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IRBs, COVID, and Experiments With New Drugs and Biologics (#1)

As we continue to report, the COVID pandemic poses new challenges for IRBs and the researchers who submit protocols for IRB review. For example, from the July 2020 HRR through the December 2020 HRRs, we presented highlights from the FDA guidance titled "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention."

That guidance covered IRB review requirements, and researcher procedures, for relevant investigational products. However, those FDA recommendations were primarily devoted to factors related to individual experiments including:

> "… FDA's current recommendations regarding phase 2 or phase 3 trials for drugs under development to treat or prevent COVID-19. This guidance focuses on patient population, trial design, efficacy endpoints, safety considerations, and statistical considerations for such trials" (85 Fed. Reg. 29950, May 19, 2020).

What Is a "Master Protocol"?

In contrast, the new final guidance we examine in the present article is titled "COVID-19: Master Protocols for Treatment or Prevention" (underline added).

> "This guidance primarily focuses on the trial design and conduct as well as statistical considerations for master protocols intended to generate substantial evidence of effectiveness and adequate characterization of safety for COVID-19.
>
> Additionally, this guidance provides administrative and procedural recommendations to sponsors of master protocols for COVID-19 ….
>
> Well-designed and -conducted master protocols can accelerate drug development by maximizing the amount of information obtained from the research effort" (86 Fed. Reg. 33309-33310, June 24).

> "For the purposes 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 inves-

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}**.

Also In This Issue

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tigational drugs in one or more disease subtypes within the overall trial structure.[7]

(FN #7: See also the draft guidance for industry; *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics* (September 2018).

When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.)" (guidance, May, 2021, pp. 2-3; see https://www.fda.gov/media/148739/download).

Certain Master Protocols Apply Best

"Types of master protocols include: umbrella trials, platform trials, and basket trials.[8,9]

(FN #8: Woodcock J, La Vange LM, 2017, *Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both*, N Engl J Med, 377(1): 62-70.

FN # 9: Basket trials study a single targeted therapy in the context of multiple diseases or disease subtypes.)

This guidance primarily focuses on umbrella trials and platform trials, as these are of particular relevance to the current landscape of COVID-19 drug development.

Umbrella trials evaluate multiple therapies simultaneously for a single disease. Platform trials evaluate multiple therapies for a single disease in a perpetual manner, with therapies entering or leaving the platform on the basis of decision algorithm.

Well-designed and conducted master protocols can accelerate drug development by maximizing the amount of information obtained from the research effort.

Compared with conducting separate standalone trials, conducting an umbrella or platform trial can increase data quality and efficiency through shared infrastructure and can reduce overall sample size through sharing of a control arm.

These efficiencies are of particular importance in the setting of a public health emergency such as the current COVID-19 pandemic, where there is a critical need for the efficient development of therapies.

FDA expects master protocols to continue to play an important role in addressing the public health needs created by the current COVID-19 pandemic, as well as to future pandemics that might occur" (supra at p. 3).

Central IRB Recommended, Not Multiple IRBs

Human subject safety is one of the main areas addressed by the guidance, including emphasis on the need for IRB oversight. For example:

"• Before involving any subjects in a clinical investigation under a master protocol, the investigator must obtain the legally effective informed consent of the subject or the subject's legally authorized representative.[18]

(FN #18: See 21 CFR 50.20. Per FDA regulations at 21 CFR 50.55, if a child is to be enrolled in a clinical investigation, the parent(s) or guardian must provide permission, with the assent of the child when appropriate.)

• FDA recommends the use of a central institutional review board to review the master protocol.[19]

(See 21 CFR 56.114. Note that 56.114 does not reflect a legal requirement.)

• The master protocol sponsor should appoint an independent, external data monitoring committee or other appropriate independent entity structured to assess safety and efficacy.[20]

(FN #20: Master protocol sponsors should review the guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* [see above citation for HRR coverage] … and the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006) for additional information.)" (supra at p. 7).

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