Guidance for Industry and Clinical Investigators

The Use of Clinical Holds Following Clinical Investigator Misconduct

DRAFT GUIDANCE

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GUIDANCE

THE USE OF CLINICAL HOLDS FOLLOWING CLINICAL INVESTIGATOR MISCONDUCT

This guidance document represents FDA's current thinking on the use of clinical holds to protect human subjects following clinical investigator misconduct in a clinical trial of a human drug or biological product. It does not confer any rights for or on any person and does not operate to bind the FDA or the public. An alternative approach may be used if it satisfies the requirements of the applicable statutes and regulations.

I. PURPOSE

This guidance provides information on the Food and Drug Administration's (FDA's) use of its authority to impose a clinical hold on a study or study site if FDA finds that a clinical investigator conducting the study has committed serious violations of FDA regulations on clinical trials of human drugs and biologics, including 21 CFR parts 312, 50, and 56, or has submitted false information to FDA or the sponsor in any required report. FDA may consider imposing a clinical hold in these situations where necessary to protect human subjects in the study from an unreasonable and significant risk of illness or injury. Such a clinical hold may be imposed on the study in which the misconduct occurred or on other studies of drugs or biological products in which the clinical investigator is directly involved or proposed to be involved. Although FDA has authority to take various enforcement actions against a clinical investigator who commits serious violations of FDA regulations, these actions may not be completed swiftly enough to protect human subjects who may be at risk in ongoing studies conducted by the investigator. Where the investigator's misconduct appears to pose an ongoing threat to the safety and welfare of such subjects, imposition of a full or partial clinical hold on ongoing or proposed studies of human drugs or biological products may be appropriate. This guidance describes the circumstances in which FDA may impose such a clinical hold.

II. BACKGROUND

This section describes the responsibilities of clinical investigators, the process for bringing an enforcement action for serious clinical investigator misconduct, and the need for a more rapid means of protecting human subjects after serious misconduct has been discovered.

A. What Are a Clinical Investigator's Responsibilities?

The regulations governing the conduct of clinical trials by clinical investigators are intended to assure adequate protection of the rights, safety, and welfare of subjects involved in those trials, as well as the quality and integrity of the resulting data, while at

the same time providing sufficient flexibility for clinical research. A brief description of the specific responsibilities of investigators follows.

Clinical investigators are responsible for protecting the rights, safety and welfare of human subjects in the studies they conduct (21 CFR § 312.60, 21 CFR Parts 50 and 56). Among other things, investigators must assure that an Institutional Review Board (IRB) that complies with FDA regulations conducts initial and continuing ethical review of the study (21 CFR Part 56 and § 312.66). An investigator must notify the IRB of changes in the research activity or unanticipated problems involving risks to human subjects or others, and must not make any changes in the protocol without IRB and sponsor approval, unless necessary to eliminate apparent immediate hazards to human subjects (21 CFR § 312.66). An investigator must also obtain informed consent from each subject who participates in the study (21 CFR § 312.60 and 21 CFR Part 50).

Clinical investigators are responsible for following the signed investigator statement (Form FDA-1572) (21 CFR § 312.60). The investigator's signed statement includes a commitment to: (1) follow the study protocol, and to make changes only after notifying the sponsor, unless necessary to protect the safety, rights, or welfare of the subjects; (2) personally conduct or supervise the research; and (3) inform sub-investigators and others assisting in the conduct of the investigation of their obligations in meeting these commitments (21 CFR § 312.53(c)). Clinical investigators are also responsible for following the investigational plan (21 CFR § 312.60).

