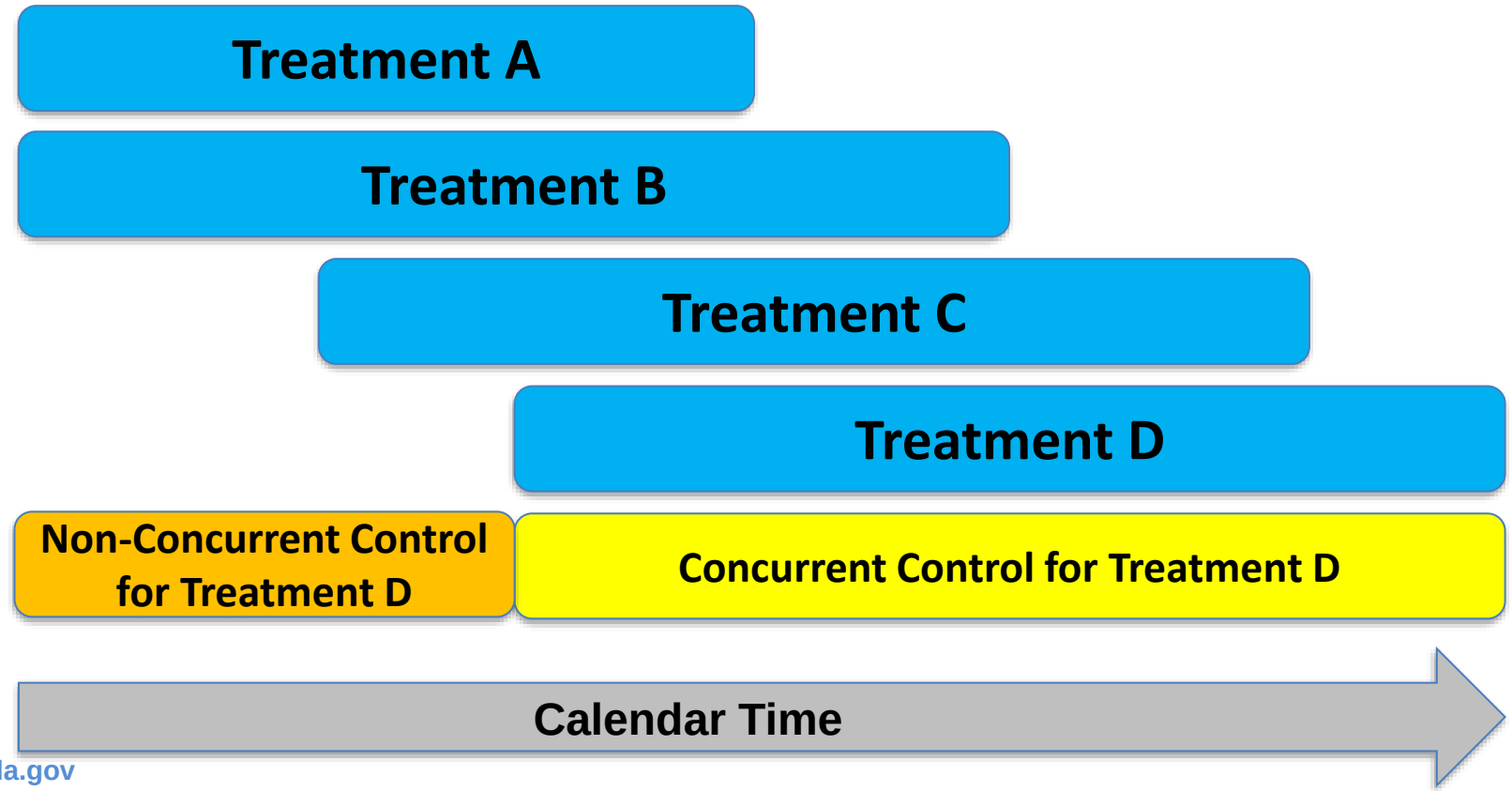
- Use of concurrent vs. non-concurrent control data
- Randomization, consent, and analysis approaches to preserve integrity of randomized comparisons
- Strategies for blinding to treatment assignment
- Ensuring typical clinical trial principles still satisfied

Primary analyses in umbrella/platform trials should utilize only concurrent control data unless there is a compelling rationale to leverage non-concurrent control data

An Example Platform Trial



An Example Platform Trial



Utilizing Concurrent Control Data

- Use of only concurrently randomized control patients* avoids potential systematic differences between drug and non-concurrent control due to changes over time in patient characteristics, trial conduct, standard of care, etc.
- Use of non-concurrent control data = non-randomized comparison
  - Temporal shifts can lead to bias in effect estimates and inflate false positive rate, even if attempts are made to account for potential trends in the analysis

* Who underwent randomization that could have assigned them to the given drug

The consent, randomization, and analysis methods should preserve the integrity of randomized comparisons

An Example of Preserving the Integrity of Randomization

- Consider a scenario where some eligibility criteria are specific to individual drugs, such as:
  - Exclusions of patients with renal or liver dysfunction
- In such a case:
  - Patients shouldn't be randomized to drugs for which they aren't eligible
  - The comparison for a given drug should be against only those control patients who were eligible for and could have been randomized to drug

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

Strategies to Incorporate Blinding

- Multiple-dummy design (complete blinding)
  - Becomes impractical as number of different administrations increases
- Distinct blinded control (e.g., 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

The typical key principles for ensuring appropriate clinical trial design, conduct, and analysis also generally apply to trials conducted under a master protocol

Example: Appropriate Adaptive Design

- Many master protocols incorporate adaptive design elements, such as:
  - Early termination of a drug due to efficacy or futility
  - Sample size modifications based on accumulating data
- Important principles for ensuring appropriate adaptive design still apply and may be more complex with a master protocol
  - See FDA Guidance *Adaptive Designs for Clinical Trials of Drugs and Biologics*

A Few Resources

- 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*
- Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med.* 377(1): 62-70, 2017.

Challenge Question #1

The following term is used to describe a clinical trial conducted under a master protocol that evaluates multiple therapies for a single disease in a perpetual manner, with therapies allowed to enter or leave the platform over time:

A. Basket trial

B. Umbrella trial

C. Platform trial

D. Backpack trial

Challenge Question #2

The following are potential advantages of some master protocols:

A. Increased efficiency due to shared design elements

B. Increased efficiency due to shared operational aspects

C. Ability to directly compare treatment options

D. All of the above

Thank you!


FDA
U.S. FOOD & DRUG
ADMINISTRATION