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What's New in GCP?
FDA Guidance Promotes Adaptive Designs for Medical Device Trials

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The FDA's Centers for Devices and Radiological Health and Biologics Evaluation and Research released a draft guidance May 15 for sponsors and FDA staff on how to plan and implement adaptive designs for device clinical studies.

"Adaptive designs, when properly implemented, can reduce resource requirements and/or increase the chance of study success," the agency said in announcing the guidance, which the centers were careful to note is not in effect now.

The guidance addresses adaptive designs for medical device clinical trials and is applicable to premarket medical device submissions, including premarket approval applications, premarket notification (510(k)) submissions, de novo submissions (evaluation of automatic class III designation), humanitarian device exemption applications, and investigational device exemption submissions and "can be applied throughout the clinical development program of a medical device, from feasibility studies to pivotal clinical trials." However, the guidance "does not apply to clinical studies of combination products or co-development of a pharmaceutical product with an unapproved diagnostic test," although "the underlying principles may be applicable to such studies."

Adaptive trial designs allow for prospectively planned modifications to trials based on accumulating study data. "In nearly all situations, in order to preserve the integrity and validity of a trial, modifications should be prospectively planned and described in the clinical trial protocol prior to initiation of the study. However, in some specific circumstances, study modifications after the trial begins can be scientifically valid if the trial design decision-makers have had no access to the outcome results by treatment." The guidance noted the "knowledge of outcome results by coded treatment groups, even without divulging which treatment is investigational, can undermine scientific validity."

The guidance cautioned that "there is a real danger that an unplanned modification to a study may weaken its scientific validity and therefore [it] may not be approved or endorsed by FDA. Sponsors should anticipate and plan for modifications based on a variety of possible scenarios that could occur during the course of the trial."

The guidance said the advantages of an adaptive design compared to a fixed design are:

- It can be more efficient, saving time, money and resources. For example, a trial with interim analyses could stop early for effectiveness in a preplanned way; a trial with two or more investigational arms could plan to drop one of them based on accumulating data; or a trial with a preplanned interim analysis could decide to stop early for futility.
- Adaptive designs can improve the chance of trial success by employing sample size reassessment. For example, based on accumulating data in the trial, planned sample size reassessment could lead to an adjustment in sample size, converting an underpowered study likely to fail into a well-designed study more likely to succeed. "This approach can salvage studies otherwise likely to be unsuccessful and as a result, help facilitate the timely assessment and marketing of medical devices demonstrating a reasonable assurance of safety and effectiveness."

- It can yield an improved understanding of the effect of the investigational treatment and a better understanding of benefit and risk.
- It may aid the transition from premarket to post-market follow-up. For example, a preplanned interim analysis that demonstrates favorable short-term study outcomes may result in a successful marketing application with continued follow-up relegated to the post-market stage.
- In some cases, planned modifications can incur no cost in either sample size increase or false positive error inflation, provided there is a strong blind to outcomes by treatment groups.
- Adaptive designs can enhance patient protection by increasing the probability that a patient is allocated to the treatment most likely to result in a better outcome for that patient.
- Adaptive designs can include a plan to modify the patient population during the study, converting what would otherwise be a failed study to one with, for example, a more targeted indication for which there are data to support both safety and effectiveness. This could help identify patients more likely to have a favorable benefit-risk profile from the use of a device.
- Adaptive studies can improve decision-making at milestones during product development or increase the chance of a successful study with the potential to improve time-to-market.

"Overall, adaptive designs may enable more timely device development decision-making and therefore, more efficient investment in resources in a clinical study," the guidance said. "From an ethical standpoint, adaptive designs may optimize the treatment of subjects enrolled in the study and safeguard their welfare from ineffective or unsafe treatments and interventions at the earliest possible stage."

However, there are also limitations:

- Preplanned study design modifications can require more effort at the design stage, although the investment can pay great dividends during study conduct.
- Adaptive study designs that are overly complicated can be difficult to plan, cost more, and be logistically difficult to carry out.
- If not done correctly, adaptive designs can introduce bias, making it difficult to characterize the true effect of the investigational device.
- A change to the study due to an adaptation may lead to results before the adaptation that are not sufficiently similar to those after the adaptation, confounding the interpretation of the study results.

