MOB Report

Office Of Clinical Site Oversight (OCSO)

National Institute of Allergy and Infectious Diseases (NIAID)

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ICH E6 R2 Impact on Study Quality and Operations

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The ICH E6 (R2) effective November 2016: Impact on Study Quality and Operations-Focusing on the changes related to Investigator responsibilities and Monitoring.

This article focuses on the bearing ICH E6 (R2) has on the investigator and on monitoring of trial activities.

The revision of ICH E6 was triggered through issues observed during audits, inspections and monitoring visits over a long period of time. Changes reflect recent methodologies focused on risk-based approaches to quality evaluation, enhanced language to accommodate modern media systems and further clarification on responsibilities for the sponsor and the investigator.

Some of the most common clinical research investigator findings include:

- Inadequate and or discrepant source documentation
- Non-compliance to the trial protocols
  - Enrolment of ineligible participants
  - Protocol Violation affecting safety
- Informed consent problems
  - Documentation errors
  - Missing informed consent
- Test article accountability
- Inadequate oversight of study and site personnel
  - Inappropriate delegation of authority
  - Inadequate or non-existent quality management systems or Standard Operating Procedures (SOPs)
- Failure to communicate with Institutional Review Board (IRB)/ Ethics Committees

ICH E6 R2 is expected to offer a solution to the ever-increasing focus on safety, quality and research cost improvements. More focus is now given to data and processes that are directly linked to participant safety, rights and welfare while circumventing obvious complexities on trial protocols and their operational feasibility.

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Adoption of this revision sets in 'modernization' of this global clinical research guideline. Newer technologies in electronic data capture and transmission are tilting the scales against the traditional methods and reliance on paper-based data collection and reporting.

The focus on the E6 R2 further includes:

- Encouraging implementation of more efficient approaches to clinical trial design, conduct, oversight
- Introducing a more formal risk management process
- Promoting a risk-based monitoring approach including centralized monitoring
- Implement improved oversight and management of clinical trials
- Continue to ensure human subject protection
- Focus on reliability of trial results and data integrity by requiring that the source data be attributable, legible, contemporaneous, original, accurate and complete (ALCOAC)
- Ensuring that both the sponsor and investigator have access to the trial data and documents
- Recognizing technology and addressing its issues like validation, back-up and security

Investigator's take home messages

Delegation of authority and supervision

This is in reference to Sections 4.2.5 and 4.2.6 newly added.

ICH E6 R2 further specifies that it is the responsibility of the investigator to supervise and provide oversight to all persons with delegated tasks. Routine protocol meetings and training should be conducted involving all study team members. There should be documentation to demonstrate participation of the investigator in such sessions. All trial staff must be qualified by education, training and experiences and they need to demonstrate capability to handle delegated trial-related tasks. Current signed and dated curriculum vitae for each study staff should be maintained in the study file.

Source data integrity

Under 'Record and Reports', a new Section 4.9.0, specifies that '*Source data should be: attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).'*

Attributable	It should be clear who made the entry. The record should identify also who modifies and why and when the record is changed.
Legible	The records and dates of an entry should be clear, easy to interpret and understood.
Contemporaneous	The data should be recorded in real-time, when the event occurred and records are signed (or initialled) and dated accurately.
Original	The record is original as it is captured, collected or is an exact certified copy of the original.
Accurate	Data including error correction and edits, should be correct, truthful and to the appropriate precision.
Complete	Up-to-date and with no omissions.

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The term 'audit trail' was added for non-paper records

Regarding clinical research quality per Section 2.13, there should be systems in place to ensure and guarantee quality in every aspect at the trial. SOPs for critical processes should be in place. The SOPs should be approved, relevant staff trained, and training documentation filed. Examples of critical processes include; Source Documentation, Informed Consent process, Screening and Enrolment process, Participant Follow-up and other processes as determined by the investigator. The sites should also have robust quality management process to ensure protocol compliance at every stage.

ICH E6 (R2) Bearing on Clinical Research Monitoring

Per Section 5.18.3, 'The sponsor should determine the appropriate extent and nature of monitoring. E6 R2 has provided for flexibility in the determination of the extent and nature of monitoring which should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.'

