Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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September 2021
Drug Safety

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Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to help clinical investigators comply with the following safety reporting requirements:

- Investigational new drug application (IND) studies[2] under § 312.64(b) (21 CFR 312.64(b))
- Investigational device exemption (IDE) studies under § 812.150 (21 CFR 812.150)

Recommendations are provided to help investigators identify the following:

1. For drugs — Identify safety information that is considered an unanticipated problem involving risk to human subjects or others and that therefore requires prompt reporting to institutional review boards (IRBs) under § 312.66 (21 CFR 312.66)
2. For devices — Identify safety information that meets the requirements for reporting unanticipated adverse device effects (UADEs) to sponsors and IRBs under § 812.150(a)(1) (21 CFR 812.150(a)(1))

This document incorporates concepts pertaining to investigator responsibilities for adverse event reporting described in the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012) (the 2012 final guidance) and in the guidance for

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] This guidance also provides relevant information for companies reporting serious adverse events (SAEs) for IND-exempt bioavailability (BA)/bioequivalence (BE) studies under § 320.31(d)(3) (21 CFR 320.31(d)(3)).

clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs—Improving Human Subject Protection* (January 2009) (the 2009 procedural final guidance).[3]

When finalized, this guidance will supersede corresponding sections in the 2012 final guidance and the 2009 procedural final guidance. Until that time, however, the 2012 final guidance and the 2009 procedural final guidance continue to represent FDA's current thinking on investigator responsibilities for safety reporting for investigational medical products.[4]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA's guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the *Federal Register* of September 29, 2010 (75 FR 59935), FDA published a final rule (referred to in this guidance as the 2010 IND safety reporting rule) amending the IND safety reporting requirements under § 312.32 and adding safety reporting requirements for persons conducting bioavailability (BA) and bioequivalence (BE) studies under § 320.31 (21 CFR 320.31). Subsequently, the 2012 final guidance was published to help sponsors and investigators comply with safety reporting requirements for INDs and for IND-exempt BA/BE studies.

Recently, the recommendations for investigators provided in the 2012 final guidance were updated, merged, and published for notice and comment purposes in the draft guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021) (the merged 2021 draft guidance).[5] The merged 2021 draft guidance does not, however, include the recommendations for investigator responsibilities that are included in the 2012 final guidance, and such recommendations on investigator responsibilities are the primary focus of this guidance.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] For combination products as defined in 21 CFR 3.2(e), safety reporting under the IDE or IND should include a complete discussion of the event with respect to the combination product as a whole, including each constituent part of the product, as appropriate, based on the available information. If you have questions related to safety reporting for your investigational product, please contact the lead review division for the IND or IDE. You may also contact the Office of Combination Products at combination@fda.gov for further assistance as needed.

[5] When final, this guidance will represent FDA's current thinking on this topic.

The IND safety reporting requirements in § 312.32 apply to sponsors,[6] not investigators. However, investigators may find it helpful to understand overall sponsor responsibilities regarding IND safety reporting requirements. The regulations in § 312.32(c)(1) require the sponsor to notify FDA[7] and all participating investigators (i.e., all investigators to whom the sponsor is providing the drug under the sponsor's INDs or under any sponsor-investigator's IND) in an IND safety report of potential serious risks identified from clinical trials[8] or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i) through (iv), which includes any of the following:

- Serious and unexpected suspected adverse reactions[9]
- Findings from epidemiological studies, pooled analyses of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug
- Findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

For IND-exempt BA/BE studies, § 320.31(d)(3) states that "[t]he person conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event, as defined in § 312.32(a), observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence."

Section 320.31(d)(3) also requires the person conducting the study (including any contract research organization) to notify FDA of any "fatal or life-threatening adverse event from the study as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence." However, the regulation does not require all investigators to be notified of such events within that time frame.

For device studies under an IDE, the regulations in § 812.150(a)(1) require investigators to submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but no later than 10 working days after the investigator first

[6] Requirements under § 312.32 also apply to sponsor-investigators, as defined in § 312.3.

[7] A sponsor-investigator who receives an IND safety report for another study for which they are not the sponsor does not need to submit that IND safety report to FDA if it has already been submitted. See the draft guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies*.

