# Protocol Deviations Working Group

**Mary Anne Luzar, Ph.D., M.S. – Chair, PDWG**
**Chief, Regulatory Affairs Branch Division of AIDS**

**Presentation to the ACTG**

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# Protocol Deviations (PD) Working Group

- Working group established in response to EMA inspection findings – noted sponsor not directly involved in PD assessment and stated we should be.
- Initiative began in 2016 in DAIDS
- Expect this issue to be reviewed by EMA in future inspections to ascertain our progress

# Working Group Objectives

- Develop a centralized DAIDS system, compliant with current regulations, for reporting and reviewing all protocol deviations that occur in DAIDS Network trials.
- Develop a DAIDS PD collection form to include “must have” requirements.
- Establish a centralized collection system within the two major DMCs, FSTRF and SCHARP, by developing a form that will becomes a CRF in Medidata Rave.
  - Eliminate the need to reconcile a separate PD database with the DMC database.
  - Provide reports and information to DAIDS, Networks and Protocol Teams.

# What is a Protocol Deviation?

- A PD “is any change, divergence, or departure from the study design or procedures defined in the protocol” (ICH E3, Q & A (R1), Q7)

- “Noncompliance may be on the part of the subject, the investigator, the study staff or a combination of these groups. It is assumed the protocol will reference key manuals used for the study and they are incorporated into this definition (e.g., Manual of Operations, Study-specific procedures, EAE Manual, and Pharmacy Manual)” (DAIDS)

  - The term “protocol violation” has been “retired” by ICH

- Good clinical practice recommends protocol deviations be summarized by site and category to determine the association of the deviation with the study findings.

- At the end of a study, the Clinical Study Report (CSR) provides information about all serious protocol deviations but not necessarily by site.

- Minor protocol deviations are to be summarized in the CSR – this is a mandatory report for filings to regulatory agencies.

# Protocol Deviation Categories
# Important vs. Not Important – Categories for DAIDS

- What is an “Important” Protocol Deviation?
  - They are PD’s that “significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being”
    - Examples: enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial (ICH E3)

- “Important” PD's must be listed in the “Clinical Study Report (CSR)” (ICH E3)
  - A central collection (database) must be available at the end of the study in order to do this
  - What is a CSR?
    - It “describes the results of a single human study and thus represents the most fundamental building block in a drug product’s argument for use in humans” (ICH E3)

# Pros of Capturing Protocol Deviations

## In EDC Together with Trial Data

- Collected data are held in central location within DMC database
- Increased consistency in protocol deviation planning, processing, analysis and reporting mechanisms
- Reduced burden associated with the interpretation of “important” deviations across all levels of a sponsor’s organization
- Single system use by site staff for clinical data and protocol deviations.

## Regulatory Authority Perspective

- Potential decreased protocol deviation reporting “noise”
- Potential increased focus on deviations associated with patient safety, reliability of study data, human subjects protections and/or data quality

## Separate Database at DAIDS

- **Easier to lockdown and freeze the database**
- **Able to search across clinical trials**
- **Uniform recording, reporting characteristics and management of deviation information**

# Cons of Capturing Protocol Deviations

## In EDC together with Trial Data

- Introduces resource intensive reconciliation process with multiple components and collaborators, between DMC, Operations Center, and Sponsor, since sites tend to over-report.
- Additional artifacts may need to be collected to ensure local IRB reporting compliance.
- Challenges for data cleaning and database lock.

## Separate Database at DAIDS

- If deviations are to be included in a CDISC regulatory submission (SDTM/ADaM), reconciled records will need to be copied back to the DMC.
- Additional resources required to implement a separate PD reporting interface and database.

# Considerations

- It is a sponsor decision in terms of how protocol deviations are collected. Currently, all networks collect PDs in some system and should continue until DAIDS communicates change to a more centralized system.
- Need to identify additional staff in DAIDS, documentation, and resources to triage deviations as they are reported regardless of the database source.
- The sponsor must adjudicate all the protocol deviations (major and minor) in a timely manner.
- Protocol deviations should be included in the study TMF regardless of the format or how they are collected.

# Regulations and ICH Requirements

- E3 Implementation Working Group ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers (R1) 2012
- ICH E6 (R2)
- ICH E3 “STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS” November 1995

# Protocol Deviations Working Group Members

- Adeola Adeyeye, M.D., Medical Officer, PSP
- Azhar Bisle, M.S.M.-H.C.A., TMF Compliance Specialist, RAB
- Bariatu Smith, R.N., M.S., Acting Chief, Monitoring and Operations Branch
- Carol Worrell, M.D., Director, OPCRO
- Dhawala Kovuri, M.S., Data Manager, OPCRO
- Edith Swann, R.N., Ph.D., Medical Officer, VRCB
- Ellen Townley, M.S.N., F.N.P., Medical Officer, PSP
- Gregg Roby, R.N., C.C.R.P., Health Specialist, OCSO
- Jane Baumblatt, M.D., Medical Officer, VCRB
- Janet O'Brien, M.P.H., Health Specialist, ProPEP
- Jui Shah, Ph.D., Chief, ProPEP
- Julia Hutter, M.D., Medical Officer, VCRB
- Karin L. Klingman, M.D., Medical Officer, TRP
- Katherine Shin, Pharm.D., Senior Pharmacist, PAB
- Kathy Smith, R.N., Nurse Consultant, TRP
- Kelly Parsons Pharm.D., Pharmacist, PAB
- Larry Chen, TMF Compliance Specialist, RAB
- Laura Polakowski, M.D., Medical Officer, VCRB
- Lynda Lahl, R.N., M.S., Policy Health Specialist, ProPEP
- Maggie Brewinski-Isaacs, M.D., Medical Officer, VCRB
- Marga Gomez, M.D., Medical Officer, VCRB
- Mark Mishkin, M.P.H., Health Specialist, RAB
- Mary Allen, R.N., M.S., Medical Officer, VCRB
- Mary Anne Luzar, Ph.D., M.S., Chief, RAB
- Peter Kim, M.D., Director, TRP
- Pia Lohse, Health Specialist, OCSO
- Ruth Ebiasah, Pharm.D., M.S., R.Ph., Chief, PAB
- Sarah Read, M.D., M.H.S., Deputy Director, DAIDS
- Sheryl Zwerski, D.N.P., C.R.N.P., Director, PSP

