C2012 Web Seminar Series

Identifying and Reporting Protocol Deviations

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monitoring/auditing and informatics support

This training has been funded with Federal funds from the National Cancer Institute, Division of Cancer Prevention.

Objectives

- Understand protocol deviations
  - ➢Its impact on participant safety, scientific integrity and/or data quality
- Explain Investigator responsibilities for protocol adherence
- Identify DCP reporting requirements
  - ➢Review some frequent reporting mistakes
- Recommend actions to prevent protocol deviations
  - ➢Discuss deviation reporting trends from 2016

Understanding Protocol Deviations

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- The term “protocol deviation” is not defined by either DHHS human subjects regulations (45 CFR 46) or FDA human subjects regulations (21 CFR 50)
- DCP Consortia 2012 SOP 4 defines a protocol deviation as any noncompliance with the study design and/or procedures of a Division of Cancer Prevention (DCP) and Institutional Review Board (IRB)-approved protocol.
  - ➢ May result from the actions of the study participant, the investigators, or the clinical staff conducting the study

Understanding Protocol Deviation Impact

- Deviations may:
  - ➢ Impact a subject's safety, rights or welfare
  - ➢ Affect scientific integrity
  - ➢ Reduce the quality or completeness of study data

Understand Protocol Deviation Impact

Commonly Reported Protocol Deviations	Impact a subject's safety, rights or welfare	Affect scientific integrity	Reduce the quality or completeness of study data
Participant enrolled but does not meet protocol eligibility criteria	✓	✓	
Informed consent (IC) not obtained prior to initiation of study-related procedures or IC process not documented properly	✓		
Study follow-up visits occurring out of protocol window or schedule of events not followed	✓	✓	✓
Participant received an excluded concomitant medication, wrong study treatment, or incorrect dose of study drug	✓	✓	✓
Participant met withdrawal criteria during the study but was not withdrawn	✓	✓	

Investigator Responsibilities

Investigator Responsibilities

- When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. *The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.* (21CFR 312.60)
- The investigator shall also assure that he or she will *promptly report to the IRB all changes in the research activity* and all unanticipated problems involving risk to human subjects or others, and that he or she *will not make any changes in the research without IRB approval*, except where necessary to eliminate apparent immediate hazards to human subjects. (21CFR 312.66)

Investigator Responsibilities

- An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. (21 CFR 812.100)

Investigator Responsibilities

- The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)). (ICH GCP [E6] 4.5.2)

- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. (ICH GCP [E6] 4.5.3)

Investigator Responsibilities: *1572 Statement of Investigator*

FDA 1572 (21 CFR 312.53(c))