[8] For the purposes of this guidance, FDA uses the terms *clinical trial* and *clinical investigation* interchangeably.

[9] Note that if the suspected adverse reaction is fatal or life-threatening, the requirement is to report as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information (see § 312.32(c)(2)).

learns of the effect. In addition, the regulations in 21 CFR 812.46(b) and 812.150(b)(1) require sponsors to conduct an evaluation of any UADE and to report the results to FDA, all reviewing IRBs, and all participating investigators within 10 working days after the sponsor first receives notice of the effect.

III. DEFINITIONS

A. DRUGS

The 2010 IND safety reporting rule defined a number of terms related to safety reporting. Although the terms defined in § 312.32 refer to sponsor reporting responsibilities, FDA is using these terms consistently for the purposes of the investigator reporting requirements for drugs[10] discussed in this guidance. These definitions, accompanied by further explanation and examples, can also be found in the merged 2021 draft guidance. For ease of reference, the following definitions from § 312.32(a) are included in this guidance as well, along with additional thinking about the meaning of these terms.

1. Adverse Event (21 CFR 312.32(a))

Adverse event (AE) means "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (§ 312.32(a)).

FDA considers an *adverse event* (also referred to as an *adverse experience*) to include any unfavorable sign (e.g., an abnormal laboratory finding), symptom, or clinical outcome temporally associated with the use of a test drug, active control, or placebo, regardless of whether the event is thought to be related to the drug. An adverse event can arise during any use of a drug or biologic (e.g., use for a purpose other than FDA-approved indication or in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

2. Adverse Reaction[11] and Suspected Adverse Reaction (21 CFR 312.32(a))

An *adverse reaction* means any adverse event *caused* by a drug. *Suspected adverse reaction* means "any adverse event for which there is a *reasonable possibility* that the drug caused the adverse event. For the purposes of IND safety reporting, *reasonable possibility* means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected

[10] For the purposes of this guidance, *drug* or *drug product* is used to refer to human drugs and human biological products that are regulated as drugs.

[11] For the purposes of prescription drug labeling, the term *adverse reaction* is defined to mean "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event" (21 CFR 201.57(c)(7); see also 21 CFR 201.80(g)).

adverse reaction implies a lesser degree of certainty about causality than adverse reaction . . . ." (emphasis added) (§ 312.32(a)).

Both an adverse reaction and a suspected adverse reaction require evidence of a causal relationship between the drug and the adverse event (§ 312.32(a)). Therefore, if no drug has been administered, an adverse event is not reportable under IND safety reporting regulations.[12,13]

The following examples provided in the safety reporting regulation (§ 312.32(c)(1)(i)) illustrate the meaning of *reasonable possibility* with respect to a determination that there may be a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).

- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

- An aggregate analysis of specific events observed in a clinical trial, indicating that they occur more frequently in the drug treatment group than in a concurrent or historical control group. Such events may be known consequences of the underlying disease or condition or events that commonly occur in the study population independent of drug therapy. Such events could also be related to an intervention or therapy that is standard of care for the disease (e.g., background treatment).

To determine whether an adverse event should be classified as a *suspected adverse reaction* or an adverse reaction, the sponsor must evaluate the available evidence (§ 312.32(b)) and make a judgment about the likelihood that the drug caused the adverse event.

3. Serious (21 CFR 312.32(a))

An adverse event, adverse reaction, or suspected adverse reaction is considered *serious*

> if, in the view of either the investigator or the sponsor, it results in any of the following: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that might not result in death, are not life-threatening, and do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention

[12] However, for clinical investigations that involve an invasive procedure that would not occur other than due to participation in the trial (e.g., intrahepatic artery administration or a kidney biopsy), FDA may request that sponsors also report SAEs associated with such a procedure, even if the investigational product is not administered.

[13] Investigator reporting requirements under §§ 312.64(b) and 312.66 may still apply even where no drug has been administered.

