MOB Report

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National Institute of Allergy
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THE FEDS

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Remote Source Document Verification (SDV)

The public health emergency that stems from the COVID 19 pandemic has a significant effect on the conduct of clinical trials, especially traditional onsite monitoring visits. A large majority of sites are not allowing onsite visits and even when permitted, monitors cannot get onsite as a result of the COVID 19 travel restrictions from the government, sponsors and/or employers. Where onsite visits are feasible and local monitors are available, maintaining physical distancing could limit the number of monitors that are allowed onsite. Additionally, the site/institutional policies that require non-essential personnel to work remotely means that key study personnel may not be available to engage monitors during an onsite visit.

Based on these factors and safety considerations, DAIDS suspended all onsite monitoring visits in March 2020, and limited remote monitoring review without source document verification was initiated in April 2020 to monitor the quality of data within the Medidata Rave system. In May 2020, DAIDS lifted the travel suspension for onsite visits, however many of the sites still could not accommodate onsite visits, either as result of the continued COVID-19 related travel restrictions or sites' policy of prohibition of onsite visits. In order to continue to fulfil one of the key sponsor obligations to adequately monitor their clinical trials, DAIDS undertook consideration of available options to conduct remote source document verification (rSDV).

The U.S. Food and Drug Administration (FDA) issued a guidance document in March 2020 (later updated in December 2020) entitled "FDA Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency", which provides the following guidance: "FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations. The regulations are not specific about how sponsors must conduct such monitoring and are therefore compatible with a range of approaches to monitoring that may vary depending on multiple factors".

In July 2020, following outreach to HIV/AIDS Network Coordination cross-network leadership and study coordinators to discuss alternative approaches to the traditional onsite monitoring visits, an initiative was launched to conduct rSDV for five priority studies with an estimated database lock date within 6 months. The sites were asked to select one or more of the following four proposed options based on their clinical research operation processes and institutional requirements:

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Remote Source Document Verification (SDV) *Continued*

1. Veeva SiteVault Platform- Available from Veeva Systems, Inc. through direct subscription by sites without a charge.
2. Site Controlled SharePoint or Cloud-Based Portal- An existing platform at the site which allows for sharing of participant source documents, that could be extended to allow monitor's access for a specific protocol and limited time.
3. Electronic Medical Record (EMR) System- Site provides monitors direct access to their EMR for a specific protocol and limited time.
4. Medidata Rave Imaging Solutions- An additional module to the existing Medidata Rave EDC system that's currently used by sites to complete eCRFs. To date, the following eight studies have been configured and are available for rSDV in Medidata Rave Imaging: HPTN 083, HPTN 084, P1093, A5359, IMPAACT 2010, IMPAACT 2014, IMPAACT 2017, and IMPAACT 2003b/A5300B.

All proposed rSDV options are 21 CFR Part 11 and HIPAA compliant. In addition, sites are required to comply with any institutional requirements regarding privacy and confidentiality; and also obtain approval for remote source document verification from their IRB/EC and national regulatory agency, if applicable. Table 1 below highlights the preference of the 66 sites that have responded to date to the request to select an rSDV option.

Table 1: Remote Source Document Verification Option by Number of Sites:

rSDV Options	# of sites
Veeva SiteVault Platform	33
Medidata Rave Imaging Solution	24
Site Controlled Cloud-Based Portal	6
Direct EMR Access	3
	66

Since the first rSDV was performed in the 3Q2020, we have performed approximately six rSDV visits for the priority protocols. Table 2 below highlights the number of visits performed by selected rSDV option.

Table 2: Remote Source Document Verification option by number of visits:

rSDV Options	# of visits
Medidata Rave Imaging Solution	1
Veeva SiteVault Platform	5
	6

As we continue to deal with the restrictions emanating from the public health emergency and to better position our sites to deal with any future disruption in onsite visits, DAIDS is currently evaluating the strategy of expanding rSDV options to all monitored protocols. In the next few weeks, the Monitoring Operations Branch (MOB) will be sending out a memo to inform sites about details of the implementation strategies and the timeline.