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

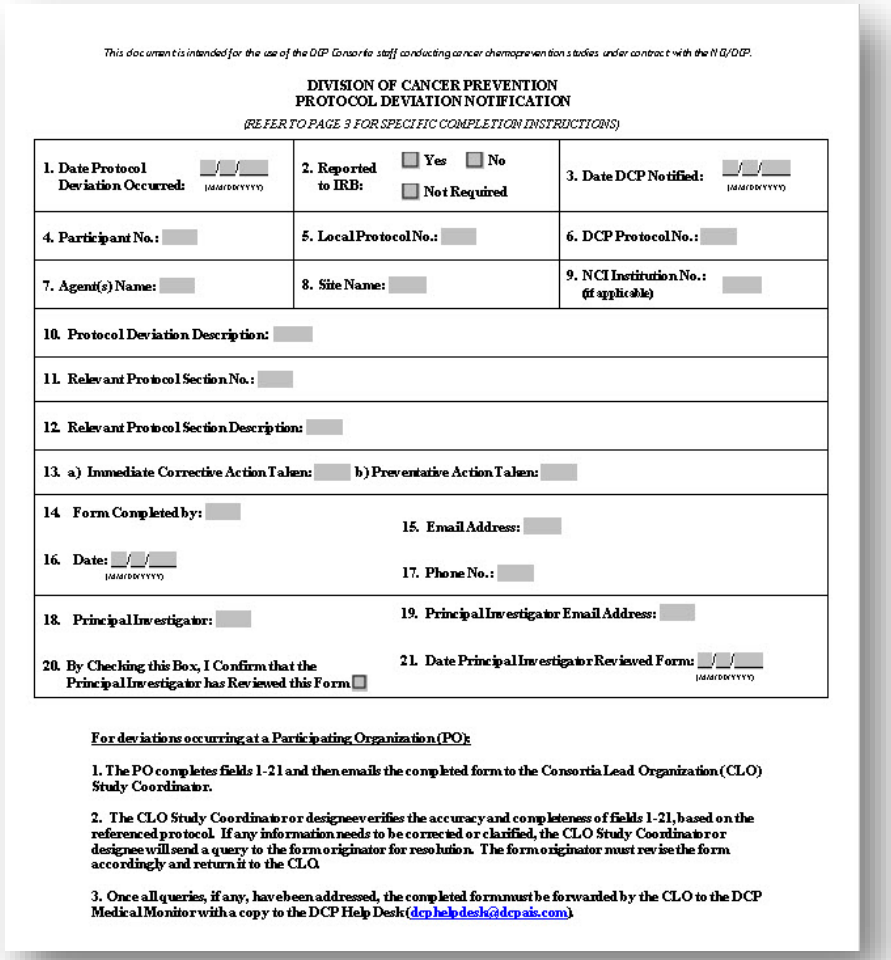
Investigator Responsibilities

- It is the responsibility of the site PI and study staff to use continuous vigilance to identify and report deviations.
- Even protocol deviations that do not meet local IRB reporting criteria must be reported to the Sponsor in accordance with DCP reporting criteria.

Reporting Protocol Deviations

DCP Reporting Requirements

- Investigators, Site Coordinators, and designees at Consortium Lead Organizations (CLOs) and Participating Organization (POs) are responsible for recording and reporting protocol deviations as soon as they are identified.
  - ➢ DCP Consortia 2012 SOP 4: Reporting Protocol Deviations
  - ➢ DCP Consortia Protocol Deviation Notification Form
- Comply with all institutional and/or CLO requirements related to the reporting of protocol deviations.



This document is intended for the use of the DCP Consortia staff conducting cancer chemoprevention studies under contract with the NIH/DCP.

DIVISION OF CANCER PREVENTION
PROTOCOL DEVIATION NOTIFICATION

(REFER TO PAGE 3 FOR SPECIFIC COMPLETION INSTRUCTIONS)

1. Date Protocol Deviation Occurred: __/__/____ (MM/DD/YYYY)	2. Reported to IRB: ☐ Yes ☐ No ☐ Not Required	3. Date DCP Notified: __/__/____ (MM/DD/YYYY)
4. Participant No.:	5. Local Protocol No.:	6. DCP Protocol No.:
7. Agent(s) Name:	8. Site Name:	9. NCI Institution No.: (if applicable)
10. Protocol Deviation Description:		
11. Relevant Protocol Section No.:		
12. Relevant Protocol Section Description:		
13. a) Immediate Corrective Action Taken:	b) Preventative Action Taken:	
14. Form Completed by:	15. Email Address:	
16. Date: __/__/____ (MM/DD/YYYY)	17. Phone No.:	
18. Principal Investigator:	19. Principal Investigator Email Address:	
20. By Checking this Box, I Confirm that the Principal Investigator has Reviewed this Form ☐	21. Date Principal Investigator Reviewed Form: __/__/____ (MM/DD/YYYY)	

For deviations occurring at a Participating Organization (PO):

1. The PO completes fields 1-21 and then emails the completed form to the Consortia Lead Organization (CLO) Study Coordinator.

2. The CLO Study Coordinator or designee verifies the accuracy and completeness of fields 1-21, based on the referenced protocol. If any information needs to be corrected or clarified, the CLO Study Coordinator or designee will send a query to the form originator for resolution. The form originator must revise the form accordingly and return it to the CLO.

3. Once all queries, if any, have been addressed, the completed form must be forwarded by the CLO to the DCP Medical Monitor with a copy to the DCP Help Desk (dcphelpdesk@dcpais.com).

DCP Reporting Requirements

A Closer Look at the PD Notification Form Completion

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(REFER TO PAGE 3 FOR SPECIFIC COMPLETION INSTRUCTIONS)

1. Date Protocol Deviation Occurred: __/__/____ (MM/DD/YYYY)	2. Reported to IRB: ☐ Yes ☐ No ☐ Not Required	3. Date DCP Notified: __/__/____ (MM/DD/YYYY)
4. Participant No.:	5. Local Protocol No.:	6. DCP Protocol No.:
7. Agent(s) Name:	8. Site Name:	9. NCI Institution No.: (if applicable)
10. Protocol Deviation Description:	Describe the deviation **and what should have occurred per protocol.**	
11. Relevant Protocol Section No.:		
12. Relevant Protocol Section Description:		
13. a) Immediate Corrective Action Taken:	b) Preventative Action Taken:	Include preventative action.
14. Form Completed by:	15. Email Address:	
16. Date: __/__/____ (MM/DD/YYYY)	17. Phone No.:	
18. Principal Investigator:	19. Principal Investigator Email Address:	
20. By Checking this Box, I Confirm that the Principal Investigator has Reviewed this Form ☐	21. Date Principal Investigator Reviewed Form: __/__/____ (MM/DD/YYYY)	

Before: Study participant 100 completed study visit 6 on June 16.

