## DCP Baseline and Adverse Event Reporting Guidelines

### Purpose

To clarify the definition and documentation of adverse events occurring after baseline assessment for clinical trials conducted by DCP.

### Definitions

|  |  |
| --- | --- |
| Adverse event (AE) | *Adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.1  Thus, an adverse event (also referred to as an adverse experience) can be any unfavorable and unintended 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 with 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 |
| CFR | Code of Federal Regulations |
| CRF | Case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Diagnosis | Determination of the nature of a disease, injury, or congenital defect |
| Disease | Illness or sickness characterized by specific signs and symptoms |
| ICH | International Conference on Harmonisation |
| Sign | An abnormality found on physical exam or an abnormal laboratory result |
| Symptom | An abnormality reported by the participant |
| Medical history | An account of past diseases, injuries, treatments, and other strictly medical facts that are or may be relevant to a patient's current state of health |
|  |  |

### Background

ICH E6(R2)3 is the definitive resource for Good Clinical Practice (GCP). A companion publication, *GCP: A Question and Answer Reference Guide*4, provides the following guidance regarding the reporting of baseline signs and symptoms:

“…protocols may also require the structured collection of signs and symptoms…to establish a baseline against which post-treatment AEs can be compared.”

DCP has adopted this interpretation in its studies to ensure that AEs are appropriately reported and evaluated for attribution. Thus, the DCP protocol template (section on Reportable AEs) states that all AEs that occur “after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.”

The following provides instructions for reporting signs, symptoms, and diagnoses/diseases documented at and after informed consent and baseline assessment(s).

1. **General Approach to Reporting Baseline Assessments *vs.* AEs**
2. A sign or symptom present at the baseline assessment(s) should be reported as such on the appropriate CRF, and not as an AE.
3. An abnormal laboratory value documented as part of the baseline assessment(s) should not be reported as an AE, regardless of clinical significance.
4. A sign or symptom documented at baseline should be reported as an AE only if the severity worsens or the frequency increases after the baseline assessment.
5. A diagnosis or disease documented at baseline should be reported as medical history on the appropriate CRF.
6. A pre-existing diagnosis or disease is reported as an AE only if the grade worsens after the baseline medical history.
7. The version of CTCAE identified in the protocol for grading the severity of AEs should be used to grade baseline signs, symptoms, abnormal laboratory values, diseases, or diagnoses.
8. **Reporting Abnormal Laboratory Values After the Baseline Assessment**
9. After the baseline assessment, all abnormal laboratory values determined to be of *clinical significance* based on the physician’s assessment are to be reported as AEs on the appropriate CRF.
10. Those abnormal laboratory values determined to be of *no clinical significance* or of *unknown clinical significance* (per the physician’s assessment) should not be reported as AEs.
11. Any laboratory value of *unknown clinical significance* should continue to be investigated/followed-up further for a final determination, if possible.
12. If the *clinical significance* is *unknown* and a retest (*i.e*., an immediate repeat of the laboratory test) is done to confirm the laboratory value, then both results should be entered into the database of record (one for the first test and one for the retest).
    1. If the retest confirms the first laboratory value and the investigator deems it as *clinically significant,* both results should be marked as *clinically significant*, and the start date for the AE should be the date the first test was done.
    2. If the retest does not confirm the laboratory value and the investigator deems the result as *not* *clinically significant*, there is no AE to report.
13. **Reporting Other Signs After the Baseline Assessment**
    * 1. Persistent Unchanged Baseline Signs or Symptoms

A baseline sign or symptom that persists unchanged throughout the study is not reported as an AE.

* + 1. Baseline Signs or Symptoms that Increase in Severity or Frequency

1. If a baseline sign or symptom increases in severity or frequency during the study, it should be reported as an AE.
2. The date on which the increase in severity or frequency was observed is reported as the onset date. For example, if a baseline sign or symptom is noted as grade 1 and is later reported as grade 3 during the study, it should be reported as a grade 3 AE with the onset date the date on which the increase in severity was observed.
3. Baseline Signs or Symptoms that Resolve

If a baseline sign or symptom resolves during the study, the resolution can be documented at the discretion of the investigator.

1. Baseline Signs or Symptoms that Resolve and Recur
   1. If a baseline sign or symptom resolves and then recurs during the study, the recurrence should be reported as a new AE.
2. The recurrence date is recorded as the onset date of the new AE.
3. **Reporting New Diagnoses or Revisions to Medical History After the Baseline Assessment**
4. Persistent Unchanged Diagnosis in Medical History

A baseline diagnosis that persists unchanged throughout the study is not reported as an AE.

1. Baseline Medical History Diagnosis that Increases in Severity

If a baseline diagnosis increases in severity during the study, it should be reported as an AE. The same version of the CTCAE used to grade AEs should be used to assign a term and grade. The date on which the increase in severity was observed is reported as the onset date. For example, if a diagnosis of seizure noted as grade 1 at baseline increases to grade 3 during the study, it should be reported as a grade 3 AE with the onset date recorded as the date on which the increased severity was observed.

1. Baseline Medical History Diagnosis that Resolves

If a baseline diagnosis resolves during the study, the resolution can be documented at the discretion of the PI.

1. Baseline Medical History Diagnosis that Resolves and Recurs

If a baseline diagnosis resolves and then recurs during the study, the recurrence should be reported as a new AE. The recurrence date should be recorded as the onset date.

1. New Diagnosis or Disease

A new diagnosis or disease after baseline is considered an AE and should be reported as such.

1. **Questions**

Questions regarding these reporting guidelines can be directed to [safety@ccsainc.com](mailto:safety@ccsainc.com).

1. **References**

121 CFR 312.32(a): IND Safety Reporting.

2FDA *Guidance for Industry: Investigator Responsibilities—Safety Reporting for Investigational Drugs and Devices* (September 2021).

3ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), 9 November 2016.

4 Malia, JS (2016). Section 9: Drug/study safety and safety reporting. In E.W. Hulihan (Ed.), *Good Clinical Practice: A Question and Answer Reference Guide* (p. 353). Needham, MA: Barnett International.