Summary of Changes Included in the Full Protocol Amendment of:

IMPAACT 2016
Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

The Amended Protocol is Identified as:

Version 2.0, Dated 13 January 2023

DAIDS Study ID #38506

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT 2016 study, including the study informed consent and assent forms, and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed, and all required approvals of this amendment must be obtained prior to initiating this study. Likewise, informed consent and assent must be obtained for this study using site-specific informed consent and assent forms that correspond to this amendment.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, study sites must submit a registration packet for protocol Version 2.0 to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for protocol Version 2.0 after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be obtained for site study activation at each site.

This Summary of Changes, Version 2.0 of the protocol, corresponding site-specific informed consent and assent forms, and all associated IRB and regulatory entity correspondence should be retained in each site's essential document files for IMPAACT 2016.

Summary and Rationale

The primary aims of this amendment are to: 1) update the background and rationale sections to incorporate recently published results from the *Kigali Imbereheza Project* (KIP) and the *Sauti ya Vijana* (The Voice of Youth) Pilot Study (SYV) — two studies of interventions that address adherence to antiretroviral therapy (ART) and mental health needs for youth living with HIV in sub-Sarah Africa; 2) add accrual monitoring procedures for the randomized trial to ensure enrollment goals are met, including criteria for an assessment of study futility; 3) incorporate language reflective of current/updated DAIDS and IMPAACT Network policies and procedures; 4) add precautions and study considerations related to the COVID-19 pandemic, and 5) incorporate other updates and clarifications regarding terminology and study implementation.

Modifications incorporated in the protocol are summarized below and are detailed in the Implementation section of this document.

- The background and rationale sections of the protocol are updated to include published results from the *Kigali Imbereheza Project* (KIP) and *Sauti ya Vijana* (The Voice of Youth) Pilot Study (SYV). KIP, conducted in Kigali, Rwanda from 2014-2017, is a six-session Trauma-Informed Cognitive Behavioral Intervention-enhanced (TI-CBT-e) to improve antiretroviral adherence for youth living with HIV. SYV was also designed to improve ART adherence among 12-24 year old living with HIV in Tanzania. Both interventions were delivered by young adults living with HIV or had experience delivering group-based interventions. Both interventions addressed mental health, although this was not the primary objective. Results from KIP were mixed, with no change in self-reported ART adherence and some improvement across all participants in mental health distress. Methodological limitations in KIP (e.g., non-biological assessment of ART adherence, strong comparison group, extensive clinic-based wrap-around services) temper the conclusions that could be drawn. SYV was a pilot study that showed trends towards efficacy with improved self-reported and objective measures of ART adherence, a slight reduction in mental health symptoms, and a 10% increase in virologic suppression for youth who received the intervention as compared to the control arm at 6 months.

  Lessons learned from both studies underscore the need for a more rigorous evaluation of trauma-informed interventions in low and middle income countries (LMICs). Guided by these lessons, IMPAACT 2016 significantly improves on prior research by: (a) ensuring greater methodological rigor in study procedures; (b) more comprehensive and detailed training and facilitator manuals; (c) restricting the participants to youth with documented mental health distress; (d) powering the study to evaluate mental health outcomes; and (e) ensuring that the comparison arm more accurately represents the standard of care in LMICs.

- The accrual monitoring procedures for youth participating in the randomized trial has been updated and enhanced to ensure timely enrollment and include specific criteria to trigger a review by the independent Study Monitoring Committee if accrual projections are not met to assess study futility.

- The inclusion criteria are updated to define the screening period and make HIV testing assays and requirements at screening consistent with current IMPAACT guidelines.

- The recruitment, screening, and enrollment procedures section for the pilot test/randomized trial section is updated with instructions and precautions required for pre-screening for potential COVID-19 or other relevant infectious disease exposures consistent with current local clinical practice, public health, and/or infection control guidelines.

- The software and mechanisms for collecting self-administered questionnaires have been modified. The questionnaires will be completed using the Medidata Patient Cloud application. The Data Management Section has been updated and throughout the protocol 'Computer assisted self-interview' (CASI) is replaced with 'electronic questionnaire',

- Ascertainment of gender identity from youth participants in the Pilot Study and Randomized Trial at entry has been added per policies in the IMPAACT Manual of Procedures. The information will be collected from participants in private, without their parent or guardian present. Sites can opt-out of the collection of this information.

