Clinical Research Deviations vs Deficiencies

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Protocol Deviation vs Audit Deficiency

Protocol Deviation

Was the protocol followed as written?

Audit Deficiency

Did you have any control over the outcome?

Disclosure to Participants

- To receive contact hours:
  - You must attend 100% (60 minutes) of the educational activity and complete all the required questions on the post-activity evaluation.
  - You can access the evaluation through the link that will be shared during the program.
  - You will receive your certificate within approximately one week after completing the evaluation.
- No one with the ability to control content of this activity has a relevant financial relationship with an ineligible company.
- This nursing continuing professional development activity was approved by the Maryland Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.
- The expiration date for the enduring activity is June 10, 2026.

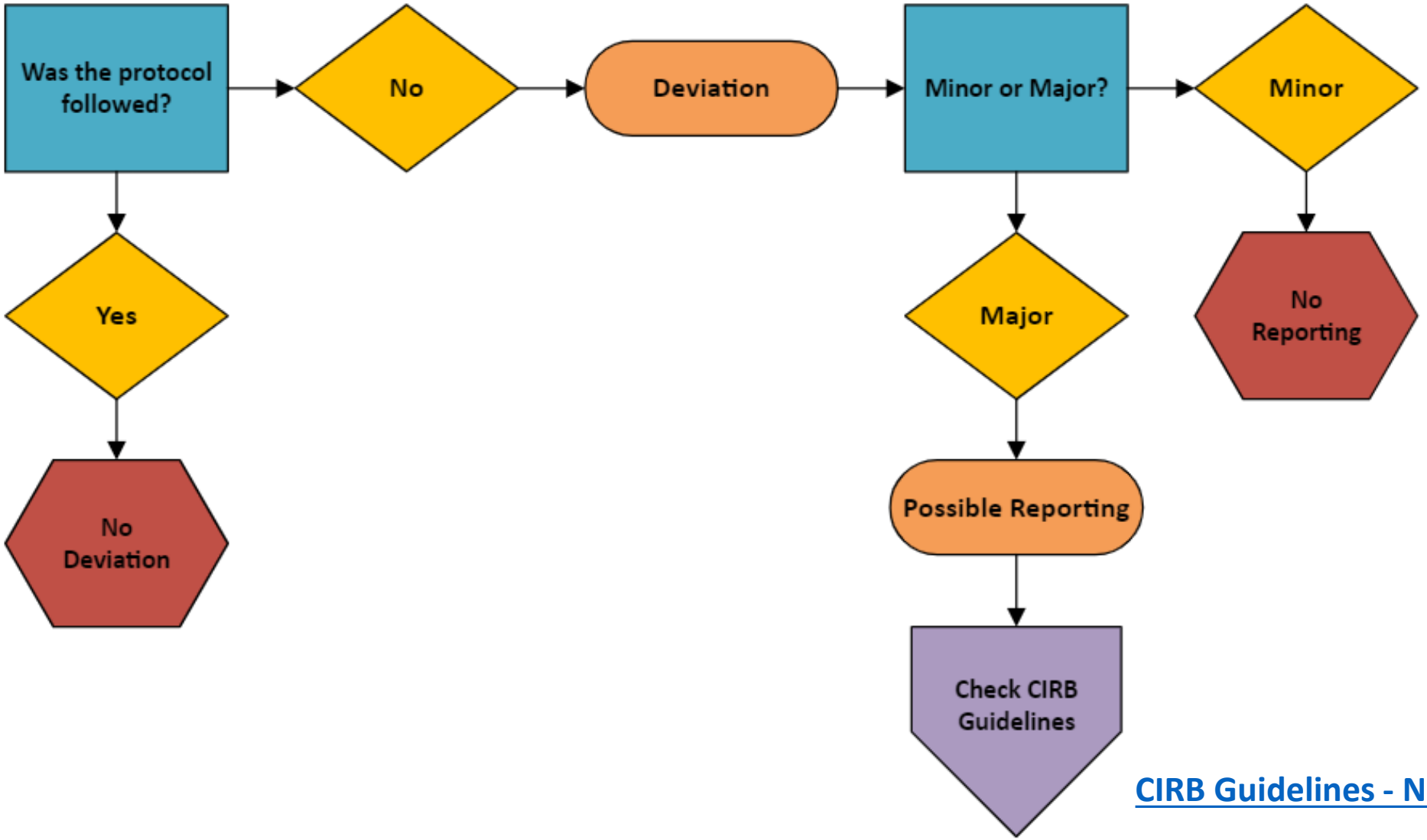
Protocol Deviation Definitions

Protocol Deviation: A protocol deviation is a failure to conduct all aspects of the study as described in the protocol. The term, “protocol violation” comes from CFR 312.64 which states that, “No changes to research are made without IRB approval except when necessary to eliminate hazards to human subjects.”

Minor Deviation: A minor protocol deviation is something that can be readily addressed, without significant consequence to the study participant or data quality. An example of a minor deviation would be a visit occurring outside the window defined in the protocol (e.g., + 3 days) because of weather or vacation. The protocol drives the importance of a protocol deviation.

Major Deviation: A major or critical protocol deviation is one that may impact participant safety, affect the integrity of study data and/or affect participant willingness to remain in the study. An example of a major violation would be failure to obtain informed consent prior to protocol treatment.

Protocol Deviation Flowchart



[CIRB Guidelines - Noncompliance]

Polling Question #1

A patient no-showed their C3D15 visit, a required timepoint per protocol.

Polling Question #2

A patient experienced an adverse event while on protocol treatment.

Audit Deficiency Definitions

Lesser Deficiency: A finding that is judged to not have a significant impact on the outcome or interpretation of the study and is not described as a major deficiency. An unacceptable frequency or quantity of lesser deficiencies should be assigned as a major deficiency.

