SECTION II: RUNNING THE TRIAL

CHAPTER 9

Adverse Event and SAE Reporting: Definitions, Timelines, and Regulatory Requirements

Safety reporting timelines are the single most frequently tested topic on the CCRP exam. This chapter covers every definition, every timeline, and every reporting pathway. Candidates who master this chapter have mastered the core of this section.

MUST KNOW

SECTION II · 50% OF EXAM

WHAT THIS CHAPTER COVERS

- SAE DEFINITION (21 CFR 312.32(A))
- 7-DAY FATAL/LIFE-THREATENING USADR RULE
- 15-DAY NON-FATAL/NON-LIFE-THREATENING RULE
- INVESTIGATOR SAE REPORTING TO SPONSOR
- UNEXPECTED VS. EXPECTED AES
- ANNUAL IND SAFETY REPORTING (21 CFR 312.33)

The Definitional Framework: AE, ADR, SAE, and SUSAR

Accurate adverse event reporting begins with precise definitions. An Adverse Event (AE) is any unfavourable medical occurrence in a trial participant administered the investigational product that does not necessarily have a causal relationship with the treatment, per ICH E6(R3) Glossary. The word "unfavourable" means unfavorable or unexpected; it does not require causal attribution, which makes AE a broad category that encompasses everything from a headache to a fatal cardiac arrest, as long as it occurs during the study period regardless of suspected cause. This is a critical distinction for documentation: if an event occurs, it gets recorded as an AE. Causality is a separate assessment made afterward.

An Adverse Drug Reaction (ADR) is an adverse event for which there is a reasonable possibility that the study drug caused the event. The threshold for "reasonable possibility" is lower than proof of causation; if the investigator cannot rule out a drug relationship, the event is treated as an ADR for safety reporting purposes. An Unexpected Adverse Drug Reaction is one whose nature, severity, specificity, or outcome is not consistent with the information in the Investigator Brochure (IB) or the product labeling. Expectedness is always assessed against the IB, not against general medical knowledge or the investigator's personal experience.

A Serious Adverse Event (SAE) meets any one of the following criteria (21 CFR 312.32(a)): results in death, is life-threatening (meaning the subject was at immediate risk of death at the time of the event, not hypothetically if it recurred), requires or prolongs hospitalization (inpatient admission), results in persistent or significant disability or incapacity, constitutes a congenital anomaly or birth defect, or is an important medical event that, based on medical judgment, may jeopardize the subject and may require intervention to prevent one of the preceding outcomes. This last criterion is commonly referred to as the "important medical event" criterion and is intentionally broad to capture events like drug-induced liver injury with significantly elevated transaminases that do not yet meet the hospitalization threshold but clearly warrant urgent safety attention. The mnemonic commonly used is DHIPP + I: Death, Hospitalization (or prolonged hospitalization), Important medical event, Persistent/significant disability, congenital anomaly (birth defect), and life-threatening (the second "I" for Immediately life-threatening).

SAE ALERT

The phrase "life-threatening" in the SAE definition means the subject was at immediate risk of death at the time of the event. An adverse event that could theoretically be fatal if it were to occur in the future does not meet the life-threatening SAE criterion unless the subject was in immediate danger at the time. This distinction is tested frequently because candidates conflate "potentially serious" with "life-threatening."

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is the highest priority safety event in clinical research. To qualify as a SUSAR, an event must simultaneously meet three criteria: (1) it is suspected to be related to the investigational product (ADR), (2) it is serious (meets at least one SAE criterion), and (3) it is unexpected (not consistent with the IB). SUSARs must be reported through the regulatory safety system with the most urgent timelines. In the ICH framework, SUSARs are the events that trigger IND Safety Reports (called ISRs) to FDA.

