Protocol Deviations

March 2017 Training

Overview of Today's Discussion

- Key resources
- Definitions
- Policy requirements for protocol deviations considered reportable by IMPAACT ("reportable deviations")
- Procedures for reportable deviations
- Scenarios
- Questions

Key Resources

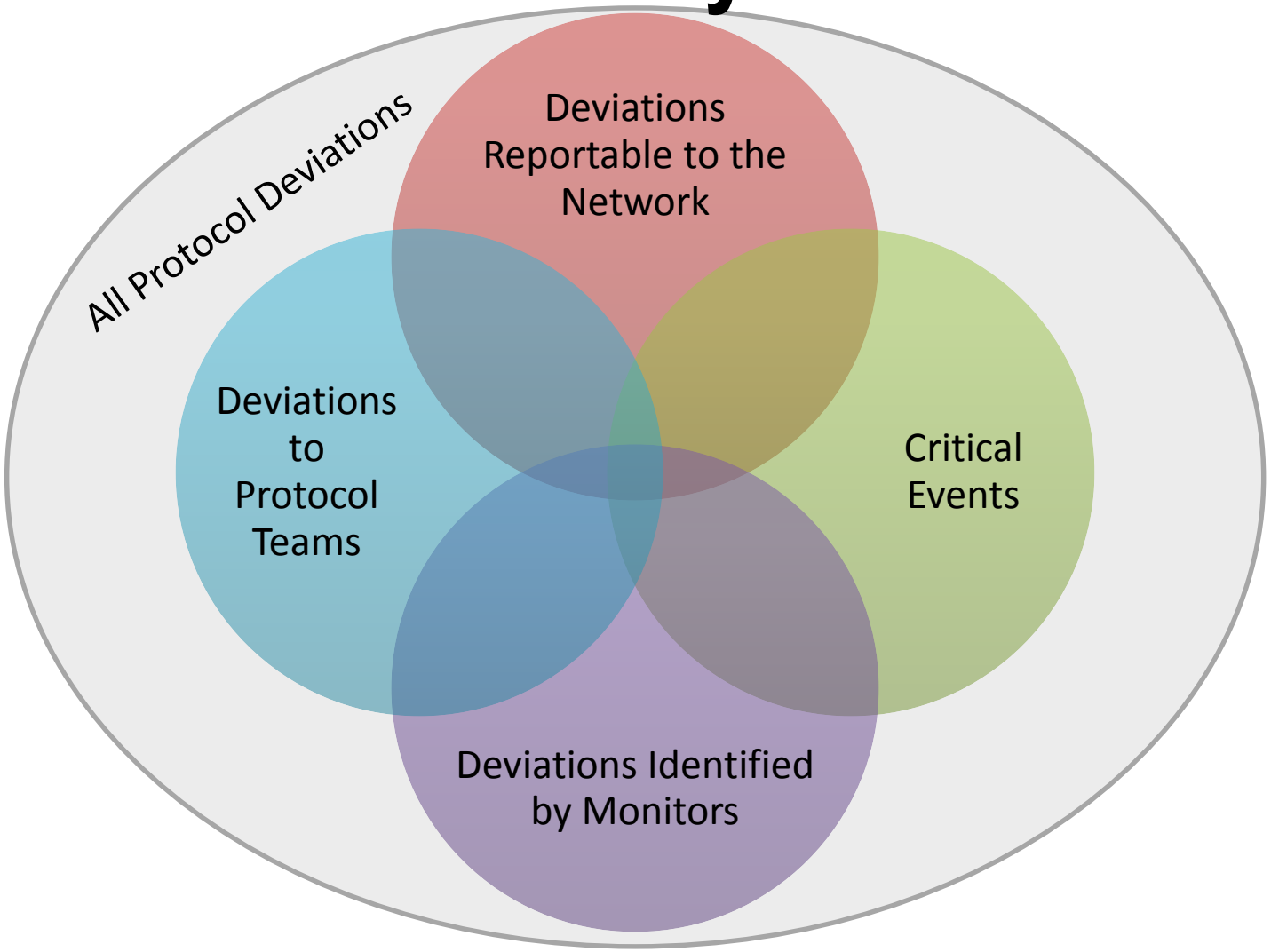
IMPAACT Manual of Procedures, Section 12.4, Protocol Deviations