Clinical investigators must ensure that the investigational drug is administered only to study subjects under the supervision of the investigator or a subinvestigator responsible to the investigator (21 CFR § 312.61). Finally, clinical investigators must keep required records of the study and make required reports to the sponsor of the investigation (21 CFR §§ 312.62 and 312.64). An investigator must prepare and maintain adequate case histories, including documentation of informed consent, and keep records of disposition of the drug (21 CFR § 312.62). These records must be maintained for 2 years from the date FDA approves the drug under study, or if FDA does not approve the drug or no application is filed for the drug, from the date the study is discontinued and FDA is informed (Id.). The investigator must make several types of reports to the sponsor, including progress reports, safety reports (prompt reports of adverse events, and immediate reports of alarming effects), and a final report (21 CFR § 312.64). The investigator must also report his or her financial interests to the sponsor to permit assessment of conflicts of interest (Id.).

In addition to FDA's regulations, the International Conference on Harmonization (ICH) Good Clinical Practice guidance document provides useful information on the responsibilities of clinical investigators.

B. What Actions Can FDA Take to Address Clinical Investigator Misconduct?

If an inspection conducted by FDA reveals that a clinical investigator has committed violations of FDA's regulations, FDA will notify the investigator of the violations and

take appropriate follow-up action. In some cases, an investigator's agreement to correct the violations may be sufficient to resolve the matter.

Where FDA finds that there have been serious violations of the investigator's obligations, and corrective action by the investigator cannot resolve the matter, FDA may conclude that it is appropriate to initiate an enforcement action against the investigator. First, if the inspection findings indicate that the investigator has repeatedly or deliberately violated FDA regulations or repeatedly or deliberately submitted false information, FDA may move to disqualify the investigator from conducting future studies regulated by FDA. Second, FDA may initiate a civil or criminal enforcement action in Federal court. Such actions can take several months and frequently years to complete.

To disqualify a clinical investigator, FDA must go through a process involving an opportunity for hearing (21 CFR § 312.70). When a Center has reviewed the inspectional findings and determined that there is evidence of repeated or deliberate violations or repeated or deliberate submission of false information, and that the pattern or severity of the misconduct warrants agency action, the Center issues a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter, which furnishes the investigator with written notice of the matter and offers the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an informal conference is held, the investigator may bring an attorney. If, after hearing the investigator's explanation, the Center still believes that the investigator's actions meet the threshold for disqualification, the Center must offer the investigator an opportunity for a regulatory hearing, whose procedures are governed by 21 CFR Part 16 (21 CFR § 312.70). The investigator may enter into a consent agreement or may request a hearing. At a regulatory hearing, the investigator may offer the testimony of witnesses, documentary evidence, and supporting briefs. After the hearing, the presiding officer issues a report or decision on whether the investigator has repeatedly or deliberately violated the regulations and should be disqualified. The report is forwarded to the Commissioner, who then issues a Commissioner's decision on disqualification (21 CFR part 16). The investigator may appeal the Commissioner's decision in Federal court. A disqualification proceeding generally takes many months or years to complete.

C. How Can FDA Protect Human Subjects Following the Discovery of Clinical Investigator Misconduct?

Initiation of an enforcement action in federal court or disqualification proceeding does not by itself halt an investigator's participation in clinical trials. Until an investigator is disqualified by FDA, the investigator remains free to participate in ongoing and new clinical investigations. There are, however, instances in which the investigator's misconduct appears to pose an ongoing risk to the safety and welfare of the human subjects under the care of that investigator. For example, where an investigator is found to have failed to monitor subjects for signs of serious toxicity associated with the experimental therapy, or falsified eligibility data, FDA may conclude that subjects under that investigator's care are at risk. Under such circumstances, protection of subjects may

demand a more rapid intervention than would be offered by an enforcement action or disqualification proceeding. One means of acting promptly to protect human subjects after the discovery of serious investigator misconduct is to impose a clinical hold on those studies or study sites involving the investigator. For example, in a multi-center trial, we would expect to place on clinical hold only those study sites that involved the investigator who engaged in serious investigator misconduct.

