18th Edition
August 2022

OFFICE OF CLINICAL SITE OVERSIGHT

MOB Report

Medidata Remote Source Review (RSR) Updates

We are excited to announce that all ongoing Targeted Source Data Verification (TSDV) studies that are sponsored/supported by DAIDS and monitored by PPD have been configured in Medidata RSR. Medidata RSR is an application hosted in conjunction with Rave EDC at the Data Management Centers (DMCs) to provide sites with a secured platform to upload source documents for remote source data verification (rSDV) by PPD monitors. The DMCs will continue to ensure that new TSDV studies are configured in Medidata RSR.

Also, in the past year, DAIDS incorporated the language regarding rSDV into the standard protocol template to ensure that an additional IRB review and approval are not required for rSDV. These actions provide us with the needed flexibility to conduct rSDV in this current environment of uncertainty regarding the COVID-19 pandemic.

Since the last newsletter, onsite monitoring visits now constitute most of all monitoring visits. At the end of 1Q2022, only 27 (11%) out of the 254 completed monitoring visits were done remotely (Table 1). However, we must recognize that with the frequent emergence of new COVID-19 variants, there remains a possibility of new travel and other restrictions which can limit the performance of onsite monitoring visits. Even in the absence of any restrictions to conduct onsite monitoring visits, rSDV may be required for timely resolution of open queries or verification of specific data points to meet database freeze/lock dates.

	VISITS	
REGIONS	Onsite	Remote
Asia Pacific	23	0
North America	97	22
EMEA	69	5
Latin America	38	0
Sub-Total	227	27
Total	254	

Table 1: 1Q2022: Number of Onsite and Remote monitoring visits by Region

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Medidata Remote Source Review (RSR) Updates Continued

A review of the site utilization of Medidata RSR, shows that only a minority of sites are using this platform for rSDV. Source documents were uploaded for 8 (19%) out of the 42 studies configured in Medidata RSR (Table 2). If your site is not currently using Medidata RSR, our expectation is that you have an alternative 21 CFR Part 11 and HIPAA compliant platform that can be used for rSDV when needed. Regardless, we continue to recommend the use of Medidata RSR when feasible and in compliance with your institutional guidelines.

Please reach out to your OCSO Program Officer (PO) and PPD monitor if you need any assistance to initiate or transition to Medidata RSR for your studies.

For questions related to technical use of Medidata RSR, please contact

SCHARP Clinical Data Management at sc.medidata.rsr@scharp.org or Frontier Science at usersprt@fstrf.org

That you have a 21 CFR Part 11 and HIPAA compliant platform that can be used for rSDV

EXPECTATION

RECOMMENDATION

The use of Medidata RSR when feasible and in compliance with your institutional guidelines

Table 2: Studies configured in Medidata RSR and Utilization by sites

ACTG

Study ID	# Sites Using RSR
A5300B	4
A5354	1
A5355	0
A5356	0
A5357	0
A5359	6
A5362	0
A5366	0
A5368	0
A5371	0
A5372	0
A5377	0
A5379	2
A5380	1
A5383	0
A5386	0
A5391	0
A5404	0

HPTN

Study ID	# Sites Using RSR
HPTN 083	4
HPTN 084	10
HPTN 084-01	0
HPTN 091	0
HPTN 094	0

HVTN

Study ID	# Sites Using RSR
HVTN 115 - Part B/C	0
HVTN 135	0
HVTN 137	0
HVTN 139	0
HVTN 140/ HPTN 101	0
HVTN 302	0
HVTN 804/ HPTN 095	0
HVTN 805/ HPTN 093	0
HVTN136/ HPTN 092	0

IMPAACT

Study ID	# Sites Using RSR
IMPAACT 2005	0
IMPAACT 2009	0
IMPAACT 2017	5
IMPAACT 2021	0
IMPAACT 2026	0
P1093	2
P1108	0
P1112	0
P1115	0

MTN

Study ID	# Sites Using RSR
MTN-042	0

Inspection Readiness
Findings from Recent Inspections

As on-site inspections resume, various regulatory agencies have conducted inspections at our sites since the start of the year. Learning from other sites' experiences and inspection outcomes can enhance inspection readiness across all sites. Some of these recent common ICH GCP and 21 CFR inspection findings with examples are noted here.

