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Documenting Clinically Significant Lab Values

By S. Eric Ceh

Adverse event (AE) documentation is the basis for determining the safety of investigational treatments. Abnormal lab results may help diagnose AEs or constitute AEs in and of themselves. Complete, accurate and informative documentation of AEs is therefore essential.

Regulatory Guidance

ICH guidelines (adopted by FDA as guidance) mention abnormal lab findings in four places:

> "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. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an 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." (ICH E6 1.2)

> "Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol." (ICH E6 4.11.2)

> "During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware." (ICH E6 4.3.2)

> "Individual Clinically Significant Abnormalities. Clinically significant changes (defined by the applicant) should be discussed. A narrative of each patient whose laboratory abnormality was considered a serious adverse event and, in certain cases, considered another significant adverse event, should be provided under sections 12.3.2 or 14.3.3. When toxicity grading scales are used (e.g. WHO, NCI), changes graded as severe should be discussed regardless of seriousness. An analysis of the clinically significant changes, together with a recapitulation of discontinuations due to laboratory measurements, should be provided for each parameter. The significance of the changes and likely relation to the treatment should be assessed, e.g. by analysis of such features as relationship to dose, relationship to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy." (ICH E3 12.4.2.3)

While these guidances confirm that abnormal lab values may constitute adverse events, they do not define "clinical significance" except with respect to toxicity grading scales (discussed below).

Documentation

The safety section of a protocol covers adverse events, including abnormal lab values. Some protocols include a specific statement concerning the review of lab results, e.g., "Clinical laboratory results that are outside of the normal ranges and are deemed clinically significant by th**e** Investigator are also AEs." Some protocols go further to provide guidance on what constitutes clinically significant lab values and when to document them as an AE. However, protocols rarely discuss how AEs should be documented on the case report form (CRF).

An abnormal lab value should be deemed clinically significant if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

Therefore, a clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken.

The process proceeds in three steps. First, a qualified physician at the investigative site, either the investigator or a subinvestigator, reviews lab test results. The investigator classifies any results that are not within their respective normal result range as either clinically significant (CS) or not clinically significant (NCS). Medical judgment is required. For example, the investigator may not classify an abnormal result as CS unless it exceeds a certain level or appears in conjunction with other observations. CS results are documented as AEs.

Second, once the investigator deems a lab value CS, he or she determines whether there is a clinical exam finding or symptom (new or pre-existing) that explains the abnormal lab value. A progress note summarizing the findings, including the reason(s), e.g., differential diagnosis, why the lab results are deemed CS, provides documentation for an adverse event report.

Third, the investigator formulates a description of the adverse event. If the investigator is able to provide a differential diagnosis for the CS lab result, describe the AE accordingly, e.g., urinary tract infection or suspected anemia. In the absence of an associated clinical sign or symptom, and if only a single lab value is deemed CS, list the abnormal lab value itself as the AE, e.g., elevated potassium or decreased calcium.

Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTCAE)[1], World Health Organization (WHO), and NIAID Division of Microbiology and Infectious Diseases (DAIDS)[2]) can be used for AE descriptions of abnormal blood, coagulation and metabolic labs. For example, the CTCAE system grades a lab abnormality on a scale of 1-5 for results that deviate above or below the normal range. Examples of appropriate AE descriptions using this system include:

- Grade 2 hemoglobin
- Grade 1 PTT
- Grade 3 hyperkalemia

Some protocols specify other grading criteria, which would supersede the use of these tables.

When several lab values are considered CS and the investigator does not have a differential diagnosis in mind, describe the AE in as specific a category as possible. Examples of such entries include:

- Abnormal CBC results: WBC, platelet, Hgb
- Abnormal chemistry results: K, Ca, Mg, Cl
- Abnormal urinalysis results: blood, ketone, WBC

An AE description of "abnormal lab result" alone is too vague to be adequate.