TABLE 1: SAE CRITERIA (DHIPP+I MNEMONIC WITH DEFINITIONS)

Letter	Criterion	Definition and Key Notes
D	Death	Results in the death of the subject. All deaths in a clinical trial require SAE reporting regardless of suspected cause. The relationship to study drug is assessed separately.
H	Hospitalization (initial or prolonged)	Requires inpatient admission or prolongs an existing hospitalization. An emergency department visit that does not result in inpatient admission does not automatically qualify, but planned hospitalizations for protocol-required procedures are typically excluded per protocol.
I	Important Medical Event	An event that, based on medical judgment, may jeopardize the subject and may require intervention to prevent death, hospitalization, disability, or birth defect. Intended as a safety net for clinically significant events that do not fit other criteria.
P	Persistent or Significant Disability/ Incapacity	Substantial disruption of the subject's ability to conduct normal life functions. "Persistent" implies the disability is lasting; "significant" implies substantial functional impairment.
P	congenital anomaly / birth defect	Abnormality present at birth. Requires pregnancy follow-up tracking in studies involving reproductive-age subjects or male subjects whose partners may become pregnant.
+I	Life-Threatening (Immediately)	

Letter	Criterion	Definition and Key Notes
		Subject was at immediate risk of death at the time of the event. Requires the most urgent reporting timeline (7 calendar days to FDA for fatal or life-threatening USADRs).

Causality Assessment: Who Decides and How

Causality assessment is the investigator's determination of whether the adverse event is likely related to the study drug. Standard causality categories used in clinical trials include "unrelated," "unlikely related," "possibly related," "probably related," and "definitely related," though protocol-specific systems may use slightly different terminology. The investigator's causality assessment is a clinical judgment, not a statistical calculation, and is based on the timing of the event relative to drug exposure, whether the event resolved upon drug discontinuation (dechallenge), whether it recurred upon rechallenge, and the biological plausibility of a drug-event relationship.

A critical principle that is frequently tested: the sponsor independently assesses causality and may disagree with the investigator's assessment. If the sponsor believes an event is related to the drug even though the investigator assessed it as unrelated, the sponsor must treat it as related for the purposes of IND Safety Reports to FDA. Conversely, if the investigator assesses an event as possibly related but the sponsor disagrees, the more conservative (related) assessment prevails — the event must be treated as related for reporting purposes. Neither party can unilaterally downgrade a relatedness finding. This dual assessment system exists because neither the investigator nor the sponsor has complete information; the sponsor has access to aggregate data across all sites and all subjects, while the investigator has intimate knowledge of the individual subject's clinical context.

Reporting Timelines: The Most Tested Content on the Entire Exam

Understanding the AE reporting timeline architecture requires knowing three distinct reporting relationships: investigator to sponsor, investigator to IRB, and sponsor to FDA. Each relationship has different triggers and timelines, and the exam heavily tests candidates' ability to apply the correct timeline to a described scenario.

Investigator to Sponsor: All SAEs must be reported by the investigator to the sponsor promptly — the widely followed standard is 24 hours of awareness — per ICH E6(R3) Annex 1, Section 2.7.2 (SAE Reporting) and 21 CFR 312.64(b). The 24-hour timeline applies to all SAEs, regardless of the investigator's causality assessment. Many protocols impose an even tighter window, such as "immediately" or "within the same business day," but 24 hours is the widely followed industry standard reflecting this promptly requirement; many protocols specify an even shorter window. Non-serious adverse events are reported per the protocol schedule, typically at study visits or weekly, and documented in the CRF.

Investigator to IRB: The investigator must report unanticipated problems involving risks to subjects or others to the IRB per 21 CFR 56.108(b). For purposes of clinical trials, this means SAEs that are unexpected and related to study participation must be reported to the IRB. The timeline is not specified by FDA regulation for this reporting pathway; it is determined by the individual IRB's written procedures, which typically require reporting within 5 to 10 working days of the investigator's awareness. Investigators must know their IRB's specific requirements. Importantly, not every SAE requires individual IRB notification; if the SAE is expected (listed in the IB) and unrelated to the study, it is reported only in aggregate via the annual study report to the IRB, unless the protocol or IRB requires otherwise.