> to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or abuse. (§ 312.32(a))

The sponsor and the investigator must evaluate whether an event meets the definition of *serious*. See §§ 312.32(c)(1)(i) and 312.64(b). Because identifying serious adverse events (SAEs) is critically important for the evaluation of potential significant safety problems, FDA considers it important to take into account both the investigator's and the sponsor's assessments. Therefore, if the sponsor or investigator believes that the event is serious, the event must be considered serious and must be evaluated by the sponsor for expedited reporting (§§ 312.32(a) and 312.32(c)(1)).

B. DEVICES

1. Unanticipated Adverse Device Effect (21 CFR 812.3(s))

An *unanticipated adverse device effect* (UADE)

> means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (§ 812.3(s))

2. Serious

What qualifies as a serious adverse effect, as that term is used in the definition of UADE, would be specific to the device and the study in which it is being used or tested. Generally, a serious adverse effect is one that is determined by the investigator or sponsor to be life-threatening, require hospitalization, result in disability or permanent damage, result in a congenital anomaly or birth defect, or require an intervention to prevent permanent impairment or damage. In the protocol, the sponsor should include information on adverse effects that helps investigators determine what would qualify as a serious adverse effect. Examples of adverse effects that could be considered serious include organ perforation and thrombus formation inside an aortic endovascular graft.

IV. INVESTIGATOR REPORTING TO SPONSORS FOR IND STUDIES[14]

Most of the information about the safety of a drug prior to marketing comes from clinical trials. Adverse event reports from investigators are therefore critically important, given that it is the investigators who observe subjects' responses to an investigational drug. The investigator must immediately report to the sponsor any SAEs,[15] regardless of whether the investigator believes the SAEs are related to the drug (§ 312.64(b)). This requirement includes those SAEs (1) listed in the safety surveillance plan as anticipated to occur in the study population independent of drug exposure or (2) listed in the investigator brochure as predicted to occur with the drug.[16] The one exception to this requirement (discussed in section IV.B of this guidance) involves study endpoints that are also SAEs (e.g., myocardial infarction, stroke, or death in trials evaluating drugs intended to treat cardiovascular conditions), which "must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event. . . . In that case, the investigator must immediately report the event to the sponsor." (§ 312.64(b)). Non-serious AEs must be reported according to the timetable for reporting specified in the protocol (§ 312.64(b)).

For the purposes of this guidance, the Agency interprets *immediately* to be as soon as feasible after the investigator recognizes an event is an SAE and obtains relevant information for the sponsor. Such information would generally include a specified subject, a suspected drug (if any), the reporting source (if not the investigator themself), and a clinical description of the event, including an assessment of whether a reasonable possibility exists that the drug caused the event. Although more data may be collected and submitted later, the initial report must be submitted as soon as possible (§ 312.64(b)). FDA recommends that this time frame for submitting such initial information also be specified in the protocol and anticipates that it will generally be no longer than 1 calendar day. Investigators are not required to determine whether an event is *unexpected* (as defined in § 312.32(a));[17] this determination is a sponsor's responsibility (see § 312.32(c)(1)(i)).

[14] Guidance provided in this section may be applicable for companies conducting IND-exempt BA/BE studies to comply with § 320.31(d)(3).

[15] Study endpoints that are SAEs must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (§ 312.64(b)).

[16] For further information about anticipated and expected adverse events, see the draft guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies.*

[17] "An adverse event or suspected adverse reaction is considered 'unexpected' if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. . . . '*Unexpected*,' as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation" (§ 312.32(a)).

A. Assessment of Causality

FDA believes that the sponsor is generally better positioned than the individual investigator to determine whether an SAE should be classified as a *suspected* adverse reaction. This is especially true for events that may warrant analysis of more than a single event to determine if any are possibly related to the drug, because the sponsor may have access to SAE reports from multiple study sites and multiple studies and would be able to aggregate and analyze these reports. Moreover, the sponsor is likely to be more familiar with the drug's mechanism of action, class effects, and other information. To determine whether an SAE meets the definition of a suspected adverse reaction, the sponsor must evaluate the available evidence (as separately required by § 312.32(b)) and make a judgment about the likelihood that the drug actually caused the adverse event. For these reasons, except for most study endpoints, investigators must immediately report any SAE to the sponsor (as mentioned previously), whether or not the investigator considers the event to be drug related (§ 312.64(b)).

