MOB Report

Office Of Clinical Site Oversight (OCSO)

National Institute of Allergy and Infectious Diseases (NIAID)

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14th Edition | July 2020

In this issue

Benefits of Remote Monitoring

By: Stacy David, Clinical Team Manager and Elandre Kok, Clinical Research Associate

To maintain Sponsor oversight responsibilities of clinical trials during the COVID-19 public health emergency, the DAIDS continues to implement remote monitoring for sites where on-site monitoring visits are not possible. Remote monitoring consists of a review of key regulatory documentation and electronic Case Report Forms (eCRFs) in the Electronic Data Capture (EDC) databases. This includes all DAIDS EDC modalities including Medidata RAVE, OpenClinica and EMMES EDC. Monitors review documents including: Protocol Registration and IRB/EC approval documents, temperature logs for pharmacies and labs, eCRFs to identify protocol deviations and Serious Adverse Events (SAEs), Delegation of Duties Log and training logs. When feasible, monitors also conduct calls to discuss key findings from the remote monitoring review with key personnel including CRS Leader, CRS Coordinator and Pharmacist of Record (as applicable).

Remote monitoring is highly beneficial in maintaining oversight of clinical sites and ensuring oversight of safety of trial participants, as well as maintaining compliance with Good Clinical Practice (GCP) and data integrity. If planned on-site monitoring visits are not possible due to various restrictions, Sponsors will optimize use of central and remote monitoring programs.

An inherent advantage of remote monitoring is enabling the monitoring teams to typically review a greater portion of entries in EDC databases per unit time in comparison to a typical on-site monitoring visit. This has the potential to more readily allow identification of trends in study data that will be a focus of subsequent monitoring visits. Furthermore it enables rapid deployment of monitoring resources to review data for protocols with higher risk levels and sites with a larger monitoring workload, allowing a comparatively larger monitoring team to focus their attention on the tasks at hand. In keeping with enabling rapid deployment of monitoring resources and the vanishing of geographical boundaries when remote monitoring tasks are undertaken, monitors are able to cover work from across the globe and spanning multiple time zones to bolster increases in productivity, albeit with the remote modality.

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Benefits of Remote Monitoring Continued

Given a possible future scenario whereby sites will allow smaller numbers of visitors upon the systematic easing of restrictions imposed due to the COVID-19 public health emergency, a hybrid approach to monitoring may be the enabler of overcoming the immediate challenges posed. The monitors will perform a remote review of the study data for trends and discrepancies prior to the on-site monitoring visit, so that the limited time on-site can be focused on significant findings from the remote review.

Upon returning to a more traditional way of monitoring beyond the COVID-19 public health emergency, remote monitoring tasks and the benefits offered may continue to serve its purpose in preparing for on-site visits and aid in maintaining adequate oversight of clinical research and maintaining the rights and safety of trial participants whilst maintaining compliance with GCP. Implementing and refining our remote monitoring processes now will allow DAIDS to be prepared in the future should a need arise where monitors are unable to complete on-site monitoring visits. The remote monitoring processes could be used in other situations such as weather-related issues or political instability.

Reference: FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020, updated June 3, 2020

Mock Inspection Audit Preparation Tips

By: Nkhafwire Mkandawire, MSc PH, Senior Clinical Team Manager- PPD

An audit is defined as a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, the Sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements (ICH-GCP 1.6).

Oftentimes before a Regulatory Agency inspection is conducted, a mock inspection audit is requested by the Sponsor. Mock inspection audits are simulations of actual inspections and are conducted to assess compliance with ICH-GCP and other applicable regulations and guidelines. Mock inspection audits in other words are trial runs for the main Regulatory Agency inspection. Sites should take mock inspection audits seriously and provide all the necessary support to the auditors, and prepare for the mock inspection audits in same way they would prepare for a Regulatory Agency inspection.

Why Mock Inspection Audits are Important

Mock inspection audits help in identifying gaps in a site's preparedness for a Regulatory Agency inspection. It can also build site confidence as it provides necessary feedback through the mock inspection audit report, especially when there are no findings. The feedback from the mock

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Mock Inspection Audit Preparation Tips Continued

inspection audit will help sites develop process improvement plans. It also provides opportunities for training in areas where weaknesses have been identified. Mock inspection audits will also help the team perform root cause analysis and formulate preventive and corrective action plans for significant findings that have been detected.