# Protocol Deviations Pilot

A5359

# Discussion
# and
# Questions from Sites

# Pilot Study for DAIDS PD Form

- Protocol A5359 will be the first protocol used to pilot the DAIDS PD Form.
- Protocol A5359 is open, the PD Form is in the database
- We will use this system for PD collection for the duration of this study.

# Protocol Deviation – Network Directives

- Each network has its own system for current PD reporting:

- Example:  For IMPAACT, deviations defined as reportable in the network MOP are collected on an eCRF and additional supporting materials are reported to FHI.  The DMC works closely with FHI to bidirectionally reconcile protocol deviations and have found this workflow to be very resource intensive and not scalable.

- For ACTG, pilot workflow for A5359 is based on a new form developed by the DAIDS PD WG.  This study is in early stages of implementation. It will provide information on:
- Ease of use of form
- Redundant areas to address
- Over-reporting – especially related to non-important PDS
- Use of database and its role for other trials or decision about a separate database.

- Industry best standards point to a model where deviations are maintained in a separate, sponsor database that may be a separate part of MDR

# DAIDS Next steps

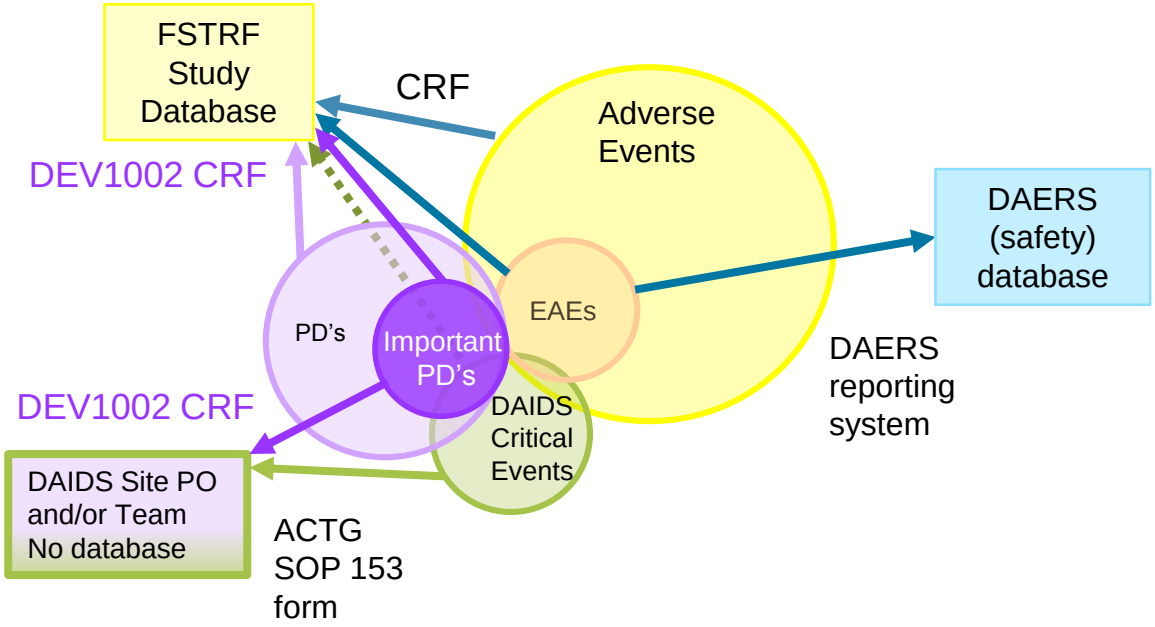
- Review pilot results, feedback session at ACTG meeting June 2019
- Work with DMC to capture PDs defined via other CRFs.
  - This will decrease need to use PD CRF for anything but Important PDs.
- Set-up groups within DAIDS/Networks to:
  - Create a process to review data from eCRF
    - Need manpower from either Network Ops (IMPAACT model) or contractor like RSC to gather information/ documentation. And develop that process with them
    - Need to develop an adjudication and documentation process for CAPA review
  - Create a PD policy; work with Monitors to use eCRF as a tool for remote monitoring
  - Work with Network site oversight committees to incorporate PD data into their site performance process.
  - Site, Investigator and DAIDS staff training on their roles and responsibilities.

# DAIDS Future Steps

- Decide how best to collect these data-
  - Separate database, housed where? DAIDS, at each DMC, or some other database contractor?
    - Ideally we would want a database that would work across networks and grants so site performance across networks and grants can be assessed.
- How will outside collaborators who need to access this database access it?
  - Create an interface that sites can use for their own QC and IRB processes
  - Ideally would want sites not to enter data in triplicate or quadruplicate—AE, SAE, PD, CE
  - An interface that allows work flow between various staff and entities, that monitors and others could query to evaluate a site or a protocol.
- Define roles of DAIDS, Networks, and contractors (if any) and training…

# Collecting Events in the ACTG

- The DEV1002 CRF puts **all PD's** in the Study Database; it defines which are Important PD's



# Thank you!

Questions?