After: Study participant 100 completed study visit 6 on June 16. **The visit should have occurred between June 1-6 as per protocol.**

Before: Study visit was held on June 16 to collect the lab samples required to assure participant safety.

After: **Staff re-educated on protocol requirements and a new, reminder trigger was added to the visit tracker log to prevent re-occurrence of missing visit windows.**

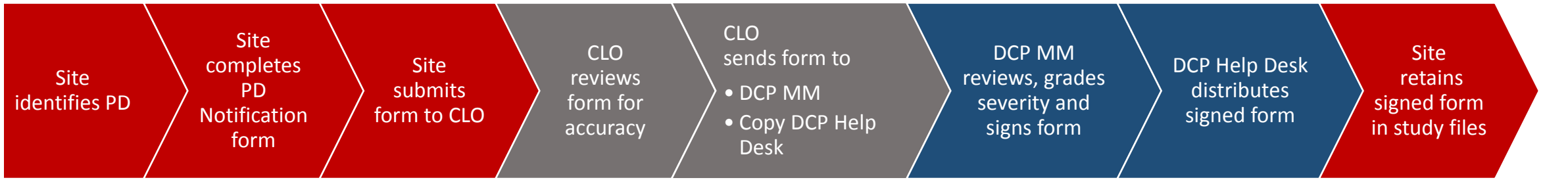
Analyze Each Deviation

- Has the specific problem been corrected?
  - ➢Take immediate steps to correct the problem (e.g., informed consent reobtained from study participants)
- Why/how did the deviation happen?
  - ➢Review the step-by-step procedure to help identify root cause
- What plan may be implemented to ensure this type of deviation/problem will not occur in the future?
  - ➢Review workflow or visit checklists to protect from re-occurrence

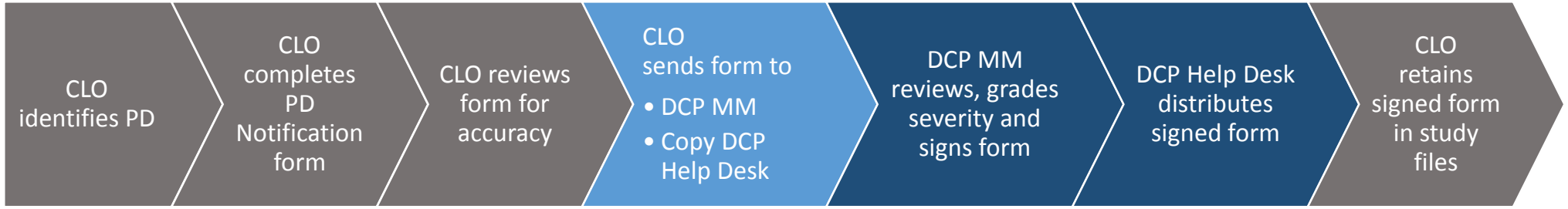
Protocol Deviation Grade

- The DCP Medical Monitor (MM) reviews and assigns the deviation severity grade:
  - 0 Not a deviation
    - Mistakenly reported as a deviation
  - 1 Minor
    - No meaningful effect on data integrity and no meaningful risk to participant safety
  - 2 Moderate
    - Potential to affect data integrity or jeopardize participant safety
  - 3 Major
    - Will affect major endpoint data integrity or will have a major impact on participant safety or ethical concerns

Protocol Deviation Process (if occurring at a PO)

