Strategies to Collaboratively Manage Protocol Deviations in Multi-site Clinical Trials-

Decreasing Burden of Protocol Deviation Collection & Reporting

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So far discussed …

- Protocol Deviations **will** occur on every study.. therefore, the reporting of PDs is needed for study integrity
- Having a streamline process for reporting PDs is **paramount** to allow for evaluating within multi-site trials and/or across protocols within a clinical trial network

Will now discuss..

Both the approach used, and the methods applied to increase efficiency in the collection and reporting of PDs

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Presentation Overview

Post-Mortem Meeting(s)

Revisions to the Protocol Deviation CRF

Update PD Sub-Categories/Leverage the EDC System

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Post-Mortem Meeting(s)

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NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK

What is a Post-Mortem?

“Project post-mortems are intended to inform process improvements which mitigate future risks and to promote iterative best practices.”

https://en.wikipedia.org/wiki/Postmortem_documentation

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Post-Mortem – Over a Yearlong Process

- Began around the timing of the Passing of the Opioid Crisis Legislation ~late 2018
  - Foreshadowing the launching of multiple trials with the CTN and the CRO
- Started by Reviewing Industry Resources
  - *Review of large academic institutions definitions/reporting procedures for PDs/PVs*
  - *Webinar on PDs*
    - *Example: The Importance of Protocol Deviations and Violations to Subject Safety and Data Integrity will Surprise You" Presented by Charles H Pierce, MD, PhD, FCP, CPI (https://www.compliance.world/en-US/Clinical-Trial)*
- Conducted a Series of Meetings with Various Stakeholders
  - Including from the CRO and the Clinical Trials Network, as represented by today's panel

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Asked ourselves **3 core** questions:

- What is going well?
- What areas could be improved?
- What should we be doing differently?

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Core Q1: What was going well?

- Standard Process for the collection, reporting, review of PDs across multi-trials
- Central repository, the electronic data capture system, for the collection of PDs
- Standard Case Report Form (CRF) for the reporting of PDs

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Core Q2: What areas could be improved?

Method for Collecting PDs

- *Improving Data Entry Elements*

Method for Summarizing PDs

- *Providing a better profile to assess study integrity*

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Core Q3: What should be we be doing differently?

Reduce Burden of Reporting and Reviewing Protocol Deviations by:

1. Revising the PD eCRF
   - *Add new questions*
   - *Update question format, e.g., Replace open text field with a drop-down menu with list of options*
2. Updating PD Sub-Categories/Leverage the EDC System
   - *Remove the protocol deviation types that do NOT require manual entry of the Protocol Deviation eCRF*
   - *Use built-in data quality metrics to collect/report PDs*

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Revisions to the PD eCRF

Original PD eCRF

1. Is this deviation related to one or more participants? ○ ☐ No ☐ Yes
2. Date deviation identified: ○ MM/DD/YYYY
3. Deviation type: ○
4. Is this deviation related to COVID-19? ○ ☐ No ☐ Yes
5. Brief description of what occurred: ○
6. Brief description of the actual or expected corrective action for this event: ○
7. Brief description of the plan to prevent recurrence: ○
8. Is this deviation reportable to your IRB? ○ ☐ No ☐ Yes

Comments:

Revised PD eCRF

1. Is this deviation related to one or more participants? ○ ☐ No ☐ Yes
2. Date deviation identified: ○ MM/DD/YYYY
3. Deviation type: ○

New Question

4. Reason for Protocol Deviation: *(select all that apply)*
   - a. Research staff error: ○ ☐ No ☐ Yes
   - b. Hospital error: ○ ☐ No ☐ Yes
   - c. Laboratory error: ○ ☐ No ☐ Yes
   - d. Pharmacy error: ○ ☐ No ☐ Yes
   - e. Equipment/supply failure: ○ ☐ No ☐ Yes
   - f. Issue with Advantage eClinical (e.g., system down, system glitch): ○ ☐ No ☐ Yes
   - g. Participant unable to comply: ○ ☐ No ☐ Yes
   - h. Participant refusal: ○ ☐ No ☐ Yes
   - i. Investigator/study decision: ○ ☐ No ☐ Yes
   - j. Other: ○ ☐ No ☐ Yes
5. Is this deviation related to COVID-19? ○ ☐ No ☐ Yes
6. Brief description of what occurred: ○
7. Was/will there be corrective action for this event? ○ ☐ No ☐ Yes
8. Brief description of the plan to prevent recurrence: *(select all that apply)*
   - a. Complete local retraining: ○ ☐ No ☐ Yes
   - b. Revise local SOP(s): ○ ☐ No ☐ Yes
   - c. Recalibrate/fix or replace faulty equipment/supplies: ○ ☐ No ☐ Yes
   - d. Remove and/or replace incorrect/outdated document(s) from file(s) ○ ☐ No ☐ Yes
   - e. No site action needed: ○ ☐ No ☐ Yes
   - f. Other: ○ ☐ No ☐ Yes
9. Is this deviation reportable to your IRB? ○ ☐ No ☐ Yes

Comments:

Replaced open text fields with a drop-down menu with list of options

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Updates to PD Sub-Categories/ Leveraging the EDC System

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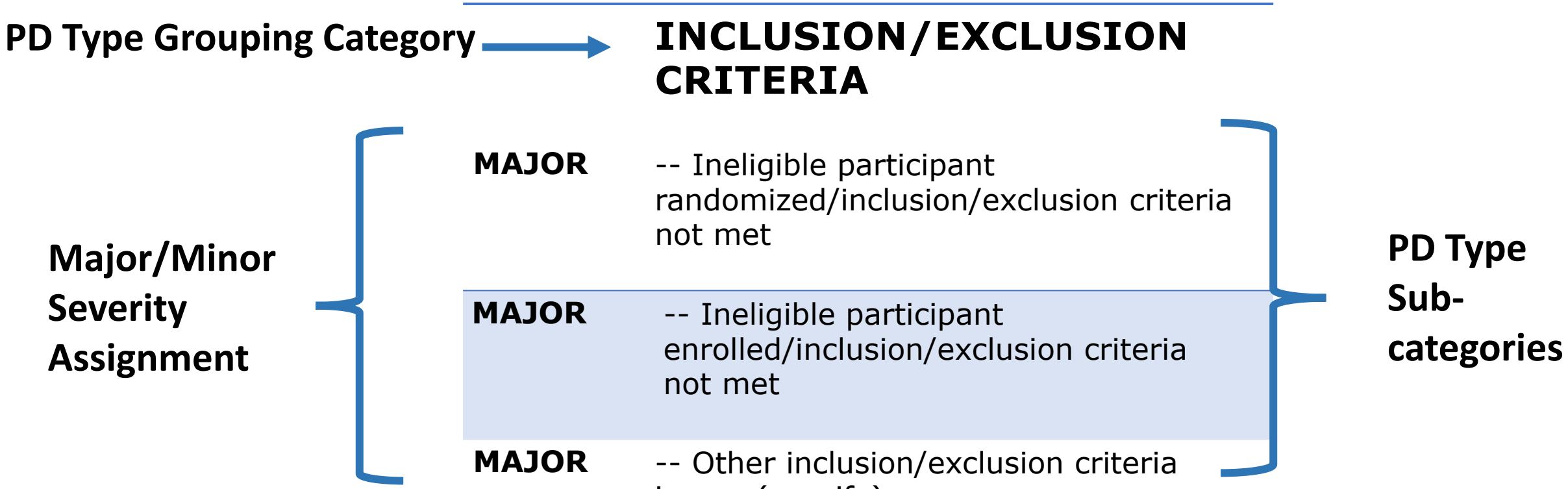
Evaluation of the PD Type Drop-Down List of Options



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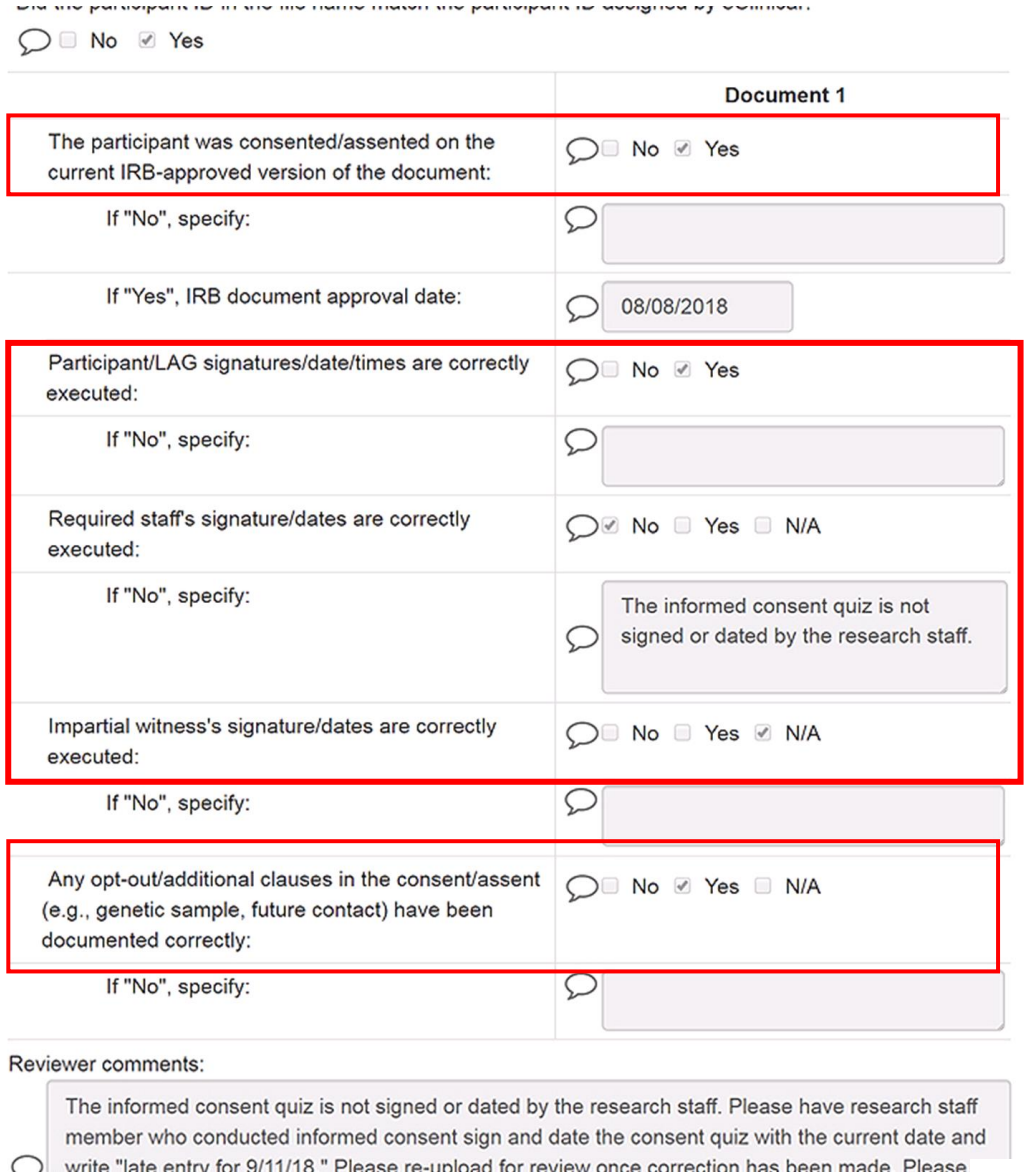
Informed Consent/Assent Procedures