Preparing for a Mock Inspection Audit

Sites must always adhere to **all** ICH-GCP guidelines and they should be "audit ready" at all times. The basic principle for sites is to ensure that the reported clinical trial data are attributable, legible, contemporaneous, original, accurate and complete. In addition to this basic principle, sites must ensure that they are adherent to:

- FDA and other Regulatory Agency statutes/guidelines
- Study Protocol, Manual of Operations, and other study-specific documents
- Applicable SOPs and Sponsor Directives

Sites must also ensure that the rights, safety and well-being of study participants are **properly** protected. This requires sites to continuously review and identify training needs within the study teams.

Various mock inspection audits have been conducted by the DAIDS at different sites in the period between Jan/2018 to Mar/2020. These audits have resulted in a number of major and critical findings as summarized in Table 1.

Per data in Table 1 , top findings from the mock inspection audits were noted in the following three categories; 1) Site Staff Qualifications, Resources and Agreements; 2) Investigational Product; and 3) Informed Consent.

Table 1: Number of issues (Major and Critical) cited per category for DAIDS sponsored Mock Inspection Audits from Jan/2018 through Mar/2020

Category of Finding	Number of Times Issue Cited	Percentage (%) of Total
Site Staff Qualifications, Resources and Agreements	48	26.4 %
Investigational Product	32	17.6%
Informed Consent	26	14.3%
Quality Management	18	9.9%
Data Management	15	8.2%
Essential Documents	12	6.6%
Inadequate Documentation of IRB Review and Approval	11	6.0%
Safety Reporting	9	4.9%
Protocol Compliance	9	4.9%
Trial Specific Issues	2	1.1%

Based on the specific issues noted in the three categories mentioned above, the following are some tips and action plans which can be undertaken to prevent these findings. The most frequent incidences noted are further expanded below.

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Mock Inspection Audit Preparation Tips

1 Site Staff Qualifications, Resources and Agreements

Per ICH GCP 2.8, 4.2.4, all individuals involved in conducting a trial should be qualified by experience, education and training to conduct their respective tasks, and per FDA guidance, the Investigator should ensure adequate study-related training for all staff. This includes training on the Protocol and other documents and training materials provided by the Sponsor. Sites should ensure evidence of staff training prior to performing any study-related task is available and on file. Based on the mock inspection audit reports, it was evident at some sites that staff training records were not available on file at the time of audits.

Further, ICH GCP 4.1.5 states that it is the Investigator's obligation to maintain a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related activities. Hence Study Coordinators and Quality Assurance Staff must not assign tasks to staff or complete the Delegation of Duties (DoD) log without proper delegation from the Investigator. The issue was identified at several sites during mock inspection audits. The Investigator should ensure that the documentation of delegated tasks is accurate and complete.

ICH-GCP 4.9.6, 8.2.6, requires the Financial aspects of the trial to be documented in an agreement between the Sponsor and the Investigator or the Institution.

The FDA also requires that all Clinical Investigators provide the Sponsor with accurate Financial information such that a complete and accurate certification or disclosure statement can be submitted and that prompt updates are provided in the event of any changes; 21 CFR 54, FDA Guidance: Financial Disclosure by Clinical Investigators (Feb 2013).

However, it was noted at several sites during mock inspection audits that the records were not up to date, especially where there had been a change of Investigators. Therefore, Investigators should ensure that all Financial agreements are on file and reflect current staff.

2 Investigational Product (IP)

Per ICH-GCP 4.6.3, 5.15, 5.14 and 21 CFR 312.62. The Investigator or a pharmacist or other appropriate individual, who is designated by the Investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the Sponsor or alternative disposition of unused product(s). Both the Sponsor and the Investigator should ensure that the IP is transported to the Investigational Pharmacy per storage requirements of the IP. Sites should also ensure documentation of chain of custody of IP.