- The study monitoring section is updated to reflect current DAIDS policies for clinical site monitoring, which allow for on-site and remote monitoring.

- The references to the retired DAIDS policies (specified below) have been removed. These policies have been replaced with instructions for sites that are now contained in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual throughout the protocol.
    - Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials
    - Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials
    - Requirements for Clinical Quality Management Plans
    - Requirements for Manual of Operational Procedures
    - Clinical Site Requirements: Enrolling Children (including Adolescents) in Clinical Research

- The reference to the DAIDS policy on identifying and classifying critical events, which has been retired, has been removed. The protocol is updated throughout with the regulatory reporting requirements that still apply for the conduct of this study.

- The clinicaltrial.gov section has been updated with the NIH and regulatory requirements for entering study results into ClinicalTrials.gov.

- Terminology and language throughout the protocol are updated for consistency with current IMPAACT processes and to remove potentially stigmatizing references.

- The sample informed consent and assent forms are updated where applicable to reflect current requirements of the Common Rule (per United States Code of Federal Regulations 45 CFR 46).

- A new appendix (Appendix IX) is added to provide guidance and operational flexibility to safeguard the health and well-being of study participants in the context of coronavirus disease 2019 (COVID-19). This guidance is intended for use at sites experiencing disruptions or limitations of usual operations due to the COVID-19 pandemic.

- The Protocol Team and Study Site Rosters are updated to reflect current membership. Cited references and links to websites are updated where applicable. Administrative and regulatory updates and corrections of typographical and other errors are incorporated throughout the protocol for accuracy, consistency, and clarity.

Implementation

The changes in the protocol text and informed consent and assent forms are summarized below, generally in order of first appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions.

1. The amended protocol is identified as FINAL Version 2.0, dated [TBA] 2023. A Version 2.0 protocol signature page is provided. The table of contents, table numbering, protocol team and study site rosters, cited references, and links to websites are updated.

2. Section 1.2, Prior Research, was updated to incorporate recent findings from KIP and SYV studies. Section 1.3, Rationale, was updated. Section 1.0 throughout was edited for clarity and to ensure language reflects the NIH language guidance.

   New references cited in Sections 1.2 and 1.3 are as follows:

   Dow DE, Mmbaga BT, Gallis JA, Turner EL, Gandhi M, Cunningham CK, et al. A group-based mental health intervention for young people living with HIV in Tanzania: results of a pilot individually randomized group treatment trial. BMC Public Health. 2020;20(1):1358.

   Willis N, Milanzi A, Mawodzeke M, Dziwa C, Armstrong A, Yekeye I, et al. Effectiveness of community adolescent treatment supporters (CATS) interventions in improving linkage and retention in care, adherence to ART and psychosocial well-being: a randomised trial among adolescents living with HIV in rural Zimbabwe. BMC Public Health. 2019;19(1):117.

   Simms V, Weiss HA, Chinoda S, Mutsinze A, Bernays S, Verhey R. Peer-led counselling with problem discussion therapy for adolescents living with HIV in Zimbabwe: A cluster-randomised trial. PLoS Med. 2022;19(1).

   Donenberg GR, Cohen MH, Ingabire C, Fabri M, Emerson E, Kendall AD, et al. Applying the Exploration Preparation Implementation Sustainment (EPIS) Framework to the Kigali Imbereheza Project for Rwandan Adolescents Living With HIV. J Acquir Immune Defic Syndr. 2019;82 Suppl 3(Suppl 3):S289-s98.

   Donenberg GR, Fitts J, Ingabire C, Nsanzimana S, Fabri M, Emerson E, et al. Results of the Kigali Imbereheza Project: a 2-arm individually randomized trial of TI-CBT enhanced to address ART adherence and mental health for Rwandan youth living with HIV. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2022;90(1):69-78.

   Gichane MW, Sullivan KA, Shayo AM, Mmbaga BT, O' Donnell K, Cunningham CK, et al. Caregiver Role in HIV Medication Adherence Among HIV-Infected Orphans in Tanzania. AIDS Care. 2017;Provisionally accepted for publication.