Investigation not conducted in accordance with the investigational plan

Participants were stratified using a previous protocol version, not the current version, thus did not meet eligibility requirements and several were incorrectly dosed;

General requirements for the informed consent process were not met – providing sufficient time/opportunity for prospective subjects to consider whether to participate or not

Inspectors reviewed documented records comparing the date/time of screening/enrollment and signature time of ICF, and an adequate reading, explanation and resolution of doubts on the part of the participants for the process of obtaining informed consent could not be guaranteed;

Failure to prepare or maintain adequate and accurate case histories for observations and data pertinent to the investigation

Documentation of the re-consenting process was inadequate; concomitant medications were listed in the source documentation but not entered into the eCRF.

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Inspection Readiness:
Findings from Recent Inspections Continued

The importance of timely documentation and thorough follow-up was demonstrated through other inspection findings.

During an FDA site inspection, an enrollment violation was noted for the first participant enrolled in the study. This enrollment violation was noted in the monitoring report, the protocol team was notified, the deviation was reported to the IRB, and eventually the protocol was updated to clarify the inclusion criteria requirement that resulted in the violation. The FDA and sponsor were already aware of the violation, and therefore the inspector did not write an FDA Form 483 citation. In this case, timely reporting of the deviation and proper documentation made available to the inspector prevented official citations.

Following receipt of a regulatory authority inspection report, sites respond to the findings and implement CAPA accordingly, as per timelines indicated in the report from the issuing agency. One agency recently conducted re-inspection of a GCP inspection completed at a site 3 months prior. The purpose of this visit was to verify if the CAPA plan on issues cited during the previous inspection visit was correctly implemented. This shows it is critical not only to communicate a thorough response with planned actions to resolve deficiencies, but also to follow through with them to ensure effectiveness.

The Monitoring 101 training course on the DAIDS Learning Portal (DLP) is a resource for Clinical Research Site (CRS) staff that provides an overview of the requirements of monitoring per International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (ICH E6). This DLP module also provides an overview of the roles and responsibilities of the sponsor, site monitors, CRS staff, and other parties who play an integral role in the monitoring process. Topics include DAIDS' risk-based approach to monitoring and activities involved in monitoring visits.

Several updates to this training module have been made to reflect current monitoring directives and processes.

DAIDS Monitoring 101 Training Course continued

These changes include the following:

- **Remote Interim Monitoring Visits (IMVs) will be included in the types of visits completed by the monitoring team.**
  - Remote IMVs can be performed under certain circumstances, for example in response to significant business disruption, such as the COVID-19 pandemic.
  - The scope of study data permitted to be monitored remotely is defined in accordance with DAIDS policies, CRS institution policies, IRB/EC, and other applicable regulations.
- **Considerations for Remote IMVs**
  - Visit preparation is key. For example, electronic platforms that will be used to support the remote ISMV must be approved for access at the site level.
  - IRB/EC approval/acknowledgement is required and should be obtained prior to the remote ISMV because without source data verification, a monitoring backlog will be created.
  - The electronic platform must also follow the CRS's own SOPs (for electronic systems use/access).
- **Co-monitoring for a multi-network approach**
  - Numerous protocols and networks may be reviewed at one monitoring visit.
- **Frequency and Duration of Monitoring Visits**
  - The duration of visits is typically 3 to 4 days. If additional visits are needed in the quarter or co-monitors are needed, these will be added to the IMVs to meet the monitoring goals. Visits may be a combination of on-site or remote.
- **Database Lock Deadlines**
  - Upcoming database lock deadlines can expedite the need for IMVs as well as increase the likelihood of co-monitoring or additional IMVs. Prior to a database lock, all data must be reviewed, source data verified and queries resolved. If your site is participating in a protocol nearing a database lock, the site must work to ensure all data is available and entered prior to the IMV and provide all source to verify.
- **Significant Findings**
  - CRS Staff should escalate significant findings to the PI/IoR and report to the IRB/EC and regulatory authority (depending on country requirements) in an expedited manner, when applicable.
  - CRS Staff should notify the protocol team of all significant findings, as applicable

