Office of Clinical Site Oversight
Monitoring Operations Branch

MOB Report

JULY 2024 · 2ND EDITION ·

Resolving Queries with Monitors During Monitoring Visits

As part of standard monitoring practices, it is customary for monitors to offer support to sites in addressing issues and queries identified during the monitoring visits, whenever feasible. What is the rationale behind this practice?

- The study team and monitor can easily discuss and answer any questions regarding the issue or query
- Decreases the number of unresolved issues subsequent to the monitoring visit
- Improves the effectiveness of the issue resolution process, thereby alleviating potential future query burdens

New NIAID Clinical Site Monitoring Contract Awarded

DAIDS Network studies are conducted in about 25 countries. As of June 2024, NIAID supports more than 50 research studies in approximately 300 domestic and international Clinical Research Sites (CRSs). A Clinical Research Organization with a regional presence, through a contract mechanism, conducts the monitoring activities at these CRS locations. The new 7-year NIAID Clinical Site Monitoring (NCSM) contract for monitoring services was awarded on February 1, 2024, to Pharmaceutical Product Development (PPD) LP, part of ThermoFisher Scientific, for monitoring services of DAIDS studies through January 2031.

PHOENIx Study Monitoring Visits

For sites participating in study A5300B/IMPAACT 2003B – Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR TB), you may expect to have more frequent monitoring visits and/or more co-monitors at the monitoring visits. The planned increase in study sample size per Version 5.0 of the protocol and the backlog of case report forms (currently over 50% pending verification at some sites) warrant additional monitoring activities. For sites that cannot accommodate additional monitors, we may schedule more than one (1) monitoring visit in a quarter. Your PPD monitor will work with you to develop a mutually agreeable plan to arrange these additional monitoring activities.

Why Monitor Screen Failures?

Screen failures occur when participants are consented for potential enrollment into a study and determined to be ineligible based on the eligibility and other study entry criteria.

International Conference on Harmonization (ICH) E6 (R2) Section 8.3.20 states that a screening log be maintained during the conduct of a trial. It should capture information on all screened participants and their eligibility status upon completion of screening assessments, including the reason for ineligibility.

Primarily, monitoring efforts are focused on enrolled participants. However, it is equally vital to monitor screen failure data to verify the following:

1 The screened population reflects the community where the trial is being conducted to ensure diversity of study participants, and leads to generalizability of the results	**2** Identify and revise specific inclusion or exclusion criteria for high screen failure rates as appropriate	**3** Lack of selection bias from screened participants

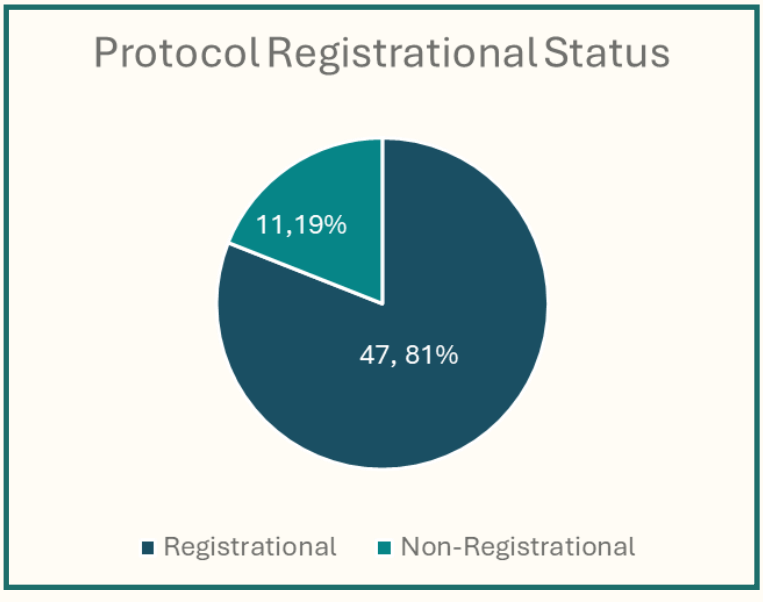
The protocol team can also analyze screen failure data to develop eligibility criteria for future studies.