When there is more than one CS lab result, the number of AE entries on the CRF depends on the abnormalities found. For example, if five abnormal lab results are clinically significant and the investigator suspects a single underlying condition, make only one entry. Note that an abnormal lab result may be CS only in the presence of other abnormal results. If so, the progress note should explain the connection.

For example, an investigator indicates that the hematocrit, hemoglobin, rbc, MCHC, and eosinphils values on a hematology report are clinically significant, and he therefore suspects anemia. The corresponding AE should be written as "suspected anemia." If the investigator did not have a differential diagnosis, an acceptable AE entry would be "abnormal CBC results: Hct, Hgb, rbc, MCHC, eosinophils." In neither of these cases would it be appropriate to make five separate AE entries, i.e., decreased Hct, decreased Hgb, decreased rbc, decreased MCHC, and increased eosinophils, since only one condition was considered to be involved. However, if one of the abnormal results appears to be unrelated to the others, it should be documented separately.

If follow-up later confirms a diagnosis, revise the AE entry on the CRF accordingly; i.e., change "suspected anemia" to "anemia." (If using an electronic CRF, understand how to make revisions before making the initial entry.) If the source of the anemia is then found to be a gastrointestinal bleed, update the AE description to show the most informative underlying cause. (Remember that the purpose of AE documentation is to help the study sponsor determine the cause of adverse events.) Write a progress note summarizing the follow-up evaluation to provide the basis for updating the CRF.

Example of Review Process

1. Ulysses Mentrite, MD, Investigator, reviews the hematology lab results for subject 001/ABC in a clinical trial at his center. He notes that the RBC, MCHC, Hct, and Hgb results are below the lower limits of the normal range and the eosinophil count is elevated; prior study visit lab test results were normal. With that, Dr. Mentrite determines that follow up evaluation and testing are warranted and marks the RBC, MCHC, Hct, Hgb and Eosinophil labs as clinically significant (CS) on the lab report; he then initials & dates the report.
2. Dr. Mentrite reviews subject 001/ABC's medical record and history for an explanation of the abnormal lab findings, but does not find any. He writes a progress note: "Subject 001/ABC, Study visit 3 lab test reviewed, CS labs noted (RBC, Hct, Hgb, MCHC, Eosinophil), negative history/physical exam, suspect anemia. Plan: notify primary care physician, repeat lab tests, follow-up exam and review of systems at next visit."

3. Dr. Mentrite reviews the visit 3 findings with the study coordinator, and instructs her to enter an adverse event, suspected anemia, on the CRF.
4. At study visit 4, lab tests yield similar abnormal results. Upon further questioning, the subject describes recently coughing up blood and markedly increasing his antacid consumption. An upper GI exam is scheduled, which reveals reflux esophagitis and an upper GI bleed. A corresponding summary progress note is written: "After further lab tests and procedures, including upper GI endoscopy on November 1, 2008, it was found that subject 001/ABC had findings of an upper GI bleed and reflux esophagitis. Surgical repair is scheduled for December. The subject will remain in the study." Note: The investigator may also include his assessment of causality for the AEs within the progress note or document it on the AE log or source worksheet, if applicable.
5. Dr. Mentrite discusses the findings with the study coordinator. He instructs her to change the CRF entry of "suspected anemia" to "upper GI bleed" and to add an additional AE entry for "reflux esophagitis." She makes the change, crossing out the previous entry with a single line, and initials and dates it.

Conclusion

Lab reports require review by a qualified investigator to determine clinical significance. If a clinically significant lab result is found, document an adverse event. Write the event description as specifically and informatively as possible, depending on the investigator's (tentative) diagnosis at the time. Revise the event description when the diagnosis is confirmed.

References

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, NIH Publication 03-5410, June 2003
2. Appendix: Division of Microbiology and Infectious Diseases (DMID) Source Documentation Guidelines, Section VIII: Monitoring and Reporting Adverse Events, NIAID, February 6, 2003.

Author

Eric Ceh is President of SEC Clinical Consulting, a provider of monitoring, quality assurance, and project management services. Contact him at 1.614.823.7937 or sec_consulting@sbcglobal.net.

