MOB Report

Office Of Clinical Site Oversight (OCSO)

National Institute of Allergy and Infectious Diseases (NIAID)

ORGANIZATION INFO

NIAID, DIVISION OF AIDS,
MONITORING OPERATIONS BRANCH

5601 Fishers Lane, Rockville, MD 20852

THE FEDS

Karen Reese

Bariatu Smith and Pia Lohse

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In this issue

What is the Purpose of Monitoring?

(The Straight Talk Version)

By Greg Lessing, PMP- Principle Clinical Team Manager
Pharmaceutical Product Development (PPD)

It could be safely said that nobody enjoys scrutiny in any form. In all aspects of our lives we experience scrutiny for different reasons, and often a misunderstanding or perception of such scrutiny can result in conflict.

According to popular research, misunderstanding is in the top 3 causes of conflict in the workplace, along with non-compliance with rules and policies and personality differences. Personality differences are always present, influenced by a virtually infinite list of qualitative factors and are thus difficult to manage. Misunderstanding and non-compliance can be addressed through communication and education.

So let's shed some light on the monitor's activities at your clinical research site. Why is the monitor scrutinizing your hard work, and why are they asking so many questions?

The primary function of monitoring is to ensure the safety of participants and integrity of data collected. This is done through ensuring compliance with a variety of guidelines, policies and procedures, the most important of which are International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), the United States Code of Federal Regulations, Division of AIDS (DAIDS) policies, Site Standard Operations Procedures (SOPs) and the Clinical Trial Protocol. It is important to note that an auditor will always ensure that the strictest of all policies and procedures impacting a single item are adhered to.

The monitor is essentially there to collaborate with sites to avoid the consequences of a 'bad' regulatory audit. In some countries, legislation states that the right to conduct research and medical licenses can be revoked due to irresponsible or inaccurate research data.

So, you might think 'that's a bit dramatic', but in fact the consequences for questionable research data are far reaching and can impact human life widely and often with traumatic effects. The research we conduct today and the data we collect are often used to determine whether a regimen or drug is safe and effective to be used in actual patients. Our responsibility as researchers to conduct research in compliance with Good Clinical Practices is thus critical and should be taken very seriously.

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You may be thinking 'still a bit dramatic' because we know we are all human, and we make mistakes. It is estimated that wherever inaccuracies or non-compliance arises, that these have been overwhelmingly unintentional. Yet, even an unintentional error could impact the safety and integrity of not only the participants in a clinical trial, but all the patients that might be treated in accordance with that clinical research data.

This is where the monitor comes in. The monitor provides a separate set of independent eyes that have been trained on the required policies and processes to assist sites to find these mostly unintentional errors. It is never the assumption of the monitor that an error has been made with intent. It is also true that a Clinical Research Organization (CRO) delegated with monitoring responsibility could also face major consequences in the event of a regulatory agency audit that resulted in critical findings.

Even the best goal keeper in the world will occasionally be beaten, and so a collaborative relationship between all stakeholders in a research project is highly prized. Sharing a common goal and working together is important to ensure we deliver responsible and valuable medical treatment solutions. Unity is strength!

Priority and Flexibility of the NIAID Clinical Site and Study Monitoring (CSSM) Work Order.

How does it work? Why are the monitors jumping around so much?

Preparation for a monitoring visit begins up to 6 weeks prior to a visit. After the monitor has established planned dates, compilation of the work order begins. During this time, the monitor and monitoring manager review the Comprehensive Record Review Summary Report, which provides an indication of the number of PIDs remaining to meet monitoring requirements for all protocols conducted at a particular site. The Protocol Specific Monitoring Plan (PSMP) (as applicable) is also reviewed for protocols conducted at a particular site, as well as any specific instructions received from the DAIDS.

The NIAID Clinical Research Management System (NCRMS) uses an algorithm to ensure that Patient Identifiers (PIDs) are included in the work order based on protocol risk level, which theoretically should enable the monitor(s) to review the PIDs consecutively from top to bottom. On occasion however, this becomes complicated due to many reasons but mostly due to;

- Sites participating in protocols where specifically trained monitors are required due to network, protocol, therapeutic area or data collection methodology. In these cases and where such a protocol appears lower down on a work order, it is possible that these charts would be requested early in the visit together with charts from other protocols. This is highly likely to occur where several co-monitors are assigned to a monitoring visit at a site conducting multiple protocols.