Traditionally clinical research monitoring has been done on-site where the activities are performed. Centralised Risk-Based Monitoring (RBM) is now an option. RBM focuses on critical data, critical processes and identified risks. Thus, effort is employed on value added activities directly supporting participant safety and reliability of trial results.

Successful RBM needs constant risk detection and evaluation to determine the approach and effort justified for the trial monitoring. The details should be well outlined in the monitoring plan.

Conclusion

ICH E6 (R2) changes are quite progressive with efforts shifting the focus to the most critical activities necessary for participant safety and data integrity. The investigator must therefore take cognisance of these changes and have plans for staff training, implementation and compliance. Strong collaboration between the sponsor, investigator and other stakeholders will boost success.

References

1. Peterson J. Getting on board with ICH GCP E6 (R2): Impact on Study Quality and operations. Clinical Researcher, 09 Oct 2017
2. Fassbender M. How to prepare for ICH E6 R2 Implementation. 21 Jun 2017
3. The FDA Group's Blog. 4 Ways ICH E6 (R2) 2016 Impacts Good Clinical Practice (GCP), 09 Aug 2017
4. CITI program. Overview-ICH GCP E6 R2 Integrated Addendum. 2017
5. International Council For Harmonisation of Technical Requirements For Pharmaceuticals For Human Use (ICH) Integrated Addendum to ICH E6 (R1): Guideline For Good Clinical Practice E6(R2), Current Step 4 version dated 9 November 2016

New Monitoring Requirements *Effective January 2018*

DAIDS contracted monitors will verify the following requirements starting 1st quarter 2018.

Informed Consent Standard Operating Procedure (SOP):

All active DAIDS network sites must develop and implement an informed consent process Standard Operating Procedure (SOP) by **November 1, 2017**. Examples of an IC process SOP are posted on the RSC's website.

Study Specific Delegation of Duties Log:

All DAIDS sites must have a study-specific Delegation of Duties Log (DL), which includes the task/ responsibility of obtaining informed consent, for ALL studies that are still enrolling participants to a given study at their site as of **November 1, 2017**. Study-specific DLs will also be required for ALL new studies, i.e. all DAIDS-approved version 1.0 studies, initiated on or after November 1, 2017, prior to enrolling participants to these studies at the site. DL examples are posted on the RSC's website.

Pennsylvania's State Informed Consent Requirements:

On 20 June 2017, the Pennsylvania Supreme Court issued a decision that significantly impacts the process for obtaining a participant's informed consent (Ref. Shinal v. Toms). Physicians working on clinical trials within the state of Pennsylvania are obliged to discuss the experimental procedure and treatment with the participant. In addition, physicians must complete, sign and date the informed consent form (ICF) during the participant discussion. These requirements are applicable unless the site has obtained a "waiver" from their IRB.

DAIDS/PPD Survey

Thank you for your participation in the DAIDS/PPD Survey. DAIDS OCSO is committed to addressing your concerns and providing information and resources on the areas of interest that were identified in the survey.

Overview of DAIDS monitoring and associated processes.

The Monitoring 101 module is available on the DAIDS LMS (link: https://daidslearningportal.niaid.nih.gov)	During the ACTG and HVTN annual meetings, OCSO MOB presented an overview of DAIDS Monitoring. Similar presentations are planned for 2018.	Upon invitation, OCSO MOB representatives are available by phone for a question and answer session.	We also answered some of your questions in this newsletter.

How to prepare for a monitoring visit.

Review the Work Order (WO) which is provided in the visit confirmation email.	Refer to a previous MOB Newsletter dated July2016, an article by a site personnel titled, "**Tips for Monitoring Visits**" which can be found here

How do I prepare for a Regulatory Inspection?

On our LMS we provide access to an FDA/EMS Inspection Awareness Course which will provide guidance and help prepare for an Inspection (link: https://daidslearningportal.niaid.nih.gov)

Whom do I contact in case of questions or comments regarding a visit report?

Please contact your OCSO PO. His or her name is listed on the Site Monitoring Visit Report and that person also receives the email notification indicating that a report is available for review.

Frequently Asked Questions

How to address citations before the citation is finalized in monitoring report?