Sponsor to FDA (IND Safety Reports): The sponsor's reporting obligations to FDA are calibrated to the severity and unexpectedness of the event. For fatal or life-threatening USADRs, the sponsor must notify FDA as soon as possible but within 7 calendar days of first receiving information about the event per 21 CFR 312.32(c)(2). A follow-up written report must be submitted within 15 calendar days of the sponsor first receiving the information — the same starting point as the 7-day clock, not 15 days after the 7-day call. For all other USADRs (unexpected serious adverse drug reactions that are not fatal or immediately life-threatening), the sponsor submits a written 15-day report per 21 CFR 312.32(c)(1)(ii). These reports are submitted in the MedWatch format (Form FDA 3500A for clinical trial reporting). The sponsor is also required to submit follow-up reports as new information becomes available on previously reported events.

SAE ALERT

The 7-day vs. 15-day distinction is one of the most frequently tested specific facts on the CCRP exam. The 7-day rule applies only to fatal or life-threatening USADRs and triggers an initial notification (21 CFR 312.32(c)) ; the full written 15-day report is submitted within 15 calendar days after the sponsor determines the event qualifies for reporting (21 CFR 312.32(c)) . The 15-day rule applies to all other unexpected serious adverse drug reactions (21 CFR 312.32(c)) . All timelines are in calendar days, not business days. A fatal USADR reported on a Friday afternoon must be notified to FDA by the following Thursday.

TABLE 2: ADVERSE EVENT REPORTING TIMELINES SUMMARY

Reporting Party	Recipient	Trigger	Timeline	Regulatory Basis
Investigator	Sponsor	Any SAE (regardless of causality)	Within 24 hours of awareness	ICH E6(R3) Annex 1, Section 2.7.2 (SAE Reporting) ; 21 CFR 312.64(b)
Investigator	IRB	Unanticipated problems involving risks to subjects; SAEs that are unexpected and related	Per IRB written procedures (typically 5-10 working days)	21 CFR 56.108(b)
Sponsor	FDA	Fatal or life-threatening USADR	Initial notification: 7 calendar days; Written report: 15 calendar days after sponsor determines the event qualifies for reporting	21 CFR 312.32(c)(2)
Sponsor	FDA	All other USADRs (unexpected, serious, related; not fatal/life-threatening)	Written 15-day safety report	21 CFR 312.32(c)(1)(ii)
Sponsor	FDA	Annual safety summary	Within 60 days of IND anniversary	21 CFR 312.33 — Annual IND Progress Report
Sponsor	All Investigators	New safety information material to subject safety	As soon as possible; updated IB or Dear Investigator letter	ICH E6(R3) Section 3 (Sponsor)

Non-Serious AE Documentation and the AE Record

Non-serious adverse events are recorded in the CRF at each study visit or according to the protocol's AE reporting schedule. The documentation for every adverse event, regardless of seriousness, must include: date of onset, date of resolution (or notation that the event is ongoing), severity graded according to the protocol's scale (commonly NCI CTCAE grade 1-5 for oncology, or mild/moderate/severe for other indications), the investigator's assessment of causality, the action taken with respect to the study drug (dose unchanged, dose reduced, dose interrupted, drug discontinued), and the outcome. Each of these data elements is a required CRF field, and missing any of them constitutes incomplete data that will generate a query.

Pregnancy Reporting and Medical Device Reporting Distinctions

Pregnancies in female subjects or in the female partners of male subjects enrolled in a trial are reportable events requiring specific follow-up. Pregnancy itself is not automatically classified as an SAE; however, protocols universally require that pregnancies be reported to the sponsor promptly (often within 24 hours of investigator awareness, similar to SAEs), and that outcomes be followed through delivery and the neonatal period for documentation of congenital anomalies or other adverse outcomes. Any adverse pregnancy outcome (spontaneous abortion, stillbirth, congenital anomaly) may constitute a protocol-reportable SAE under the birth defect criterion.