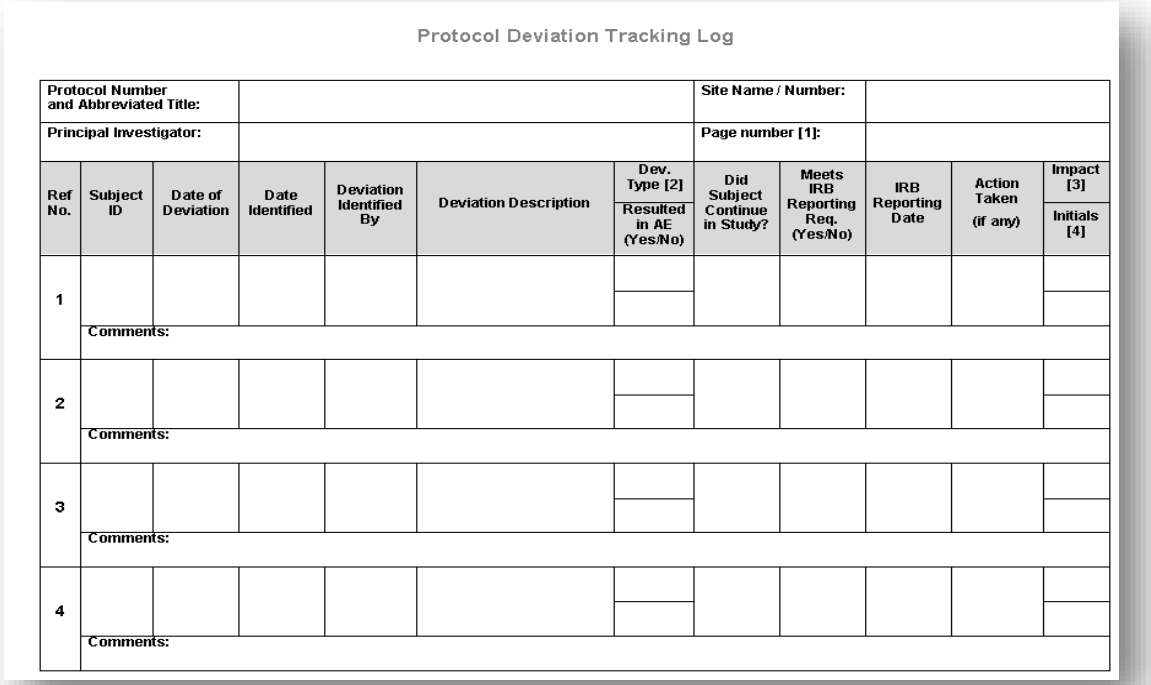


Protocol Deviation Process (if occurring at the CLO)



Documentation

- Each CLO/PO will retain a copy of the signed PD Notification Form and related communications in their study files.
- Recommendations:
  - Record protocol deviations in the tracking log as they occur, to track the process.
  - Number each page and maintain this log in the Essential Documents (Regulatory) Binder, behind the 'Protocol Deviations' tab.



Protocol Deviation Tracking Log

Protocol Number and Abbreviated Title:							Site Name / Number:				
Principal Investigator:							Page number [1]:				
Ref No.	Subject ID	Date of Deviation	Date Identified	Deviation Identified By	Deviation Description	Dev. Type [2] / Resulted in AE (Yes/No)	Did Subject Continue in Study?	Meets IRB Reporting Req. (Yes/No)	IRB Reporting Date	Action Taken (if any)	Impact [3] / Initials [4]
1											
	Comments:										
2											
	Comments:										
3											
	Comments:										
4											
	Comments:										

Frequent Reporting Mistakes

Frequent Mistakes in Form Completion

Before

This patient experienced a myocardial infarction which required hospitalization and elevated his cardiac enzymes. After this patient was discharged from the hospital, his labs continued to be elevated for several weeks. The patient experienced study drug interruption for 27 days. This all occurred as this patient was beginning Study Visit #2. The research nurse and PI discussed allowing this patient to restart study drug once his lab results returned to normal range and to continue taking study drug for the days he missed (27) then perform Visit #2. This patient's labs returned to normal on January 1st and he restarted study drug on January 2nd. He was scheduled to undergo Visit #2 endoscopy on February 6th but the technician was going to be out February 5th-10th, so the test was rescheduled for February 14th.

After

- Study drug administration was interrupted for 27 days due to rehospitalization to treat a reported SAE (myocardial infarction).
- Study Visit #2 protocol-required endoscopy was performed outside of protocol window due to lab scheduling conflicts.

Frequent Mistakes in Form Completion

Before

Participants 100, 103, 105 and 110 completed study visit 6 outside of protocol window on the following respective dates: June 16th, June 19th, July 24th, and August 4th. The first two participants missed study visit 7 and the third participant completed study visit 7 and 8 late. Study participants 118 and 124 completed study visit 6 on April 4th and April 17th respectively. The last dose of study drug was taken one week and two weeks before their respective visit, deviating from the protocol specific time point.