http://impaactnetwork.org/DocFiles/MOP/12_Implementation.pdf

Definitions

Protocol deviation	Any departure from an IRB-approved protocol
Reportable protocol deviation	Deviations that require additional reporting by the IoR or designee as described in Section 12.4.3. Defined by IMPAACT as deviations that result in: • Significant increased risk to the study participants or others • Significant non-compliance with IRB-approved protocol requirements • Significant non-compliance with Good Clinical Practices or Good Clinical Laboratory Practices and all applicable regulations

Deviations, Violations, Critical Events… Oh My!



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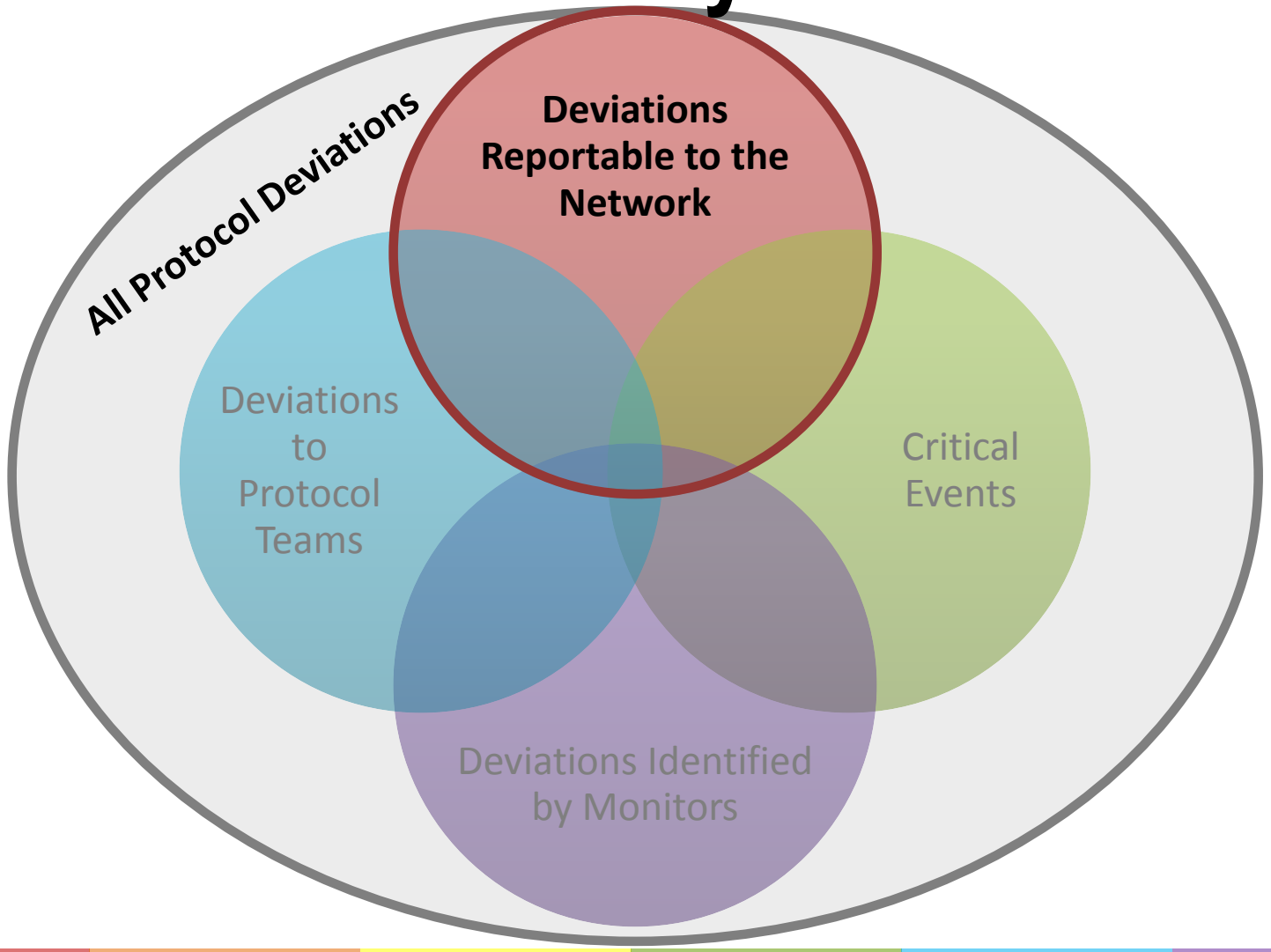


