Letter of Amendment #2 for:

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

Version 2.0, dated 29 May 2017

DAIDS Study ID # 20735
IND # 133,017 Held By DAIDS

Letter of Amendment Date: 22 April 2020

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2008 study and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT 2008. If the IMPAACT 2008 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

DAIDS Study ID #20735

Version 2.0, Letter of Amendment #2
Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record	Date

Name of Investigator of Record
(printed)

Summary of Modifications and Rationale

The primary purpose of this LoA is to update guidelines for monitoring by the Study Monitoring Committee (SMC). Following the first regularly scheduled SMC review of this study, the SMC identified no safety concerns and recommended that the third trigger for an SMC safety review specified in protocol Section 9.5.2 be revised to specify separate thresholds for hematologic adverse events (anemia and neutropenia) and non-hematologic adverse events. The SMC also recommended that the Protocol Team set a higher threshold for triggering a review of anemia and neutropenia events. This LoA reflects the Protocol Team's response to the SMC recommendations.

A second purpose of this LoA is to add batch antiretroviral (ARV) resistance testing at study Entry and at Week 14 for infants with plasma HIV-1 RNA greater than 500 copies/mL. Combination antiretroviral therapy (cART) regimens are selected for infants in this study by primary care providers, consistent with local standards of care. At many sites, resistance testing is not routinely performed before or during ARV treatment as standard of care. Routine review of cART regimens received by the Protocol Team and the SMC has identified diversity in regimens selected across sites and participants. Information on ARV resistance mutations present at study Entry (baseline) and at Week 14 (when the primary study outcome measure is assessed) will facilitate interpretation of the primary study results.

ARV resistance testing will be performed in batch at a designated centralized laboratory. This testing was not explicitly listed as a study-specific evaluation in protocol Version 2.0 but is generally consistent with the use of stored blood specimens as described in the protocol and sample informed consent forms. No additional blood will be collected for this testing. Results will be provided to participants' parents or guardians and primary HIV care providers.

This LoA also incorporates minor and administrative updates of the following:

- Clinical Management Committee (CMC) monitoring of antiviral activity and a description of performing sensitivity analyses of antiviral activity
- Protocol team and site rosters
- Websites where DAIDS resources for key aspects of study implementation can be accessed
- References to the NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL)

All of the above are addressed in Sections A-C of this LoA.

Section D of this LoA incorporates the contents of protocol Clarification Memorandum (CM) #2, which was issued on 01 April 2020 to safeguard the health and well-being of study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic. CM #2 provided operational flexibility for conducting study visits and procedures when needed to ensure ongoing contact with participants and to prioritize the conduct of clinically and scientifically important evaluations when possible. Per the study Sponsor, sites were instructed to implement the guidance provided in CM #2 immediately. All sites should continue to follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures during the COVID-19 pandemic, with utmost importance placed on the health and well-being of study participants and study staff. Consistent with the instructions provided in CM #2, implementation of Section D of this LoA is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT 2008 Protocol Team will determine when, in the future, the guidance provided in Section D is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform their IRBs/ECs.

Implementation

Modifications of protocol text are shown in three sections (A-C) of this LoA. Within each section, modifications are generally shown in order of appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions. Operational guidance for conducting study visits and procedures during the COVID-19 pandemic is provided in the fourth section (D) of this LoA; conventions for use of strikethrough and bolding do not apply in this section.

A. Update of Guidelines for Monitoring by the SMC

1. In protocol Section 9.5.2, Monitoring by the SMC, Participant Safety, third, fourth, and fifth paragraphs:

   Triggered SMC reviews will occur in the following scenarios:

   1. Any infant in Arm 1 dies or has a Grade 4 adverse event that is judged by the CMC to be related to the study product (excluding neutropenia, anemia, and fever)

   2. Three or more infants in Arm 1 have a Grade 3 or higher adverse event that is judged by the CMC to be related to the study product (excluding neutropenia, anemia, and fever)

   3. After at least 25 participants have been enrolled~~, 20% (across arms) have Grade 3 or higher adverse events~~**:**

      a. 20% across arms have Grade 3 or higher adverse events excluding anemia and neutropenia
      b. 50% across arms have Grade 3 or higher anemia or neutropenia

   Because Grade 3 and higher neutropenia and anemia are common among infants on ART, and Grade 3 and higher fever is common due to inter-current illnesses, these events will not be counted in scenarios (1) and (2). ~~These events~~ **Grade 3 or higher fever** will be counted in scenario (3**a**). **Grade 3 or higher anemia and Grade 3 or higher neutropenia will be counted in scenario (3b).**

   If ~~either~~ scenario (1)**,** ~~or~~ scenario (2)**, or scenario (3a)** occurs, accrual into the study and administration of study product will be paused, and an SMC review will take place within seven days. If scenario (3**b**) occurs, accrual into the study and administration of study product will not be paused, and an SMC review will take place within seven days. **After a safety trigger has been met and the required SMC review has taken place, the threshold for future triggered safety reviews will be reset (i.e., the events that triggered a safety review will not be re-counted toward future reviews).**

B. Addition of ARV Resistance Testing

1. In the Schedule of Evaluations in Appendix I, the listing of infant evaluations to be performed with stored plasma and PBMCs for primary, secondary, and other evaluations is updated to include ARV resistance testing at Entry and at Week 14, and a new footnote 10 is added, as shown on the next two pages of this LoA.