   Libous JL, Montañez NA, Dow DE, Kapetanovic S, Buckley J, Kakhu TJ, et al. IMPAACT 2016: Operationalizing HIV Intervention Adaptations to Inform the Science and Outcomes of Implementation. Frontiers in Reproductive Health. 2021;3.127.

3. Section 3.2, Randomized Trial, 1st paragraph, the sentence below is added at the end.

   Mixed gender groups will be required to have a minimum of two participants of each gender.

4. Section 4.1, Inclusion Criteria: Youth Participants (Pilot Test/Randomized Trial), 1st paragraph

All of the criteria listed below must be met in order for youth to be included in the Pilot Test and Randomized Trial. **The screening period begins when informed consent/assent is obtained and ends immediately prior to enrollment. For criteria involving a potential participant's medical history, it is expected that each inclusion condition will be assessed at screening and subsequently reviewed and confirmed on the day of study entry, prior to enrollment.**

5. Section 4.1.3, Inclusion Criteria: Youth Participants (Pilot Test/Randomized Trial)

Confirmed **to be living with** HIV ~~infection~~ based on **test results from** ~~documented testing of~~ two samples collected **from two separate blood collection tubes per Sample #1 and Sample #2, as described below**. ~~at different time points as documented in medical records or by confirmatory testing~~

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One enzyme immunoassay (EIA) OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and the third rapid test must be from a third manufacturer or based on a third principle or epitope. **The use of combination antigen-antibody based rapid tests is allowed.**

- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

All study-specific samples tested to determine HIV status must be whole blood, serum, or plasma. Testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center. Testing methods should be FDA-approved, if available.
Note: Test results may be obtained from medical records or from testing performed during the study screening period, as follows:

- **For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., Good Clinical Laboratory Practices [GCLP], or Virology Quality Assurance [VQA]) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.**

- **If adequate source documentation is not available, Sample #1 and/or Sample #2 must be collected during the study screening period and tested in the study site's designated testing**

laboratory. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to GCLP guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the study site's VQA-certified laboratory.

~~All samples tested must be whole blood, serum, or plasma. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a VQA-approved laboratory. For tests performed in other (non-GCLP-compliant or non-VQA-approved) settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.~~

6. Section 4.1.4, Inclusion Criteria: Youth Participants (Pilot Test/Randomized Trial)

   At screening, aware of **their** ~~his or her~~ HIV infection **status**, as **determined** ~~confirmed~~ by **the site** ~~I~~**i**nvestigator. ~~of Record or designee.~~

7. Section 4.1.5, Inclusion Criteria: Youth Participants (Pilot Test/Randomized Trial)
   At screening, has been prescribed ART for a minimum of 24 weeks prior to screening **as determined by the site investigator** based on **participant/parent or guardian report and/or** medical records. ~~documentation.~~

8. Section 4.2, Exclusion Criteria: Youth Participants (Pilot Test/Randomized Trial), 1st paragraph

   Youth who meet any of the following criteria will be excluded from the Pilot Test and Randomized Trial; **in these criteria, "at entry" is used to refer to the day of enrollment in the study:**

9. Section 4.6, Recruitment, Screening, and Enrollment Process (Pilot Test/Randomized Trial), 2nd paragraph is added

   Before initiating in-person contact with a potential youth participant, caregiver, parent and/or guardian, study site staff are expected to follow institutional policies for pre-screening for potential COVID-19 or other relevant infectious disease exposures consistent with current local clinical practice, public health, and/or infection control guidelines. This may involve, for example, pre-screening prior to a scheduled visit by telephone and/or pre-screening prior to entry into the site facility on the day of a scheduled visit. Potential participants identified with current symptoms suggestive of COVID-19, or with recent test results or contacts that require quarantine, should not initiate the study screening process until symptoms have resolved and quarantine requirements have been completed. Likewise, if COVID-19 symptoms, test results, or contacts requiring quarantine are identified after the study screening process has been initiated, screening should be suspended until symptoms have resolved and quarantine requirements have been completed.