Protocol deviations may include …

- Administrative inconsistencies or minor study implementation errors (e.g., visit or procedure performed outside of window)
- Departure from specified treatment, examination, data collection, or reporting procedures
- Violation of inclusion/exclusion criteria

Protocol Deviations

- Deviations may or may not render a participant ineligible and may be considered significant or serious when they increase potential risk to participants or affect the integrity of study data
- An isolated deviation may not be significant by itself but significance may increase with numerous deviations of the same nature

Examples of Protocol Deviations

- Hair collection for study drug levels was missed in error for participant who was off treatment/on study
- Infant's washout PK sampling was obtained within the specified window but it was not possible to perform a physical exam within the window
- Procedures required to be performed within 48 hours of birth were performed between 49 and 50 hours of birth

Protocol Deviations

- All protocol deviations must be adequately documented in study records consistent with DAIDS SOPs for source and essential documentation, including
  - Description of the deviation
  - Reasons why it occurred
  - Corrective and preventive actions taken in response

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

Protocol Deviations

- Deviations must also be reported to site IRBs/ECs and other regulatory entities, following their policies and procedures

Now let's look at protocol deviations defined as reportable by IMPAACT …

Reportable Protocol Deviations

Protocol deviations are reportable to the IMPAACT Network if they result in

- Significant increased risk to participants or others
- Significant non-compliance with IRB-approved protocol requirements
- Significant non-compliance with GCP or GCLP and all applicable regulations

Participant Non-Compliance

- Participant non-compliance (e.g., participant misses study visits or does not take study drug) is considered a protocol deviation but is not considered a reportable protocol deviation
- Participant non-compliance should be documented and reported per usual site procedures (and any applicable protocol requirements) but should not be reported to the Network

Examples of Reportable Protocol Deviations (1)

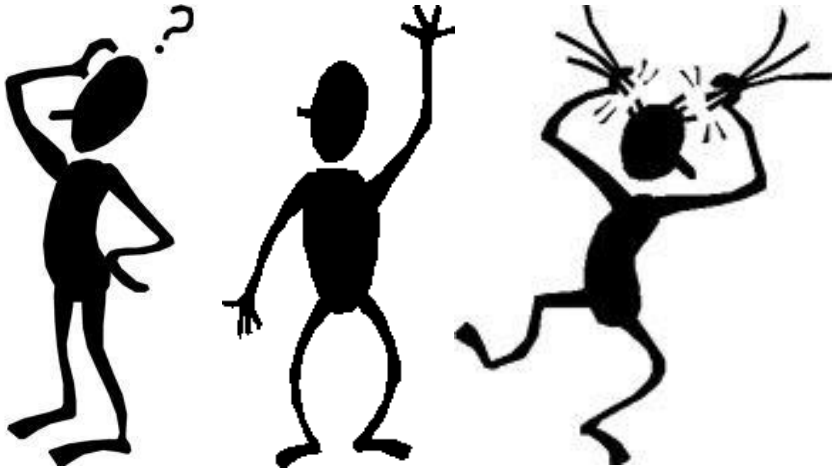
- Enrollment of an ineligible participant
- Failure to obtain informed consent or assent from the participant, legal guardian, or other legally authorized representative prior to performing protocol-specified procedures
- Performing procedures not specified in the IRB-approved protocol and not otherwise clinically indicated for the participant

Examples of Reportable Protocol Deviations (2)

- Knowingly reporting of an inaccurate laboratory result
- Failure to follow protocol-specified procedures for participant safety monitoring, management, or reporting (including failure to report expedited adverse events within 3 reporting days)
- Breach of participant confidentiality

Questions?
Or not sure about reportability?