After

Submit separate PD Notification Forms for each unique event:

- Participant 100 completed visit 6 outside of protocol window and missed visit 7.
- Participant 103 completed visit 6 outside of protocol window and missed visit 7.
- Participant 105 completed visits 6, 7 and 8 outside of protocol window.
- Participant 110 completed visit 6 outside of protocol window.
- Participant 118 took visit 6 study drug dose outside of protocol timeframe.
- Participant 124 took visit 6 study drug dose outside of protocol timeframe.

Frequent Mistakes in Form Completion

Before

This patient initiated study drug on March 22nd. Study Visit #3 timeframe for this patient was from March 24th to April 4th. The study coordinator tried to contact the patient via phone and text messages on the following dates: March 30th, April 12th, September 12th, September 19th, October 2nd. The study coordinator called and left messages on his sister's (*Amy Grant*) cell phone at *(301) 123-4567*. This patient gave his verbal permission on February 28th that the study coordinator could speak to his sister on his behalf. The research nurse was unable to completed Visit #3 secondary to the patient and his sister not responding to phone calls or text messages.

After

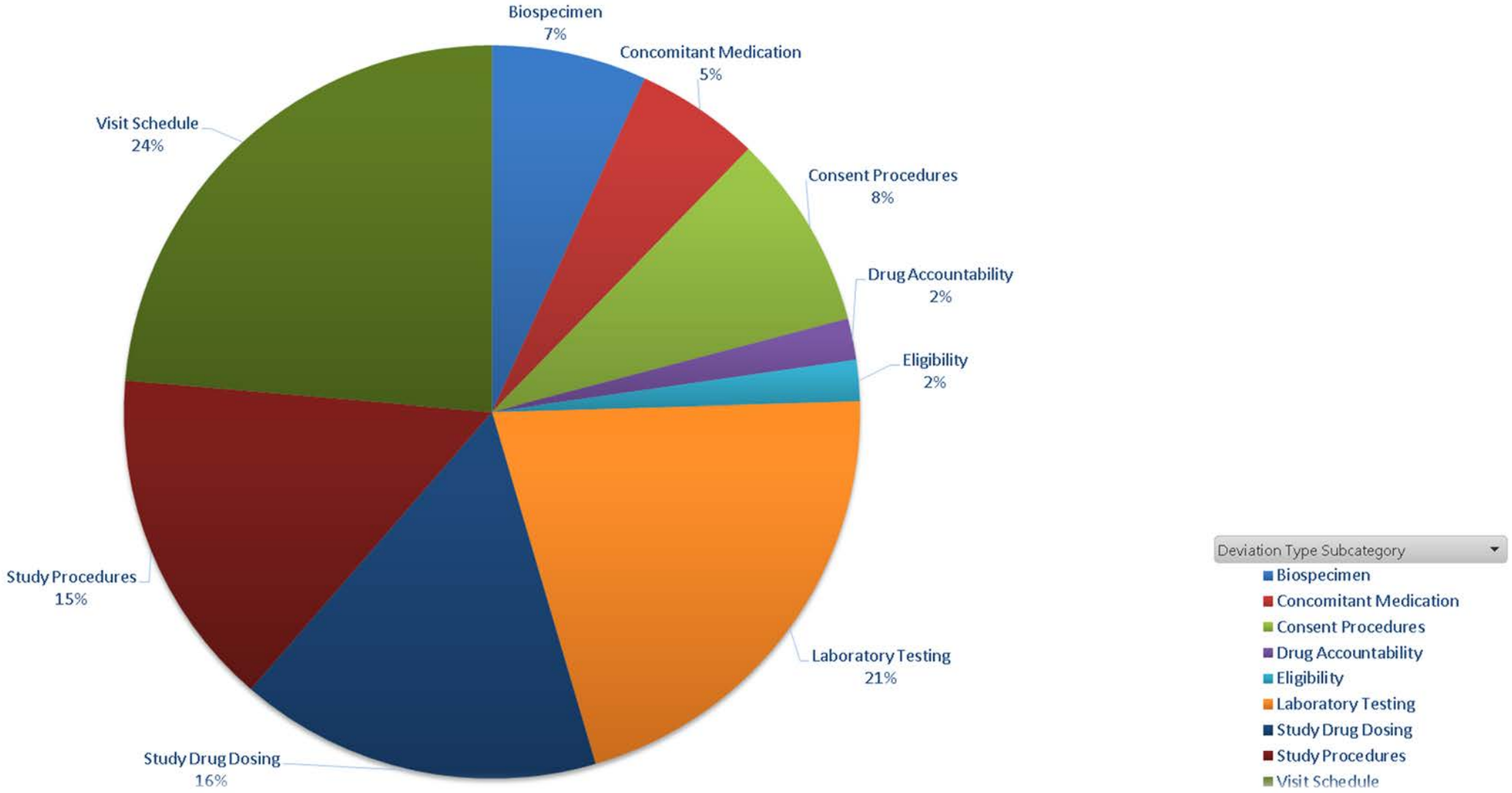
Study Visit #3 was not completed because patient could not be contacted after multiple attempts via phone call and text messages.

