19th Edition
December 2022

MOB Report

OFFICE OF CLINICAL SITE OVERSIGHT

Regulatory File Reminders

A Regulatory File refers to the essential documentation related to the conduct of the research study at your site (also known as Regulatory Binder, Investigator Site File). Per ICH GCP, Essential Documents are "those documents that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced." Regulatory files are typically organized by sections following ICH GCP Section 8.0: Essential Documents, but organization should be tailored to meet your site's needs of the protocol at your institution. The organization and contents of the regulatory file should be easy to understand by someone who is not familiar with the study.

With complex and numerous documents generated throughout the course of a study, keeping the Regulatory File current and up to date is an ongoing challenge. The Regulatory File should be stored in a safe and secure location, and made accessible to regulatory authorities, IRB/EC, institution, and monitors to enable evaluation of study conduct and compliance to GCP and applicable regulatory requirements. Monitors on the NIAID Clinical Site Monitoring (NCSM) contract conduct routine Regulatory File Reviews and a more in-depth Annual Regulatory File Review.

Although the name Regulatory File may imply a physical binder with hard-copy documents, investigators should determine the most appropriate method to meet recordkeeping obligations. Some sites use a hybrid version where hardcopy documents are signed, scanned and uploaded to an electronic file management system. In a hybrid system, the physical binder should include a placeholder noting all documents stored in electronic format only, with the electronic pathway to each item's location.

Fully electronic regulatory binder systems need to be 21 CFR part 11 compliant. Electronic regulatory binder platforms such as Advarra eReg, Complion and Veeva Site Vault, provide a way of managing a large volume of documents in an efficient fashion. They can help in tracking documents, reducing physical storage requirements, providing secure record retention, and permitting remote access for monitoring visits and audits.

NIH National Institute of Allergy and Infectious Diseases

A Brief Review of Recent Significant Events

A total of 58 significant events were reported from monitoring visits for the second quarter of 2022 (April – June). The top 2 major categories of significant events were **informed consent violations** and **IRB/EC lapse approvals**, constituting 67% of the reported significant events for the quarter.

Table 1: 2Q2022: Number of reported Significant Events

Significant Events	Number	Percentage (%)
Informed Consent and Subsequent Consent violations	29	50
IRB/EC lapses	10	17
Enrollment violations	4	7
Pharmacy findings	3	5
Other (related to participant safety or site procedures that impact data)	12	21
Total	58	100

Based on a review of the underlying reasons for these top two significant event categories, we suggest the following tips to reduce their occurrence at your site:

Informed Consent Violations:

- All staff conducting consent should be adequately trained on the requirements for obtaining informed consent.
- Initial and subsequent consenting should be conducted within the timeframe specified in the Protocol Registration Manual, Network MOP, or Site SOP whichever one is earlier.
- Use a checklist as a quality control measure to prevent and/or decrease errors during each instance of informed consent administration for initial and subsequent consenting:
    - Is reconsenting required with a subsequent ICF approved by the IRB/EC?
    - Has the process of obtaining informed consent been adequately recorded in the source notes?
    - Has the delegation of duties been appropriately documented for staff obtaining consent?
    - Are the study staff or the sub-investigators obtaining consent listed on the Form FDA 1572?
    - Is the most recent approved version of the consent document being used?
    - Are all pages of the consent document present?
    - Have all required fields been completed throughout the consent document?
    - Has the participant been offered a signed copy, and the original consent document retained at the site?
    - Has someone at the site reviewed the checklist before the participant leaves the clinic?
    - Have all dates on the ICF been confirmed to be complete, and correct?