III. USE OF CLINICAL HOLDS TO PROTECT HUMAN SUBJECTS

A. What Is a Clinical Hold?

A clinical hold is an order by FDA that immediately suspends or imposes restrictions on an ongoing or proposed clinical study. FDA has promulgated regulations authorizing clinical holds for studies involving drugs and biological products (21 CFR § 312.42). Section 312.42(a) describes the scope and effect of a clinical hold order:

> A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

A clinical hold may be complete or partial. Delay or suspension of all clinical work under an IND is considered a complete clinical hold. Delay or suspension of only part of the clinical work under an IND is considered a partial clinical hold. A partial clinical hold could, for example, be imposed to delay or suspend one of several protocols in an IND, a part of a protocol, or a specific study site in a multi-site investigation.

FDA's regulation authorizing clinical holds on studies of drugs and biological products sets forth grounds for imposing a hold. Those grounds vary depending on the nature of the study.[1] For all types of studies, however, FDA may impose a clinical hold if it finds that "[h]uman subjects are or would be exposed to an unreasonable and significant risk of illness or injury" (21 CFR §§ 312.42(b)(1)(i), (b)(2)(i), (b)(3)(i)(A), (b)(3)(ii)(E)(2), (b)(4)(i), (b)(5)(i), (b)(6)(i)).

[1] The types of studies covered by §312.42 include: Phase 1 studies, §312.42(b)(1), Phase 2 and 3 studies, §312.42(b)(2), proposed and ongoing treatment use, §312.42(b)(3)(i)-(iii), studies that are not designed to be adequate and well-controlled, §312.42(b)(4), studies involving an exception from informed consent under §50.24, §312.42(b)(5), and studies involving an exception from informed consent under §50.23, §312.42(b)(6).

B. Under What Circumstances Would FDA Consider Imposing A Clinical Hold Following Discovery Of Clinical Investigator Misconduct?

FDA believes that, in some situations, clinical investigator misconduct may be sufficiently serious to conclude that human subjects under that investigator's care are or would be exposed to an unreasonable and significant risk of illness or injury. In this section, FDA provides guidance on the circumstances in which the agency could reach such a conclusion and impose a clinical hold on the study or study sites in which an investigator is involved.

1. Before an enforcement action is initiated.

After FDA obtains evidence of investigator misconduct, but before a decision to bring an enforcement action in federal court or to issue a NIDPOE letter has been made, there may or may not be reason to believe that human subjects under the care of the investigator are or would be exposed to an unreasonable and significant risk of illness or injury. At this stage in an inquiry into investigator misconduct, FDA would consider two factors in deciding whether to issue a clinical hold.

First, FDA would look at the nature of the violation and its significance for the safety and rights of human subjects. Certain types of violations may pose such a significant threat to subjects in the trial that suspending that part of the trial under the investigator is justified, even where the investigation into the violations is at an early stage. For example, FDA may conclude that suspending the trial is necessary to protect subjects from a significant and unreasonable risk of illness or injury, if FDA finds evidence of one or more of the following:

?? Failure to report serious or life-threatening adverse events;

?? Serious protocol violations, such as enrolling subjects who do not meet the entrance criteria due to conditions that put them at increased risk from the investigational drug or other important failure to follow the approved protocol;

?? Repeated or deliberate failure to obtain adequate informed consent, including:

  ?? falsification of consent forms;

  ?? repeated or deliberate failure to disclose serious risks of the investigational drug in the informed consent process;

?? Falsification of study safety data; and

?? Failure to obtain IRB review and approval for significant protocol changes.

Conversely, some types of violations would be less likely to justify a clinical hold at an early stage in FDA's investigation. For example, certain kinds of record-keeping

violations or failure to disclose certain types of financial interests would be unlikely to suggest such a significant risk of illness or injury to subjects in the trial that a clinical hold would be justified.

Second, FDA would consider the degree of certainty that there has been investigator misconduct that poses a significant risk to subjects. Early in the process of evaluating inspectional findings, for example, FDA may not have had an opportunity to assess the significance of the alleged violations or to hear the investigator's response to the allegations. FDA is more likely to impose a clinical hold where there is greater certainty about whether a violation occurred and its signficance to the safety of subjects. Nonetheless, protecting the safety of patients at imminent risk is of great importance, and even preliminary (e.g., pre-inspectional), but credible evidence raising concerns that patients may be placed at substantial risk may warrant a hold while further information is being obtained.