Medical device adverse events follow a different regulatory architecture. Under 21 CFR Part 803 (Medical Device Reporting), manufacturers must report deaths and serious injuries to FDA within 30 calendar days. Certain device types with higher risk profiles require 5-day reporting. Malfunctions that could cause or contribute to a death or serious injury must also be reported within 30 days. These timelines are categorically different from the drug-trial timelines under 21 CFR 312.32 — IND Safety Reporting. Candidates conducting device trials must be explicitly aware that 312.32 does not apply; Part 803 governs. This distinction is occasionally tested on the CCRP.

EXAM TIP

For calculation-style exam questions about SAE reporting deadlines, remember that all FDA safety reporting timelines are counted in calendar days, not business days. Day 1 is the day the sponsor first receives the information (or for the investigator-to-sponsor timeline, the day the investigator becomes aware). If a fatal USADR is reported to the sponsor on Monday, the 7-day FDA notification deadline is Sunday (Day 7). Weekends and holidays do not extend the timeline. When the question asks about the investigator's deadline to the sponsor, the answer is always "within 24 hours," with Day 1 being the day of awareness (same calendar-day counting convention as the sponsor-to-FDA clock).

KEY TERMS

Adverse Event (AE)

> Any unfavourable medical occurrence in a trial participant administered the investigational product without necessarily having a causal relationship to the investigational product per ICH E6(R3) Glossary.

Serious Adverse Event (SAE)

> An adverse event that results in death, is life-threatening, requires hospitalization, results in persistent disability, is a congenital anomaly, or is an important medical event per ICH E6(R3) Glossary and 21 CFR 312.32(a).

SUSAR

> Suspected Unexpected Serious Adverse Reaction: an adverse reaction that is serious, unexpected (not in IB), and suspected to be causally related to the investigational product.

IND Safety Report (ISR)

> The sponsor's regulatory submission to FDA reporting USADRs, submitted on 7-day or 15-day timelines per 21 CFR 312.32(c).

Expectedness

> Whether an adverse event's nature, severity, specificity, or outcome is consistent with the current Investigator Brochure. Always assessed against the IB, not general medical knowledge.

Chapter 9 Review Questions

A study coordinator is notified on a Monday at 9:00 AM that a subject was admitted to the hospital on Sunday evening for a hypersensitivity reaction suspected to be related to the study drug. Per ICH E6(R3) Annex 1, Section 2.7.2 (SAE Reporting) and 21 CFR 312.64(b), what is the deadline for the investigator to report this SAE to the sponsor?

A. Within 24 hours of the subject's hospital admission (i.e., by Monday evening)

B. Within 72 hours, since the weekend delays the clock

C. Within 24 hours of the investigator's (site's) awareness (i.e., by Tuesday at 9:00 AM)

D. At the next monitoring visit

A subject in a Phase III oncology trial develops fulminant hepatic failure and dies. The sponsor receives the fatal SAE report from the investigator on a Wednesday. The sponsor's medical team determines the event is an unexpected serious adverse drug reaction. What is the FDA notification deadline?

A. 7 calendar days from Wednesday (the following Tuesday)

B. 30 calendar days from Wednesday

C. 5 business days from Wednesday

D. 15 calendar days from Wednesday

Which of the following adverse events meets the SAE criterion for "life-threatening"?

A. A subject who experienced cardiac arrest during infusion and required immediate defibrillation to survive

B. A subject with moderate hypertension controlled by medication withdrawal, which the investigator notes "could become life-threatening if untreated"

C. A subject who developed severe nausea requiring a dose reduction

D. A subject who is hospitalized for elective surgery unrelated to the study

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A newborn delivered to a female subject enrolled in a Phase II trial is found to have a ventricular septal defect. The mother was exposed to the study drug during the first trimester before the pregnancy was known. Under SAE reporting criteria, how should this event be classified?