- In some protocols PIDs are identified as priority for review. For example participants with Grade 2 or higher adverse events, pregnancies, or have had medication stopped for any reason. In these cases, the system is not designed to customize to this extent and monitors will need to 'pick and choose' from the list of PIDs in order to meet these requirements.

- Certain protocols might not populate on the work order due to the risk ranking being low by comparison to other protocols and the monitor may have received specific instructions to custom add those protocols and PIDs.

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What is the Purpose of Monitoring? *continued*

An army of monitors has arrived at my site,

why?

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Co-monitors are assigned to monitoring visits based on a number of factors. Factors considered include, but are not limited to;

- Number of networks and protocols, and risk ranking of protocols conducted at a site.
- Enrollment performance and the number of PIDs remaining to meet monitoring requirements.
- Trends in the number of PIDs remaining to meet monitoring requirements in relation to monitoring resources assigned during previous site visits. For example, where 3 monitors have been traditionally assigned but no progress is made toward meeting monitoring goals, a decision is made to add additional monitors.
- Number of assessments, including pharmacy, regulatory, lab specimen verifications and special assignments.
- Complexity of assessments. For example, in some networks there is a substantial difference in complexity of pharmacy assessments.
- Site visit frequency. Site visit frequencies for the NIAID CSSM contract includes annual, bi-annual, 3 times annually, quarterly and enhanced. For an enhanced site visit frequency, more monitors will be assigned and occasionally sites prefer to have all those monitors at one visit rather than fewer monitors at two separate visits per quarter.
- Number of follow-up or quality issues noted at the site.

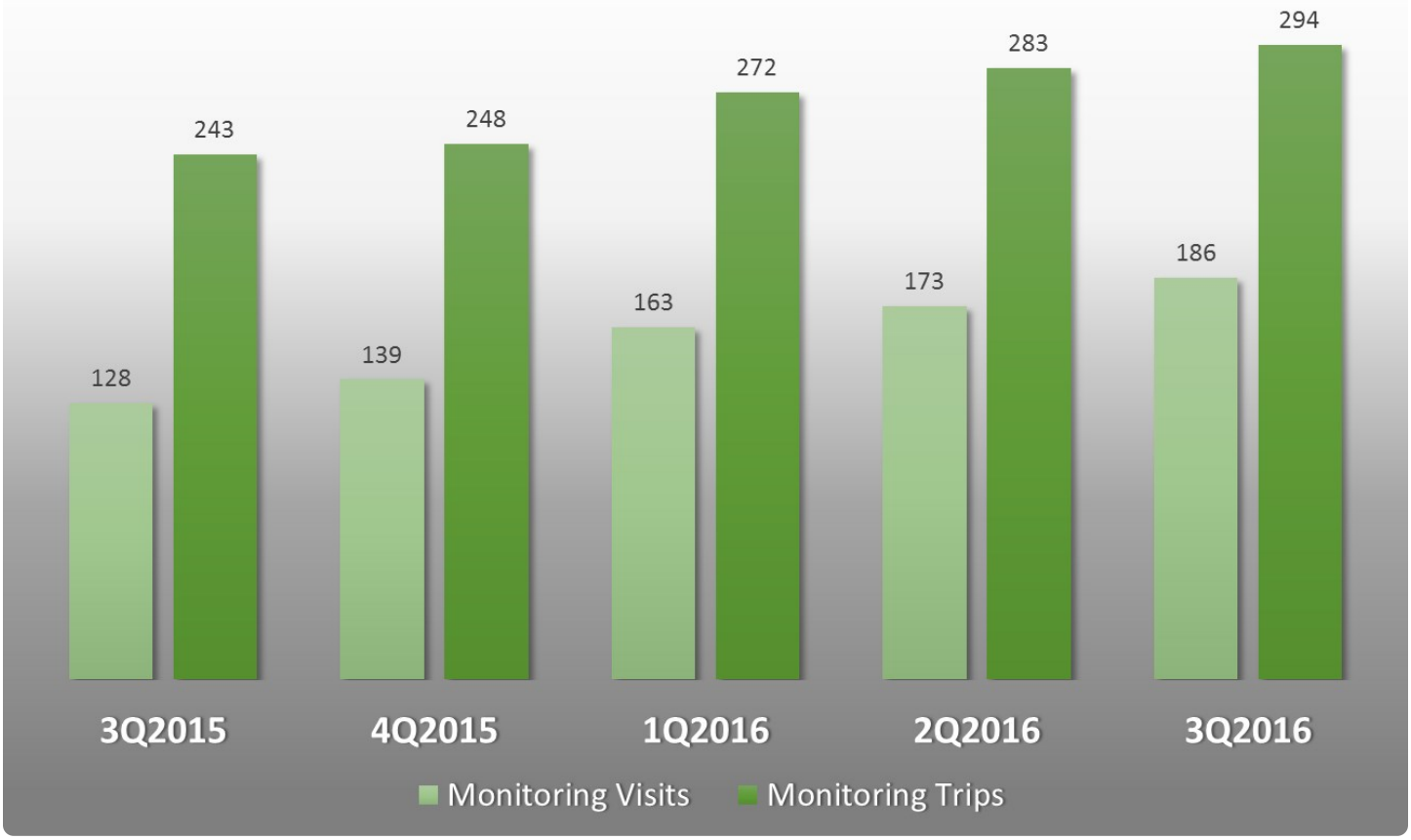
That said, it is understood that the attendance of several monitors at a site visit can place a strain on site staff during a monitoring visit. The number of co-monitors in attendance is communicated to sites via the Pre-Visit Letter released to sites 21 days prior to a site visit. Sites are encouraged to discuss any concerns they have regarding the number of monitors attending site visits with their DAIDS Program Officer in real time so that contingency plans can be made. Wherever possible, an optional approach can be considered to ensure the monitoring team does not overwhelm site accommodations.

