



THE ROCKEFELLER UNIVERSITY HOSPITAL

CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE



Protocol Deviations and Protocol Violations Made Simple

Donna Brassil, MA, RN, CCRC
Rhonda G. Kost, MD



Objectives

Upon completion of this class, the learner will be able to:

- verbalize the difference between a deviation and a violation
- identify GCP/IRB reporting requirements for deviations/violations
- suggest actions to prevent violations/deviations



Definitions

- A **protocol deviation** occurs when the activities during a study diverge from the IRB-approved protocol; a variance from protocol
- A **protocol violation** occurs when there is divergence from the IRB-approved protocol (a deviation) *that also*:
 - reduces the quality or completeness of the **data**
 - impacts a subject's **safety, rights or welfare**
 - affects the **scientific integrity**



Examples of Protocol Deviations

- Vital signs obtained prior to informed consent
- Weighing participant with shoes on
- Urine dipstick is completed, but not sent for formal U/A
- Targeted physical exam documented instead of complete PE
- Conjugated bilirubin, part of the protocol, is left off the lab request form, but total bilirubin was drawn and is normal



Examples of Protocol Violations

- Inadequate informed consent
- Enrollment of subjects not meeting the inclusion /exclusion criteria
- Initiation of study procedure prior to completion of informed consent
- Unreported SAE's
- Improper breaking of the blinding of the study
- Use of prohibited medication
- Incorrect or missing tests
- Mishandled samples
- Multiple visits missed or outside permissible windows
- Inadequate record-keeping
- Intentional deviation from the protocol, GCP or regulations by study personnel in a non-emergency setting
- Repeated noncompliance by the subject
- Repeated deviations of the same nature
- Falsification



ICH GCP Regulations

ICH GCP 4.5 Compliance with protocol

4.5.1 Investigator should conduct the trial in compliance with the protocol agreed to and approved by an IRB

4.5.2 Investigator should not implement any changes or **deviations** from the protocol unless agreed to by the IRB, sponsor, etc. except when necessary to eliminate immediate hazards to trial subjects, or when the changes are administrative or logistical



ICH GCP Regulations

- ICH GCP 5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of non-compliance, the sponsor should notify promptly the regulatory authority(ies).
- ICHGCP *section 5.20.2*, the sponsor must view protocol non-compliance as a 'violation' of agreed responsibilities.



FDA

- Does not distinguish between a violation and a deviation; all protocol variances are violations
- Any deviation not reported and later discovered by an audit is considered non-compliance with the FDA



Who Discovers Deviations/Violations?

- Study team
- Hospital staff:
 - Nursing
 - Bionutrition Staff
 - Pharmacy Staff
 - Regulatory Staff
- Auditors, monitors
- Participants



Interdisciplinary Safety Net

- Assure protocol compliance
- Identify non-compliance
- Who should be involved: Nursing, Bionutrition, Pharmacy, Medical Director, Coordinators, Facilitators, Recruitment staff, Regulatory Support staff, Informatics, Biostatistics, IRB, Investigators



Interdisciplinary* Safety Net

- Safety check examples
 - Re-affirm consent for each visit, procedure, participant
 - Confirm consent forms for the right study, before and after consent
 - Do the 5 “R”s of the study medication match the protocol?
 - Do the labs being drawn match what is in the protocol?



What Do You Do if You Discover a Deviation/Violation in the Making?

- Bring non-adherence to the protocol to the attention of the study team
 - they may not be aware
 - the deviation/violation may still be averted
 - If instructed to proceed with a deviation/violation, check with your supervisor, CRO or facilitators; the orders should always reflect the action
 - In an emergency, the occurrence of a deviation is secondary to the delivery of immediate care



What Do You Do if You Discover a Deviation/Violation Has Occurred?

- Bring non-adherence to the protocol to the attention of the study team
 - They may not be aware
 - Participate in the analysis of the deviation/violation:
 - How/why did it happen?
 - Could it have been prevented?
 - Does workflow need to be altered?
 - Does the protocol or ICF need to be amended?
 - How will the safety net watch for/prevent repeated variances?



RU IRB Reporting Requirements

All deviations/violations must be reported to the IRB

➤ Violations

- report to the IRB via iRIS within 5 working days of the detection of the event

➤ Deviations

- report in iRIS – as soon as reasonably convenient

➤ A pattern of repeated protocol deviations of the same nature may constitute a protocol violation



Preventing Deviations

- Review and understand protocol
- Identify any procedures in the protocol that differ from standard practice at your establishment
- Staff Training and Initiation Meetings
 - Special procedures
- Use well-designed study-specific forms for documentation including I/E checklists
- Perform study-required procedures and visits within the required window
 - A large number of out-of-window procedures/visits may indicate too tight a window or poor planning/scheduling
- During Navigation:
 - be sure eligibility criteria are clear and not subject to interpretation
 - predict possible deviations during Navigation and prior to IRB submission and create contingency plans in the protocol!
- Internal Monitoring-start as soon as you enroll



Assuring Protocol Adherence

- Review and understand protocol
- Identify any procedures in the protocol that differ from standard practice
- Thoroughly train study staff
- Study initiation meetings
- Is the staff who are conducting the procedures credentialed?
- Carefully review amendments
- Use the correct version of the protocol



Assuring Protocol Adherence

- During Navigation
 - Be sure eligibility criteria are clear and not subject to interpretations
 - Predict possible deviations during Navigation and prior to IRB submission and create contingency plans in the protocol
- Internal Monitoring –
 - Start as soon as enrollment begins



Assuring Informed Consent Is Obtained Correctly

- Assure that Study-specific procedures are performed after the ICF has been signed
- Confirm that the informed consent discussion is conducted by someone who is authorized on the DOA
- Assure that the consenting discussion takes place in a confidential setting
- Review the signatures/dates promptly
- Confirm that the subject received a copy of the signed ICF



Assuring Drug Accountability

When providing study meds to take home, assure:

- Subjects received proper dose/route
- Subjects received correct instructions
- Pill bottles/unused pills/blister packs, etc. have been returned
- Drug accountability has been completed



Review of Examples

- Subject signed an outdated version of a consent
- Incorrect storage of study medication
- Use of prohibited concomitant medication



Review of Examples

- Investigator implemented revisions to procedure after submitting amendment but before IRB approval of change to protocol.
- Study team member performs procedure beyond scope of practice listed on DOA
- Subject returns incomplete study drug diary
- Over-enrollment of protocol



Deviations/Violations: Summary

- Variances from protocol
- Prevent them
- Identify them
- Report them
- Develop and implement a corrective action plan
- Amend the protocol moving forward, if necessary



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Resources

Please call us if you need assistance in identifying deviations/violations and/or the reporting requirements

Arlene, Kathy, Jenny, Donna
Kim, Rhonda