MOB Report

Office Of Clinical Site Oversight (OCSO)

National Institute of Allergy and Infectious Diseases (NIAID)

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In this issue

Informed Consent Violations: The root of it all

By: Greg Lessing

Sampling & Methodology:

443 Informed Consent Violations recorded during PPD monitoring occurring between February 2017 and May 2018 were examined and a root cause analysis was done to determine and provide suggestions on how to address the underlying reasons for the significant number of Informed Consent Violations.

Table 1: Informed Consent Violations by observation category

Number of observations	Observation Category	Category Description	Percentage of Total
87	A1A	Level 1* Informed Consent Violation (ICV)	20%
69	A1B	Level 2* ICV	16%
104	A51A	Level 1* Subsequent ICV	23%
183	A51B	Level 2* Subsequent ICV	41%

*Level 1: Significant monitoring finding that constitutes increased risk by compromising participant safety, rights and welfare, and/or data integrity

*Level 2: Significant monitoring finding that compromises data integrity and constitutes noncompliance with DAIDS policies, ICH/GCP or applicable regulations but is unlikely to compromise participant safety

Are IC violations protocol-specific?

IC Violations were noted for 39 protocols during the period specified above however, 5 protocols contributed to 66% of all IC Violations noted.

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Informed Consent Violations

Table 2: Number of IC Violations and percentage of total by protocol

Protocol Number	Number of Observations	Percentage of Total
A5332 (REPRIEVE)	102	23%
HVTN 704/HPTN 085	66	15%
HVTN 703/HPTN 081	62	14%
HVTN 702	33	7%
HPTN 083	31	7%
Others	149	34%

Protocol specific number of charts reviewed was calculated as a percentage of all charts reviewed between 01-Feb and 31-May-2018 and the top 5 protocols are noted in Table 3. When compared with the data illustrated in Table 2 (Number of IC Violations noted by protocol), it is evident that the number of IC Violations by protocol was directly proportional to the number of charts reviewed. Therefore, protocol-specific prevalence does not seem to be a significant contributing factor of IC Violations.

Table 3: Percentage of charts reviewed by protocol during the period 01-Feb-2017 to 31-May-2018

Protocol	% of total charts reviewed
A5332 (REPRIEVE)	22%
HVTN 704/HPTN 085	11%
HVTN 703/HPTN 081	6%
HVTN 702	5%
HPTN 083	6%
Others	50%

Are IC Violations related to announced or unannounced chart reviews?

In general charts are selected for review on an announced/ unannounced basis at a ratio of 1:1. Although this practice is changing due to the use of various electronic data capture systems it could be considered to still be generally true for this analysis.

Table 4: Number & Percentage of IC Violations noted by unannounced or announced chart reviews

	Number of ICVs noted	Percentage
Announced chart reviews	278	63%
Unannounced chart reviews	165	37%

As the number of IC Violations noted in announced chart reviews was greater than unannounced, it is unlikely that sites planning for a monitoring visit, had an impact. This can therefore be excluded as a factor influencing the number of IC Violations reported.

With the exclusion of protocol and visit preparation as possible reasons, the 443 IC Violations observed were categorized to identify a root cause.

The 443 IC Violations noted during the period referenced above could be broadly categorized into 11 categories per Table 5

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Informed Consent Violations

Table 5: Categories of IC Violations noted

Category	Number of Observations	Percentage of total
Inadequate documentation of Informed Consent Process in source documents	103	23%
Incorrect or unapproved version of the Informed Consent used	95	21%
Delay in obtaining subsequent consent	93	21%
Site staff obtaining consent not appropriately delegated	31	7%
Blank or incomplete fields within informed consent form (e.g. permission to store and use samples) not including signature or date fields	30	7%
Signature, date or time missing (Site Staff)	22	5%
Signature, date or time error (Site Staff)	19	4%
Site staff obtaining consent not appropriately qualified to conduct consent (local regulations)	17	4%
Signature, date or time missing or error (Participant)	12	3%
Site copy of consent form partial or missing	7	2%
Study procedures conducted prior to consent, Subject not consented at transfer site or other	14	3%

79%

The top 5 categories of informed consent findings noted accounted for 79% of all violations noted. To address issues related to the informed consent process, DAIDS issued a memo dated August 21, 2017 which requires that all active DAIDS sites develop and implement an informed consent Standard Operating Procedure by November 1st, 2017. All staff conducting consent should be intensively trained on the requirements for obtaining informed consent. The SOP also should outline subsequent informed consent process and procedure for obtaining consent in a timely manner.