Appendix I
IMPAACT 2008 Schedule of Evaluations: Screening through Week 14

Study Visit	Screen	Entry	Entry +3d	Week 1	Week 2	Week 2+3d	Week 3	Week 6	Week 6+3d	Week 7	Week 10	Week 10+3d	Week 11	Week 14[9]
Visit Window	-30 d	Day 0	-1/+3 d	±3 d	±3 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	-7/+14 d
Urinalysis		X		X										X
Infant Evaluations (continued)														
Stored plasma and PBMCs for primary, secondary, and other evaluations		3-5 mL[5]			1 mL			1 mL			1 mL			5 mL
ARV resistance[10] (plasma)		**X**												**X**
VRC01 resistance (plasma)		X												
VRC01 level (plasma)		X			X			X			X			X
Anti-VRC01 antibodies (plasma)		X												X
HIV-1 DNA (PBMC)		X												X
HIV-1 RNA (spliced/ unspliced; PBMC)		X												X
HIV-1 RNA (inducible; PBMC)		X												
Neutralization (plasma)		X												X
ARV levels (plasma, adherence)														X
Stored serum for ADCC		1 mL												1 mL
Stored plasma and PBMCs for exploratory evaluations[6]		0-2 mL[6]			X[6]			X[6]			X[6]			0-2 mL[6]
Cerebral spinal fluid storage for exploratory evaluations														
Total Infant Blood Volume	**3-6 mL**	**5-9 mL**	**—**	**5 mL**	**1 mL**	**—**	**2 mL**	**4 mL**	**—**	**2 mL**	**4 mL**	**—**	**2 mL**	**12-14 mL**

Appendix I Footnotes

1. At Entry and Weeks 2, 6, and 10, for infants in Arm 1, blood collection must precede administration of VRC01.
2. Refer to Section 6.16.
3. CD4 and CD8 cell counts and percentages are generally expected to require 1 mL of blood. At sites where a complete blood count (CBC) is needed to obtain both cell counts and percentages, 1 mL may be collected to perform the CBC at Week 36 and Week 48 (at other sites, the CBC is not required at these visits).
4. At Entry, collect 1 mL and dilute as needed to perform the HIV-1 RNA assay. At all other time points, collect 3 mL and process specimen for storage of PBMCs in addition to plasma for the RNA assay, if possible.
5. At Entry, collect 3 mL for storage for primary, secondary, and other evaluations if the infant weighs <3 kg; collect 5 mL if the infant weighs ≥3 kg.
6. At Entry and Week 14, collect 2 mL for storage for exploratory evaluations only if the infant weighs ≥ 3 kg at the visit; otherwise, do not collect any blood for exploratory evaluations at these visits. At Weeks 2, 6, 10, and 16, no additional blood is collected for exploratory evaluations but any plasma and PBMCs remaining from specimens collected for primary, secondary, and other evaluations will be stored for exploratory purposes (indicated with "X^{6}").
7. Refer to Section 6.13. Infants who are withdrawn or terminated before completing the Week 24 Visit should have urinalysis performed and 5 mL of blood drawn for storage for primary, secondary, and other evaluations; infants who are withdrawn or terminated after the Week 24 Visit should not have urinalysis performed and should have 7 mL of blood drawn for storage for primary, secondary, and other evaluations. For all infants, laboratory evaluations that have been performed within the two weeks prior to the Early D/C Visit need not be repeated.
8. Refer to Section 6.12.
9. The Week 14 Visit is targeted to take place on Day 98, with a preferred window of ±7 days and an allowable window of -7 to +14 days. Every effort should be made to conduct this visit as close as possible to the target date and within the preferred window. If the visit cannot be conducted within the preferred window, the visit may be conducted within the allowable window with approval in advance from the CMC. Also note that the Week 14 and Week 16 allowable visit windows overlap by a period of seven days. The Week 14 Visit should preferably be conducted before this period of overlap. However, if this is not possible, the Week 14 Visit may be conducted during the period of overlap and, in this case, the Week 14 and Week 16 Visits may be combined (i.e., all Week 14 and Week 16 visit procedures may be performed on one day).
10. **Resistance testing will be performed at Entry and at Week 14 for infants with HIV-1 RNA >500 copies/mL.**

2. In Section 5.7.1, Concomitant ARVs, second paragraph:

   Site clinicians may order **real-time non-study-provided** ARV resistance testing at their discretion to inform regimen management and ARV selection; if such testing is performed, results will be entered into eCRFs. The details of each regimen change will be source documented and entered into eCRFs, including the specific reason for the change.

