JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 11, No. 8, August 2015 "Happy Trials to You"

What's New in GCP?
FDA Clarifies Risk-Benefit Factors, Risk Mitigation for Device Studies

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In a draft guidance released June 18, the FDA clarified the factors it uses to assess the risks and anticipated benefits for device studies and how uncertainty can be offset by risk mitigation measures.

"FDA believes use of this benefit-risk framework in an [Investigational Device Exemption (IDE)] application will facilitate the incorporation of evidence and knowledge from different domains — clinical, non-clinical and patient — to support a comprehensive, balanced decision-making approach," the guidance says. "FDA envisions this will facilitate a common understanding between FDA and sponsors/sponsor-investigators by highlighting which factors are critical in the benefit-risk assessment for a specific application, and clearly explaining how these factors influence a regulatory decision. FDA also believes implementation of this guidance document will improve the predictability, consistency and transparency of the review process for IDE applications."

The FDA will disapprove an IDE if "'[t]here is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained' [21 C.F.R. §812.30(b)(4)]. In many cases, the agency believes that effective risk management, including the application of risk controls and risk mitigation measures, can result in a favorable IDE benefit-risk determination."

The guidance said the informed consent process is a "key tenet of FDA's IDE benefit-risk framework," as it provides "adequate information about the study, including pertinent information about the investigational device, its risk and benefits, alternatives and what is expected of the subject" in the study. The subject "must be given sufficient opportunity to consider whether or not to participate in the clinical study under circumstances that minimize the possibility of coercion or undue influence" (21 C.F.R. §50.20).

What to Consider?

When making IDE benefit-risk assessments, FDA considers the stage of development of the device; the maturity of the proposed technology, and the availability of nonclinical testing to complement or replace the need for clinical testing.

The guidance said the benefit-risk assessment "should be tailored to the stage of device development," as different stages of development "are generally associated with different types of risk, and different levels of uncertainty. Specifically, a greater degree of uncertainty is expected for novel technologies, and at earlier stages of device development, such as first in human or early feasibility trials, while relatively more certainty is expected in traditional feasibility and pivotal trials. At earlier stages, the focus is on appropriate risk mitigation measures for anticipated possible risks and unanticipated risks, whereas in later stages focus shifts increasingly to mitigating the most probable risks."

"FDA intends to permit appropriate latitude for the conduct of IDE studies within the boundaries of applicable laws and regulations. In considering whether risks outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained,

absence of definitive evidence of benefit or the presence of purely hypothetical risks are not sufficient justification, in and of themselves, to disapprove an IDE application," the guidance said.

The "inherent uncertainty" of clinical investigations "can often be offset by appropriately tailored risk control/risk mitigation measures," the FDA said.

In considering benefits of research, the FDA considers the direct benefits to subjects in the study as well as the benefits to others "to the extent they are indirect benefits to subjects or reflect the importance of knowledge to be gained."

The FDA assessment also considers the contextual setting, including characterization of the disease or condition under study and the availability of alternative therapies, including their associated benefits and risks.

Assessment Should Be Part of IDE Application

The FDA recommends that IDE sponsors include a section in the IDE application that summarizes the key considerations for the benefit-risk assessment. The summary should address:

- the context of the investigation, including the disease or condition to be treated or diagnosed, a description of the device in the context of available options, and a description of the objective and design of the study;
- assessment of risks;
- assessment of benefits;
- consideration of patient preference information;
- assessment of uncertainty; and
- conclusions on how the consideration of the benefit-risk factors justify the decision to proceed with the study.

"Deficiencies related to an incomplete or inadequate investigational device description are the single most common type of nonclinical deficiency in IDE applications that fail to attain full approval," the FDA noted.