A. Non-serious AE; birth defects are not included in the SAE definition

B. Only reportable if the defect is fatal

C. SAE meeting the congenital anomaly/birth defect criterion

D. Protocol deviation, not an adverse event

The PI determines that a hospitalization was likely caused by the study drug. The sponsor's medical officer reviews the same event and believes it is unrelated to the study drug based on aggregate safety data. For IND Safety Report purposes, whose assessment prevails?

A. The investigator's assessment always governs, as they have direct clinical knowledge of the subject

B. The IRB must resolve the disagreement

C. The event is not reported until the disagreement is resolved

D. The sponsor's assessment governs; if the sponsor considers the event related, it must be reported accordingly. If the sponsor considers it unrelated and the PI considers it related, the more conservative (related) determination is used

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An investigator determines that a subject's adverse event is "possibly related" to the study drug and "unexpected" based on the current IB, but does not involve hospitalization, death, or disability. The event fully resolves within 2 days. Does this event require an IND Safety Report to FDA?

A. Yes, because it is unexpected and related

B. No, because the event is non-serious; IND Safety Reports are required only for unexpected serious adverse drug reactions

C. Yes, because any unexpected related AE requires a 15-day report

D. Only if the investigator assesses it as "probably" or "definitely" related

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A subject enrolled in a medical device trial experiences a serious device-related injury. The site coordinator is preparing the safety report. Which regulation and timeline govern this report to FDA?

A. 21 CFR 312.32; 15-day written report

B. 21 CFR Part 803; 7-day report for all device injuries

C. 21 CFR 812.150(b) (IDE Reporting); device-related serious injuries in IDE trials reported to FDA within 10 working days

D. ICH E6(R3) Annex 1, Section 2.7.2 (SAE Reporting); 24-hour report directly to FDA

The PI was notified of a subject's fatal outcome (suspected USADR) on a Monday. The sponsor receives the report from the PI on Tuesday. What is the latest date by which the sponsor must make the initial notification to FDA?

A. The following Monday (7 days from Tuesday, counting Tuesday as Day 1)

B. The Wednesday of the same week

C. The following Sunday

D. 15 calendar days from Tuesday

Which of the following SAE reports does an investigator need to report to the IRB?

A. All SAEs within 24 hours

B. Only SAEs resulting in death

C. SAEs that the sponsor determines require an IND Safety Report to FDA

D. Unanticipated problems involving risks to subjects or others, including SAEs that are unexpected and related to study participation

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A female subject of childbearing potential enrolled in a double-blind trial reports a positive pregnancy test at Week 8 of the study. The protocol requires immediate reporting to the sponsor. This pregnancy report is:

A. Not required, as pregnancy is a normal physiological event

B. Only reportable if the subject is also experiencing an adverse event

C. An SAE by definition because it involves a reproductive outcome

D. Required per protocol; pregnancy is reportable even if it does not meet SAE criteria, and outcomes must be tracked through delivery

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ANSWER KEY

Answers & Explanations

QUESTION 1

Correct Answer: C. The 24-hour reporting clock starts from the moment the investigator (or their designee at the site) becomes aware of the event. The coordinator was notified Monday at 9:00 AM; the deadline for reporting to the sponsor is Tuesday at 9:00 AM. The event occurred Sunday, but the site's clock begins at first awareness, not at event occurrence. Weekends do not pause the timeline.

QUESTION 2

Correct Answer: A. Fatal USADRs require an initial notification to FDA within 7 calendar days per 21 CFR 312.32(c)(2). Day 1 is Wednesday; the 7-day deadline is the following Tuesday. A full written 15-day IND Safety Report must then be submitted within 15 calendar days after the sponsor determines the event qualifies for reporting per 21 CFR 312.32(c)(2). All timelines are in calendar days.