The memo also states the requirement for:

- A study specific delegation of duties log which includes the task/responsibility of obtaining informed consent.
- Informed Consent Quality Assurance (QA)/ Quality Control (QC) checks should be part of the sites overall Quality Management Plan.

Further recommendations for sites to decrease the number of Informed Consent Violations noted are the use of checklists for staff obtaining informed consent:

- Has the process of obtaining informed consent been adequately recorded in the source notes?
- Delegation of duties appropriately documented for staff obtaining consent?
- Is the most recent approved version of consent document being used?
- Are all pages of the consent document present?
- Have all fields requiring input been completed throughout the consent document?
- Has the participant been offered a signed copy, and the original consent document retained at site?
- Has someone at site reviewed the checklist before participant leaves the clinic?

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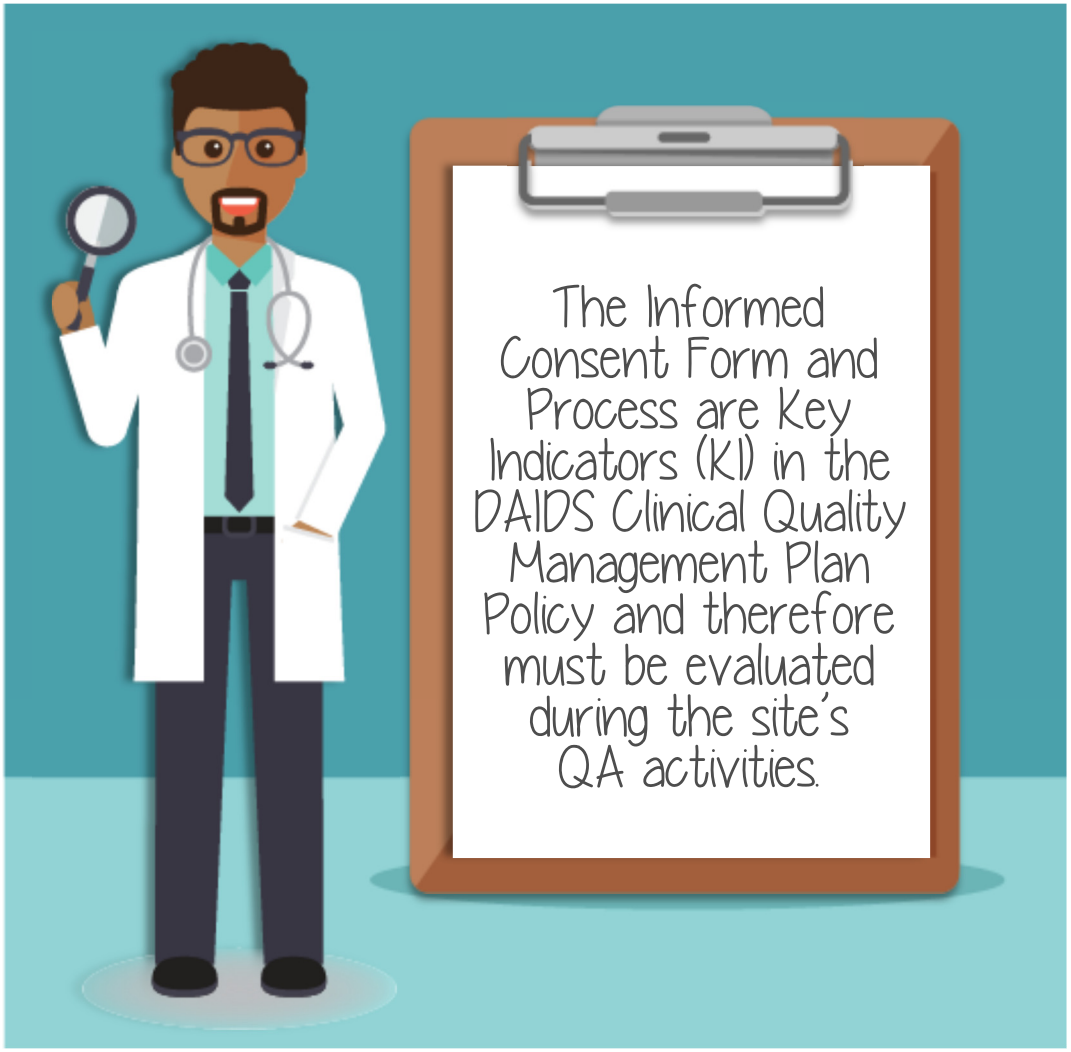
Informed Consent Violations