Major Deficiency: A variance from a protocol-specified procedure that makes the resulting data questionable or causes concern for patient safety.

Critical Deficiency: Any condition, practice, process, or pattern that adversely affect the rights, safety, or well-being of the patient/study participant and/or the quality and integrity of the data; this includes manipulation and/or serious violation of safeguards in place to ensure the safety of a patient/study participant and/or intentional misrepresentation of data.

Audit Deficiencies

- An audit deficiency may be assigned prior to or during a SWOG audit.

- When assigning deficiencies, auditors take into consideration whether your site had any control over the events.
  - If a patient refuses anything at any timepoint – no deficiency.
  - If a patient's insurance denies any procedure or test – no deficiency.

- If your site did have any level of control over the events, a deficiency may be assigned.
  - If the primary coordinator is out of office when an SAE occurs, and the backup coordinator did not report it on time – deficiency.
  - If a research specimen is missed because the phlebotomy staff is short-handed that day – deficiency.

Major Audit Deficiencies – Eligibility/Treatment

Eligibility

- Patient did not meet eligibility criteria as specified by protocol (e.g., pre-study tests done late).
- Unable to confirm eligibility due to missing documentation.

Treatment

- Incorrect agent/treatment used.
- Additional agent/treatment used which is not permitted by protocol.
- Greater than +/- 10% dose deviations or dose modifications.
- Unjustified dose modifications or failure to modify doses according to protocol.
- Timing and sequencing of treatment not per protocol.
- Unjustified delays in treatment.

Major Audit Deficiencies – AEs/Disease Outcome

Disease Outcome/Response Assessment

- Inaccurate documentation of initial sites of involvement.
- Tumor measurements/evaluation of status of disease not performed according to protocol.
- Failure to detect cancer (as in prevention study) or failure to identify cancer progression.
- Claimed response (PR, CR) cannot be verified.

Adverse Events

- Failure to obtain required baseline and follow-up studies to effectively assess AEs.
- Grades, types, or dates/duration of serious AEs inaccurately recorded.
- AEs cannot be substantiated.
- Recurrent under or over-reporting of AEs.
- Failure to report a Serious Adverse Event within the required timeframe.