- **Removed 3 PD sub-categories and replaced with a report**

Severity Classification	Sub-Category Label	Change Applied
Major	-- No consent/assent obtained	None
Minor	-- Invalid/incomplete informed consent/assent form	**Removed/Replaced with report**
Major	-- Unauthorized assessments and/or procedures conducted prior to obtaining informed consent/assent	None
Minor	-- Non-IRB approved/outdated/obsolete informed consent/assent documents used	**Removed/Replaced with report**
Minor	-- Informed consent/assent process not properly conducted and/or documented	**Removed/Replaced with report**
Minor	-- Other informed consent/assent procedures issues (specify)	None

HOW?

Identify Informed Consent/Assent Procedures PDs via the Secure Document Upload Review Form



	Document 1
The participant was consented/assented on the current IRB-approved version of the document:	☐ No ☑ Yes
If "No", specify:	
If "Yes", IRB document approval date:	08/08/2018
Participant/LAG signatures/date/times are correctly executed:	☐ No ☑ Yes
If "No", specify:	
Required staff's signature/dates are correctly executed:	☑ No ☐ Yes ☐ N/A
If "No", specify:	The informed consent quiz is not signed or dated by the research staff.
Impartial witness's signature/dates are correctly executed:	☐ No ☐ Yes ☑ N/A
If "No", specify:	
Any opt-out/additional clauses in the consent/assent (e.g., genetic sample, future contact) have been documented correctly:	☐ No ☑ Yes ☐ N/A
If "No", specify:	

Reviewer comments:

The informed consent quiz is not signed or dated by the research staff. Please have research staff member who conducted informed consent sign and date the consent quiz with the current date and write "late entry for 9/11/18." Please re-upload for review once correction has been made. Please

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Updates to the “Study Procedures/ Assessments” PD Category

- **Removed 1 PD sub-category and replaced with report**

Severity Classification	Original Sub-Category Label	Change Applied	Revised Subcategory Label
Minor	Protocol required visit/assessment not scheduled or conducted	Removed/Replaced with report	
Minor	Study assessments not completed/followed as per protocol	Modification to language	Study assessments/procedures not followed in accordance with the study protocol
Major	Inappropriate unblinding	None	
Minor	Other study procedures/assessments issues (specify)	None	

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Listings/Reports
Replacing PD Sub-Types: Parameters

Participant ID

Study Phase PD occurred (Screening, etc.)

Report Type (ICF Errors, Missed Assessments, Out of Window Visits, etc.)

Tier Categorization (primary outcome, safety, etc.) *to resemble PD severity Classification*

Summary of Updates to PD Categories

1. INFORMED CONSENT/ASSENT PROCEDURES
2. INCLUSION/EXCLUSION CRITERIA
3. LABORATORY ASSESSMENTS
4. STUDY PROCEDURES/ASSESSMENTS
5. **ADVERSE EVENT**
6. **RANDOMIZATION PROCEDURES**
7. STUDY MEDICATION MANAGEMENT
8. **STUDY BEHAVIORAL INTERVENTION**
9. **STUDY DEVICES**
10. SAFETY EVENT
11. OTHER SIGNIFICANT DEVIATIONS

- *11 PD Categories with respective sub-categories reviewed*
- *4 categories listed in **red** did **not** incur changes to sub-categories*
- *7 categories incurred revisions to at least one respective sub-category either:*
  - *Modified subcategory description/label*
  - *Removed subcategory **and** replaced with data report*

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Thank you!

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