10. Section 5.5, Study Evaluations and Measures

    Outcome measures for the Randomized Trial are described below and in Sections 5.5.1-5.5.3. Feasibility and acceptability measures for TI-CBT adaptation are described in Section 5.5.4.

Youth Participants

Measures collected during the Randomized Trial only (not Pilot Test) form the basis for study evaluation.

Outcome measures include self-reported mental health symptoms [PHQ-9 (136); UCLA PTSD-RI (64); GAD-7 (141)]; self-reported ART adherence (138); barriers to adherence; report of caregiver behavior; AIDS-related stigma scale (139); gender-based violence (140, 141); gender roles; sexual risk behavior and drug/alcohol use (142); demographics; and HIV status disclosure. Measures will be translated and back translated in the local language prior to study use as needed. Measures will be collected at baseline, immediately post-last group session, and at 6- and 12-months post-first group session, with demographics collected once at baseline. **Questionnaires will be self-administered and electronic; refer to Section 10.1 for data collection procedures.** ~~Youth will complete self-report measures via Computer-Assisted Self-Interview (CASI), but trained research staff will remain in the room to answer participants' questions or read questionnaire items to participants as needed. In the event CASI is inaccessible due to environmental interference (e.g., power outages) or other unforeseen cause, paper versions of the questionnaires will be administered to participants, and data will be entered into CASI by study staff when CASI is next accessible.~~

Laboratory based evaluations include quantitative drug concentration levels from hair samples as a biologic measure of adherence; HIV-1 RNA (viral load); and biomarkers of inflammation (e.g., hsCRP, sCD14, IL1β, IL6, D-dimer, and TNFα). ~~Measures are further described throughout Section 5.5 below.~~

Caregiver Participants

Measures collected during the Randomized Trial only (not Pilot Test) form the basis for study evaluation.

Outcome measures include caregiver-reported HIV attitudes, knowledge, and beliefs, and AIDS-related stigma (143), caregiver involvement in youth adherence using a measure developed for the KIP study in Rwanda, and caregiver report of youth behavior (CBCL) and demographics. Measures will be translated and back translated in the local language prior to study use as needed. Measures will be collected at baseline, immediately post-last group session, and at 6- and 12-months following the first youth group session of the caregiver's youth, with demographics collected once at baseline. **Questionnaires will be self-administered and electronic; refer to Section 10.1 for data collection procedures.** ~~Caregivers will complete measures via CASI, but trained research staff will remain in the room to answer participants' questions or read questionnaire items to participants as needed. In the event CASI is inaccessible due to environmental interference (e.g., power outages) or other unforeseen causes, paper versions of the questionnaires will be administered to participants, and data will be entered into CASI by study staff when CASI is next accessible. Measures are further described throughout Section **Error! Reference source not found.** below.~~

11. Section 6.1.2, Youth Pilot Test: Pre-Entry Visit, the text below is added

Youth Pre-Entry Visit Procedures for Pilot Test (up to 14 days prior to enrollment)	
Clinical	• Obtain targeted medical/medications history per Section **Error! Reference source not found.** ***If applicable*, ascertain gender identity**

Gender identity should be ascertained at the Pre-Entry visit; however, this procedure should not be performed at sites that have formally opted out of collection of gender identity data, in accordance with policies specified in the IMPAACT Manual of Procedures. Gender identity data should be collected from participants in private, without their parent or guardian present.

12. Section 6.3.2, Youth Randomized Trial: Pre-Entry Visit, the text below has been added.

Youth Pre-Entry Visit Procedures for Randomized Trial (up to 14 days prior to enrollment)	
Clinical	• Obtain targeted medical/medications history per Section **Error! Reference source not found.** ***If applicable*, ascertain gender identity**

Gender identity should be ascertained at the Pre-Entry visit; however, this procedure should not be performed at sites that have formally opted out of collection of gender identity data, in accordance with policies specified in the IMPAACT Manual of Procedures. Gender identity data should be collected from participants in private, without their parent or guardian present.

13. Section 7.2, Safety Related Data Collection, the last paragraph below is added

In addition, for any event that is assessed as serious as defined in Version 2.0 of the DAIDS EAE Manual due to the event resulting in hospitalization or prolongation of hospitalization, data regarding the hospitalization will be entered into eCRFs.

