20th Edition, August 2023

MOB Report

OFFICE OF CLINICAL SITE OVERSIGHT

Recent EMA Site Inspections

In early March of this year, two DAIDS sites underwent site inspections by the European Medicines Agency (EMA) as part of a review of the application of Apretude (cabotegravir extended-release injectable suspension). The Committee for Medicinal Products for Human Use (CHMP) requested routine GCP inspections be carried out on the conduct of the *HPTN 084 clinical trial: A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women*. The purpose of the inspections was to verify the efficacy and safety data reported in the marketing authorization application, and verify compliance with GCP and applicable regulations, particularly where it may have impacted the data's validity or the ethical conduct of the study.

Three inspectors from the EMA visited two sites, Botswana Harvard AIDS Institute Partnership in Gaborone, Botswana and Emavundleni Research Centre in Cape Town, South Africa, for 5 days at each site. The inspectors reviewed the contents of the investigator site file and the medical records of randomized participants (6 records at one site, 10 records at the other), focusing on the compliance with the eligibility criteria, HIV tests and pregnancy, the primary evaluation criterion and safety reporting. Additionally, the inspectors conducted interviews of key personnel at the sites, asking them to describe how study tasks were done and how this was documented.

Great Job!

There were no critical findings, and the inspectors concluded that at the sites' level, the study was conducted at an acceptable level of compliance with GCP and internationally accepted ethical standards. Congratulations to the site leadership and staff!!

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NIH National Institute of Allergy and Infectious Diseases

EMA Site Inspections Continued

The inspection process can be stressful, however, there were several steps taken to help the sites and ensure their readiness for a smooth inspection.

Prior to the Inspection

The EMA informed DAIDS in December 2022 of the sites selected to be inspected, and then in February 2023 provided specific dates of the inspections, to occur in March. After receiving the site inspections announcement including the dates, DAIDS coordinated Site Preparation Visits before the EMA planned to be on site. These include Pre-inspection Visits and Mock Inspections targeted for each site's needs. These visits can be time-consuming but prove invaluable in training site staff and identifying gaps or deficiencies to be addressed and documented. PPD Quality Assurance (QA) colleagues conducted these preparation visits, with assistance from the PPD Monitoring group. They provided feedback on the sites' CAPAs and practiced potential interview questions.

Following these preparation visits, OCSO held weekly calls with the sites to review site progress made on resolution of findings. The assigned Program Officer worked with the site staff to develop storyboards for complicated site issues that may have required more explanation. The DMCs provided data listings of SAEs, protocol deviations, Lost to Follow-up participants, and seroconverters prior to the inspection for cross-checking against site records to ensure complete data and documentation.

During the Inspection

To provide real-time guidance to site staff during the inspection, DAIDS QA team members traveled to the sites to be present during the inspections. DAIDS and the sites held daily debrief calls to address questions and/or provide additional information requested by inspectors, or to triage the questions to the appropriate party or subject matter expert. A tool that proved helpful for telling the story of the study at the site was a document with protocol and site-specific milestones during the study (protocol amendments, site activation dates, enrollment pauses and training dates).

Following the Inspection

In May, the sites received the official inspection reports from the EMA. The report outlined the various elements of the inspection, with summary, discussion and conclusion, which the Investigators of Record reviewed and acknowledged. The DAIDS POs continue to work with the sites on any minor observations noted to improve processes and ensure inspection readiness.

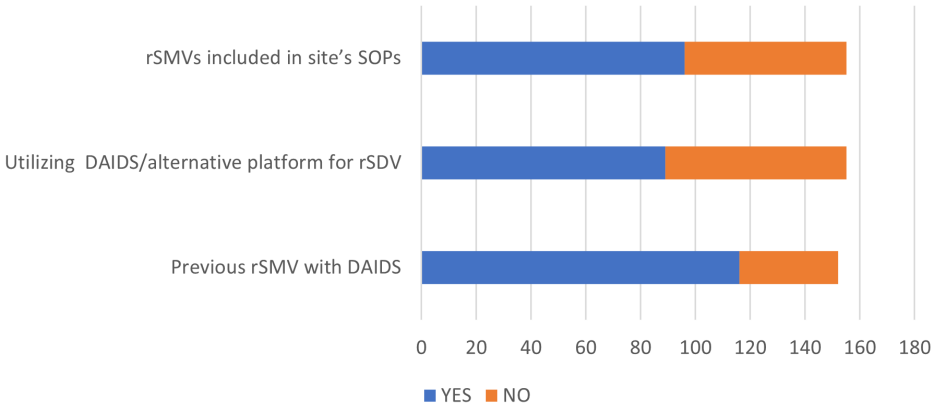
No critical findings by the inspectors was a great outcome, made possible by the diligent work of the site personnel in preparing for the inspection and by the partnership between the sites, DAIDS and our PPD colleagues. With all the hard work over the years of the HPTN 084 trial duration, culminating in these positive inspection experiences, we are now one step closer to making this drug accessible to more communities in need.