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A Brief Review of Recent Significant Events *Continued*

Lapse in IRB/EC Approval:

Several reasons are responsible for the reported lapse in IRB/EC approval, but the resulting outcome is the same, which is inadvertent continuation of the study without IRB/EC approval. To avoid these lapses, we suggest the following tips and guidelines:

- Create a tracker for all ongoing studies that includes the dates of initial review approval, approval expiration, continuing review, study document submission deadline, and the IRB/EC review meeting.
- Understand the time requirements for the multi-step IRB/EC review and approval process to allow for sufficient time to complete the review process
- Be sure of the final study approval date - IRB/EC versus Country approval. If in doubt, confirm with your institution and site monitor.
- Determine the timing of the first and subsequent continuing review dates based on the initial review approval date. Especially if your site IRB/EC has the policy to maintain a fixed date for the expiration of annual approvals/renewals.
- Set up auto reminders for key dates to ensure IRB/EC approval is obtained prior to the expiration date (the DAIDS Protocol Registration System is set to automatically send out email notifications to designated site staff of IRB/EC renewals starting 90 days out from expiration)

Continuing Review Guidance

Additional information on IRB continuing review of research can be accessed here: Continuing Review Guidance (2010) | HHS.gov

NCSM Moving with the Times

By: Dore Shinners, Clinical Team Manager
PPD, part of Thermo Fisher Scientific

With the easing of COVID-19 public health and travel restrictions in most countries, Clinical Research Associates (CRAs) have appreciated the ability to resume onsite Site Monitoring Visits and conduct an in-person review of regulatory documents and pharmacy assessments. However, performing one hundred percent of the review onsite, suddenly seemed very time-consuming and CRAs were left with a slight feeling of limitation.

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NCSM Moving with the Times Continued

After being thrown into the deep end in March 2020 and quickly pivoting to a remote review of minimal scope of regulatory and pharmacy documents, we soon realized the potential value of remote review in the future, pending the resources and approvals required to expand the scope. Being able to do remote, partial review of documents prior to an onsite regulatory and/or pharmacy assessment has proven to be very beneficial to both the CRAs and the site staff. Per the NIAID Clinical Site Monitoring (NCSM) traditional way of continuously assessing our efficiencies and pushing our boundaries, this was no exception. The initial "emergency" remote review of regulatory and pharmacy documents rolled into the next logical step of assessing if this could bring value to our contract going forward. If so, how could we incorporate it into our pre-COVID-19 assessment process to increase efficiency?

During the third quarter progress review meeting between PPD (part of Thermo Fisher), and DAIDS, PPD shared presentations to outline the benefits and challenges surrounding the idea of incorporating remote review as a standard into the Monitoring Plans. Bearing in mind that remote verification is limited at times due to a variety of factors (approvals not being in place, limitations to the shared platforms and nature of required review as in the case of inventory checks during pharmacy assessments), PPD developed the idea of a hybrid assessment. A hybrid assessment would allow sites to share documents on a secure shared platform for CRAs to review before the Site Monitoring Visit, and then physically verify other information during the onsite Site Monitoring Visit. The total time spent by CRAs on performing pharmacy and regulatory assessments would likely not be reduced, however the time spent in the pharmacy or at the site's regulatory office is reduced, timeframe for sites to respond to questions/queries are expanded and Site Monitoring Visits are experienced as much less invasive by site staff and less time consuming for CRAs.

A survey conducted by PPD, Part of Thermo Fisher Scientific, in Sep/2022 revealed the following site preferences.

Region	100% onsite	75% onsite and 25% remote	50% onsite and 50% remote	25% onsite and 75% remote	Total
APAC	8	2	0	1	11
EMEA	29	8	4	0	41
LA	4	2	1	0	7
NA	75	8	8	7	98
Total	116	20	13	8	157

Additional feedback from sites preferring the 100% onsite option included that they experienced it being time consuming to upload documents and extra resources (staff) are needed to do this. In general, sites felt that communication is better with face-to-face meetings and facilitates the resolution of issues in real time.

DAIDS will continue to consider feedback from the sites including benefits and challenges to remote review, balancing this with the efficiencies experienced by the CRAs. Entering a new year, DAIDS and PPD, part of Thermo Fisher Scientific, commit to continuous evaluation of efficient and effective new monitoring strategies.