Although the sponsor is ultimately responsible for determining whether an SAE should be classified as a *suspected* adverse reaction, the investigator's view is important for the sponsor to carefully consider when assessing the safety of the drug and determining whether to report an event expeditiously to FDA. The investigator, who monitors the subject's response to the drug, is knowledgeable about the subject's clinical state (e.g., medical history, concomitant medications, symptoms, pertinent test results, timing of events relative to drug exposure). Therefore, the investigator may be sensitive to distinctions between events that may be related to study drug exposure versus those caused by the underlying disease process and/or concomitant therapies.

For these reasons, the investigator must include in the report to the sponsor an assessment of whether there is a reasonable possibility that the drug caused the event (§ 312.64(b)). For the purposes of § 312.64(b), FDA interprets *reasonable possibility* to mean there is evidence to suggest a causal relationship between the drug and the adverse event. This interpretation is consistent with the definition of *suspected adverse reaction* in § 312.32(a). Factors that should be considered when making a causality assessment include, but are not limited to, temporal relationship of the event to drug administration; biologic plausibility, based on the mechanism of action of the drug or similar drugs in the same class; nonclinical evidence; and dechallenge-rechallenge information.

B. Study Endpoints

In studies where trial endpoints meet the criteria for SAEs (such as myocardial infarction or death), the investigator must report these as endpoints, in accordance with the protocol, and not as SAEs to the sponsor (§ 312.64(b)). An exception to this requirement, however, is when there is evidence suggesting a causal relationship between a drug and an event (e.g., death from anaphylaxis after exposure). Even if such an event is a component of the endpoint (e.g., all-cause mortality), SAEs meeting this criterion must be immediately reported to the sponsor (§ 312.64(b)).

C. Nonserious Adverse Events

The investigator must record nonserious adverse events and report them to the sponsor according to the timetable specified in the protocol (§ 312.64(b)). Often, nonserious events are recorded and are submitted to the sponsor and reviewed at regular intervals throughout the course of the investigation.

V. INVESTIGATOR REPORTING TO INSTITUTIONAL REVIEW BOARDS FOR IND STUDIES[18]

Investigators are required to "promptly report to the IRB . . . all unanticipated problems involving risk to human subjects or others" (§ 312.66), including adverse events that represent unanticipated problems, as further described in this section.[19] Note that the requirements for IND safety reporting under § 312.32 do not address safety reporting by investigators to IRBs. The types of unanticipated problems that must be reported to the IRB are discussed in sections A and B below.

A. Adverse Events as Unanticipated Problems That Must Be Reported to the IRB

Investigators are required under § 312.66 to report all "unanticipated problems involving risk to human subjects or others" to the IRB. FDA considers a serious and unexpected adverse event that meets the criteria for sponsor reporting to FDA and all investigators in an IND safety report under § 312.32 to be an unanticipated problem involving risk to human subjects or others that therefore must be reported to the IRB by the investigator.[20]

IND safety reports and reports of SAEs from IND-exempt BA/BE studies[21] provide FDA and participating investigators with important information relevant to the safety of human subjects receiving the investigational drug. IND safety reports provide information on potential serious risks, including unexpected SAEs for which there is a reasonable possibility that the

[18] Guidance provided in this section may be applicable for companies conducting IND-exempt BA/BE studies to comply with § 320.31(d)(3).

[19] We note that IND-exempt BA/BE studies are not subject to the requirements in § 312.66. However, they must still be conducted in compliance with the requirements for review by IRBs established in 21 CFR part 56. See § 320.31(d)(2). Section 56.108(b)(1) provides that an IRB will ensure the prompt reporting to the IRB of "any unanticipated problems involving risks to human subjects or others. . . ." FDA interprets this language in a manner consistent with the interpretation of § 312.66 laid out in this guidance.

[20] In general, the occurrence of an SAE is very unusual in a BA/BE study because the number of subjects enrolled is small, the subjects are usually healthy volunteers, and drug exposure is typically brief, but often at the highest available dosage. For these reasons, FDA considers the occurrence of any SAE in a BA/BE study that is subject to an IND to be an unanticipated problem involving risk to human subjects. Accordingly, the investigator of a BA/BE study that is subject to an IND must report to the IRB any SAE that occurs in the study (21 CFR 312.66).