The updated Monitoring 101 Module will be available on the DAIDS Learning Portal in Fall 2022.

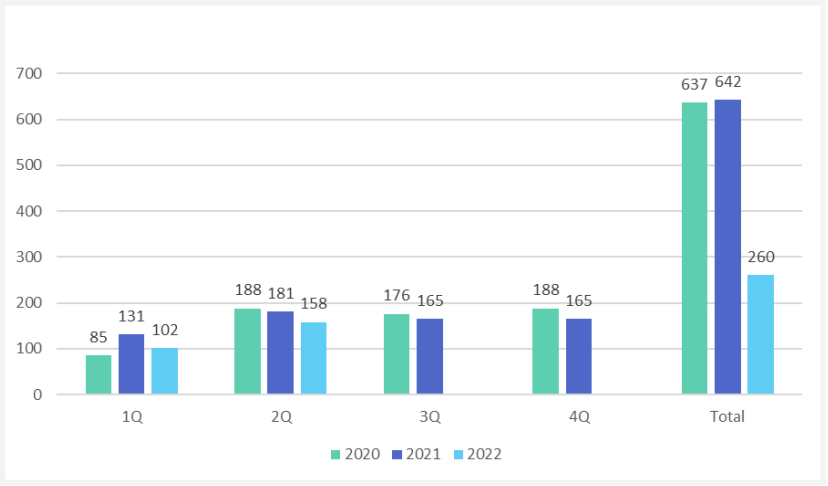
Monitoring Metrics

Year to Date Monitoring Metrics

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

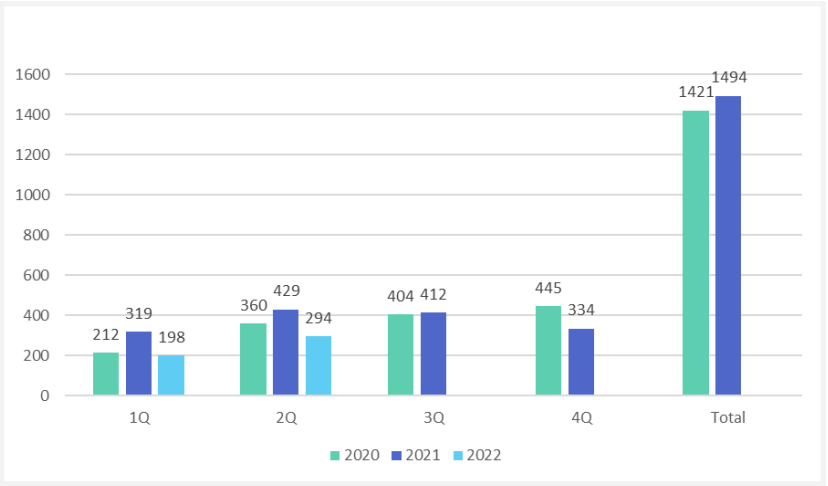
Monitoring Visits

Any time monitoring is conducted during a site visit.