Monitoring Metrics

Overview of Monitoring Visits and Trips to Date

Monitoring Trips and Visits

Over the past 5 quarters, PPD has conducted a total of 789 Monitoring Visits and 1,340 Monitoring Trips



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.

Record Review 2015

(Running Total)

1Q	2Q	3Q	4Q
2,102	4,356	6,296	8,812

Record Review 2016

(Running Total)

1Q	2Q	3Q	4Q
2,197	4,268	6,270	?

Pharmacy Assessment 2015

(Running Total)

1Q	2Q	3Q	4Q
351	782	1,162	1,602

Pharmacy Assessment 2016

(Running Total)

1Q	2Q	3Q	4Q
457	1,001	1,542	?

Regulations, Policies & SOPs

ICH E6: Good Clinical Practice Finalized Addendum

Since ICH E6 was implemented in 1996 the development of medicine has become globalized, the location of clinical trials has expanded, clinical trials have become more complex, and there have been tremendous advancements in technology. Modernizing the ICH E6 via an addendum was essential 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 data integrity.

The recent update to the guidance is being implemented in an addendum integrated format. The addendum text follows the original wording for a given section.

The ICH E6: Good Clinical Practice Finalized Integrated Addendum and a 20 minute recorded presentation outlining the addendum contents can be accessed on the ICH E6 web page.

High Level Summary of Addendum	
Introduction	• Describes rational of the addendum and the addendum objective has been incorporated.
Glossary (Section 1)	• Definitions for certified copy, monitoring plan, monitoring report, and validation of computerized systems have been added or expanded.
GCP Principles (Section 2)	• Clarifies that this principle applies to all records (paper or electronic).
Investigator Responsibilities (Section 4)	• Topics addressed in this section include: Supervision of tasks delegated, ensure qualification of any party performing study tasks and implement procedures to ensure the integrity of study and data.
Sponsor Responsibilities (Section 5)	• Topics addressed in this section include: Quality management systems, focus on essential trial activities, ensure methods used to assure and control quality of trial is proportionate to risks, avoid unnecessary complexity, use risk based approach to quality management, oversight of trial, approve subcontracting by CRO, use of computerized systems including training, follow-up of non-compliance, risk based, centralized and on-site approach to monitoring.
Essential Documents (Section 8)	• Topics addressed in this section include: Record maintenance, additional documentation for trial master file depending on trial activities, investigator control of Case Report Form (CRF) data, certified copies, investigator control of essential documents.