- DAIDS has instructed monitors to list all issues noted during a monitoring visit, including the issues that were addressed during the visits
- Sites should discuss these findings with the monitor and provide clarification and/or additional documentation to support their stance
- The site may also contact their OCSO Program Officer (PO) to discuss the finding
- The monitor may also escalate the finding to their PPD manager for input. Monitors have been requested to always provide a reference to a regulation, guideline, DAIDS policy, etc. to support findings in question

What is the communication channel between site, monitor and DAIDS regarding citations?

- The site should always contact their OCSO PO to discuss
- The OCSO PO may request input from the Monitoring Operations Branch (MOB)
- The MOB will research the issue and discuss with PPD. MOB will provide response back to OCSO PO and the PO will provide further explanation to site

Should the review sequence follow the order as listed in the monitor's Work Order?

- PIDs on the Full WO can be reviewed in any order by the monitor
- If a chart is not available for review the monitor will move on to another PID. It will be noted in monitoring report that chart was not available, along with the reason
- If the monitor has time he/she may request additional PIDs for review during the visit, even if not previously included on the Full WO

Happy Holidays

Monitoring Metrics

Year to Date Monitoring Metrics

February, March	1Q2017 (1Q consist of 2 months)
April, May, June	2Q2017
July, August, September	3Q2017

479
Monitoring Visits

1Q2017: 119
2Q2017: 174
3Q2017: 186

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

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

821
Monitoring Trips

1Q2017: 207
2Q2017: 293
3Q2017: 321

6395
Records Reviewed

1Q2017: 1526
2Q2017: 2233
3Q2017: 2636

1631 Pharmacy Assessments

Type of Pharmacy Assessment	1Q2017	2Q2017	3Q2017
Pharmacy Special Assignment	2	0	4
Site-Specific Investigational Pharmacy Assessment	0	6	6
Investigational Pharmacy Inventory and Storage Assessment	194	298	303
Protocol-Specific Investigational Drug Audit	196	301	308
Site Initiation Investigational Pharmacy Assessment	8	3	2
Total	**400**	**608**	**623**

Manager and Monitor Spotlight: South Africa

Bridget Daniell attended B.G. Alexander Nursing College in Johannesburg, South Africa, where she received a Diploma in General Nursing and Midwifery. Nursing years were spent working in private hospitals, mostly in post-natal maternity care units and general surgery wards. In the latter years of Bridget's nursing career, she became a Nursing Unit Manager in a surgical day ward and gastroenterology unit. In 2005, she started working on a part time basis in research as a Research Nurse and Study Co-ordinator. Bridget joined PPD as a Research Assistant in 2006 and went on to become a Clinical Research Associate (CRA) on the DAIDS contract in 2007 and a Clinical Team Manager (CTM) in 2012. As a Manager, she partook in tasks such as resourcing for the EMEA region and more recently she oversees the global resource process for visits and trips on the DAIDS contract as well as having the role of EMEA function lead. Bridget enjoys travelling, learning to play the piano, reading, embroidery and spending time with her family and friends.

Lorraine Africa is a registered nurse who joined PPD in 2010, and has fulfilled the role of Principal CRA since 2015. In this capacity, she has served as a mentor to several new starters at PPD South Africa. Prior to her research career which began in 2001, Lorraine worked in the Managed Health Care Sector as a Case Manager and as an Intensive Care Nurse in the private hospital sector. Her qualifications include diplomas in Midwifery, Psychiatric and Community Health Nursing Science and Intensive care Nursing Science. She holds a B Cur Nursing Degree in Nursing Education and Administration, BA (Hons) degree in Corporate Communication as well a Master of Science degree in Bioethics and Health Law. During her recreational time, she enjoys reading, walking and travelling.

Benny Tjale has a Bachelor of Science Honours Degree from the University of Limpopo. He began working in the pharmaceutical research industry as a Clinical Data Manager in 2009 and later as a CRA in 2013 both at Quintiles. He joined PPD in 2015 as a CRA on the DAIDS contract. Benny is homebased in Hazyview, Mpumalanga, some 30 minutes drive from the Kruger National Park, one of Africa's largest game reserves. Away from the office Benny spends his time with his wife and their 18 month year old baby boy. Benny enjoys reading, sports and listening to music.