The initial lessons learned to date on rSDV from both the site and the CRA's perspectives are as follows:

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Lessons Learned From Remote Source Data Verification

1. Generally the system is user-friendly however requires sufficient time to be allocated for visit preparation.

2. Once PVL is released and PID visits are known, assign dedicated site staff to start uploading documents prior to the visit start date to ensure all requested documents are available during the monitoring call.

3. Allow adequate time to upload documents, as large files take time to upload thereby limiting the number of PIDs that can be uploaded during normal working hours.

4. Daily communication between monitors and site staff is key to ensure both parties plan each day ahead.

5. Ensure continuous QC is performed when un-stapling, scanning and naming documents to ensure they are scanned and uploaded properly into the system.

6. Once source documents have been uploaded, allocate adequate resources to re-stapling and re-filing to reduce potential for mis-filing errors.

7. PID Numbers and associated visits for risk-ranked and TSDV studies will be specified in the Work Order for efficient use of site resources in uploading source documents to be reviewed at each visits.

8. Review uploaded documents for missing or poorly scanned pages.

9. Source documents for E2 follow-up issues from a remote monitoring review are to be prioritized for upload, however source documents should also be uploaded for all related visits pending SDV. For example: if source document was uploaded for E2 follow-up issue for a week 030 visit that has been eCRF reviewed only, the monitor can only resolve this in NCRMS if SDV was performed for all visits prior to week 030 follow-up visit.

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
Remote modality	(r)
Combination modality	(c)

Monitoring Visits

	2019	2020
1Q	128	85
2Q	187	9+179 (r)
3Q	182	61+103 (r) + 12 (c)
4Q	229	TBD
Total	**726**	**TBD**

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

Monitoring Trips

	2019	2020
1Q	232	189
2Q	397	20+337 (r)
3Q	419	124+218 (r) + 52 (c)
4Q	502	TBD
Total	**1550**	**TBD**

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

Records Reviewed

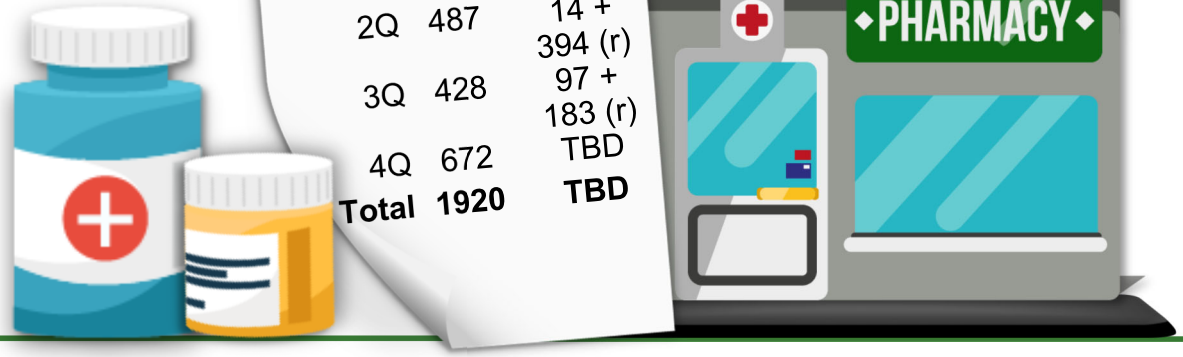
	2019	2020
1Q	2410	1241
2Q	2593	137+3079(r)
3Q	2930	1201+1530(r)
4Q	3459	TBD
Total	**11392**	**TBD**

Regulatory Files Reviewed

	2019	2020
1Q	221	149
2Q	288	9 + 251 (r)
3Q	281	69 + 112 (r)
4Q	302	TBD
Total	**1092**	**TBD**

Pharmacy Assessments

	2019	2020
1Q	333	216
2Q	487	14 + 394 (r)
3Q	428	97 + 183 (r)
4Q	672	TBD
Total	**1920**	**TBD**



Remote Regulatory Authority Inspections

As participant clinic visits and onsite monitoring visits have pivoted to remote modalities during the COVID-19 public health emergency, so have onsite inspections by regulatory authorities. The US FDA is continuing to support regulatory decisions on applications by utilizing remote inspection of sites when travel or onsite access is restricted. The FDA conducts Remote Regulatory Assessments by accessing de-identified versions of key study documents using a secure online portal (e.g., box.com), with additional staff interviews via secured video conference calls (e.g., WebEx). Alternatively, key study records (certified copies) could be transferred to a US Agent for inspection at a US location. With either approach, FDA conducts their review in a manner consistent with sites' local requirements and national regulations.