[21] See § 320.31(d)(3).

investigational drug caused the event. Reports of SAEs from IND-exempt BA/BE studies provide information on SAEs that occur in those studies, all of which are important to consider for human subject protection reasons because the occurrence of SAEs in BA/BE studies is unusual: the number of subjects enrolled is small, the subjects are usually healthy volunteers, and drug exposure is typically brief, but often at the highest available dosage.

Reviewing IND safety reports and reports of SAEs from IND-exempt BA/BE studies is essential for protecting the safety of human subjects because each report represents important safety information regarding the investigational drug. FDA considers the review of these reports critical to fulfilling the investigator's responsibility under § 312.60 (21 CFR 312.60) to protect the safety of subjects under their care. For these reasons, investigators must review all IND safety reports and reports of safety information from IND-exempt BA/BE studies received (see § 312.60). In addition, investigators must submit these reports to the IRB because the reports describe important safety information representing unanticipated problems involving risks to human subjects or others (§ 312.66). Many study protocols specify that the sponsor will submit IND safety reports to the IRB on the investigator's behalf. In these situations, where the investigator receives confirmation that the report has been sent to the IRB (e.g., the investigator is copied on the report sent to the IRB by the sponsor), FDA would not expect an investigator to provide the IRB with a duplicate copy of the report.[22]

B. Other Unanticipated Problems Requiring Reporting to the IRB

Some events not meeting the criteria for reporting in an IND safety report or as a BA/BE study premarket SAE would still be considered unanticipated problems involving risk to human subjects or others and, under § 312.66, would require reporting to the IRB by the investigator. Such events may occur at the subject, site, and/or study level. Some possible examples may include reports of medication errors (such as receipt of wrong dose or contaminated study medication), breach of privacy/confidentiality (such as disclosure of personally identifiable information), untimely destruction of study records, and other scenarios. The investigator must report any unanticipated problems involving risk to human subjects or others. This requirement applies regardless of whether the unanticipated problem is related to the study drug or related to study procedures. Such unanticipated problems may include serious unexpected adverse events that occur prior to test article administration or during a washout period or that are attributable to a screening procedure (e.g., renal failure after receipt of an imaging contrast agent).

Finally, the IRB's written procedures or institutional policy may require the investigator to submit to the IRB other unanticipated problems in addition to those that qualify for reporting under § 312.66. The investigator should be familiar with and adhere to the IRB's written procedures for reporting unanticipated problems involving risks to human subjects or others to the IRB (see 21 CFR 56.108(b)(1)). Also, as part of their clinical trial monitoring responsibility, we understand that sponsors generally require that investigators report such unanticipated problems to the sponsors as well.

[22] Note that such an agreement should be documented.

VI. INVESTIGATOR REPORTING TO SPONSORS AND INSTITUTIONAL REVIEW BOARDS FOR IDE STUDIES

The IDE regulations require investigators to report UADEs to both sponsors and IRBs. Similar to the handling of SAEs described previously for IND studies, FDA believes that the sponsor is generally better positioned than the individual investigator to assess UADEs, given that the sponsor has access to UADE reports from multiple study sites and multiple studies and is able to aggregate and analyze these reports. Therefore, UADE reports are critical to the process, and the IDE regulations require not only timely reporting for investigators, but also timely evaluation by sponsors, described as follows:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (§ 812.150(a)(1)).

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and all participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b) and 812.150(b)(1)).

What qualifies as a UADE is expected to vary depending on the specific device and the way the device is used within the study. Therefore, sponsors are required to include risk information in the investigational plan, which may help investigators identify and assess potential UADEs (§§ 812.25(c) and 812.45).

In addition to reporting UADEs, according to § 812.150(a)(3), investigators are to provide progress reports to sponsors, monitors, and IRBs[23] at regular intervals, and no less than yearly. Such reports should provide information to sponsors about both anticipated and unanticipated adverse device effects.

[23] The terms *sponsor*, *monitor*, and *IRB* in the context of device studies are defined in § 812.3.