14. Section 7.3.1. EAE Reporting to DAIDS, 1st and 2nd paragraphs

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 (January 2010) of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual), which is available on the DAIDS RSC website at **https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids** ~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.~~

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 using the DAIDS EAE Form. This form is available on the DAIDS RSC website at **https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-rportineg**. ~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.~~

15. Section 9.3, Randomizations, the sentence below is modified

Randomization will be stratified by gender to assure approximate balance between study arms.~~; there will be no accrual limits for the strata.~~

16. Section 9.3.1, Sample Size, under Randomized Trial, 4th paragraph, the formula in the 4th sentence is corrected.

This means that if the required sample size for a study without clusters is N, then the required size for a cluster randomized trial to have the same power will be $N_c=N*(1 + (\sout{m}\ \mathbf{n} - 1)*ICC)$ and the average group size will be $n=N_c/m$.

17. Section 9.4.1, Monitoring by the Protocol Team, under *ADAPT-ITT Progress, the text below is modified.*

    Designated ~~The Core~~ protocol team **members and site staff** will monitor the outcomes of the ADAPT-ITT process. If the TI-CBT Intervention is **deemed** not acceptable or feasible at one of the sites, **the CMC will be convened**. **The CMC may recommend** ~~team will discuss either~~ adding a site or increasing the number of TI-CBT and Discussion Control groups at other sites**.**

18. Section 9.4.1, Monitoring by the Protocol Team, under *Randomized Trial Progress and Quality of Study Conduct and Participant Retention*, the text in these sections was removed and the text below added.

    The CMC is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct.

    The CMC has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. Accrual performance will be reported by the DMC, by site and across sites at least monthly. Each site is expected to accrue one TI-CBT group and one discussion control group within three months of the first participant screening at the site. For any site that may not meet this expectation, the SMC will be informed, and the CMC will communicate with the site to identify barriers to enrollment and operational strategies and action plans to address these. If the site is subsequently not able to accrue one TI-CBT group and one discussion control within the next three months (approximately six months from the first screening) the team will request a SMC review of operational futility

    The CMC will also monitor participant retention, and other key indicators of the quality of study conduct (e.g., data and specimen completeness) based on reports (pooled across the TI-CBT and the Discussion Control Arms) generated at least monthly by the DMC. The CMC will take action with study sites as needed to ensure high-quality study conduct throughout study implementation.

19. Section 9.5.1, Primary Outcome Measures, 2nd paragraph, 2nd sentence is corrected.

    For cluster randomized trials, one valid method for analyzing intervention effects is to compute the mean for each ~~site~~ **group** and then do a two-sample t-test on the site-specific measures.

20. Section 9.5.2, Secondary and Other Outcome Measures, 2nd sentence is corrected.

    For dichotomous measures (e.g., viral suppression), the first stage of the cluster-level analyses will involve calculating the proportion with that outcome ~~at~~ **in** each ~~site~~ **group**, and then proceeding as above using t-tests.

21. Sections 10.1, 10.2, 10.3, 13.3 and 13.4 refer to DAIDS policies that have been retired and replaced with instructions for sites that are now included in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual. Throughout the protocol, references to these policies are replaced with requirements specified in the DAIDS SCORE Manual. The SCORE Manual is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

22. Section 10.1, Data Management

As described in Section 4.6, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the **DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual which is available at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations. p**~~olicy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 10.2).~~

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs using Medidata Rave (refer to Table 6, Table 7, Table 8, and Table 9 below) with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS. **The Protocol Team and/or study oversight bodies (e.g., SMC) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation**

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the ~~Subject~~ **Study** Enrollment System is available on the DMC portal at: https://www.frontierscience.org.

Self-administered electronic questionnaires will be completed by youth and caregiver participants using the Medidata Patient Cloud application (app) on a site-provided compatible device (i.e. iPad, iPhone, or Mac). Electronic questionnaires will be translated into local languages prior to study use, as needed. The site will pre-install the app on a device and provide youth and caregiver participants with additional instructions for completing the questionnaires as needed. Youth and caregiver participants will complete the questionnaires at the site with trained research staff present to answer participants' questions or read questionnaire items to participants as needed. If the questionnaires are inaccessible due to environmental interference (e.g., power outages, app not accessible) or any other unforeseen cause, paper versions of the questionnaires will be administered to participants, and the data will be entered by study staff when the app is next accessible.