DAIDS Monitoring Visit Modalities

Over the recent years, DAIDS has expanded our monitoring modalities from the traditional onsite visit to a combination of onsite, remote, and hybrid (onsite/remote) approaches. A monitoring visit that may have previously been completed onsite could be changed to a fully remote or hybrid approach, where a remote review of study documents is conducted a few days ahead of the onsite visit. Remote Site Monitoring Visits (rSMVs) have monitoring activities completed remotely instead of on site. With these flexibilities, rSMV is one of the examples of alternative monitoring techniques that will be used to supplement onsite visits, as per the FDA Risk-Based Monitoring Guidance.

In April, our PPD colleagues surveyed the network sites to assess their experience with rSMVs: previous use of rSMVs, types of platforms, benefits, and concerns. There was a good response rate of 85% to the survey, with 198 sites responding out of 231 sites contacted. Some of the survey results are presented below.

Figure 1: Sites with prior remote monitoring visit



155 of the 198 (78.28%) have completed a Remote Site Monitoring Visit. Of note, 19 of the 89 sites with a secured platform are utilizing Medidata RSR. Additional information is shown in Figure 1

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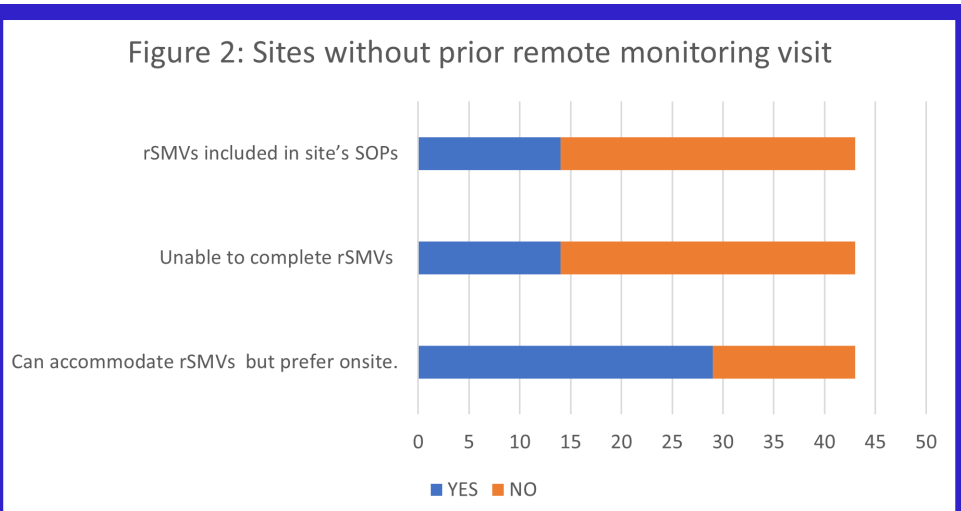
DAIDS Monitoring Visit Modalities Continued



43 of the 198 sites (21.72%) have not completed a Remote Site Monitoring Visit. Figure 2 shows that 29 of the 43 sites prefer onsite visits but can accommodate rSMV.

The responses received through the survey are valuable as we continue to improve our monitoring modalities. We heard back that remote visits allow for more flexibility when scheduling, reduce the burden of having a monitor onsite allowing for site staff to focus on daily activities, and require similar preparation for the visit (in some cases). We also acknowledge the potential challenges some sites shared with implementing remote monitoring, such as time constraints, paper source documents, labor-intensive uploading of source documents, and limited staffing.

Remote SMVs will not replace onsite monitoring visits, instead they will supplement onsite monitoring.

To facilitate remote monitoring capabilities at sites, Remote Site Monitoring visit language is included in all active protocols. DAIDS has also made the Medidata Remote Source Review (RSR) platform available to all DAIDS supported sites for all network protocols through the DMCs. We are strongly recommending that sites use the Medidata RSR platform to facilitate remote site monitoring activities. Advantages to sites in 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 pre-configured according to the protocol.
- Automatic creation of subject ID from Medidata Rave EDC.
- Built-in redaction functionality to decrease errors and increase productivity.
- Pharmacy folder pre-configured to meet specific study requirements.
- Regulatory folder pre-configured to support review of essential documents.
- Technical support available through the DMCs.