2. After an enforcement action is initiated.

In general, when FDA concludes that there is sufficient evidence of repeated or deliberate violations of the regulations or of repeated of deliberate submission of false information to take an enforcement action, typically it will issue a NIDPOE letter and begin a disqualification proceeding. In this case there will be a strong presumption that human subjects are or would be exposed to an unreasonable and significant risk of illness or injury. The types of violations that warrant the issuance of NIDPOE letters are always significant and, with rare exceptions, jeopardize the safety and rights of the subjects involved. Those exceptions involve violations that compromise data integrity alone without jeopardizing subjects. Minor violations of an investigator's responsibilities do not alone give rise to a NIDPOE letter. One or more of the following types of violations may give rise to NIDPOE letters, and may also give rise to clinical holds if the circumstances show that the violations pose a significant risk to subjects:[2]

?? Repeated or deliberate failure to obtain or document informed consent from human subjects, which may include:

   ?? Repeated or deliberate omission of a description of serious risks of the experimental therapy when obtaining informed consent;

   ?? Repeated or deliberate failure to provide informed consent in a language understandable to the subject;

?? Repeated or deliberate failure to limit administration of the investigational article to those subjects under the investigator’s supervision;

?? Repeated or deliberate failure to comply with conditions placed on the study by the IRB, sponsor, or FDA;

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[2] This list is not intended to be all-inclusive.

?? Repeated or deliberate failure to obtain review of a study plan by an IRB, the body responsible for overseeing the rights and safety of human subjects;

?? Repeated or deliberate failure to follow the signed investigator statement or protocol, e.g., by enrolling subjects who should have been excluded because of concomitant illnesses that put those subjects at greater risk;

?? Repeated or deliberate failure to maintain accurate study records or submit required adverse event reports to the sponsor; and

?? Repeated or deliberate falsification or concealment of study records, e.g., by substituting in study records the results of biological samples from subjects who met the inclusion criteria for samples of subjects who did not meet the inclusion criteria, or by fabricating subjects.

When such violations, or others of similar gravity, have occurred, FDA may determine that human subjects under the care of the investigator are or would be exposed to an unreasonable and significant risk of illness or injury and may impose a clinical hold.

C. What Steps Will FDA Take Before Imposing A Clinical Hold to Protect Subjects from Investigator Misconduct?

The general regulations governing clinical holds require that, where FDA concludes that there may be grounds for imposing a clinical hold, "FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order" (21 CFR 312.42(c)). In most cases in which a clinical hold might be imposed following investigator misconduct, the threat to subjects will be serious. If possible, as in all cases where a clinical hold is considered, FDA contacts the sponsor and attempts to resolve the matter in a way that adequately protects study subjects before imposing a clinical hold.

D. When Will FDA Lift a Clinical Hold that Was Imposed to Protect Subjects from Investigator Misconduct?

FDA will lift a clinical hold imposed to protect subjects from investigator misconduct when the grounds for the hold no longer apply. The sponsor of the affected study may, during the pendency of the clinical hold, present evidence to FDA to show that it has taken steps to protect study subjects, e.g., by replacing the investigator who is charged with the misconduct or, for example, in the case of a sponsor-investigator, by hiring a monitor to oversee the clinical trial. If FDA concludes, based on this evidence, that the study subjects are no longer exposed to an unreasonable and significant risk of illness or injury, the hold will be lifted. In all instances, if a sponsor of a study that has been placed on clinical hold requests in writing that the clinical hold be removed and responds to the issues identified in the clinical hold order, FDA will respond in writing to the sponsor within 30 calendar days of receipt of the request and response (21 CFR 312.42(e)). FDA

will either remove or maintain the clinical hold and will state the reasons for its decision (Id.).