Delay in obtaining subsequent informed consent is another significant category. Subsequent informed consent is necessary either due to an amendment to the protocol or changes made by a site that result in a change to the content of the initially signed consent document.

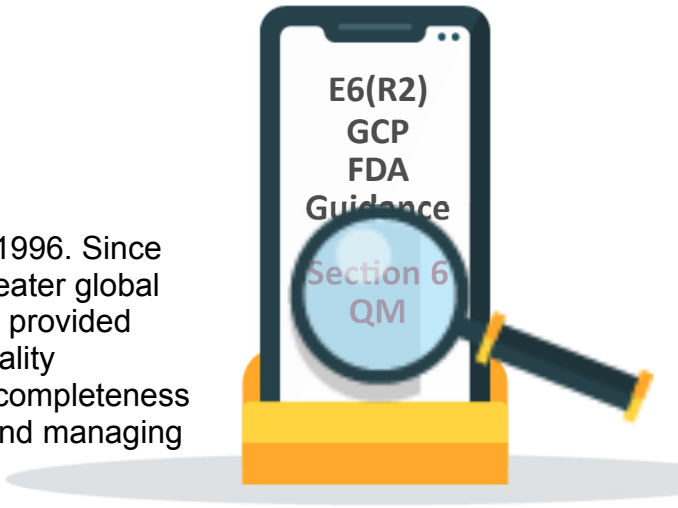
Delayed signing of subsequent informed consent has a risk for potential safety issues, delay in communication of information which may change the participants willingness to participate in the trial and the potential to conduct study related procedures prior to obtaining consent. It is therefore recommended that sites develop a mechanism which supports current site procedures and which complies with DAIDS requirements, to ensure that subsequent informed consent is obtained at the very earliest opportunity, following appropriate ethics/regulatory approvals. Examples could be a note placed in each participants folder or in a calendar used by the site for scheduling participant visits. This should also be part of the sites' SOP on IC and sites should follow the procedure in their SOP consistently.



Per the US Food and Drug Administration (FDA), Bioresearch Monitoring (BIMO) Fiscal Year 2017 Metrics, inadequate recordkeeping and inadequate subject protection due to informed consent issues and failure to report AEs are among the common investigator deficiencies resulting in the issuance of an FDA Form 483 at close of inspections.

It is thus of critical importance that sites develop detailed standard operating procedures for informed consent, ensuring that all processes are clearly described and consistently implemented and that all staff are adequately trained.

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry (March 2018) (FDA)



ICH Guidelines for Good Clinical Practice were first adopted in 1996. Since then, clinical trials have evolved substantially with regards to greater global coverage, complexity and advancements in technology. ICH E6 provided flexibility to sponsors to implement innovative approaches to quality management however actual implementation often focused on completeness and accuracy of trial data without comprehensively identifying and managing the risks impacting data integrity.