Refer to Error! Reference source not found.**,** Error! Reference source not found.**,** Error! Reference source not found.**, and** Error! Reference source not found. **below for source and data entry documentation requirements**.

~~Data collected on questionnaires administered to participant via CASI will be stored in the central database at the DMC and transferred through standardized mechanisms to the protocol statistician for analysis. The data will not be entered into eCRFs (refer to Table 6, Table 7, Table 8, and Table 9 below). In the event CASI is not accessible due to environmental interference (e.g. power outage, off-site visit) at the time of administering to participants, paper versions of the questionnaires will be administered to participants, and data will be entered into CASI by study staff when CASI is next accessible.~~

23. Section 10.1, Table 6 and Table 7, the following row under baseline is added.

Gender identity (if applicable) **eCRF**

24. Section 11 Clinical Site Monitoring

Under contract to ~~DAIDS~~ **NIAID or NICHD** site monitors ~~under contract to NIAID~~ will ~~visit study sites to~~ inspect study **site** facilities and review participant study records— including **informed** consent **and assent** forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. ~~The~~ Monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by ~~the~~ monitors.

Monitoring visits may be conducted on-site or remotely. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity [ref]. The site will make available study documents for site monitors to review utilizing a secure platform.

Reference added for the section above: US Department of Health and Human Services. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. March 2020, Updated on August 30, 2021.

25. Section 12.1, Institutional Review Board/Ethics Committee Review and Approval, 1st paragraph

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific **informed consent forms** ~~ICFs~~ **and assent forms** in accordance with 45 CRF 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and **must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following:** ~~any~~ unanticipated problems involving risks to participants or others**; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.**

26. Section 13.5 Critical Event Reporting is removed

27. Section 13.5 Clinical Trials.gov was renumbered and updated as specified below.

The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The Protocol Team will comply with this policy as well as the requirements of 42 CFR 11.

This **study** ~~protocol~~ is not subject to the Food and Drug Administration Amendments Act of 2007 **or the NIH Policy on Dissemination of NIH-funded Clinical Trial Information**. ~~(FDAAA).~~ However, it will be registered in ClinicalTrials.gov to meet International Committee of Medical Journal Editors requirements.

28. Appendix III, Sample Informed Consent form for Youth and Caregivers in Pilot Test

— Under Introduction, the text below is added

Here is some important information about the Focus Group for the study:

- **The study is being done to find out if group sessions led by older peers can help youth living with HIV.**
- **The Focus Groups are being done to prepare for the study.**
- **As part of the Focus Group, you will be told about the study and asked to give your opinion about how different parts of the study are planned to be done.**
- **There will be two focus groups conducted separately. One group will consist of youth living with HIV and the other group will consist of caregivers of youth living with HIV.**
- **Each group will meet for 2 hours.**
- **There are possible risks to participating in the Focus Group. One possible risk is that some topics discussed during the Focus Group may make you feel uncomfortable, embarrassed, or upset.**
- **There may be no benefit to participating in the Focus Group.**
- **The decision to participate is voluntary (your choice). Your decision on participation in the Focus Group will have no effect on the services you or your youth would normally receive.**

— Under About the Focus Group, the text below is added

The study is being done to find out if group sessions led by older peers can help youth living with HIV. The study will look at the effects of the group session on mental health and how well youth are able to take their medicines for HIV (ARVs). The study will include about 200 youth from Botswana, Malawi, South Africa, and Zimbabwe. The study will also include caregivers of these youth.

The purpose of the Focus Group is to see how you feel about specific parts of the study. This information will be reviewed and may be used to inform changes in how parts of the study are planned to be done.

— Under What happens in the Focus Group, the text below is modified

About ~~5~~ **8** people will take part in each Focus Group and each group will meet for about 2 hours.

