

Clinical Trial Standards Applied During Audit *Proceedings*

Major and Minor Violations

The guidelines below, a compilation of ECOG, CALGB and NCI definitions, were created at the DFCI in July 1994 to help define major and minor violations. An exhaustive list of examples is not given, but the examples are intended to guide the reviewers in their assessment and categorization of specific violations. A major violation is generally defined as that violation which significantly alters the clinical effectiveness of the treatment or the evaluation of its toxicity. Minor violations occur when the protocol is not followed exactly, but the data are usable and valid.

MAJOR VIOLATIONS

A. IRB/Consent

- Failure to document properly obtained patient consent
 - Consent dated after registration/treatment of pt.
 - Consent not obtained in a language fully understood by the patient.
 - Outdated consent used
- Failure to comply with Institutional Review Board (IRB) approval and reapproval guidelines, including lapsed or expired annual continuing reviews, inappropriate use of less than full-board review and approval and improper review of appropriate amendments or revisions (i.e. patient entered prior to IRB approval.)

B. Eligibility

- Does not meet eligibility criteria

C. Pre-therapy

- Pre-therapy tests of major importance were not done or not done prior to therapy
- Unacceptable frequency of minor violations

D. Registration/Randomization/Stratification

- Patient not registered prior to treatment
- Information given at registration is inconsistent with actual data in medical records chart (wrong stage, diagnosis, cell type, etc..)

E. Forms/Data Submission/Special Requirements

- Submission of data outside of protocol guidelines
- Incorrect data (substantial amounts of data are incomplete or inaccurate for 1 or more forms)

MINOR VIOLATIONS

A. IRB/Consent

- Consents do not have date/witness signature
- Consents do not have unique patient identifiers on each page

B. Eligibility

- Small variations of criteria with reasonable explanation/approval (Phase II and III only)

C. Pre-therapy

- Missing a small number of minor tests

D. Registration/Randomization/Stratification

- Date of birth/date of diagnosis inconsistent

E. Forms/Data Submission/Special Req.

- Incorrect data (sporadic pieces of data are incomplete or inaccurate)

F. Treatment

- Inappropriate administration of non-protocol anticancer treatment (additional drugs, radiation, etc.)
- Failure to modify doses according to protocol, (especially where doses are expected to have a major impact on outcome)
- Failure to dose reduce in the face of severe toxicity
- Failure to dose escalate on a dose-intensification study
- Inappropriate dose reduction on a dose intensity study
- Repetitive or systemic errors in dosing
- Repetitive or serious errors in dosing, timing or schedule
- Wrong route in administration
- Failure to document drug administration
- Error in Concomitant Medications
- Failure to administer an important medication or the administration of a prohibited medication or treatment

G. Toxicity

- Failure to obtain the required protocol baseline studies required to effectively assess toxicity
- Failure to get necessary follow-up studies to assess toxicity as required by protocol
- Unreported major toxicity (Grade 4)
- Repetitive failure to report Grade 2 & 3 toxicities
- Serious or repetitive failure to properly characterize toxicity or grade
- Failure to file required NCI Adverse Reaction Reports according to protocol when applicable

H. Required Evaluation

- Unacceptable frequency of required evaluation violations

I. Response/Follow-Up

- Failure to assess disease status according to the required protocol guidelines either pre-therapy or in response to treatment
- Failure to obtain baseline CT scan to document pre-therapy tumor size
- Failure to obtain the required follow-up CT scan to document persistent reduction in tumor size to define a response as specified in the protocol
- Inaccurate assessment of tumor response
- Substantial inaccuracy in the detection of cancer (as in a prevention study) or determination of cancer progression

J. Data Quality

- Unacceptable level of missing documentation
- Missing charts
- Repetitive failure to obtain protocol specified laboratory tests or diagnostic studies
- Frequent inaccuracies or errors in submitted data

F. Treatment

- Wrong antiemetic given as per protocol
- Wrong doses (<25% deviation without explanation for one dose; or 25% deviation from dose reduction indicated)
- Wrong timing (<2 week delay with acceptable explanation (i.e. holiday, bad weather, flu sx))

G. Toxicity

- Not reporting occasional grade 3 toxicities
- Frequent non-reporting of grade 1 & 2 toxicities

H. Required Evaluation

- Missing a small number of minor required evaluations or tests

I. Response/Follow-Up

- Missing minor measurements
- Missing one of several measurements used to assess response and scans unavailable for review

J. Data Quality

- Acceptable level of missing documentation with explanation
- Minor and sporadic missing tests
- Infrequent errors in submitted data