Major Audit Deficiencies – Consent/Data Quality

Informed Consent

- Consent form missing.
- Consent form not signed and dated by patient.
- Consent form signed after patient was registered.
- Consent form not the current IRB-approved version at the time of registration.
- Consent form does not include updates required by protocol modifications

Data Quality

- Recurrent missing documentation (i.e. missing charts, insufficient source documentation).
- Protocol-specified research/advanced imaging studies not done or submitted appropriately.
- Delinquent data submission > 3 months for baseline and on treatment data, > 6 months follow-up data.
- Missing or delinquent specimen submission.

Polling Questions #3 & #4

A patient missed their appointment due to a snowstorm.

Patient Safety Principles

Risk Management
Infection Control
Medication Management
Environment/Equipment Safety
Patient Education/Participation
Skincare Integrity
Nutrition
Teamwork Amongst Healthcare Providers
Accountability/Reporting Errors

Implications for Patient Safety

- Failure to meet eligibility criteria
- Incorrect treatment agent/dose
- Failure to modify dose per protocol
- Missed disease assessments
- Failure to assess adverse events
- Labs not drawn prior to treatment

Implications for Patient Safety cont.

Eligibility	Patient has already had lifetime maximum dose of doxorubicin.
Treatment	Patient received 200% of the intended dose.
Treatment	Dose not held for G4 hypertension.
Disease Outcome	CT done 2 months late, showing progression.
Adverse Events	Patient hospitalized for sepsis.
Adverse Events	Protocol treatment given despite acute renal failure.

Follow-Up Actions to Protect Patients

Patient Safety > Protocol Adherence

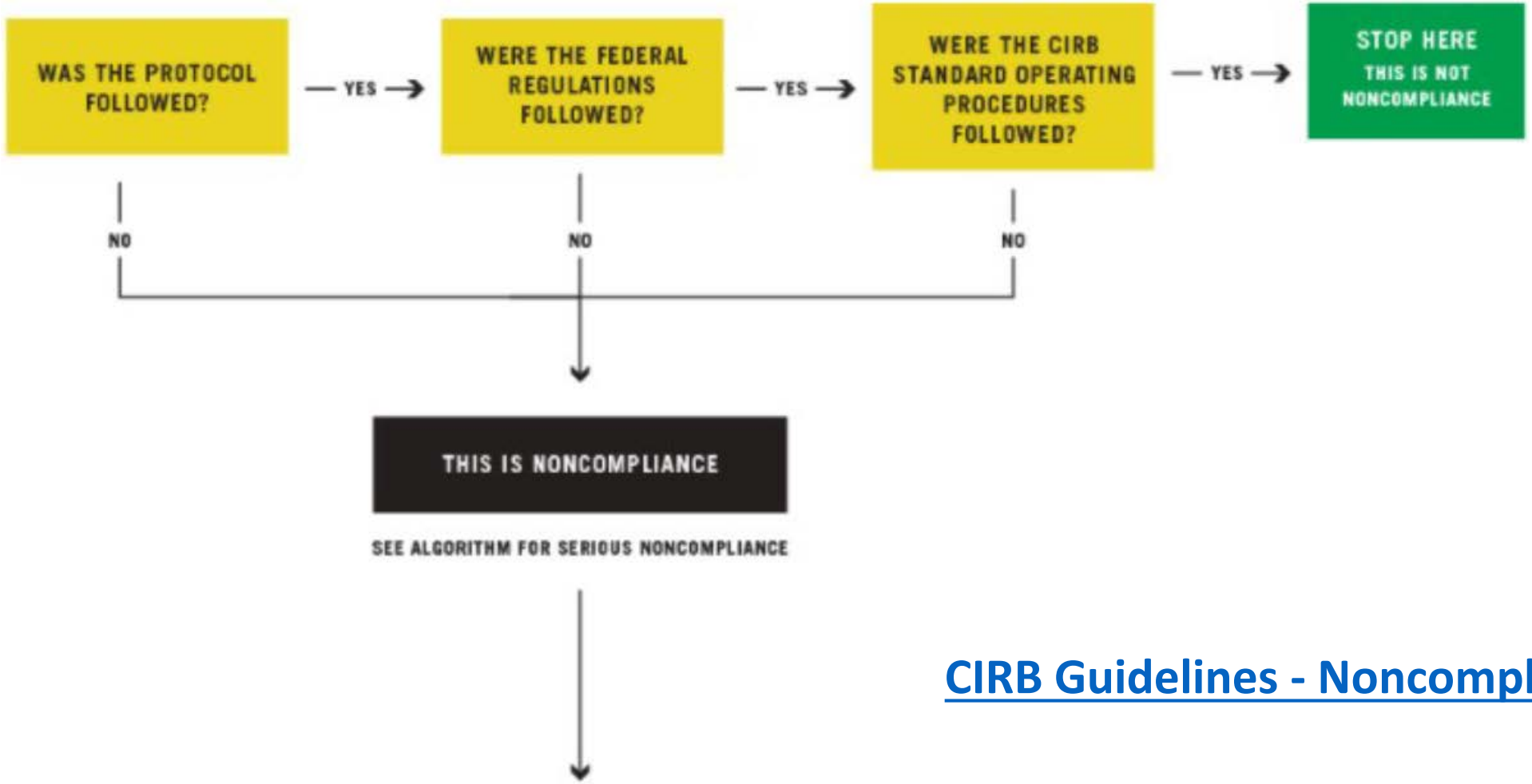
- **Always take care of the patient first.** If that means deviating from the protocol, so be it.
- Some AEs and SAEs can be critical for patients and require immediate reporting to regulatory entities.
  - Note that this reporting should occur after the patient has been medically stabilized.
- Check the CIRB Guidelines for reporting serious noncompliance to determine if reporting is required.
- Check with your local IRB to ensure no site-specific reporting is also required.

