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IRBs and Assessment of Benefit-Risk Ratios (#1)

Traditionally, the assessment of benefit-risk ratios for human subject study participation has been at the heart of IRB reviews of research protocols.

A recent draft FDA guidance addresses numerous aspects of such judgments, emphasizing benefit-risk evaluations in the development of new drugs and biological products.

The guidance is titled "Benefit-Risk Assessment for New Drug and Biological Products." We find this guidance to be of particular interest because it includes a focus on an increasing phenomenon in clinical trials; namely, the use of human subject self-reports by IRBs and researchers in evaluating study results and the resultant justification of experimental designs.

As we have reported recently, the increasing predominance of using "PROs" (patient reported outcomes) in evaluating research results is posing special challenges for IRBs.

Hence, this new guidance may prove especially useful to IRBs involved in reviewing drug and biologics experiments.

Use of Subject/Patient Experience in Making Benefit-Risk Assessments

"This guidance articulates important considerations that factor into the Center for Drug Evaluation and Research and the Center for Biologic's Evaluation and Research's benefit-risk assessments for drug products, including how patient experience data may be used to inform benefit-risk assessment.

It discusses how sponsors can inform FDA's benefit-risk assessment through the design and conduct of the development program, as well as how they may present benefit and risk information in the marketing application ….

The guidance concludes with additional considerations on benefit-risk assessments that inform regulatory decision making that occurs in the postmarket setting" (86 Fed. Reg. 54212, September 30, 2021).

For IRBs reviewing studies that may lead to researcher submissions to FDA, understanding the agency's views on benefit-risk analyses can be quite useful.

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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Therefore, we present below the guidance's discussion of factors that IRBs may have to weigh as well.

"B. The Impact of Uncertainty on Benefit-Risk Assessment

FDA's benefit-risk assessment carefully considers the strength and quality of the evidence available and takes remaining uncertainties into account in every dimension of the Benefit-Risk Framework" (guidance, September, 2021, p. 10 of 20; on the Web at https://www.fda.gov/media/152544/download).

"Uncertainties" and Their Impact Upon Benefit-Risk Assessments

"Uncertainties that can affect benefit-risk assessments may include, but are not limited to:

- Limits on scientific understanding of the patient population and natural history of the condition, e.g., due to heterogeneity of disease manifestations and progression in the patient population, or lack of identification of risk factors or prognostic biomarkers.
- Aspects of the program or study design, such as the population, choice of controls, endpoints, duration, and data sources, as well as any differences between the clinical study and real-world use.
- Reliability of the estimates of benefit or risk, based upon variability in estimated effects due to sampling (statistical uncertainty) or issues with trial conduct such as missing data, poor protocol compliance, etc.
- Limited understanding of the effects of the drug that may be used in combination with existing therapies (e.g., potential beneficial adjunctive effect, potential for adverse drug-drug interactions, etc.).
- Proposed risk management strategies, such as patient monitoring, which have not been studied in clinical trials, or that have been studied in clinical trials but would be potentially difficult to implement in practice.
- Limited patient input on disease burden and unmet medical needs, meaningfulness of potential benefits, and acceptability of risk tradeoffs and uncertainty …." (ibid).

Accepting Some Uncertainty

"Many sources of uncertainty can be anticipated and potentially avoided with careful attention to trial design during product development stages, as discussed further in section IV. At other times, uncertainties become apparent only after the trial evidence has been generated, such as the appearance of an unexpected safety signal ....

Therapeutic context plays an important role in FDA's assessment of the acceptability of uncertainty. For a drug intended to treat a serious disease with unmet needs, FDA may accept greater uncertainties about benefit or risk at the time of approval, for example through the accelerated approval pathway[22].

[FN #22: For more information about accelerated approval, see FDA's guidance for industry *Expedited Programs for Serious Conditions -- Drugs and Biologics* (May 2014), available at the FDA guidance web page.]

A higher degree of uncertainty is common in drug development programs for rare diseases, where the prevalence of disease, and consequent limitations of study size, can limit the precision of safety and efficacy characterizations.

FDA recognizes that when a drug is developed to treat serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable provided that the substantial evidence standard has been met.

FDA therefore often exercises greater regulatory flexibility in these cases, in particular by accepting clinical trials that have lower sample sizes" (supra at pp. 10-11). © {TBC}