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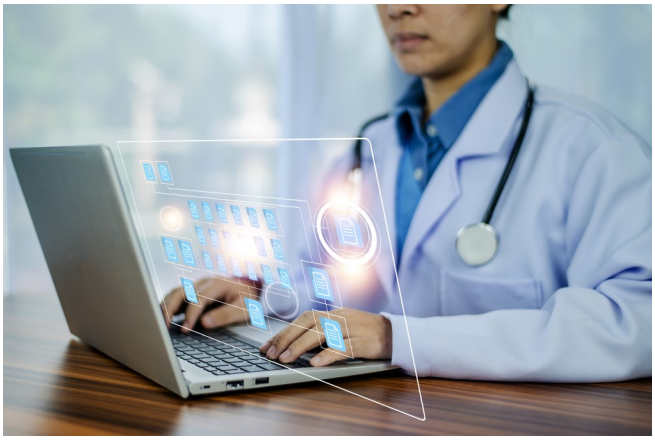
DAIDS Monitoring Visit Modalities Continued

OCSO MOB presented "**DAIDS Remote Site Monitoring Visits"** sessions at the recent HPTN and ACTG network meetings. We heard feedback directly from attendees with a main takeaway that implementing remote monitoring would be easier if DAIDS included all PIDs to be reviewed in the announced work order. We are working on this programming change within the NCRMS system, to provide a single full work order with the Pre-visit letter. This will allow sites to start uploading source documents for all PIDs to be reviewed well in advance of the visit.



As rSMVs supplement onsite monitoring, our monitoring modalities will now include onsite monitoring visits, hybrid monitoring visits, and rSMV starting in 4Q2023. DAIDS will require one remote site monitoring visit per site annually. This allows DAIDS to fulfill our monitoring obligations as Sponsor, to ensure continuity of monitoring operations when situations arise preventing onsite monitoring. We will continue outreach and engagement on this initiative through future network meetings and HANC calls.

Medidata RSR FAQs

Is redaction required by DAIDS?

DAIDS does not require redaction since the upload is to a secure HIPAA and 21 CFR Part 11 compliant platform. In addition the standard DAIDS protocol language and consent form regarding remote monitoring does not limit remote monitoring to de-identified data.

If redaction is not required, do we need to inform our local IRB/EC?

Even though Medidata RSR is 21 CFR Part 11 and HIPAA compliant, our recommendation is to inform your IRB/EC in the event there are institutional policies or agreements that require uploaded documents to be redacted.

Is there a place where we can get more information about how the Medidata RSR platform works?

Link for general information on Medidata RSR: https://www.medidata.com/en/clinical-trial-products/clinical-operations/rbqm/remote-source-review/

For questions related to technical use of Medidata RSR, contact SCHARP Clinical Data Management at sc.medidata.rsr@scharp.org or Frontier Science at usersprt@fstrf.org. The DMCs developed FAQs for reference, available here: Frontier Science Portal under Site Support > Medidata Rave Resources; For HVTN studies, on each protocol page on the HVTN Members' Site; For HPTN studies, to be posted on Microsoft Teams.

A user training will be provided prior to granting access to the platform.