C2012 Reporting Trends for 2016

Protocol Deviation Subcategory Descriptions

Category	Definition	Categorization Examples
Laboratory Testing	Any deviation impacting integrity, collection or assessment of laboratory samples	Laboratory tests were not done or collected outside of protocol window or sample was mislabeled.
Biospecimen	Any deviation impacting bio specimen integrity, collection or assessment	Site sent biospecimen, which was returned by carrier due to bad address. Shipment exceeded the designated assessment window.
Study Procedures	Any procedure conducted outside the protocol design	Ex. 1. Not taking study vital at designated time point such as collecting at 2 and 4 hours instead of designated 1 and 3 hours. Ex. 2. Procedures done out of sequence.
Study Drug Dosing	Not receiving drug within the protocol time point(s)	Participant missed their morning study drug dosing.
Visit Schedule	Any visit not held within the study designated time point	Participant did not show for study visit and rescheduled visit fell outside allowable visit window.
Consent Procedures	Any deviation of Human Subject Protection, versions, signature/dates/copies	Outdated consent document used to consent.
Eligibility	Any deviation from eligibility criteria	Inadvertent violation of study eligibility criteria.
Concomitant Medication	Any drug taken OTC/prescribed that is indicated in the protocol as prohibited	Subject reported taking aspirin, which is prohibited in the protocol.
AE/SAE Reporting	Any untoward event that was not reported per protocol	Subject was hospitalized and the site did not report within the designated timeframe.
Drug Accountability	Issues related to study drug integrity, distribution, missing units	Distribution of expired study drug.

C2012 Protocol Deviations Reported by Subcategory Type
(January 2016 - September 2016)



Preventing Protocol Deviations

Preventing Protocol Deviations: *Root Cause Identification*

Deviation	Cause	Recommended Remediation
Study visits conducted outside of protocol window or not done	Participant scheduling conflicts; Visit scheduled late due to Investigator error	Amend protocol to include visit windows; Provide visit calendars to participants
Laboratory tests not done or collected outside of protocol window	Testing missed due to lab or staff error; Sample was not processed due to mislabeling	Develop laboratory manuals/SOPs, checklists, tools; Provide protocol training to staff
Participant missed study drug dosing	Study drug dose missed due to participant error; Participant discarded study drug	Review protocol requirements with participants; Reminder phone calls/emails from study staff; Provide pill diary and study calendars
Study-required procedures performed out of sequence or not performed	Procedures missed due to staff error or participant scheduling conflicts	Develop checklists and study tools; Reminders in Outlook or shared study calendar; Provide protocol training to staff

Preventing Protocol Deviations

- Know and understand the protocol
  - Initial and ongoing training
- Identify vulnerabilities
  - Watch where protocol procedures differ from standard practice at your site
  - Amend study protocol, if necessary
- Maximize protocol compliance with well-designed visit checklists
  - Develop collaboratively to assure protocol adherence at site level
  - Conduct ongoing internal monitoring and quality control checks
  - Update regularly to align with applicable protocol amendments or address QA gaps

In Summary

- Site PI and study staff are responsible for preventing, identifying, and reporting deviations
- Follow DCP Reporting requirements per DCP Consortia 2012 SOP4
- Protocol Compliance is an ongoing, proactive process that includes
  - ➢ Identifying vulnerabilities
  - ➢ Establishing processes to support protocol adherence in a busy clinic setting
  - ➢ Assuring continuous training and support

Save the Date: Upcoming C2012 Web Seminar

Date/Time	Webinar	Presenter
Jan. 19, 2017 1pm – 2pm EST	SAE Reporting	Gary Della-Zanna, DO, MSc

What topics would you like to see in the next C2012 Web Seminar Series?

- Please take a moment to consider your CLO and PO educational needs and send your webinar topic recommendations to DCPhelpdesk@dcpais.com.

Acknowledgments

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- Liz Walsh
- Lauren Dresser
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Questions?

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