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SBIA CHRONICLES

FEBRUARY 26TH, 2019

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Resources:

1. Draft Guidance for Industry – Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Cancer Drugs and Biologics

2. FDA in Brief

3. Federal Register Notice

Upcoming Events:

1. Regulatory Education for Industry (REdI) Generic Drug Forum – April 3 -4 2019; College Park MD

2. FDA-OCE: Childhood Cancer Advocacy Forum, March 15, 2019 – Silver Spring MD

3. Save the Date: REdI Annual Conference; May 29-30; Boston MA

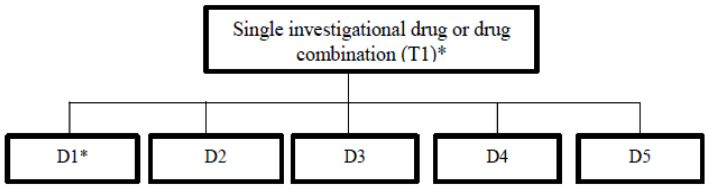
FDA Modernizes Clinical Trials with Master Protocols

The innovative regulatory approaches resulting from the 21st Century Cures Act are modernizing new drug development. The use of clinical trials with Master Protocol design is one example of a modern approach to expedite the development of oncology drugs and biologics. Because of the complexity of these trials and the potential regulatory impact, it is important that such trials are well designed and well conducted to ensure patient safety and to obtain quality data that may support drug approval.

Traditionally, oncology drug development involves a series of clinical trials studying one or two drugs in a single disease. Other clinical trials are intended to simultaneously evaluate more than one investigational drug and/or more than one cancer type within the same overall trial structure in adult and pediatric cancers. The *Draft Guidance for Industry – Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Cancer Drugs and Biologics* provides recommendations on the design and conduct of the latter type of clinical trials. Master protocols may incorporate specific design features that require special considerations. Examples of types of master protocol design include trials commonly referred to as *basket trials* and *umbrella trials*:

A ***Basket Trial*** involves a single investigational drug or drug combination that is studied across multiple cancer populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics. It is usually designed as a single-arm, activity-estimating trial with overall response rate as the primary endpoint. A strong response signal seen in a sub-study may allow for expansion to generate data that could potentially support a marketing approval.

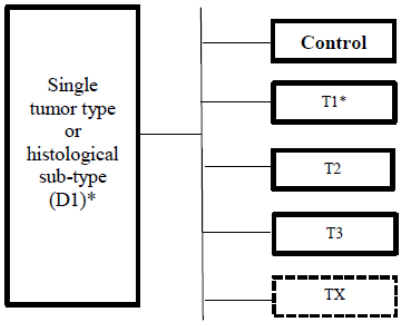
Figure 1: Schematic Representation of a Master Protocol With *Basket Trial* Design



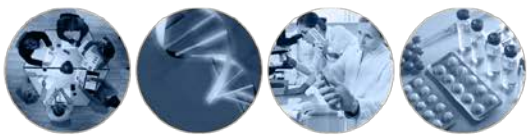
* T = investigational drug; D = protocol defined subpopulation in multiple disease subtypes.

An ***Umbrella Trial*** is designed to evaluate multiple investigational drugs administered as single drugs or as combination drugs in a single disease population. Sub-studies can include dose-finding components to identify safe doses of an investigational drug combination before proceeding with an activity-estimating component.

Figure 2: Schematic Representation of a Master Protocol with *Umbrella Trial* Design



* T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border depicts future treatment arm.



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Design Considerations in Master Protocols:

- ***Dosing***: FDA strongly recommends that the recommended phase 2 dose (RP2D) of each investigational drug be established before evaluation in a master protocol.

- ***Common Control Arm***: In trials where multiple drugs are evaluated simultaneously in a single disease, sponsors can use a common control, which should be the current standard of care (SOC) for the target population. This may change over time if newer drugs replace the SOC. Comparative analyses should be conducted between a test drug and the common control rather than between experimental treatment arms.

- ***Novel Combinations***: The sponsor should provide strong scientific rationale for studies intended to evaluate the concomitant administration of two or more investigational drugs. The sponsor should also ensure that the RP2D has been identified for each drug that may have antitumor activity.

- ***Adding and Stopping Treatment Arms***: The master protocol and statistical analysis plan should describe conditions where treatment arms may be added, expanded, or discontinued based on findings from prespecified interim analyses or external new data.

- ***Independent Data Monitoring Committee***: If a sponsor anticipates that results from one or more sub-studies will form the basis of a marketing application, the master protocol should describe and provide the charter for an independent radiologic review committee to perform blinded tumor-based assessments, along with a charter for an independent data monitoring committee to monitor the efficacy results.

- ***Biomarker Development***: Master protocols evaluating biomarker-defined populations should explain why use of the biomarker is appropriate and employ in-vitro diagnostic tests that are analytically validated. A sponsor interested in pursuing the development of a specific biomarker test for marketing as a companion diagnostic device should consult the appropriate FDA Center responsible for the review of the in-vitro diagnostic test.

The guidance document also describes additional aspects of master protocol designs; trial conduct; and related considerations, such as biomarker co-development, statistical analysis, safety considerations, and master protocol content. It provides advice on how sponsors can interact with FDA to facilitate efficient review. It also discusses challenges with the conduct and analysis of master protocols, such as concerns with assessing the rapidly emerging safety profile of investigational drugs.

FDA strongly encourages sponsors to discuss their plans to develop drugs under a master protocol with the clinical review division early in the development program to obtain feedback on the design of such a protocol before submission. We encourage sponsors to read through the guidance document for details.

Cheers,
Renu Lal, Pharm.D.
CDER Small Business and Industry Assistance

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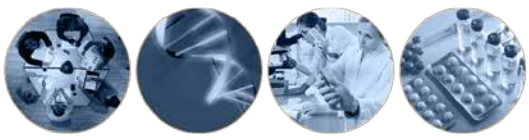

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