Updates to the Monitoring 101 training course on the DAIDS Learning Portal

The revised module is now live! Clinical Research Site staff may access the updated module which provides an overview of the requirements of monitoring per ICH GCP (ICH E6). Topics include DAIDS' risk-based approach to monitoring and activities involved in monitoring visits. Several updates to the training module have been made to reflect current monitoring directives and processes.

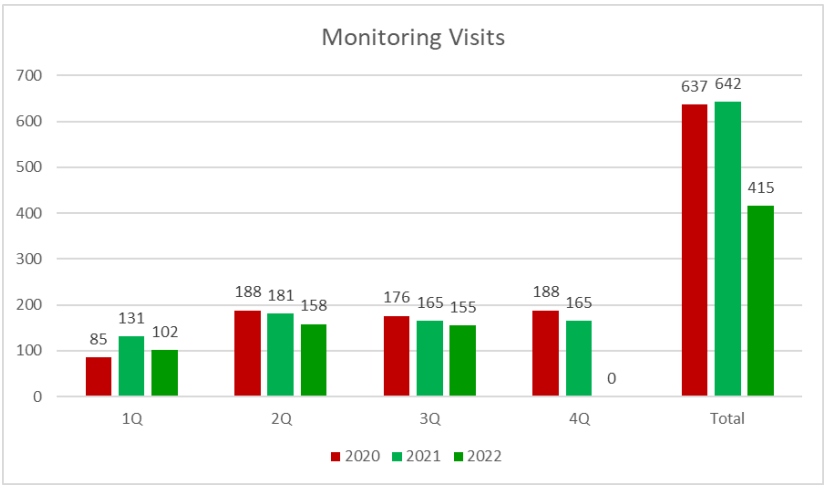
Monitoring Metrics

Year to Date Monitoring Metrics

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

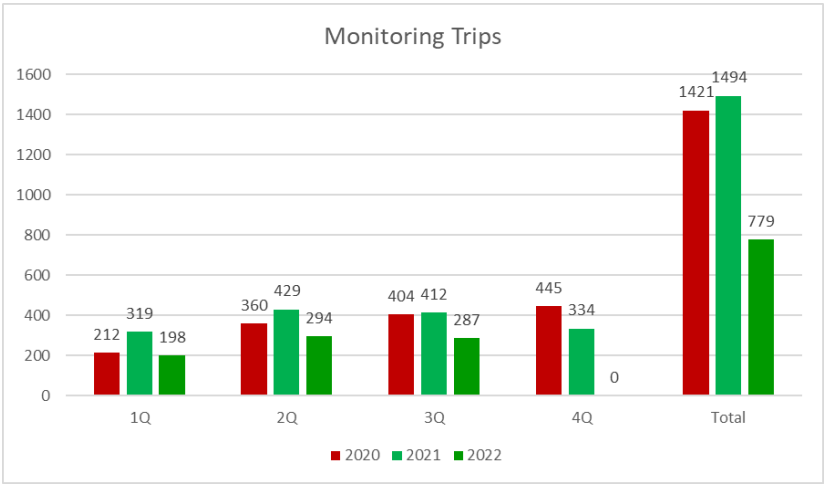
Monitoring Visits

Any time monitoring is conducted during a site visit.

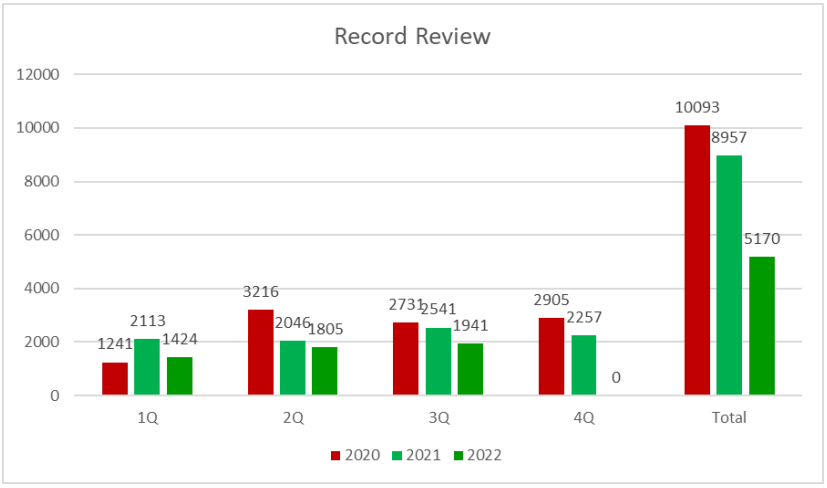


Monitoring Trips

Includes the total number of monitors conducting monitoring during a site visit.