Recent Remote Inspection Experience

Two DAIDS network sites in South Africa recently underwent remote regulatory inspections. Following email notification of being selected for inspection, the FDA scheduled an introductory call with the site personnel to relay the study selected for inspection and to discuss logistics. The inspections were scheduled to occur within the next two weeks, at agreed upon dates with the Clinical Research Site (CRS) leader and inspection team.

The CRS leader was requested to share the site's capacity for transmitting documents and availability for video calls during the inspection. The sites were directed to confirm with their national and local regulatory oversight bodies that the remote inspection is acceptable and share any requirements they may have. The FDA requested that all documents containing subject identifiers be redacted prior to scanning, including Subject Name, Initials, Date of Birth/Death, Medical Record Number, and any other identifying information (except when required to verify a participant's eligibility, e.g. date of birth). For one site inspected, 377 documents were uploaded to the FDA's Box site for 10 participants (Mother-Infant pairs) reviewed. The sites reported that the inspectors were understanding of the workload of uploading documents during this time, with reduced staffing and other COVID-19-related impacts.

Document Submission and Preparation

Inspectors will request provision of documentation to support inspection for the trials identified for detailed review. This documentation helps 'tell the story' of the trial, such as records which describe the handling and decision making associated with important issues. See Table 1 for the list of sources of information and select key documents generally requested for review. As with onsite inspections, sites should maintain for their records a log of documents submitted to the inspectors.

Table 1

Complete study subjects' records such as: • Informed Consent Documents • Documentation of all study visits and activities • Original medical records • Laboratory and Consultation (x-ray, cardiology, etc.) reports • Case report forms • Diaries or other study drug administration records	Records of test article shipment, dispensing, dosing, accountability, and storage conditions
	Sample collection, processing, and storage records/ logbooks

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Remote Regulatory Authority Inspections *continued*

Other common documents requested for inspector review are the site monitoring reports (SMRs). As the SMRs do not contain any personally identifiable information, there is no need to redact these reports. The SMRs may contain findings for DAIDS studies being conducted at the site other than the study identified for inspection. While sites may not wish to share this information pertaining to other studies, it is DAIDS position that the Network visit reports be submitted in full, without redaction.

Recommendations for Remote Inspection

Remote inspections are likely to be more labor intensive than face-to-face inspections. Scanning and uploading documents can be very time-consuming. DAIDS recommends at the start of the inspection that sites provide to FDA a document log which details the specific documents at their site (e.g. signed consent form = 10 pages, medication log = 4 pages, Study Product shipment records = 22 pages). This helps the FDA understand the types of documents to expect and the number of pages the site would be required to upload. During the daily debriefs with the inspectors, keeping open communication regarding document upload progress is recommended. Sites may want to consider how they will label the document files before uploading, as once posted, the file names cannot be edited nor can the files be removed. Additionally, while inspectors adhere to site business hours during onsite inspections, with remote inspections, time zone differences should be considered. Flexibility of CRS staff will be key to meet the demands of the inspection. Following the inspection, the site's access to the FDA Box site is revoked, so it is important to maintain a complete record of submitted documents.

Guidance and Resources

Remote inspection processes and requirements will vary by regulatory authority. In October 2020, the European Medicines Agency issued guidance on remote inspections during COVID-19, found here: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/good-clinical-practice-gcp-inspection-procedures. Adapting to virtual inspections may be challenging, but the basics of inspection preparation remain the same and DAIDS is here to support you! Sites are encouraged to review inspection guidelines, such as the FDA's Bioresearch Monitoring Program (BIMO) Compliance Program Guidance Manual and inspection readiness related training on the DAIDS Learning Portal.