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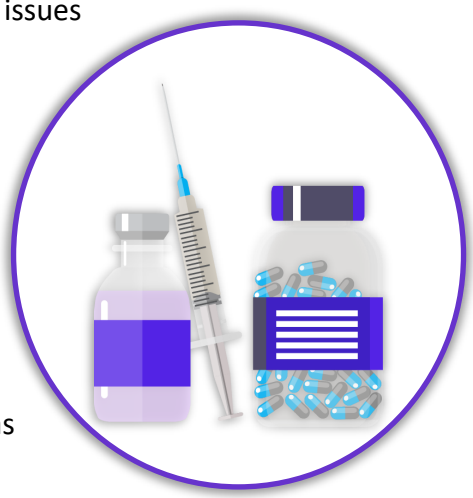
Mock Audit Preparation Tips Continued

Per review of some of the mock inspection audit reports, the following IP issues were noted:



- Signatures and dates on study transfer documents were missing, especially from the central pharmacies to the study clinics
- Product delivery and inventory records were not maintained appropriately
- Study products had not always been documented on the accountability records at the time of each dispensing as required by Pharmaceutical Affairs Branch (PAB) guidelines
- Temperature monitoring of the study product storage rooms, refrigerators and freezers had not been performed and/or documented as required by PAB guidelines
- Incorrect doses and treatments dispensed to study participants

Pharmacist of Records (PoRs) should therefore put in place adequate quality management procedures in the pharmacy to assure good pharmacy practices and adherence to all relevant pharmacy instructions. PAB guidelines Section B1.16 and ICH GCP 2.13 state "systems with procedures that assure the quality of every aspect of the trial should be implemented."

3 Informed Consent

Per ICH GCP 4.8, 21 CFR part 50.27: The Investigator in obtaining and documenting informed consent, should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

However, per review of some of the mock inspection audit reports, the following main informed consent issues were noted:

- Informed consent documents not complete or attributable.
- Informed consent documentation not completed contemporaneously.
- Correct version of the Informed Consent not always used.

Also, Investigators not ensuring that participants are re-consented to updated versions of the informed consent form (ICF) in a timely manner was another issue cited. Per DAIDS Protocol Registration Manual, amendments including any revised site-specific ICFs must be implemented immediately. Participants should be re-consented without delay no later than 5 business days, usually at the participant's next scheduled study visit.

Careful attention to the information provided above will assist sites with preparation for regulatory agency inspections and maintaining continual inspection readiness.

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

	2019	2020
1Q	128	85
2Q	187	191
3Q	182	TBD
4Q	229	TBD
Total	**726**	**276**

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

Monitoring Trips

	2019	2020
1Q	232	189
2Q	397	360
3Q	419	TBD
4Q	502	TBD
Total	**1550**	**549**

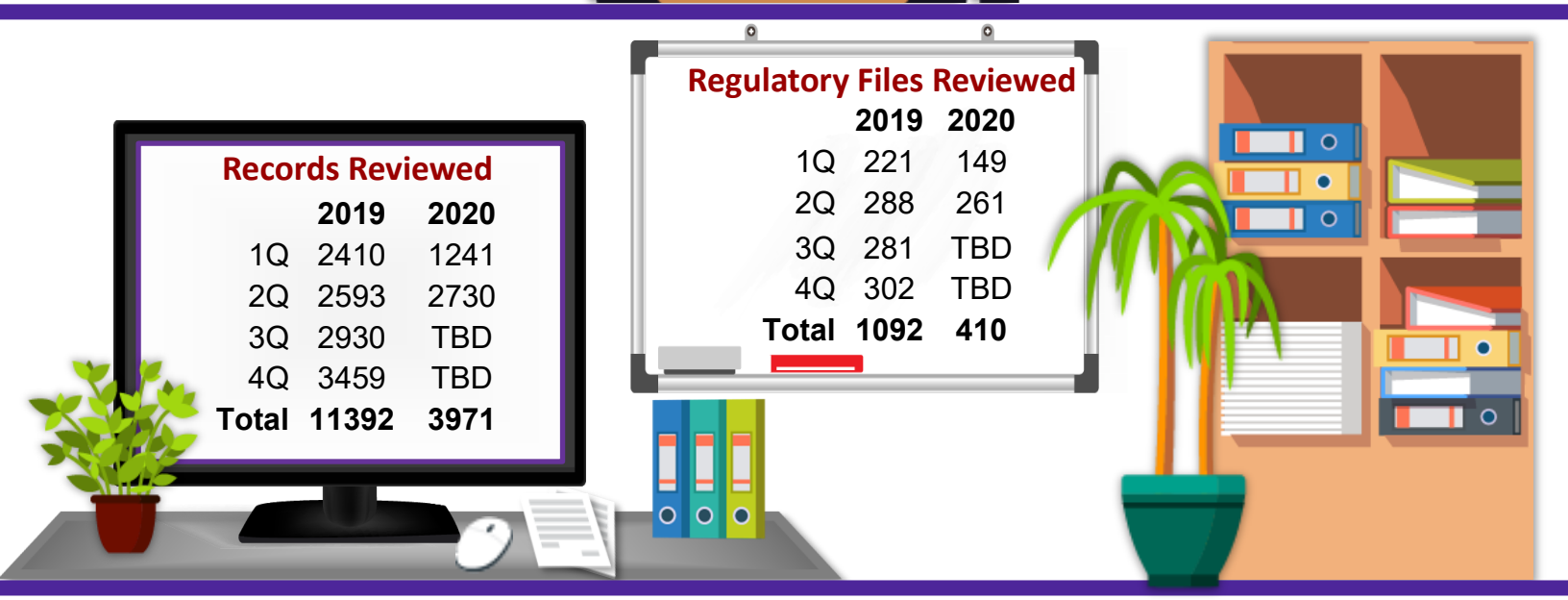
Monitoring Trips: Includes the total number of monitors traveling to a site to conduct a site monitoring visit.