Records Reviewed



Monitoring Metrics

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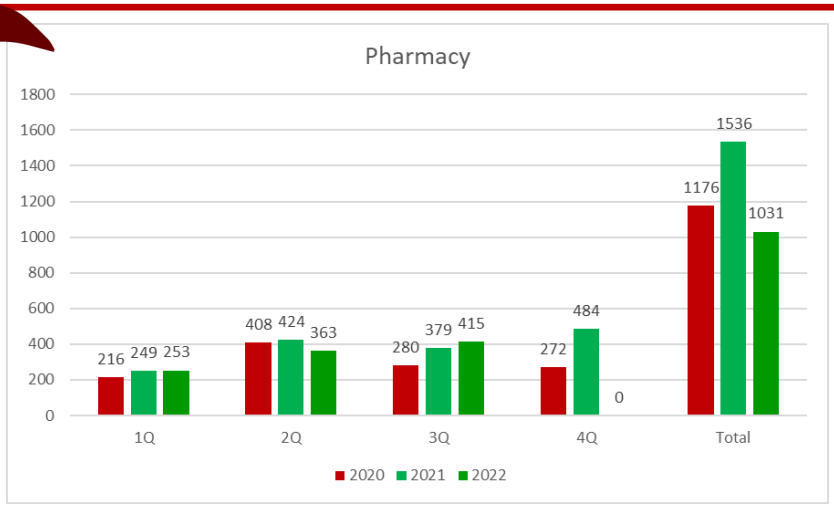
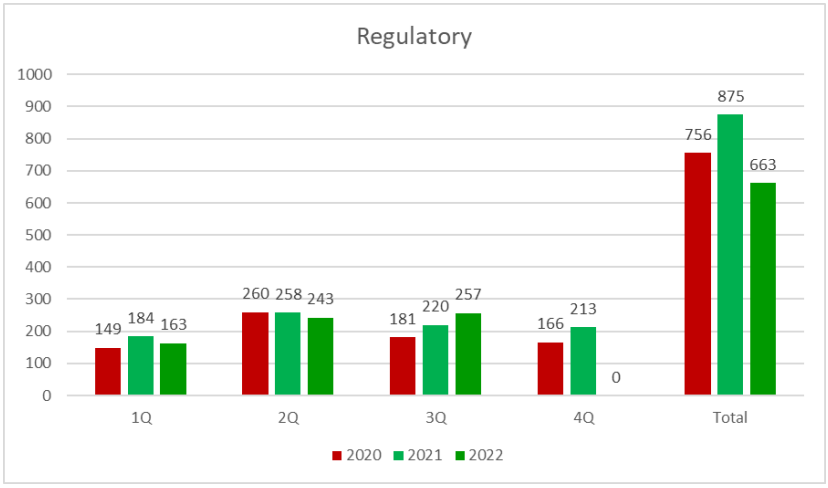
Pharmacy Assessments



Regulatory Files



ORGANIZATION
NIAID, DIVISION OF AIDS,
MONITORING OPERATIONS BRANCH
5601 FISHERS LANE, ROCKVILLE, MD 20852
EMAIL: OCSOMOB@NIAID.NIH.GOV

National Institute of Allergy and Infectious Diseases

THE FEDS
BARIATU SMITH, KAREN REESE,
PIA LOHSE, GRACE ROY,
DOREEN CAMPBELL*, KAYODE KOLEOSO*

* contractor