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IRBs and Reviewing Protocols That Include "Real World Evidence" (#1)

With this article we introduce a topic that is relatively new for HRR; namely, the use of "real world evidence" in human subject studies and the review of same by IRBs.

"Real world evidence" (RWE) is increasingly in use in the US. If an IRB has not already seen its appearance, we predict that -- sooner or later -- RWE will be something that it will have to consider during protocol reviews.

Perhaps in recognition of this growing trend, FDA recently issued three new draft guidances on this topic. These new guidances are titled:

- "Data Standards for Drug and Biological Product Submissions Containing Real-World Data," (October, 2021);
- "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products," (November, 2021); and
- "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products," (December, 2021).

All of these guidances, albeit still in draft stage, have different areas of interest for IRBs. For now, we will concentrate on the most recent one (i.e., "Considerations for the Use of …") and deal with the prior two guidances in future HRRs as time and events permit.

"RWE" Is Part of a Bigger FDA Program

First, just what is an "RWE"? Most relevant for IRBs is how FDA defines it and how the agency treats it, both in creating new human subject research regulations and in reviewing study submissions for FDA approval.

> "FDA is issuing this guidance as part of its Real-World Evidence (RWE) Program and to satisfy, in part, the mandate under the Federal Food, Drug, and Cosmetic Act (FD&C Act) to issue guidance about the use of RWE in regulatory decision making. FDA created a framework to evaluate the potential use of RWE to help support the approval of a new indication for a drug already approved under the FD&C Act or to help to support or satisfy postapproval study requirements.

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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This guidance discusses the applicability of FDA's investigational new drug application (IND) regulations to various clinical study designs that utilize real-world data (RWD), and clarifies the Agency's expectations regarding clinical studies using RWD submitted to FDA in support of a regulatory decision regarding the effectiveness or safety of a drug (e.g., as part of a new drug application or a biologics license application) that are not subject to the IND regulations" (86 Fed. Reg. 70131, December 9, 2021).

"Interventional" and "Noninterventional" Human Studies Are Both Included

The guidance itself describes real-world data (RWD) and real-world evidence (RWE) as follows:

"• RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

• RWE is the clinical evidence about the usage and potential benefits or risks of medical products derived from analysis of RWD.

This guidance discusses the applicability of FDA's investigational new drug application (IND) regulations under part 312 (21 CFR part 312) to various clinical study[6] designs that utilize RWD.

[FN #6: For the purposes of this guidance, the term *clinical study* means research that evaluates human health outcomes associated with taking a drug of interest.

Clinical studies include interventional (clinical trial) designs and noninterventional (observational) designs (see section II in this guidance) ….]" (guidance, p. 2; on the Web at https://www.fda.gov/media/154714/download).

"Noninterventional" Studies Can Require IRB Review Too

"The guidance also clarifies the Agency's expectations concerning clinical studies using RWD submitted to FDA in support of a regulatory decision regarding the effectiveness and safety of a drug (e.g., as part of a new drug application (NDA) or biologics license application (BLA)) when such studies are not subject to part 312.

This guidance focuses primarily on clinical study designs that are non-interventional …." (supra at p. 2).

We realize, of course, that most (if not all) of the studies that many IRBs review are interventional in nature.

However, certain noninterventional studies do require IRB review and approval for FDA-regulated products. We shall discuss this further after we present the guidance's clarification of just what kinds of activities involving RWD or RWE might be submitted to IRBs.

"For the purposes of this guidance, the term *interventional study* (also referred to as a clinical trial) is a study in which participants, either healthy volunteers or volunteers with the disease being studied, are assigned to one or more interventions, according to a study protocol, to evaluate the effects of those interventions on subsequent health-related biomedical or behavioral outcomes" (ibid).

Agency Lists Several Types of Noninterventional Studies

"One example of an interventional study is a traditional randomized controlled trial, in which some participants are randomly assigned to receive a drug of interest (test article), whereas others receive an active comparator drug or placebo.

Clinical trials with pragmatic elements (e.g., broad eligibility criteria, recruitment of participants in usual care settings) and single-arm trials are other types of interventional study designs.

For the purposes of this guidance, a *non-interventional study* (also referred to as an observational study) is a type of study in which patients receive the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol.

Examples of non-interventional study designs include (1) ***observational cohort stud-***