Frequently Asked Questions

The following are answers to questions that have been asked at network meetings .

How are protocols and PIDs selected for the Work Order?

The NCRMS has an automated algorithm that randomly selects protocols and PIDs based on the Protocol Risk Rank (Risk Level 1, 2, or 3) and last review date. Additionally, Protocols and PIDs can be custom added to the Work Order based on requirements to meet protocol monitoring goals set by the DAIDS.

When can sites gain access to the unannounced PID list?

Sites can access the unannounced PID list at midnight Eastern Standard Time (EST) on the visit start date.

Are monitors permitted to ask for anything on the work order (Announced vs. Unannounced) as soon as they arrive on site?

Yes, however if the records for the PIDs on the announced work order are made available upon the monitor's arrival they can start reviewing those records while the site retrieves the records for the unannounced PIDs.

Why monitors cannot conduct extensive training for Site Personnel?

While the PPD monitors cannot conduct extensive trainings during a monitoring visit, they can provide guidance and training points based on deficiencies identified during a monitoring visit. DAIDS as the sponsor has a regulatory obligation to monitor the studies conducted at the site and the review of participant's records along with pharmacy assessments and regulatory file reviews is time consuming and must take precedence. DAIDS has also not tasked the monitors to provide extensive training during a monitoring visit. There are multiple training modules on the DAIDS Learning Portal which can be accessed at daidslearningportal.com. Training modules available at the DAIDS Learning Management System (LMS) include but are not limited to GCP, source documentation, Clinical Quality Management, DAIDS policies etc.

When did completed Financial Disclosure Forms at the beginning and end of a DAIDS sponsored and/or supported IND study become effective?

Title 21 Code of Federal Regulations (CFR) 54.4 has been a regulatory requirement for a while. Based on the requirements outlined in this CFR for IND sponsors, DAIDS has developed a process to ensure that financial disclosure forms/statements are completed by all investigators listed on all Form FDA 1572s for any DAIDS sponsored and/or supported study where DAIDS is the IND holder.

This process became effective July 1, 2014, and this action is not retrospective to IND studies that started prior to July 1, 2014. During regulatory reviews monitors will verify that every investigator listed on all Form FDA 1572s has accurately completed and signed either the DAIDS approved network financial disclosure form or the drug company-specific financial disclosure form/statement for that clinical trial.

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Manager and Monitor Spotlight: North America

Lisa Gilligan received her Bachelor of Science Degree in Clinical Research along with a minor in Psychology from University of North Carolina Wilmington. She has been at PPD since 2008 and began her career in the clinical administration group. During her time at PPD Lisa has worked on Phase II – Phase IV studies as a Clinical Research Associate (CRA) and gained experience in digestive, circulatory and infectious disease studies. Lisa joined the government group as a Clinical Team Manager (CTM) in July 2016. During her free time she enjoys being with her family. She also enjoys the outdoors especially boating and fishing.

Lori Karpinecz has a Bachelor's and Master's Degree in Art History but found her career in research. She worked in many different research roles including Clinical Research Coordinator, Institutional Review Board (IRB) Coordinator, and CRA prior to joining PPD in March 2016 as a CRA. Lori is a runner and serves as both a coach and co-organizer for a local marathon/half marathon training program in her hometown of Cleveland, Ohio.

Karen Baker has a Degree in Nursing from The College of Health Sciences in Roanoke, VA. She worked as a critical care nurse in the Cardiac/Open Heart Intensive Care Unit and Cath lab for 18 years prior to working as a research nurse/ coordinator in a wide verity of disciplines. She worked as a research coordinator in the Infectious Disease Department and received certification from ACRP as a Certified Clinical Research Coordinator (CCRC). Karen came to PPD as a CRA on the CSSM contract. She enjoys spending time with her family and traveling.