In addition, the guidance said, there are several key concepts that are commonly not well described in IDE applications:

- Harms — specifying how a hazard could lead to clinical sequelae or other harmful events is estimation of risk severity and likelihood;
- Likelihood — focusing on severity of a risk along with likelihood is important for a complete estimation of the risk; and
- Residual risk and completeness of risk control – many identified risks are reduced to an acceptable level through effective risk controls. The FDA's benefit-risk assessment of IDE applications focuses on completeness of risk control measures and whether residual risk outweighs anticipated benefits to the subjects.
- "Assessment of benefits and risks should not necessarily be made in comparison to the most technologically advanced alternative but rather to commonly used therapies and treatments," the FDA advised.

Investigational Plan Must Have Risk Analysis

The investigational plan must include "a risk analysis, which describes and analyzes all increased risks to which subjects will be exposed by the investigation, the manner in which

these risks will be minimized, a justification for the investigation, and a description of the patient population, including number, age, sex, and condition" (21 C.F.R. §812.25).

The assessment of risks to IDE subjects focuses on risks whose existence and characteristics are supported by objective scientific evidence, the guidance said. The assessment of risks must include a description and analysis of all incremental risks to which subjects will be exposed, as well as how those risks will be minimized.

"While it is not necessary to include specific mitigations for hypothetical risks that are not supported by scientific evidence or risks that are determined to be negligible due to a low probability of occurrence and low severity of harm, it is helpful to identify all possible risks in the risk assessment and include information on how the level of risk was determined," the guidance said.

The FDA said the risk assessment involves describing the relationships between a hazard (a potential source of harm) and the ultimate consequences in terms of physical injury or damage. "This relationship should specifically describe the foreseeable sequences of events, hazardous situations, and associated possible harm. This may include: the initiating hazard, failure mode, or circumstance; the sequence of events that could lead to a hazardous situation occurring; the likelihood of such a situation arising; the likelihood that the hazardous situation leads to harm; and the nature of the harm that could result."

The extent of risks/harms associated with a study is assessed by considering, both individually and in aggregate:

- the types of risks and their severity regarding basic safety, device-related serious adverse events, device-related non-serious adverse events, procedure-related complications due to the investigation, risks associated with the study, and risk from false positive or negative results for diagnostics;
- the likelihood or probability of risks;
- the duration of risks;
- risk management; and
- residual risk evaluation.

Risk Mitigation Detailed

"Sponsors should conduct an initial determination regarding which risk controls are appropriate for their proposed IDE study," the guidance said. Benefit-risk assessment for IDE decisions should focus on residual risk, and whether residual risk has been reduced to acceptable levels relative to the anticipated benefits to the subjects."

Risk mitigation can include device design features and modifications; protective measures, such as study design features; and the communication of safety information through training of investigational staff. "

The preferred hierarchy of risk mitigation is to first attempt to eliminate the risk, then if this is not possible, to design and implement protective measures, and communicate the residual risk to patients and operators, such as by labeling," the guidance said.

After risk control measures are applied, the measures that may be considered when evaluating residual risk, particularly in cases where there are substantial risks associated with the study, are:

- risk communication and disclosure of residual risk during the informed consent process;
- consideration of the subject perspective on assuming risk relative to anticipated benefit;

- performance of initial limited study in subjects most likely to experience benefits; and
- selection of a participant subset where the benefit/risk profile is more favorable.

Patient Preference Differs

As to patient preferences, the guidance said, "it is important to acknowledge that individual patient preferences vary, and that a patient may not assign the same values to various risks and anticipated benefits as their physician, family member, or other individual. Furthermore, patient preferences vary, both in preferred modality of treatment/diagnostic procedure [and] some patients are willing to take on higher risks to potentially achieve a small benefit, whereas others are more risk averse. In certain circumstances, some patients may be willing to participate in clinical studies that offer no or limited direct benefit to subjects but have anticipated societal benefits in advancing medical science."

The guidance added that "it may be appropriate to approve an IDE application where only a subset of the eligible study subject population would accept the risks as weighed against the benefits, provided there is enough information and an adequate informed consent process in place for study patients to make informed decisions. However, if, for a certain IDE application, the risks outweigh the anticipated benefits for all subjects, FDA would disapprove the IDE application" (21 C.F.R. §812.30(b)).