Records Reviewed

	2019	2020
1Q	2410	1241
2Q	2593	2730
3Q	2930	TBD
4Q	3459	TBD
Total	**11392**	**3971**

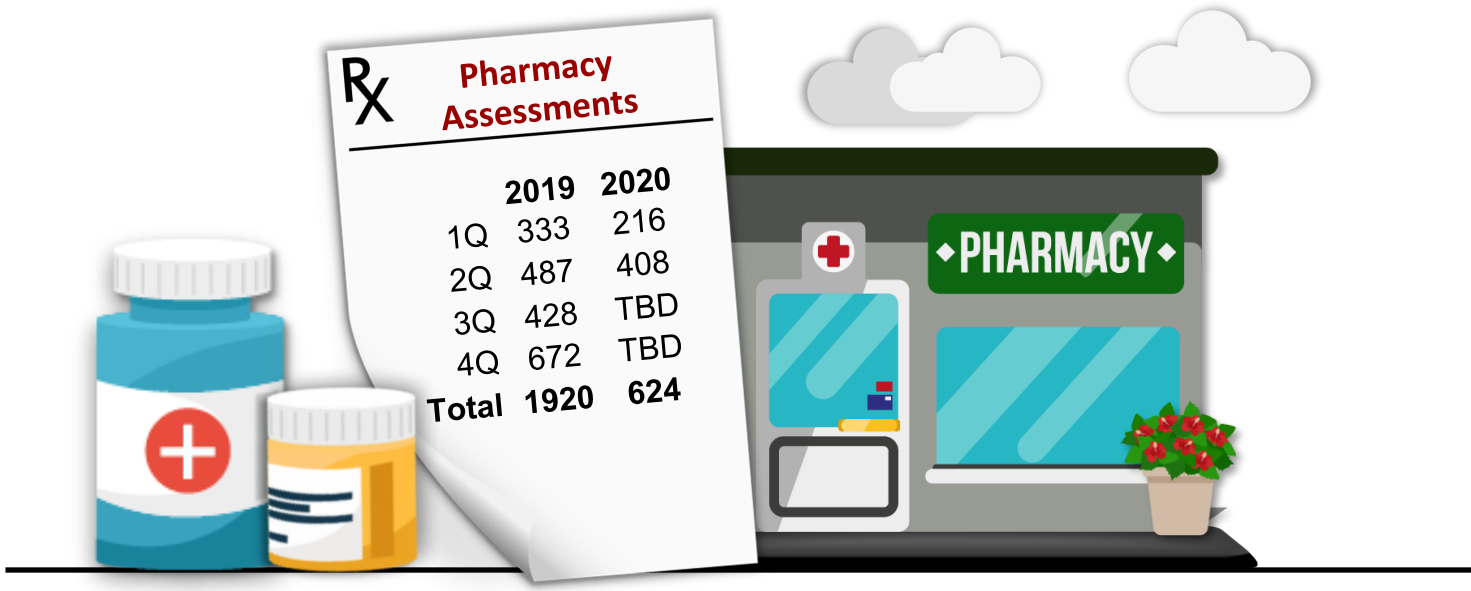
Regulatory Files Reviewed

	2019	2020
1Q	221	149
2Q	288	261
3Q	281	TBD
4Q	302	TBD
Total	**1092**	**410**



Pharmacy Assessments

	2019	2020
1Q	333	216
2Q	487	408
3Q	428	TBD
4Q	672	TBD
Total	**1920**	**624**



Spotlight
Monitoring During Coronavirus (COVID-19) Pandemic

Mustapha Kamara and Kamarin Mam were our first monitors in North America to conduct an on-site visit during the COVID-19 Pandemic. They conducted the visit together in Houston, TX. Learn a little more about them and their experience:

Mustapha Kamara

Mustapha holds a Bachelor of Science in Health Science from Stephen F. Austin State University and has nearly completed his master's degree in Public Health with a concentration in Health Management & Policy. He has worked in the clinical research industry for about five years - three years with PPD and within infectious diseases and two years in oncology. He began as a coordinator whose role was to ensure data accuracy and patient safety, much like a remote site monitor. At that time, he worked on various government sponsored cancer prevention trials.

In his free time, he loves spending his time with family. He is an avid Eagles and Sixers fan and loves to listen to music. He likes to travel and experience new food and cultures. He is passionate about Public Health and is very interested in helping to make a positive difference in any capacity.

When asked about what it was like being one of the first monitors to conduct an on-site visit during the Coronavirus Disease 2019 (COVID-19) pandemic this is what he had to say:

I think it is safe to say that dealing with the COVID-19 pandemic has been challenging. Irrespective of gender, ethnicity, age, geographic location, or socioeconomic status we have all been tasked with defeating an invisible enemy that has threatened public health and claimed the lives of so many. Whether mandated or voluntarily we have altered our lives from the norm and have implemented preventative measures such as social distancing or wearing face masks. No matter how much you try to avoid COVID-19 it is ubiquitous. After being on lockdown for about two months due to the pandemic, it felt good to be able to do something "normal" again. Given the circumstances, these were the most notable changes in conducting an on-site visit: increased security (every door required badge access), almost everyone wore a face mask, and debriefing was conducted on-site, but via Zoom rather than face to face. I live in Houston and was able to drive to the site and home with no issues. Although I was able to drive, I'm very interested to see how air travel will be affected once restrictions are lifted especially if COVID-19 is not adequately mitigated.