Reporting Protocol Deviations/Noncompliance

- SWOG follows the NCI CIRB guidelines for reporting protocol deviations (noncompliance).
- This includes protocols where the CIRB is not the IRB of record.
- SWOG does not require reporting of minor deviations.
  - We understand that some sites are required to track and submit these to SWOG, but we do not require it.

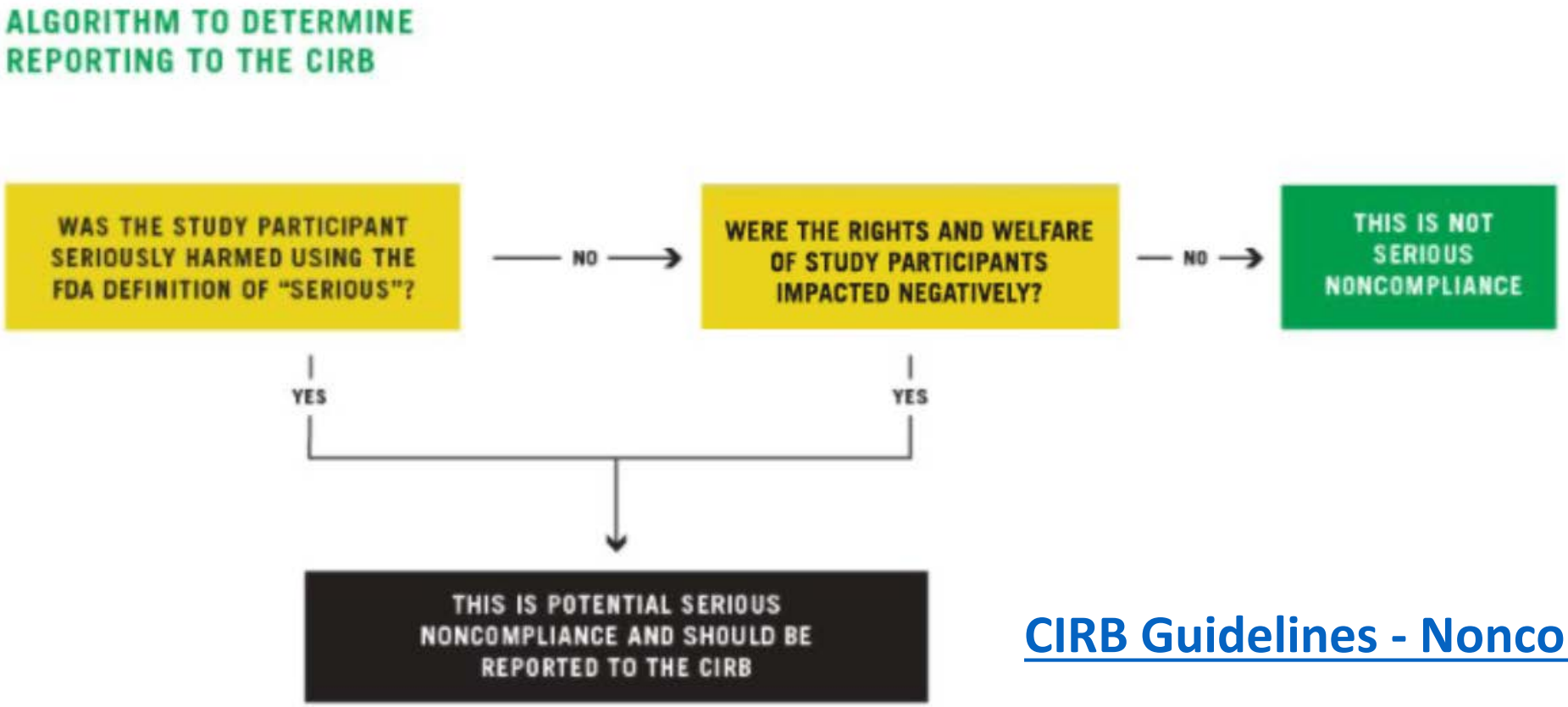
CIRB Guidelines - Noncompliance

Reporting Protocol Noncompliance



[CIRB Guidelines - Noncompliance]

Reporting Protocol Noncompliance cont.



[CIRB Guidelines - Noncompliance]

Reporting Audit Deficiencies

[NCI CIRB - Reporting Audit Findings]

BEFORE YOU BEGIN

Collect the audit report, the response to the audit report, and the management plan that outlines how the findings will be addressed and future occurrences prevented.

Reporting Audit Deficiencies cont.

NCI CIRB - Reporting Audit Findings

STEPS

1 PI OR DESIGNEE REVIEWS AUDIT REPORT

The Principal Investigator (PI) or designee reviews the audit report issued by the institution, a Network, the Office for Human Research Protections (OHRP), or the Food and Drug Administration (FDA) for a study open under the CIRB.

2 PI OR DESIGNEE IDENTIFIES MAJOR AUDIT FINDINGS

There are two categories of audit findings: major and minor. Any major finding based on the Clinical Trials Monitoring Branch audit guidelines should be submitted to the CIRB as potential serious noncompliance. Any finding that had been documented in a previous audit report should be submitted to the CIRB as potential continuing noncompliance.

3 PI OR DESIGNEE COMPLETES THE UNANTICIPATED PROBLEM AND/OR NONCOMPLIANCE WORKSHEET

The PI or designee submits any findings (potential serious or continuing noncompliance) using the Unanticipated Problem and/or Noncompliance Worksheet available in IRBManager. For more information, go to the Completing the Unanticipated Problem and/or the Noncompliance Reporting Worksheet.

Reporting Audit Deficiencies cont.

[NCI CIRB - Reporting Audit Findings]

4 CIRB OPERATIONS OFFICE CONDUCTS ADMINISTRATIVE REVIEW

The Worksheet is reviewed by the CIRB Operations Office. This review typically takes two weeks. The CIRB Operations Office may send the submitter an email request for additional information. Revisions to the Worksheet are completed in IRBManager.

