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IRBs and Assessment of Benefit-Risk Ratios (#6)

We continue here with more of our coverage of highlights from a draft FDA guidance titled "Benefit-Risk Assessment for New Drug and Biological Products."

IRBs can find themselves facing the guidance's protocol review issues on assessing benefit-risks for research subjects.

This is true no matter who is funding and/or directing the research in question.

We begin by concluding the guidance's section on "Structured Benefit-Risk Planning During Drug Development," as follows:

> "In addition, various qualitative structured approaches and supporting tools tailored for drug development and evaluation (e.g., value trees, effects tables, forest plots) have been developed and may be useful to support sponsors' benefit-risk planning, assessments, and communications with FDA[27]" (guidance, September, 2021, p. 14; on the Web at https://www.fda.gov/media/152544/download).

Early Identification of Subject Safety Issues

> "[FN #27: Hughes, D.E., … [et al.], 2016. Recommendations for Benefit-Risk Assessment Methodologies and Visual Representations, *Pharmacoepidemiol Drug Saf*, 25(3): 251-262.]

B. Appropriate Interactions Between a Sponsor and FDA During Drug Development To Inform Benefit-Risk Planning

FDA can provide insight and regulatory perspective that can inform a sponsor's benefit-risk planning appropriate to the issues identified at a particular stage of development.

The End of Phase 2 (EOP2) meeting is typically a critical timepoint where discussions with FDA on benefit and risk considerations may be especially important and can influence the design of phase 3 studies in ways that can enhance the characterization of the drug's benefits and risks, including decisions on study design, selection of appropriate patient populations, enrichment strategies, clinically meaningful endpoints, trial duration, dose-response assessment, and trial sizes ....

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

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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These discussions at EOP2 can be particularly important when preclinical, early clinical, or other data identify a potential safety issue that would require greater certainty about the drug's benefits and/or risks to support approval" (supra at p. 14).

Research on Rare or Serious Diseases, As Well as With Pediatric Patients

"Although it is important to discuss benefit-risk planning at EOP2, in some situations there may be earlier points in a product's development when communication between the Agency and the sponsor regarding benefit and risk considerations would be useful.

These communications could involve deliberations regarding the clinical meaningfulness of a purported benefit or concern for non-clinical safety signals at the pre-IND phase for first-in-human studies.

They could also resolve considerations on the best design to characterize benefits and risks where the population is limited or vulnerable, such as for rare or serious diseases or pediatric populations.

Typically, discussion of benefit-risk considerations and benefit-risk planning occurs within the standard processes for formal meetings between FDA and sponsors.

Sponsors can add 'benefit-risk considerations' as a proposed question and/or agenda item and provide relevant supplementary information in the meeting package" (supra at pp. 14-15).

Value of "Patient Experience Data"

"The type of input that FDA can provide on benefit and risk considerations depends on the product, indication, current therapeutic context, stage of product development, and uncertainties associated with the benefit, risk, or other development issues.

FDA's input on these topics may evolve as more information becomes available throughout development. FDA's final premarket benefit-risk assessment is based on complete information submitted as part of an NDA or BLA.

C. Collecting Patient Experience Data During Development To Inform Benefit-Risk Assessment

Patient experience data can help inform critical aspects of a drug development program, and benefit-risk assessment more broadly.

For example, patient experience data collected early in the development program can help identify unmet patient needs and define the target patient population.

Patient experience data can also inform the assessment of the clinical relevance of the study endpoints, that is, to help identify endpoints that measure or predict clinical outcomes of importance to patients" (supra at p.15).

Benefits of Early Communications

"FDA encourages sponsors who are considering collecting and utilizing patient experience data as part of their evaluation of effectiveness or safety to have early interaction with FDA during the design phase of such studies and obtain feedback from the relevant FDA review division on appropriate research design and any applicable regulatory requirements.

As part of the Patient-Focused Drug Development[29] and Science of Patient Input[30] initiatives, FDA is working to advance the development and use of systematic approaches to better incorporate the patient's voice into drug development and evaluation and is developing a series of methodological guidances on these approaches" (ibid).

FDA Developing New Recommendations

"[FN #29: More information on patient-focused drug development is available at https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

FN #20: More information on the science of patient input is available at https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/center-biologics-evaluation-and-research-patient-engagement-program.]" (ibid). © {TBC}