While the FDA does not expressly require the submission of screen failure data, it is implied by recommending a standard format for screen failure data in the Study Data Technical Conformance Guide (2018). Also, the Bioresearch Monitoring Technical Conformance Guide (2022) recommends that screen failures be included in the clinical site listings of consented participants. In addition, the EMEA guidance on the Structure and Content of Clinical Study Reports (1996) recommends that appropriate screen failure data should be included in the overall disposition of study participants.

By monitoring screen failure data, we can ensure that data submitted to the regulatory agencies are complete, accurate, and verifiable from the source. This is even more vital for registrational studies which are conducted with the purpose of submitting trial data for review by regulatory agencies; hence meeting the requirement to source data verify the screen failure data.

Currently there are 58 DAIDS sponsored studies in on-going monitoring status, of which 11 (19%) are registrational studies (see chart).

Across these registrational studies, monitors are required to verify demographics, informed consents, eligibility criteria, and other data fields deemed relevant by the protocol team to meet DAIDS sponsor obligations.



Remote Monitoring Visits: Redaction and Medidata Remote Source Review System Validation

DAIDS kicked off the year with the new annual requirement for one fully remote monitoring visit. As we reach the second half of the year, MOB aims to address concerns and facilitate the capability of all sites to conduct remote monitoring visits.

For remote monitoring visits completed to date, it is noted that redacted documents were uploaded in about 18% of completed remote visits, and we are providing guidance regarding redaction of uploaded source documents. DAIDS does not require redaction for source documents uploaded into secure platforms that are HIPAA and 21 CFR Part 11 compliant.

Medidata Remote Source Review (RSR) is a secure, 21 CRF Part 11 and HIPAA-compliant module of Medidata hosted by the DAIDS Data Management Centers (DMC) to facilitate remote access to source documents and is available to all sites. It is designed with stringent security measures to ensure confidentiality and privacy of all study-related information. This will enable your site to upload unredacted source documents so that monitors can verify source documents remotely while protecting participants' privacy and confidentiality. During the monitoring visit, access to the Monitor platform is limited to "view only" mode, with no ability to download or print. This access privilege to view source documents is removed upon the conclusion of the visit.

Some of the benefits of using Medidata RSR include:

- One login for both Medidata Rave EDC and RSR
- No separate site user agreement for initial use or upgrades
- Study-specific visit folders are pre-configured according to the protocol
- Automatic creation of subject IDs from Medidata Rave EDC
- Pre-configured Regulatory Folders
- Pharmacy Folders are pre-configured to meet specific study requirements
- Technical support available through DMCs

Additional details on Medidata RSR can be reviewed here: https://www.medidata.com/en/clinical-trial-products/clinical-operations/rbqm/remote-source-review/

At study completion, there is a process for systematic permanent document removal. Once a study has reached the final database lock, all uploaded source documents are deleted from the Medidata RSR platform and the records are no longer available.

For sites moving forward with Medidata RSR, it may be helpful to provide validation certifications to your local IRB/EC or institution which document the platform's systems that ensure security and compliance of site data. This certificate contains all the validated Medidata Rave modules including the Medidata RSR module.

For ACTG/IMPAACT studies, your site can find these validation certifications on the Frontier Science portal (under **Systems** select **Validation Certificate,** then select **Medidata Rave**). Or contact user.support@fstrf.org.

For HPTN/HVTN studies, the SCHARP contact is Kristine Donaty at kdonaty@fredhutch.org.

Monitoring Metrics

February, March and April 2024

169 **Monitoring Visits**
Anytime monitoring is conduced during a site visit

301 **Monitoring Trips**
Total number of monitors conducting monitoring during site visit.

1902 **Records Reviewed**

382 **Pharmacy Assessments**

240 **Regulatory File Reviews**

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