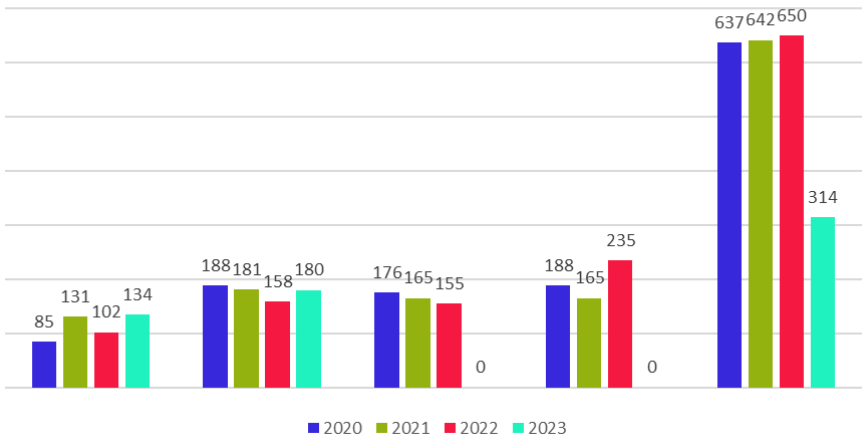
Monitoring Metrics

Year to Date Monitoring Metrics

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

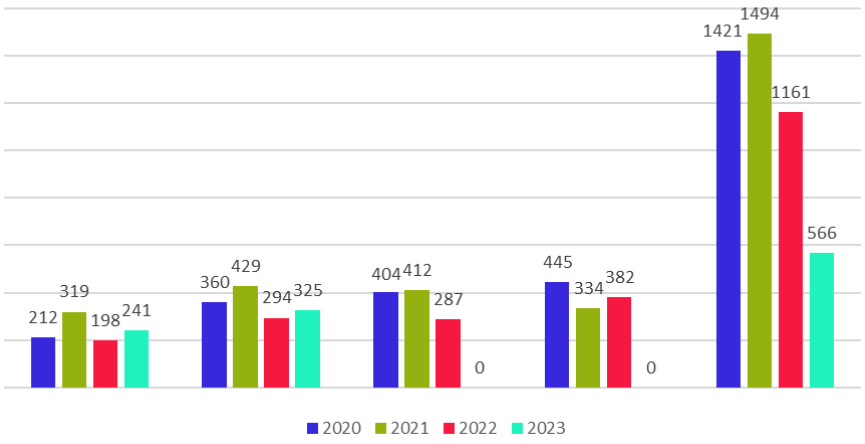
Monitoring Visits

Any time monitoring is conducted during a site visit.

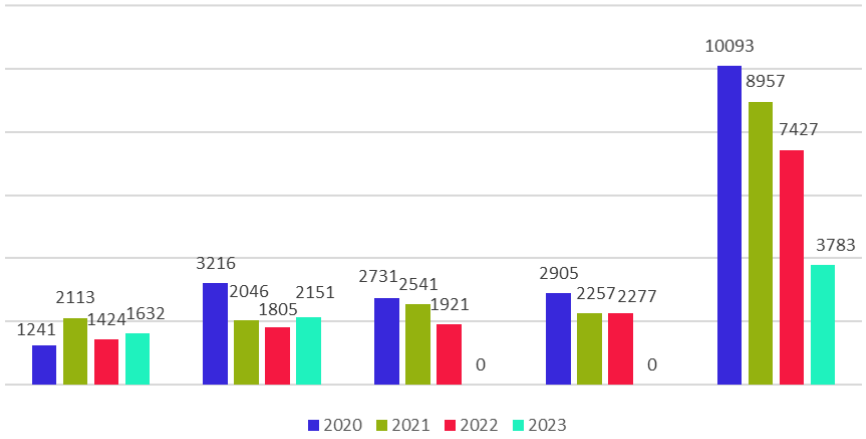


Monitoring Trips

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



Records Reviewed



Monitoring Metrics

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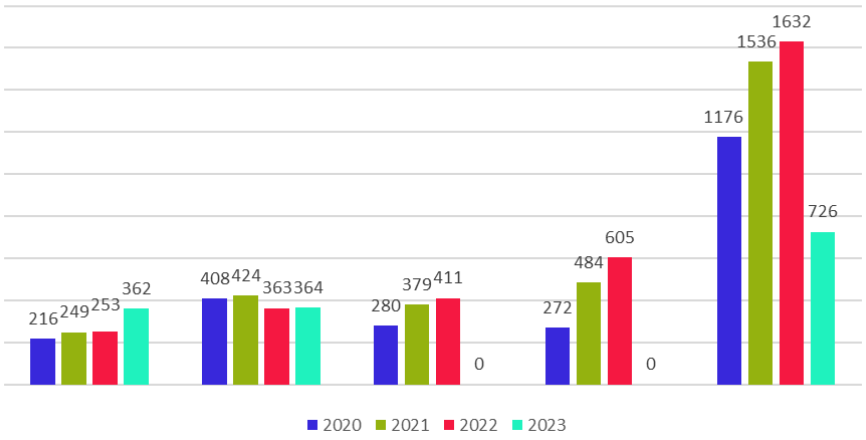
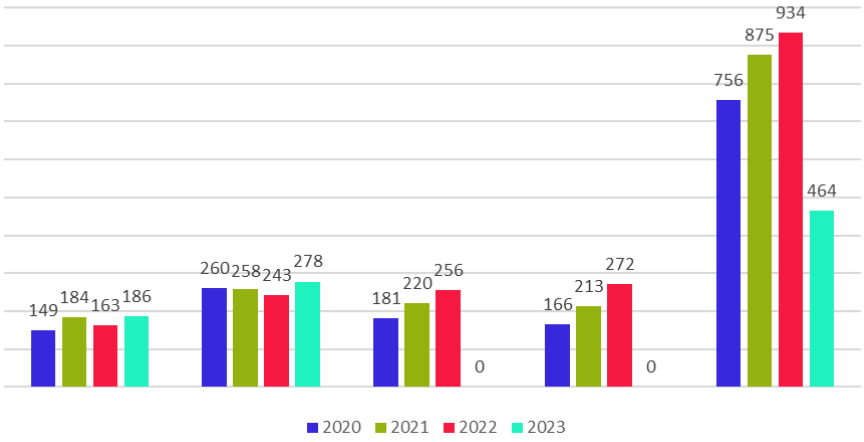
Pharmacy Assessments



Regulatory Files



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