If your site has questions about a deviation, email the protocol Clinical Trials Specialists or the Deviation Group: IMPAACT.deviation@fstrf.org



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- **Procedures for reportable deviations**
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- Questions

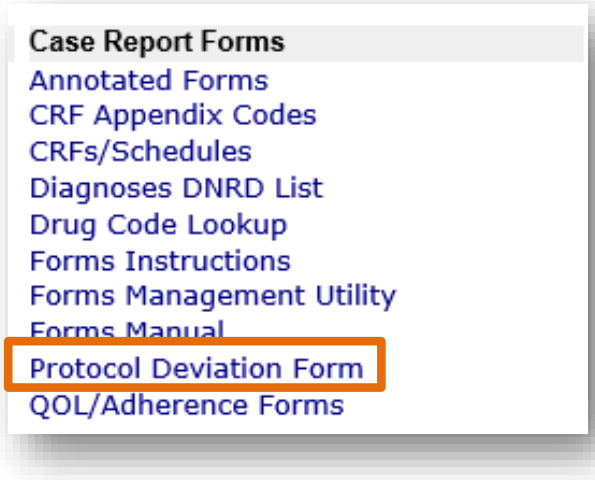
Procedures for Reportable Protocol Deviations

- Report within 10 working days of site awareness
- Complete and enter a protocol deviation case report form (CRF) into the database **AND** email a copy of the completed CRF to IMPAACT.deviation@fstrf.org
- Email any additional supplemental documents (e.g., IRB correspondence) with the completed CRF
- See network MOP for exceptions for deviations involving >25 participants or not involving specific participants

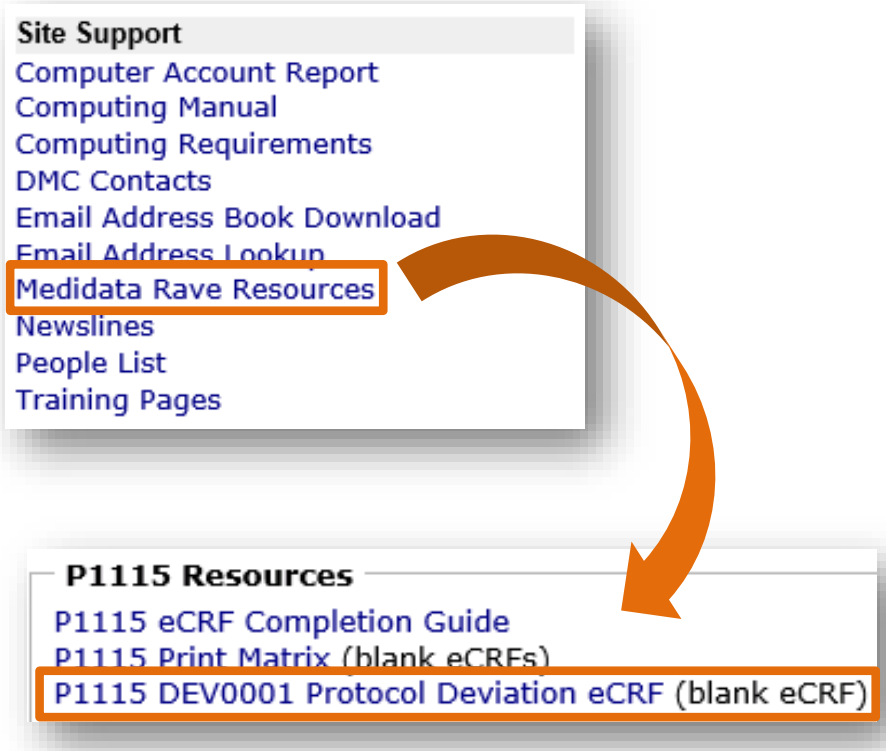
Where is the CRF Located?

www.frontierscience.org

eData Studies:



Medidata Rave Studies:



eCRF in Medidata Rave

P1115_V1.5.4.0: Protocol Deviation
Folder: Protocol Deviations
Form: DEV0001: Protocol Deviation

Site Awareness Date (dd-mmm-yyyy)	
Form Week	
Step Number	

NOTE: For a deviation that applies to a single date, please enter the same date for both the start and stop dates below.