Sponsor responsibilities related to **Quality Management** have been expanded. The E6R1 guidance has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and reliability of trial results.

Development of a quality management plan through the identification and management of risks is a critical precursor to quality management in ICH E6 R2 which provides supplemental guidance to sponsors. Guidance include sponsor implementation of a quality management system throughout the design, conduct, recording, evaluation and archiving of clinical trials. Listed below is a summary of the other FDA guidance outlined in Section 5.0 Quality Management.

Section 5.0 Quality Management Summary:
The sponsor should implement a quality management (QM) system that uses a risk based approach throughout all stages of the trial. The QM system should focus on trial activities essential to ensuring human subject protection and include efficient protocols, tools, and procedures for data collection.

The methods developed to assure and control the quality of the trial should be proportionate to the risks and the importance of the information collected. Sponsors should ensure all aspects of the trial are operationally feasible and operational documents should be clear, concise, and consistent.

The risk based approach should include:

- *Critical Process and Data Identification – identify critical process and data to ensure human subject protection*
- *Risk Identification – identify system and clinical trial risks*
- *Risk Evaluation – evaluate risks against existing risk*
- *Risk Control – approach should be proportionated to significance of risk and risk reduction should be incorporated in various stages throughout the trial*
- *Risk Communication – document and communicate QM activities to those involved and affected by activities*
- *Risk Review – periodic review of risk control is essential to ensure QM activities remain effective*
- *Risk Reporting – QM approach, deviations and remedial action taken should be reported in the clinical study report.*

For more details, you can review the Quality Management section, which begins on page 30, in the E6(R2) GCP Guidance Document.

Site Management (Program Officer (PO) responsibilities) vs Site Monitoring (PPD responsibilities)

The NIAID Clinical Site Monitoring (NCSM) contract (PPD) monitoring approach at DAIDS sponsored clinical research sites differs operationally from traditional full-service commercial clinical monitoring. DAIDS directs the PPD tasks and assignments through a suite of Standard Operating Procedures (SOPs), Policies, Monitoring Plan and in accordance with ICH E6 R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry research. The scope of monitoring services encompasses approximately **80** ongoing studies at **275** active sites in **21** countries. Due to the large number of sites and studies differentiating NCSM monitoring scope from a traditional commercial research opportunity, research scientific agenda is structured to be more site and network than protocol-specific. Broadly summarized, PPD is contracted to provide monitoring services at DAIDS sites and report findings to the DAIDS in network specific monitoring reports. Site management activities are conducted by the DAIDS via the DAIDS Program Officer. To provide a better understanding, a summary of PPD vs. DAIDS Program Officer responsibilities are further detailed below.

SITE MANAGEMENT
PO's Responsibilities

- Implement and coordinates a range of clinical site-management activities; advises PI on clinical site start-up and relevant operational and regulatory issues including assurance of site quality management activities, resource allocation, administrative issues and compliance with relevant regulations and policies.
- Provide leadership for planning, organizing, and conducting site visits to effectively fulfill site management responsibilities.
- Provide guidance on site queries regarding DAIDS research polices, SOPs and directives, training requirements and questions regarding PPD monitoring and monitoring reports.
- Review and interpret observations noted in SMRs.
- Identify significant findings requiring resolution and follow-up including corrective action plan developed by investigators and provide guidance as necessary.
- Enter findings into the DAIDS Clinical Site Monitoring (CSM) System Issue Resolution Tracking system.
- Follow-up on critical events identified by the Monitoring Contractor or through other sources.
- Direct and conduct formal evaluations of the clinical trials units' organizational structures and modes of operations in relationship to the achievement of the Division's goals and objectives in the areas of administration, clinical site management, and recruitment of participants.