Spotlight
Monitoring During Coronavirus (COVID-19) Pandemic

Kamarin Mam

Kamarin holds a Bachelor of Arts in Communications with a minor in psychology from the University of Houston. After college, he worked as a phlebotomist in a plasma center familiarizing himself in the biopharmaceutical industry. From there, he moved to PPD as a Project Assistant where he was eventually accepted into the CRA Academy. He has been with PPD for over 5 years now, but says it feels more like 10. In his free time, Kamarin likes to be outdoors playing sports or camping.

Being one of the first monitors to return to an on-site visit since COVID-19, he was asked to share his experience:

My first on-site visit since COVID-19 was to Houston, TX. Having grown up in Houston, the drive in from Austin felt more like a trip "home" than work. I even stopped by my parents' place to load up on food and water and sanitizing supplies that may prove useful in this landscape.

The hotel (Marriott Medical Center) was a ghost town. Outside of a few people in the lobby, I never saw anyone else, not even on the elevators. Once at the site, it was business as usual. The coordinators would bring binders, we'd review them, bring them back and ask for more.

It's unsettling to say the only normal part of the trip was reviewing PIDs.

I advise other monitors conducting on-site visits at this time to drive, if you can. You can load your car with cleaning supplies, food (to avoid having to go out), and as big of a suitcase as you need. I wouldn't call myself a germaphobe, but I did Lysol everything in my hotel room (including myself) after returning from the site. I think if you're cautious and wear your PPE, on-site visits won't be so daunting.

Due to the COVID-19 public health emergency, on-site monitoring visits were suspended through May 15, 2020. Remote monitoring visits were initiated and are continuing, to include remote regulatory file review and review of CRFs in Medidata or other EDC systems. DAIDS is pursuing options for implementation of remote Source Data Verification with an initial focus on several priority protocols.