Deviation start date (dd-mmm-yyyy):	
Deviation stop date (dd-mmm-yyyy):	
Has or will this deviation be reported to local IRB/EC?	Yes ☐ No ☐
Has or will this deviation be reported to DAIDS as a critical event?	Yes ☐ No ☐
Type of deviation:	Inappropriate enrollment ☐
	Failure to follow trial randomization or blinding procedures ☐
	Study product management deviation ☐
	Study product dispensing error ☐
	Conduct of non-protocol procedure ☐
	Breach of confidentiality ☐
	Physical assessment deviation ☐
	Lab assessment deviation ☐
	Use of non-IRB/EC-approved materials ☐
	Informed assent/consent process deviation ☐
	Other ☐

NOTE: Please include the following information in your description below:

- Explain the reason for deviation
- Risk/benefit ratio for the participant(s)
- Integrity of the research data
- Participant's willingness (or parent/legal guardian's willingness) to continue study participation

Description of deviation [800]:	
Describe any corrective actions taken to address this deviation [800]:	
Describe any preventive actions taken to prevent recurrence [800]:	
Deviation reported by (staff name) [70]:	

NOTE: The deviation should be reported by the responsible/communicating site staff member (IoR or other designee).

Report date (dd-mmm-yyyy):	09 Feb 2017

eData CRF – Page 1

DEV0001/11-04-16

PROTOCOL DEVIATION
NIAID AIDS CLINICAL TRIALS GROUP

Patient Number ☐☐☐ ☐☐☐☐ ☐ Site Awareness Date ☐☐ dd ☐☐☐ mmm ☐☐☐☐ yyyy

Protocol Number ☐☐☐☐☐☐ Institution Code ☐☐☐☐☐☐

Form Week ☐☐☐☐ **Seq No. ☐☐ ***Step No. ☐☐ Key Operator Code ☐☐☐

NOTE: For a deviation that applies to a single date, please enter the same date for both the start and stop dates below.

Deviation start date (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Deviation stop date (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Has or will this deviation be reported to local IRB/EC? ..... (1-Yes, 2-No) ☐

Has or will this deviation be reported to DAIDS as a critical event? ..... (1-Yes, 2-No) ☐

Type of deviation ..... ☐☐

11-Inappropriate enrollment
12-Failure to follow trial randomization or blinding procedures
13-Study product management deviation
14-Study product dispensing error
15-Conduct of non-protocol procedure
16-Breach of confidentiality
17-Physical assessment deviation
18-Lab assessment deviation
19-Use of non-IRB/EC-approved materials
20-Informed assent/consent process deviation
99-Other

Description of deviation:
NOTE: Please include the following information in your description below:

- Explain the reason for deviation
- Risk/benefit ratio for the participant(s)
- Integrity of the research data
- Participant's willingness (or parent/legal guardian's willingness) to continue study participation

[100]: _____

[100]: _____

[100]: _____

[100]: _____

[100]: _____

[100]: _____

[100]: _____

[100]: _____

eData CRF – Page 2

PROTOCOL DEVIATION

Pt. No. ☐☐☐☐☐☐☐ *Seq. No. ☐☐ **Step No. ☐☐ Date ☐☐ dd ☐☐☐ mmm ☐☐☐☐ yyyy

Describe any corrective actions taken to address this deviation:

[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____

Describe any preventive actions taken to prevent recurrence:

[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____
[100]: _____

Deviation reported by (staff name):

[70]: _____

NOTE: The deviation should be reported by the responsible/communicating site staff member (IoR or other designee).