   Note: ARV resistance testing will also be performed in batch using stored samples at Entry and at Week 14 for infants with plasma HIV-1 RNA >500 copies/mL. The results of this testing will be provided to site clinicians for entry into eCRFs and provision to participants' parents or guardians. Site clinicians will also provide the results to participants' primary HIV care providers if agreed to by the parent or guardian.

3. In Section 6.17.2, Specimen Preparation, Testing, Storage, and Shipping, third paragraph:

   Specimens stored at site laboratories for the primary antiviral activity outcome — concentration of HIV-1 DNA in PBMCs at Week 14 — are expected to be requested for shipment once all enrolled infants have reached Week 14 of follow-up; specimens for ARV drug concentration assays**,** ~~and~~ VRC01 resistance assays**, and ARV resistance assays** are also expected to be requested at this time.

4. In Section 13.9, Management of Incidental Findings, first paragraph:

   Site clinicians will inform infants' parents or legal guardians of all clinically meaningful physical exam findings and laboratory test results, including hematology and chemistry test results, CD4/CD8 cell counts, ~~and~~ HIV-1 RNA levels**, and ARV resistance test results. Site clinicians will also provide ARV resistance test results to infants' primary HIV care providers if agreed to by the parent or guardian.** When applicable, site clinicians will provide referrals to non-study sources of medical care further evaluation and/or treatment of these findings.

C. Other Minor and Administrative Updates

1. In the Abbreviations and Acronyms listing, reference to the NIAID Vaccine Immune T-Cell and Antibody Laboratory is removed:

   ~~NVITAL NIAID Vaccine Immune T-Cell and Antibody Laboratory~~

2. On the Protocol Title Page and in the Protocol Team Roster, updates are incorporated to reflect current team membership:

   Protocol Title Page

   NIAID Medical Officer**s**: Mary Elizabeth Smith, MD
   Dwight Yin, MD, MPH

   NICHD Medical Officer: ~~Rohan Hazra, MD~~ **Sai Majji, PhD**

Protocol Team Roster

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3. In the Site Roster, the member listing is updated to reflect a change of site investigator:

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4. In several protocol sections, references to websites are updated:

Section 7.3.1, EAE Reporting to DAIDS, first and second paragraphs

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at:
~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual~~
https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at:
~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.~~
https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting

Section 7.3.3, Grading Severity of Events, first paragraph

For infants in both study arms, adverse events will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.1, dated March 2017, which is available on the **DAIDS** RSC website:
~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables~~
https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

Section 11.2, Essential and Source Documents and Access to Source Data, first paragraph

All DAIDS policies referenced in this section are available at:
~~www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures~~
https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

Section 11.3, Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at:
~~www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures~~
https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

Section 14.2, Protocol Registration, fourth paragraph

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available **at** ~~on the RSC website~~:
~~http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual~~
https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

5. In protocol Section 9.5.1, Monitoring by the Protocol Team, Antiviral Activity:

   The CMC will monitor plasma HIV-1 RNA levels as a real-time measure of antiviral activity. The SDMC will generate individual RNA profiles for each infant ~~and summary descriptive statistics for the change from baseline (Week 0) across arms~~ for routine review by the CMC.

6. In protocol Section 9.6.3, Other Analyses, Antiviral Activity, third paragraph:

   Other analyses will additionally include sensitivity analyses of the primary outcomes, in particular restricting the VRC01 analysis set to ~~those~~ **infants** who received all four injections; **excluding infants who received suboptimal antiretroviral treatment; including infants who comprise** the intent-to-treat ~~analyses~~ **population**; and **performing** analyses with alternative censoring and imputation methods. **These analyses will be further specified in the statistical analysis plan.**

7. In Section 10.2, Pharmacology Data, reference to the NIAID Vaccine Immune T-Cell and Antibody Laboratory is removed and replaced with more general references to the laboratory specified in the Laboratory Processing Chart (LPC):

   Data expected to be used for PK analyses include the following: demographics (sex and age); height and weight; VRC01 dosing details (date, time, dose administered, administration location); and sample collection details (date and time of collection). For each infant randomized to Arm 1, seven samples are expected to be collected for PK evaluations, at study Entry (Day 0) and Weeks 2, 6, 10, 14, and 16. Samples collected at Entry and Weeks 2, 6, and 10 will be collected prior to VRC01 dosing. All sample collection data will be documented in LDMS.