5 CIRB LOCAL CONTEXT COMMITTEE CONDUCTS REVIEW

After the administrative review, the Worksheet is sent to the CIRB Local Context Subcommittee for review. This process typically takes five days. The CIRB Operations Office may send the submitter an email request for additional information. Revisions to the Worksheet are completed in IRBManager.

6 CIRB SENDS DETERMINATION LETTER TO INSTITUTION

After the CIRB Local Context Subcommittee approves the Worksheet, the CIRB Operations Office sends a determination letter to:

- the PI
- the person submitting the Worksheet,
- the Signatory Institution Primary Contact(s), and
- OHRP and FDA if the event is determined to be reportable.

Reporting Audit Deficiencies cont.

NCI CIRB - Reporting Audit Findings

CIRB REPORTING - USEFUL TIP

You can usually expect to receive the determination letter within a month of submitting the Unanticipated Problem and/or Noncompliance Worksheet. If the submission is incomplete or if there are questions raised during the administrative or local context review, the process will take longer.

Polling Question #5

A patient demanded to reschedule their treatment due to an upcoming vacation.

Polling Question #6

Informed consent was not signed by the patient until two hours after registration.

Polling Question #7

Patient has received prior anti-cancer treatment that is specifically excluded in eligibility criteria.

Polling Question #8

During a lab draw, a patient stated “Nope. You won’t get another tube from *me* today.”

Polling Question #9

Patient experienced Grade 3 colitis following C1D15 treatment, but C2D1 treatment was not held/reduced per protocol.

Polling Question #10

Baseline data was entered into Rave 124 days after registration.

Resources/References

Questions?
QAMail@swog.org

- CTEP's Policy on Issuance of Waivers for Protocol Deviations
- Completing the NCI CIRB Unanticipated Problem and/or Noncompliance Reporting Worksheet
- NCI CIRB - Algorithm to Assess Potential Noncompliance
- NCI CIRB - Reporting Audit Findings
- CTSU Protocol Deviation Guide
- Protocol Deviations: A Holistic Approach from Defining to Reporting
- Clinical Trials Monitoring Branch Audit Guidelines - Patient Case Review
- Nurses' Adherence to Patient Safety Principles: A Systematic Review

Resources/References

Questions?
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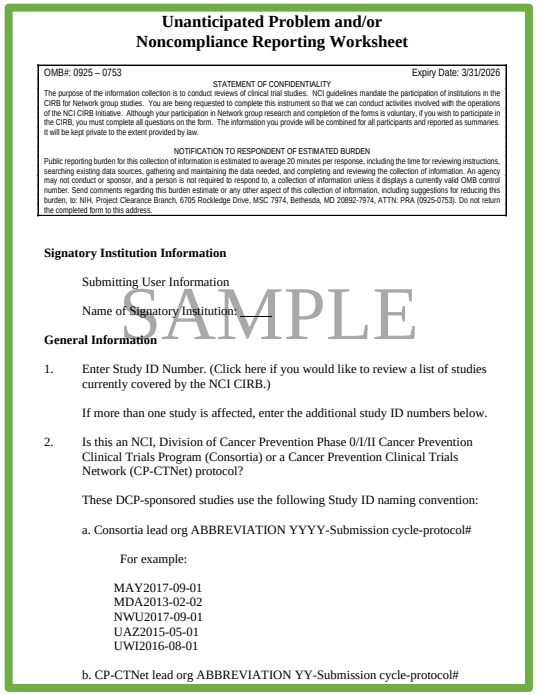
CIRB Reporting Worksheet



Unanticipated Problem and/or Noncompliance Reporting Worksheet

OMB#: 0925 – 0753 Expiry Date: 3/31/2026

STATEMENT OF CONFIDENTIALITY

The purpose of the information collection is to conduct reviews of clinical trial studies. NCI guidelines mandate the participation of institutions in the CIRB for Network group studies. You are being requested to complete this instrument so that we can conduct activities involved with the operations of the NCI CIRB Initiative. Although your participation in Network group research and completion of the forms is voluntary, if you wish to participate in the CIRB, you must complete all questions on the form. The information you provide will be combined for all participants and reported as summaries. It will be kept private to the extent provided by law.