QUESTION 3

Correct Answer: A. "Life-threatening" means the subject was at immediate risk of death at the time of the event. Cardiac arrest requiring defibrillation is the paradigmatic example; the subject would have died without immediate intervention, placing them in immediate risk of death during the event. Theoretical future risk (answer B) does not qualify. Severe nausea and elective surgery meet other SAE criteria (hospitalization for elective surgery is typically excluded per protocol).

QUESTION 4

Correct Answer: C. Congenital anomaly/birth defect is explicitly listed as one of the SAE criteria per ICH E6(R3) Glossary and 21 CFR 312.32(a). A ventricular septal defect is a congenital anomaly. This event must be reported as an SAE to the sponsor within 24 hours and, if it meets SUSAR criteria, must be reported to FDA.

QUESTION 5

Correct Answer: D. The sponsor independently assesses causality and expectedness. If either the sponsor or the investigator concludes the event is related, it must be treated as a related event for reporting purposes. The more cautious assessment prevails. If the sponsor disagrees with the investigator's causality assessment, the sponsor must document the rationale for their determination.

QUESTION 6

Correct Answer: B. IND Safety Reports (ISRs) under 21 CFR 312.32(c) are triggered by unexpected SERIOUS adverse drug reactions. An adverse event that is unexpected and related but not serious does not trigger a 7-day or 15-day ISR. It is documented in the CRF and included in the IND Annual Report, but it does not rise to the level requiring an individual expedited report to FDA.

QUESTION 7

Correct Answer: C. For medical device clinical trials conducted under an Investigational Device Exemption (IDE), adverse device effects involving death or serious injury must be reported by the IDE sponsor to FDA under 21 CFR 812.150(b) within 10 working days. This is distinct from the post-market MDR framework under 21 CFR Part 803 (which applies to manufacturers, not trial sponsors) and from the drug-trial 7-day/15-day USADR reporting framework under 21 CFR 312.32. Device-trial coordinators must know that Part 312 does not apply; 21 CFR Part 812 governs. Answer A is incorrect because 21 CFR 312.32 governs drug trials, not device trials. Answer B is incorrect because the 7-day timeline applies to fatal/life-threatening drug USADRs under 21 CFR 312.32, not to device trials. Answer D is incorrect because ICH E6(R3) Annex 1 does not specify a 24-hour FDA reporting deadline; that is the investigator-to-sponsor timeline.

QUESTION 8

Correct Answer: A. The 7-day clock for fatal/life-threatening USADRs per 21 CFR 312.32(c)(2) begins when the sponsor first receives the information. If the sponsor received the report on Tuesday, Tuesday is Day 1. Seven calendar days from Tuesday means Day 7 is the following Monday (Tuesday = Day 1, Wednesday = Day 2, Thursday = Day 3, Friday = Day 4, Saturday = Day 5, Sunday = Day 6, Monday = Day 7). The initial notification to FDA is due by the end of that Monday. Calendar days are used; weekends do not pause the clock.

QUESTION 9

Correct Answer: D. Per 21 CFR 56.108(b), investigators must report unanticipated problems involving risks to subjects or others to the IRB. For clinical trials, this standard encompasses SAEs that are both unexpected and related to study participation. Expected SAEs (consistent with the IB) that are not unexpected are generally not reported individually to the IRB; they may be included in periodic safety reports or annual study summaries per IRB requirements.

QUESTION 10

Correct Answer: D. Pregnancy in a trial subject (or a partner of a male subject) is not automatically an SAE, but protocols universally require its reporting to the sponsor, typically within 24 hours of awareness, because of the potential teratogenicity risk of the investigational product. Pregnancy outcomes, including miscarriage, termination, or congenital anomalies at delivery, must be followed and reported. If a congenital anomaly or adverse pregnancy outcome occurs, it is then evaluated as a potential SAE.