Report date (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Date Form Keyed (DO NOT KEY): _____ / _____ / _____

General Instructions

- Enter the form in eData or Medidata Rave, as needed
- Remember to email PDF of completed CRF and supplemental materials to the Operations Center
- Ops and DMC communicate frequently regarding deviations reported:
  - Expectation that data reported to both Ops and DMC will match
  - If there are inconsistencies, they will be queried

Changing or Deleting a Form

eData

- Online Correct
- Delete Form 

Medidata Rave

- Change data and save
- Inactivate form 

Questions on Protocol Deviation Forms

- Contact the protocol data manager for questions on using eData or Medidata Rave to submit or modify a form
- Contact the Operations Center regarding questions about what to report: IMPAACT.deviation@fstrf.org

Procedures for Reportable Protocol Deviations

- You will receive a confirmation message within 24-48 hours of emailing
- If the deviation is reportable:
  - The deviation report will be sent by the Operations Center to Network Leadership
  - The Operations Center will follow-up with the site on any further clarifications and next steps

Procedures for Reportable Protocol Deviations

- If the Operations Center assesses the deviation as not reportable:
  - The Operations Center will communicate this assessment to the site
  - However, the site Investigator of Record (IoR) retains responsibility for final determination of reportability
  - The Operations Center will ask the site to reply with the site IoR's determination

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Reportable or Not?

(1) In a PK study, a participant is reminded over the phone to switch her study drug to morning dosing beginning 3 days before her visit. She confirms her understanding. However, when she comes to the clinic for the PK visit, she reports her last dose of study drug was last night.

Reportable or Not?

(1) In a PK study, a participant is reminded over the phone to switch her study drug to morning dosing beginning 3 days before her visit. She confirms her understanding. However, when she comes to the clinic for the PK visit, she reports her last dose of study drug was last night.

Not reportable because the deviation is due to participant non-compliance

Reportable or Not?

(2) Hair collection for study drug levels was missed for one participant

Reportable or Not?

(2) Hair collection for study drug levels was missed for one participant

Likely not reportable because the deviation only involved one missed collection from one participant

Reportable or Not?

(3) Hair collection for study drug levels was missed for all participants enrolled at the site

Reportable or Not?

(3) Hair collection for study drug levels was missed for all participants enrolled at the site

Likely reportable because the deviation involves all participants at the site and may effect data integrity

Reportable or Not?

(4) During a monitoring visit, an informed consent form is identified as having an incorrect year in the date of signature

Reportable or Not?

(4) During a monitoring visit, an informed consent form is identified as having an incorrect year in the date of signature

Likely not reportable because is an administrative error not otherwise associated with increased risk to the participant

Reportable or Not?

(5) During a monitoring visit, an informed consent form is identified as not signed by the participant

Reportable or Not?

(5) During a monitoring review, one informed consent form is not signed by the participant

Likely reportable because of the significance of the omission with respect to GCP compliance and potential risk to the participant

Reportable or Not?

(6) Three participants did not have a screening HIV RNA assay performed within the time period specified in the study inclusion criteria

Reportable or Not?

(6) Three participants did not have a screening HIV RNA assay performed within the time period specified in the study inclusion criteria

Likely reportable because of the significance of the error with respect to eligibility, potential risks to the participants, and potential impacts on data integrity

Reportable or Not?

(7) For a study in which the protocol-specified window for the Labor and Delivery (L/D) visit is 3 days after delivery, all participants at the site were scheduled for their L/D visit 5 days after delivery

Reportable or Not?

(7) For a study in which the protocol-specified window for the Labor and Delivery (L/D) visit is 3 days after delivery, all participants at the site were scheduled for their L/D visit 5 days after delivery

Likely reportable because of the significance of the error with respect to data integrity (and potential risk to the participants)

Reportable or Not?

(8) Participant 630 was inadvertently given study drug intended for Participant 360 (the PIDs were similar)

Reportable or Not?

(8) Participant 630 was inadvertently given study drug intended for Participant 360 (the PIDs were similar)

Likely reportable because of the significance of the error with respect to data integrity and potential risk to the participant

Key Resources

- US Code of Federal Regulations (www.ecrf.gov/)
  - 21 CFR 312.60
  - 21 CFR 58.108
  - 45 CFR 46.113
  - 45 CFR 46.103(b)(4)(iii)
  - 45 CFR 46.103(b)(5)
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (http://ichgcp.net/)
- US Food and Drug Administration (www.fda.gov)
- US Health and Human Services (www.hhs.gov/ohrp/)

Questions?

If your site has questions about a deviation, email the protocol clinical trials specialists or the Deviation Group:
IMPAACT.deviation@fstrf.org