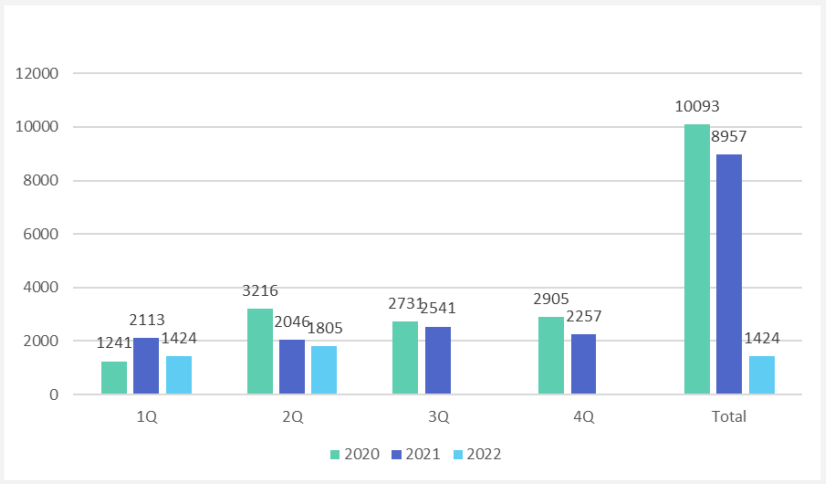


Monitoring Trips

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



Records Reviewed



Monitoring Metrics

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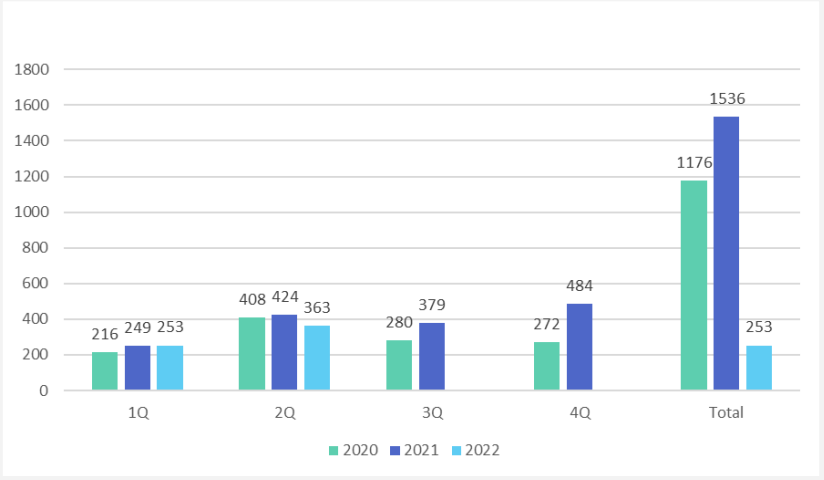
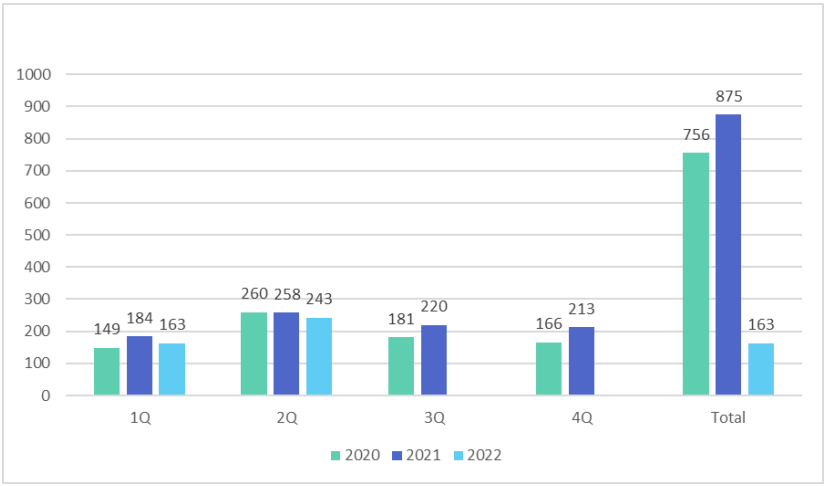
Pharmacy Assessments



Regulatory Files



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