NOTIFICATION TO RESPONDENT OF ESTIMATED BURDEN

Public reporting burden for this collection of information is estimated to average 20 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0753). Do not return the completed form to this address.

Signatory Institution Information

Submitting User Information

Name of Signatory Institution:

SAMPLE

General Information

1. Enter Study ID Number. (Click here if you would like to review a list of studies currently covered by the NCI CIRB.)

   If more than one study is affected, enter the additional study ID numbers below.

2. Is this an NCI, Division of Cancer Prevention Phase 0/I/II Cancer Prevention Clinical Trials Program (Consortia) or a Cancer Prevention Clinical Trials Network (CP-CTNet) protocol?

   These DCP-sponsored studies use the following Study ID naming convention:

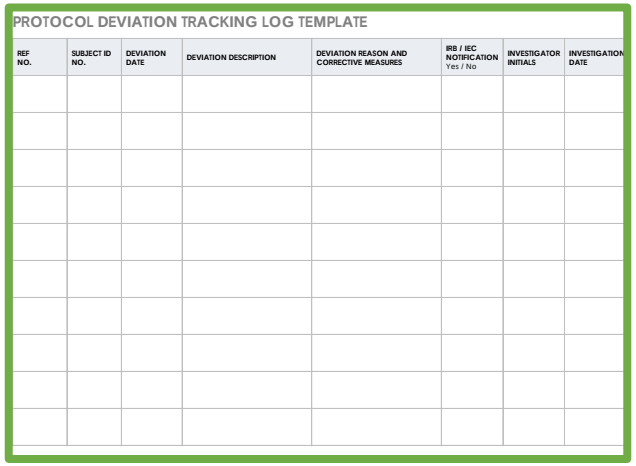
   a. Consortia lead org ABBREVIATION YYYY-Submission cycle-protocol#

      For example:

      MAY2017-09-01
      MDA2013-02-02
      NWU2017-09-01
      UAZ2015-05-01
      UWI2016-08-01

   b. CP-CTNet lead org ABBREVIATION YY-Submission cycle-protocol#

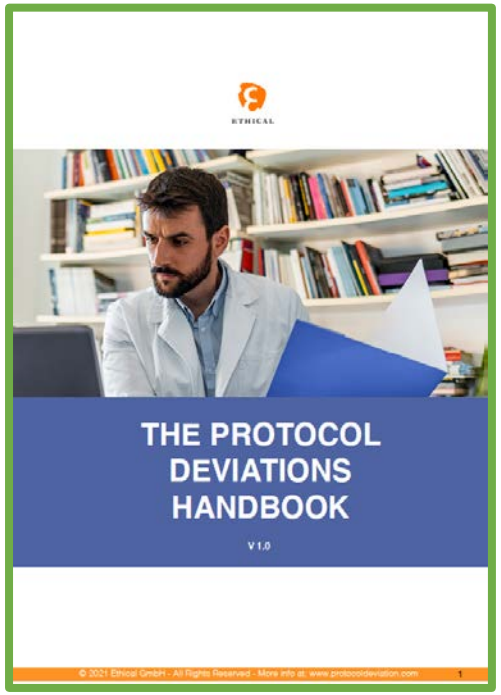
Protocol Deviation Tracker



PROTOCOL DEVIATION TRACKING LOG TEMPLATE

REF NO.	SUBJECT ID NO.	DEVIATION DATE	DEVIATION DESCRIPTION	DEVIATION REASON AND CORRECTIVE MEASURES	IRB / IEC NOTIFICATION Yes / No	INVESTIGATOR INITIALS	INVESTIGATOR DATE

The Protocol Deviations Handbook



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Q & A