The assessment of anticipated benefits to IDE subjects "does not include purely hypothetical benefits, and instead focuses on those direct benefits whose existence and characteristics are supported by objective scientific evidence. FDA's assessment of anticipated benefits of study participation includes the direct benefits to the subject — benefits that may be realized by the subjects participating in the research," including:

- the type of benefit;
- the magnitude of the benefit;
- the probability of the subject experiencing one or more benefits; and
- the duration of effect.

An IDE benefit-risk assessment also includes consideration of anticipated benefits to others. "One should consider the possibility that study subjects will receive no direct benefit from study participation. However, subjects may still be willing to participate because of the indirect benefits, such as the importance of the knowledge to be gained. Studies that are well-designed may be considered to have greater benefits in this regard, because it generates knowledge that can inform safe use and may lead to earlier patient access to high quality, safe and effective devices," the guidance said.

Patient preference information "may be particularly informative in helping to assess the trade-offs between risks and benefits in certain challenging device areas," such as: life-saving but high-risk devices; devices intended to yield improvements in health-related quality of life; devices intended to yield benefits in terms of health; aesthetic devices; and devices for use in conditions where alternatives include non-device options, such as surgical procedures or medical therapy.

"When available, information characterizing subject tolerance for risk and perspective on benefit may provide useful context for assessing the benefits and risk of a proposed clinical investigation," the agency added.

How to Weigh Uncertainty

The guidance noted that "there is always some uncertainty when weighing benefits and risks prior to clinical study conduct. However, the degree of certainty is a factor we consider when assessing benefit-risk for IDE applications," including:

- the quality of prior non-clinical and clinical investigations;
- the predictive capability of evidence from prior investigations; and
- different uncertainty considerations at different stages of development.

Other factors to consider when assessing benefit-risk are:

- Characterization of the disease — The treated or diagnosed condition, its clinical manifestation and severity (e.g., temporary or permanent loss of function), how it affects the subjects who have it, how and whether a diagnosed condition is treated, and the condition's natural history and progression (i.e., does it get progressively better or worse for the subject and at what expected rate). Conditions with more severe symptoms that run a natural course, relatively fewer and less effective treatment options, and less chance of responding to current treatment options may warrant tolerating greater risk in a study.
- Availability of alternatives — When characterizing the availability of alternatives, the FDA considers important factors, including treatment (or diagnostic) options, treatment strategy (if applicable, such as for chronic diseases) and the safety and effectiveness of alternatives, including the potential for adverse events. If alternative therapies (or diagnostic options) exist, are effective for the subject population, and are associated with relatively fewer adverse events, subjects may not tolerate a higher degree of risk of study participation.
- Subject tolerance for risk and perspective on benefit — Risk tolerance varies among subjects and will affect individual subject decisions to participate in a study. When evaluating benefits and risks, the FDA "recognizes that tolerance for risk and a subject-centric assessment of risk may reveal reasonable individuals who are willing to tolerate a high level of risk to achieve an anticipated benefit, especially if that benefit results in an improvement in quality of life or achieves societal benefit from knowledge gained. In addition, a thorough informed consent process serves to assure that prospective subjects are informed of, among other information, the risks and benefits of study participation and agree to the risks of study participation given other factors, including the potential benefits."
- Least burdensome study design – When elements of study design are considered, incorporating additional elements often involves trade-offs in terms of time, cost and practicality of study conduct, which may affect other aspects of clinical trial start-up, such as institutional review board approval and feasibility of subject enrollment. "While FDA does not consider cost when deciding to approve an IDE application, the potential impact of study design elements on trial start-up, IRB approvability, and feasibility of subject enrollment should be considered," the guidance said.

Find Out More

The draft guidance is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationand-Guidance/GuidanceDocuments/UCM451440.pdf.

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