Title: Baseline and Adverse Event (AE) Reporting Guidelines

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REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
1.0	AUG-05-2020	Original version of document

1. INTRODUCTION AND PURPOSE

To clarify the definition and documentation of AEs occurring after baseline assessment for clinical trials conducted via the Cancer Prevention Clinical Trials Network (CP-CTNet).

2. DEFINITIONS

Adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment[1,2] An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product[1,2]
Clinical Significance	Indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken[3]
eCRF	Electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
Diagnosis	Determination of the nature of a disease, injury, congenital defect, or any untoward medical occurrence
Disease	Illness or sickness characterized by specific signs and symptoms
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
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

3. BACKGROUND

ICH E6(R2)[2] 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 for CP-CTNet studies to ensure that AEs are appropriately reported and evaluated for attribution. All AEs that occur after the informed consent is signed must be recorded on the AE eCRF, 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).

4. GENERAL APPROACH TO REPORTING BASELINE ASSESSMENTS *VS.* AEs

1. A sign or symptom present at the baseline assessment(s) should be reported as such on the appropriate eCRF, and ***not*** as an AE.
2. An abnormal laboratory value documented as part of the baseline assessment(s) should ***not*** be

reported as an AE, regardless of clinical significance.

3. 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.
4. A diagnosis or disease documented at baseline should be reported as medical history on the appropriate eCRF.
5. A pre-existing diagnosis or disease is reported as an AE only if the grade worsens after the baseline medical history.
6. 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, disorders, or diagnoses.

5. REPORTING ABNORMAL LABORATORY VALUES AFTER THE BASELINE ASSESSMENT

1. 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 eCRF.
2. 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.
3. Any abnormal laboratory value of *unknown clinical significance* should continue to be investigated/followed-up further for a final determination, if possible.
4. If the *clinical significance* is *unknown* and a retest (i.e., an immediate repeat of the laboratory test) is done to confirm the abnormal laboratory value, then both results should be entered into the database of record (one for the first test and one for the repeat).
    a. If the retest confirms the first abnormal 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.
    b. If the retest confirms the first abnormal laboratory value and the investigator deems it as *not clinically significant* or *unknown*, there is no AE to report.
    c. If the retest does not confirm the abnormal laboratory value and the investigator deems the result as *not clinically significant*, there is no AE to report.

6. 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.

2. Baseline Signs or Symptoms that Increase in Severity or Frequency
    a. If a baseline sign or symptom increases in severity or frequency during the study, it should be reported as an AE.
    b. 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.

4. Baseline Signs or Symptoms that Resolve and Recur
   a. If a baseline sign or symptom resolves and then recurs during the study, the recurrence should be reported as a new AE.
   b. The recurrence date is recorded as the onset date of the new AE.

7. REPORTING NEW DIAGNOSES OR REVISIONS TO MEDICAL HISTORY AFTER THE BASELINE ASSESSMENT

1. Persistent Unchanged Diagnosis in Medical History

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

2. 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.

3. 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.

4. 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.

5. New Diagnosis or Disease

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

Please address questions regarding these reporting guidelines to:
DataManagement_CP-CTNet@frontierscience.org.

8. REFERENCES

- [1]ICH E2A *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting,* 27 October 1994.
- [2]ICH E6(R2) *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*, 9 November 2016.
- [3]Ceh SE. 2009. Documenting clinically significant lab values. *J Clin Res Best Pract* 5(1):1–4
- [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.
- [5]CP-CTNet Chemoprevention Protocol Template.

9. APPENDICES

- None