The guidance noted that "adaptive studies can be especially useful in the pivotal stage if there are uncertainties about one or two aspects of the study. In some cases, an adaptive design can obviate the need for a feasibility study (or a second feasibility study), and instead can allow the uncertainties to be scientifically addressed in an adaptive pivotal study." However, "if there are numerous uncertainties, an adaptive design may be difficult to plan and implement. In such cases, it may actually be more efficient and increase the overall likelihood of success to conduct one (or more) additional feasibility studies to resolve some of these uncertainties before embarking on a pivotal trial," the agency said.

Statistical Challenges Considered

The guidance said the control of the rate of false-positive conclusions "can be a major statistical challenge, and inflation of this error rate can arise from various sources." Most commonly, they arise due to "multiplicity," which occurs when study data are examined and

analyzed multiple times during a study without appropriate statistical preplanning, and the study is stopped at any time point where nominal statistical significance appears to have been achieved.

There are multiple sources of multiplicity in adaptive trial designs: multiple endpoints, multiple subgroups, multiple exposures or dosages, or a combination of these features that could be dropped or added at an interim analysis. "Another type of multiplicity would be an increase in sample size at an interim analysis without any statistical adjustment; this could also lead to the inability to control erroneous conclusions," the guidance said.

"It is advantageous for both the sponsor and the FDA to understand the operating characteristics of a study design," including the chances of false positive and negative conclusions.

The guidance said it is also important that "bias of all kinds be reduced or eliminated because the presence of bias can distort the findings of a clinical study and undermine its scientific validity." The guidance said "knowledge that the size of the study has been increased may help participants to estimate the magnitude of the interim treatment effect, which in turn, can then affect the ongoing conduct of the study in various ways. If not blinded to the patients' treatment assignment, the investigator may, unintentionally and without being aware, change the decision about whether to enroll a subject in the study or start treating the subjects in the investigational treatment group in manner that is different from that applied to subjects in the control group."

In addition, if analysts of the study data have access to the unblinded results of an adaptive trial during its conduct, it is vital that policies and procedures be in place to insulate this information from the study sponsor and investigators. Furthermore, it is important to assure regulatory authorities and other stakeholders that there are safeguards in place to ensure that those with legitimate access to unblinded data do not share information about these data with others," the guidance said.

"Sponsors are encouraged to consider adaptations that use baseline data and aggregate outcomes for studies that do not break the blind" and are "strongly advised that such a study be conducted under an approved Investigational Device Exemption, when appropriate. While it is strongly preferred that such adaptations be preplanned at the start of the study, it may be possible to make changes during the study's conduct as well. In such instances, the FDA will expect sponsors to be able to both justify the scientific rationale why such an approach is appropriate and preferable, and demonstrate that they have not had access to any unblinded data (either by coded treatment groups or completely unblinded) and that the data has been scrupulously safeguarded."

The guidance noted that adaptive designs based on accumulating unblinded results "require thoughtful planning. Sponsors are encouraged to consult with FDA prior to embarking on an adaptive design, in general, and for several types of adaptations in particular: group sequential designs, sample size adaptation, group sequential design with sample size reassessment, dropping a treatment arm, changing the randomization ratio, changing the hypothesis, adaptive enrichment, planning to adapt based on the total information, adaptation of the device or endpoint, and seamless studies. All of these are detailed in the guidance.

The guidance also covers a number of special considerations: changes to pivotal clinical studies that are not preplanned using blinded data, changes to pivotal clinical studies that are not preplanned with unblended data, simulations in planning an adaptive design, adaptive designs for safety endpoints, adaptive designs for open-label randomized studies, adaptive designs for observational comparative studies, adaptive designs for one-arm studies without a control, diagnostic devices, adaptation to prevalence and the entire

disease spectrum, blinded sample size reassessment based on interim estimates for the comparator, and adaptation and staged designs.

DMC and IRB Considerations

The guidance noted that data monitoring committees and institutional review boards will have special considerations for adaptive designs.

"Even in cases where another entity is charged with the logistics of the adaptation, the DMC is tasked with safeguarding the trial participants and should monitor their safety during the adaptive trial," the agency said, noting the DMC should be appropriately constructed to assure that its members possess the necessary expertise and experience for an adaptive study design.