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Site Management (Program Officer (PO) responsibilities) vs Site Monitoring (PPD responsibilities)

SITE MONITORING
PPD's Responsibilities

PPD Contractual Requirements:

✓	PPD is contracted through the NIAID Clinical Site Monitoring (NCSM) contract to provide monitoring services for DAIDS sponsored research. The primary purpose of PPD monitoring is to ensure that DAIDS sponsored clinical research is conducted as required by ICH/GCP, DAIDS SOPs, any specific in-county requirements and the clinical trial protocol.
✗	PPD is not contracted to perform tasks in other functional areas that may be associated with a full-service commercial type project for example pharmacovigilance, medical writing and protocol development, data management & statistics, investigational product supply management, laboratory services, IT systems management (e.g. IVRS), medical and regulatory affairs, feasibility and site selection and activation.

PPD Role:

✓	PPD's role on the NIAID Clinical Site Monitoring (NCSM) contract is largely to verify, observe and report. PPD monitors review PID documentation and conduct assessments per the NCRMS generated Work Order, evaluating the following: • Accuracy and completeness of reportable data on Case Report Forms (CRFs) • Maintenance of appropriate source documentation • Documentation of objective findings, including verification of protocol endpoints • Documentation of and adherence to informed consent procedures • Adherence to inclusion and exclusion criteria • Reporting of protocol violations and deviations • Reporting critical findings, per DAIDS policy, to the DAIDS Program Officer and COR (Contracting Officers Representative) via e-mail, twenty-four (24) hours of becoming aware of the event • Adherence to Federal and country-specific regulatory requirements, ICH Harmonised Guideline for Good Clinical Practice, and DAIDS policies • Documentation and reporting of Serious Adverse Events (SAEs), EAEs and Adverse Events (AEs) • Adherence to other protocol-specific requirements, including specimen collection and reporting of clinical laboratory test results and storage of clinical specimens • Adequacy of pharmacy operations, performance and management related to protocol-specific requirements Report all monitoring findings via the monitoring report and components distributed to the DAIDS and sites via the NIAID CRMS system.
✗	Unless requested to do so via special assignment, PPD is not responsible for site management activities such as providing guidance on document management, training, review and editing of procedural documents etc.
✓	While PPD does not provide training to sites as part of the NCSM Contract, monitors can provide advice regarding ICH/GCP, regulatory requirements, how to avoid and resolve queries as part of the routine process of resolving queries during a monitoring visit.

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Site Management (Program Officer (PO) responsibilities) vs Site Monitoring (PPD responsibilities)

SITE MONITORING
PPD's Responsibilities

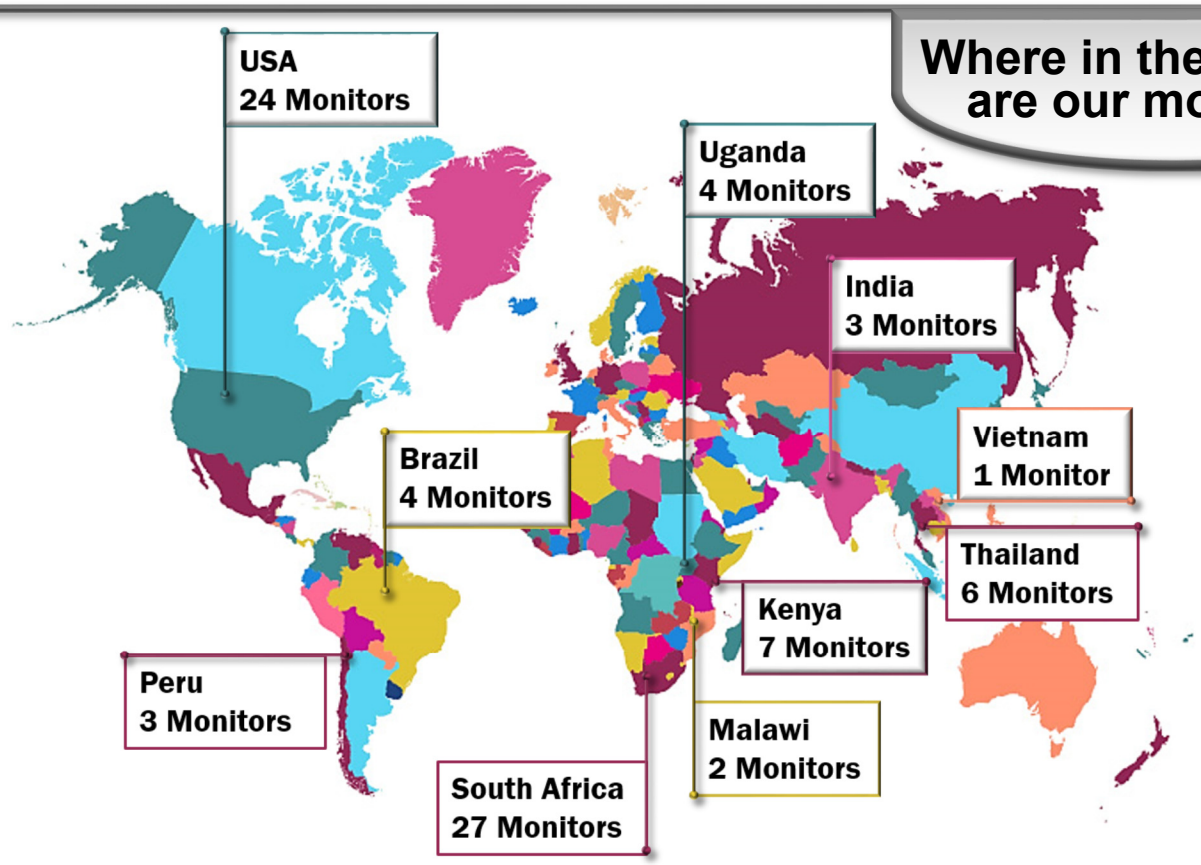
Review of outcomes from monitoring observations:

- Only those monitoring observations marked with E2-Follow-up code will be reviewed for resolution during subsequent visits.
- The DAIDS Program Officer will identify other monitoring observations and issues for follow-up via the issue resolution process in the NIAID CRMS system.

Communication:

- PPD's Communication with the site pre-and post-visit is limited to approved processes e.g. site visit scheduling, N-CRMS and sending the RRT Change Notification Form.
- PPD sends a pre-visit letter to clinical sites via N-CRMS which includes the following:
  - site-specific activities/protocols to be reviewed
  - data and other information to be collected/assessed
  - description of any other materials to be made available to monitors
  - site personnel need to be available during the visit
- While on site, PPD monitors may schedule an opening meeting with site staff to ensure all monitors and site staff have the same expectations of the visit and to confirm activities planned. Monitors also review a summary of site visit activities having been completed with site staff during debriefing.
- If a debriefing was not completed with the CRS Leader during the visit, DAIDS has asked that the monitor, if possible contact the CRS Leader post-visit to complete the debriefing during the week following the monitoring visit.

Where in the WORLD are our monitors?



Monitoring Metrics

Year to Date Monitoring Metrics

February, March	1Q
April, May, June	2Q
July, August, September	3Q
October, November, December, January	4Q
To be determined	TBD

Monitoring Visits

	2017	2018
1Q	119	141
2Q	174	182
3Q	186	TBD
4Q	208	TBD
Total	**687**	**323**

Monitoring Visits: Any time a monitor travels to a site to conduct monitoring.

Monitoring Trips

	2017	2018
1Q	207	255
2Q	293	317
3Q	321	TBD
4Q	326	TBD
Total	**1147**	**572**

Monitoring Trips: Includes the total number of monitors traveling to a site to conduct a site monitoring visit.

Records Reviewed

	2017	2018
1Q	1526	1927
2Q	2233	2411
3Q	2636	TBD
4Q	2554	TBD
Total	**8949**	**4338**

Regulatory Files Reviewed

	2017	2018
1Q	183	213
2Q	247	265
3Q	320	TBD
4Q	345	TBD
Total	**1095**	**478**

Pharmacy Assessments

	2017	2018
1Q	400	453
2Q	608	453
3Q	623	TBD
4Q	712	TBD
Total	**2343**	**906**

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