U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

Master Protocols for Drug and Biological Product Development

Draft Guidance

What Is Recommended In This Guidance?

This guidance provides recommendations on the design and analysis of trials conducted under a master protocol. It focuses on randomized umbrella and platform trials (see definitions below) intended to contribute to evidence of safety and effectiveness of drugs. The document also provides guidance on the submission of master protocol documents for FDA review.

Why Is This Guidance Important?

Compared with traditional stand-alone trials under separate protocols, trials conducted under master protocols can share control arms, protocol elements, infrastructure, and oversight, thereby maximizing the amount of information obtained from a research effort. This document provides guidance to support well-designed, well-conducted trials using master protocols to accelerate drug development, particularly in certain settings, such as where subject recruitment is challenging.

What Is A Master Protocol?

A protocol designed with multiple substudies:

- These substudies may have different objectives
- These substudies are coordinated within an overall study structure to evaluate:
  - One or more medical products
  - One or more diseases or conditions

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about master protocols, **read the draft guidance**. To see additional Guidance Snapshots, check out the **pilot program**.

Examples of trial types that could utilize a master protocol

Umbrella trial

Evaluates multiple medical products at the same time for a single disease or condition

Platform trial

Evaluates multiple medical products for a disease or condition and medical products can enter or leave the platform in an ongoing manner

Basket trial

Evaluates a medical product for multiple diseases, conditions, or disease subtypes

Trial Design Considerations

Randomization

- Removes systematic imbalances between treatment arms to ensure reliable inference.
- Consider a randomization scheme that allocates more subjects to the control arm than each individual drug arm (can increase power for each drug versus control comparison for a given sample size).
- Randomization ratios can change when products enter or exit a platform trial. Comparisons should account for time periods of different randomization ratios.

Control Group

Platform trials in which products enter and exit should generally only use concurrent control subjects who meet drug-specific eligibility criteria for primary comparisons.

Blinding to Treatment Assignment

Critical to avoid bias, but complex strategies may be needed as the number of drugs, routes of administration, and dosing schedules increases.

Multiplicity

FDA generally does not recommend controlling for multiplicity across comparisons of different drugs to the control, but multiplicity control across different analyses (e.g., of different endpoints) for a given drug remains important.

Comparison Between Drugs

Not required, but may be useful and if conducted, should be prespecified in the statistical analysis plan. Sponsors should consider entering into data-sharing agreements to allow for leveraging of information across drugs.

Independent, External Data Monitoring Committee (DMC)

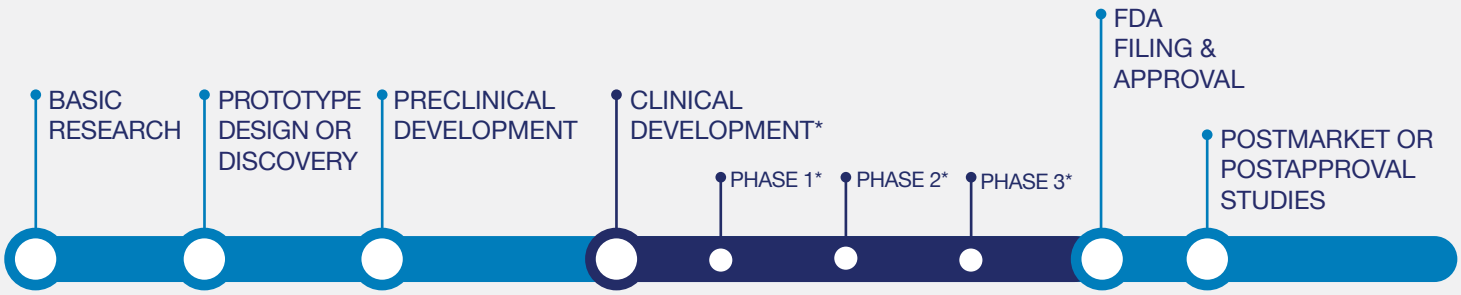
Recommended to oversee data access plans, analyses, and communication of results while maintaining trial integrity and preventing inadvertent dissemination of information when multiple drugs are being studied.

Background About the Guidance

In May 2021, FDA published the guidance for industry COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention, which focused on master protocols evaluating drugs for the treatment or prevention of COVID-19. That guidance was intended to remain in effect only for the duration of the public health emergency related to Coronavirus Disease 2019 declared by the Secretary of Health and Human Services under section 319 of the Public Health Service Act, which has now expired. FDA is issuing this draft guidance because many of the recommendations set forth in the 2021 guidance are applicable outside the context of the section 319 public health emergency and are applicable to other therapeutic areas, not just COVID-19.

Drug Development Timeline

***When to Apply the Guidance Recommendations**



Recommendations From the Guidance Apply to Clinical Development

The regulatory considerations for a master protocol have increased complexity compared to those for a protocol for a stand-alone trial given the involvement of additional stakeholders, the potential for frequent changes, and the quantity of documentation. Because of these complexities, each master protocol should be submitted as a new IND to FDA, and a master protocol sponsor should request a pre-IND meeting to discuss the protocol and submission details.

Guidance Recap Podcast

Hear highlights from FDA staff

Speaker: *Gregory Levin, PhD, Associate Director for Statistical Science and Policy in the Center for Drug Evaluation and Research's Office of Biostatistics*

Click here to listen

Click here to read transcript

Continue the Conversation

Share your thoughts on the draft guidance (docket opens on 12/22/2023)

Click here to provide official comments to the FDA Docket

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about master protocols, **read the draft guidance**. To see additional Guidance Snapshots, check out the **pilot program**.