In cases where adaptations are based on interim analyses of unmasked outcomes, robust prespecified and well-documented procedures must be in place before initiation of the clinical trial or review of the data. Critical aspects include: assurance of a robust "firewall" for managing access to unblinded interim data/analysis since DMC interactions with a sponsor have the potential to adversely impact study integrity; and the shielding of investigators and study participants as much as possible from knowledge of the adaptive changes that are implemented. "The DMC charter should include a complete description of standard operating procedures relating to implementation of the adaptive design protocol. The protocol should state the role of the DMC, with particular emphasis on how the DMC will be involved in the conduct/analysis of the adaptation. A clarification on whether or not a DMC will review any interim analyses and who will conduct the adaptation of the design should be provided," the guidance said.

"Although the DMC may be tempted to recommend changes to the adaptive design or to the fundamental study type (e.g., from a fixed study to an adaptive one) during study conduct, once the DMC has access to coded or unmasked outcomes, such recommendations can imperil the scientific integrity of the study," the agency said.

The guidance noted there are "several steps that study sponsors can take in advance of initiating an adaptive clinical study that can minimize or avoid critical IRB-related delays during the study. As an initial step when seeking IRB approval, sponsors should clearly describe the adaptive nature of the study and provide an informed consent document that accurately reflects the study's risks and meets other informed consent requirements. Potential planned adaptations should be described to the IRB, and sponsors are encouraged to clearly articulate the circumstances under which protocol amendments will be submitted to the IRB for review."

The guidance added that "an IRB's familiarity with adaptive design clinical studies may impact the efficiency with which they are able to review such studies and study modifications. For example, some IRBs may require the resubmission of the study protocol for full board review when an adaptation is made. If prespecified adaptations were not disclosed to the IRB during the initial approval process, the sponsor risks critical IRB-related delays that can hinder study progress. Failure to disclose the adaptive nature of the study and its associated risks in the initial informed consent document may result in an IRB-mandated reconsenting of study subjects or subject notification related to the study modifications or identified risks. Advanced planning and good communication with the IRB can mitigate these potential IRB-related issues," the guidance said.

What the FDA Needs

The guidance recommends sponsors have a risk-based monitoring plan in place that focuses on specific aspects of adaptive studies that are of particular importance and may not be present in traditional (non-adaptive) trial designs. "For adaptive studies, sponsors should have a pre-determined monitoring plan in place to ensure adequate monitoring if the pre-planned changes do occur. When an adaptation is planned, sponsors should consider adopting procedures, such as pre-planned site visits scheduled to verify adequate documentation and execution of blinding procedures to ensure blinding was appropriately maintained."

In addition, "the monitoring plan should include procedures that confirm that data firewalls have not been breached and that statistical changes were made according to the study statistical analysis plan.

Sponsors also should provide the FDA with "sufficient evidence of a 'firewall' and documented policies and information in advance that will assure personnel are appropriately blinded/masked during the conduct of the adaptive study. Changes in study design that occur after an unblinded interim analysis of study data are not considered adaptive and, in many cases, may undermine the scientific validity of the study," the guidance said.

"Sponsors are strongly encouraged to discuss the planning of adaptive clinical study designs with the appropriate FDA review division in advance, and the agency has established mechanisms to conduct such interactions in a timely and efficient manner."

The guidance said submissions to the FDA for adaptive study designs "should clearly identify that the clinical study employs an adaptive design and should provide details of the proposed adaptations. Information provided should address what, when, how and why the adaptation will be performed. The adaptation should be prospectively described at least generally in the protocol and in detail in the statistical analysis plan, which should include the operating characteristics of the design."

Submissions also should address key issues related to study monitoring and the role of the DMC. In addition, decision points should be delineated and documented for inclusion in the final study report to be submitted as evidence of safety and effectiveness to FDA. "If a firewall is part of the design, a mechanism and an implementation plan for the firewall should be provided.

If a firewall is intended to provide only limited information to the investigators, a general clinical protocol and a separate detailed statistical analysis plan (SAP) could be used, with the SAP not widely distributed.

Computer systems can be employed to monitor, document and limit access and can provide audit trails and firewalls."

At the conclusion of an adaptive study, the documentation that should be sent to the FDA should include a description of how the adaptation was implemented, the data sets for the study, the baseline population characteristics for pre- and post-adaptation subgroups, the prespecified statistical analysis, and any deviations that may have occurred from the protocol's adaptive plan and how they have been addressed in additional analyses.

Find Out More

The draft guidance — Adaptive Designs for Medical Device Clinical Studies — is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446729.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery.

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