   Assay Location: Plasma samples will be shipped to the ~~NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL)~~ **laboratory specified in the LPC,** where they will be assayed for concentrations of VRC01.

   Assay Methods: All assay methods will be immune-based, standardized with a filed Methods Report, and performed under Good Clinical Laboratory Practice conditions at ~~NVITAL~~ **the laboratory specified in the LPC**.

   Reporting of Assay Data: Real-time PK evaluations will not be performed in this study. Assay data are expected to be evaluated at two time points:

   - An interim PK analysis will be undertaken when six infants randomized to Arm 1 have received two doses of VRC01 and have specimens available for analysis through Week 6. At this time, all PK samples collected from all infants thus far will be shipped and assayed at ~~NVITAL~~ **the laboratory specified in the LPC**. These results will be compared to those predicted from IMPAACT P1112 with an emphasis on VRC01 concentrations, and their variability, prior to dosing at Weeks 2 and 6. As described in section 9.5, results will then be reported to the CMC and SMC for purposes of assessing whether a dose adjustment may be indicated.

   - A final PK analysis will be undertaken after study completion. All remaining PK samples will be shipped and assayed at ~~NVITAL~~ **the laboratory specified in the LPC** after completion of follow-up. All VRC01 concentration data (including data from the interim analysis) will be combined for final analysis and final results will be reported to the Protocol Team.

D. Operational Guidance from Protocol Clarification Memorandum (CM) #2, dated 01 April 2020

This CM provides operational guidance to study sites from the IMPAACT 2008 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the Clinical Management Committee (impaact.2008cmc@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

Visit Scheduling

- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the allowable visit window. Visits conducted prior to opening of the allowable window would also be preferred to completely missing a visit at a later date.
- Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the allowable visit window. Visits conducted after closing of the allowable window would also be preferred to completely missed visits.
- Effective with the issuance of this CM, the allowable window for the Week 24 and Week 36 visits is broadened to ±6 weeks; the allowable visit window for the Week 48 visit is broadened to -6 to +12 weeks.
- In the event that any scheduled visits or procedures are missed, all participants should remain on-study for the full duration of follow-up (i.e., through the Week 48 visit) if possible.

Prioritization of Study Visit Procedures

- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Sites may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, site staff should communicate with participants' caregivers to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.
- Sites with limited capacity to conduct study visits should prioritize the visits outlined below for participants in <u>both study arms</u>. When applicable, specimen collection should be prioritized per protocol Section 6.17.1.
  - First priority visits:
    - Weeks 2, 6, and 10: These visits include VRC01 administration (for Arm 1 participants) and specimen collection (for all participants). **VRC01 administration must be performed on-site** with personnel and supplies available in case of an immediate hypersensitivity reaction. If these visits cannot be conducted on-site, procedures other than VRC01 administration may be performed off-site if the requirements listed above, particularly the requirements pertaining to specimen collection and transport, can be met. If specimen collection cannot be

performed off-site, other visit procedures (e.g., history taking, cART adherence assessment) may be performed remotely rather than in-person.
    - Week 14: These visits include specimen collection for assessment of primary study outcome measures. These visits may be conducted off-site if the requirements listed above, particularly the requirements pertaining to specimen collection and transport, can be met. If specimen collection cannot be performed off-site, other visit procedures (e.g., history taking, cART adherence assessment) may be performed remotely rather than in-person.
    - Weeks 3, 7, and 11: These visits should be conducted in-person (on-site or off-site) whenever possible. If in-person visits are not possible, reactogenicity assessments and history taking may be performed remotely.
  - Second priority visits:
    - +3-Day Contacts after Weeks 2, 6, and 10: Per protocol Section 6.16, these contacts may be conducted remotely.
    - Weeks 24, 36, and 48: These visits involve specimen collection and may be conducted off-site if the requirements listed above can be met. If specimen collection cannot be performed off-site, other visit procedures (e.g., history taking, cART adherence assessment) may be performed remotely rather than in-person.
  - Third priority visits:
    - Weeks 16 and 20: These visits are of lowest priority. They involve specimen collection and may be conducted off-site if the requirements listed above can be met. If specimen collection cannot be performed off-site, other visit procedures (e.g., history taking, cART adherence assessment) may be performed remotely rather than in-person.

Study Drug Supply

- No changes in procedures for preparing, dispensing, or administering study product (VRC01) are permitted. These procedures must be performed on-site to ensure adherence to product temperature requirements. In addition, study product must be administered in a clinical setting to ensure appropriate management in the rare event of an acute hypersensitivity reaction.

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2008.
- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
- In consultation with the Division of AIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.