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IRBs and the Use of "Master Protocols" in Cancer Drug and Biologics Research (#1)

The final version of an FDA guidance has been issued that will affect IRBs. The guidance is titled "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics." These "master protocols" pose special challenges for IRBs.

> "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" (87 Fed. Reg. 11722, March 2).

"Ad Hoc" IRB Meetings Have Specific Role and Consent Changes Made

As we will see, IRBs will be affected by a number of changes made to the guidance due to previous comments received by FDA.

> "Changes from the draft to the final guidance include adding information about a dose-finding or safety lead-in component in basket trials when evaluating an investigational drug combination, and comparison between experimental arms in umbrella trials and acceptable statistical approaches.
>
> Revisions were also made to various sections of the draft guidance to clarify the information to be submitted to FDA to support amendments to expand the protocol, the frequency of cumulative safety updates, the role of ad hoc institutional review board meetings, the role of the safety assessment committee, and informed consent requirements" (supra at p. 11723).
>
> "There is increased interest in expediting late-stage drug development (i.e., trials intended to provide substantial evidence of effectiveness) through developing trial designs that test multiple drugs and/or multiple cancer subpopulations in parallel under a single protocol without a need to develop new protocols for every trial. The term *master protocol* is often used to describe the de-

NOTE #1: Quoted materials in this newsletter appear exactly as originally published in source documents, including any misspellings, grammatical errors, missing words, etc. However, we will on occasion insert words or edit text/formating in brackets [ ] to make the material easier to read, or to add an underline emphasis.

NOTE #2: Emphases are added to articles by HRR by underlining or adding ***bold/italics*** to selected text, unless stated otherwise.

NOTE #3: Articles **T**o **B**e **C**ontinued in subsequent issues are marked at the end of the article with **{TBC}**.

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sign of such trials, with a variety of terms such as *umbrella*, *basket*, or *platform* describing specific designs ….

Because of the complexity of these trials, which evaluate multiple drugs and/or disease populations, and their intent to support regulatory approval, it is important that such trials be well designed and well conducted to help ensure human subject safety and to generate data that meets regulatory standards for demonstrating each investigational drug's safety and effectiveness" (guidance, pp. 2-3; on the Web at https://www.fda.gov/media/120721/download).

Design May Heighten Subject Risks

As FDA warns in the following excerpt, master protocols can pose special risks for human research subjects and, hence, pose special requirements for IRB reviews.

"For the purpose of this guidance, a master protocol is defined as a protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure ….

A master protocol may be used to conduct the trial or trials for exploratory purposes or to support a marketing application and can be structured to evaluate, in parallel, different drugs compared with their respective controls or to a single common control ....

The potential advantage of a master protocol is flexibility and efficiency in drug development, consistent with FDA's goal of helping to make safe and effective drugs and drug combination treatments available to the public" (supra at pp. 3-4).

IRBs Must Address Level of Subject Risk

"A master protocol provides an opportunity to incorporate efficient approaches, such as a shared control arm and/or the use of centralized data capture systems to enhance efficiency.

However, a master protocol can also create challenges in the conduct and analysis of the trial that, if not properly addressed, can increase risk to human subjects or delay the development of the drug.

Sponsors should establish procedures for sample acquisition, handling, and the testing and analysis plans as early as possible in the biomarker development program.

Sponsors should discuss with the [applicable FDA] review division whether to submit the IVD's analytical validation data for FDA to determine whether the clinical results will be interpretable.

Further, when the trial uses an investigational IVD, sponsors and institutional review boards (IRBs) should assess what investigational device requirements apply using the definitions in 21 CFR 812.3 and the criteria found in 21 CFR 812.2 that address the level of risk that the device presents to trial subjects (i.e., significant risk, nonsignificant risk) and address exempted device investigation ....

Clinical investigations of devices that pose a significant risk generally require both FDA and IRB approval before initiation.[19]

[FN #19: 21 CFR 56.103 and 812.20]" (supra at p. 9).

Amendments Must Be Reported to IRB

"A clinical trial being conducted under a master protocol IND must not be initiated until an IRB or independent ethics committee has reviewed and approved the protocol, and the trial remains subject to continuing review by an IRB.[29]

[FN #29: 21 CFR 56.103(a); 21 CFR 312.66]

After initiation, modifications to the master protocol must be approved by the IRB or independent ethics committee before implementation, with the exception of protocol amendments that are necessary to eliminate apparent immediate hazards to trial participants, which can generally be immediately implemented but are required to be reported to the IRB afterward" (supra at p. 13). © **{TBC}**