29. Appendix IV, Sample Informed Consent form for Youth in Pilot Test:

— Under Introduction, the text below is added

Here is some important information about the study:

- **This study will look at the effects of group-based counseling sessions led by study staff on the mental health of youth living with HIV and adherence to their medication.**
- **The purpose of the Pilot Test is to practice conducting procedures that will be done in the study and to help us learn the best way to conduct the study.**
- **As part of the Pilot Test, youth will attend a 'counseling' group led by an older peer. The group will consist of about 8 youth participants, ages 15-19 years living with HIV.**
- **Youth will attend six, two-hour sessions over eight weeks. A final two-hour session will take place six months later.**
  Youth participants will complete questionnaires about their mental health, and no information collected will be analyzed.
  There may be no benefit to participating in the Pilot Test.

- **There are possible risks to participating in the Pilot Test. One possible risk is that some topics discussed during the group sessions may make you feel uncomfortable, embarrassed, or upset.**
- **The decision to participate is voluntary (your choice). Your decision will have no effect on the services you would normally receive.**

— Under #5, the below text is added

[You/Your youth] will answer questions about taking ART, violence in relationships, roles of men and women, stigma, alcohol and drug use, sexual activity, and [your/their] caregiver behaviors. These questions will be answered on a computer **and no information will be analyzed. At the end of the last session, you will be asked questions on how you felt about the group sessions**. We will review medical records to confirm changes in [your/your youth's] health and/or medications. We will also pretend to collect [your/your youths] hair and blood, but we will not cut any hair or draw blood.

***[Sites that have opted out of collection of gender identity data should remove this paragraph; sites may also modify the explanation of gender identity to reflect locally applicable gender options and descriptions.] W*e will ask [you/your] youth about their gender identity. Gender identity is the internal sense people have of whether they are male, female, gender non-binary, or something else. A person's gender identity may be different from their sex at assigned birth. We will ask you/your youth about their gender identity in private.**

— Under #10, the below text is modified

All people who take part in the group session are asked respect the privacy of others in the group. However, it is possible that people in the group could talk about the group with others, **including a parent or guardian**. If this happens, others could find out that [you/your youth] took part in a group. [You/Your youth] could be treated badly or unfairly. [You/Your youth] could feel stress or embarrassment.

— Under #14, the below text is added

[Your/your youth's] study information may be disclosed to other authorities if required by law. *[Sites may add more specific detail here describing local laws that may be applicable]*

30. Appendix V, Sample Informed Consent form for Caregiver in Pilot Test:

— Under Introduction, the text below is added

Here is some important information about the study:

- **This study will look at the effects of group-based counseling sessions led by study staff on the mental health of youth living with HIV and adherence to their medication.**
- **The purpose of the Pilot Test is to practice conducting procedures that will be done in the study and to help us learn the best way to conduct the study.**
  If youth agree, their caregiver will also participate in separate group sessions, along with other caregivers. As part of the Pilot Test, caregivers will attend group sessions led by study staff. The sessions will discuss topics such as HIV knowledge, stigma, and how to support youth living with HIV in taking their medication.

Each group will consist of about 8 caregivers.

- **Caregivers will attend two, two-hour sessions on two separate weeks and within the time that youth groups are taking place.**
- **Caregivers will complete questionnaires about HIV knowledge and stigma, medication adherence, and youth behavior, and no information will be analyzed. There may be no benefit to participating in the study.**
- **There are possible risks to participating in the study. One possible risk is that some topics discussed during the group sessions may make you feel uncomfortable, embarrassed, or upset.**
- **The decision to participate is voluntary (your choice). Your decision on participation in the study will have no effect on the services you or your youth would normally receive.**

— Under #3, the below text is added

At the end of the last session, you will be asked questions on how you felt about the group sessions.

31. Appendix VI, Sample Informed Consent Form for Youth in Randomized Trial:

— Under Introduction, the text below is added.

Here is some important information about the study:

- **This study will look at the effects of group-based sessions led by older peers on the mental health of youth living with HIV and adherence to their medication.**
- **In this study, there are two different types of groups- that youth may be placed in. One group is called a 'counseling' group and the other group is called a 'discussion' group.**
- **The older peer who leads the counseling group will be trained in a type of therapy called trauma-informed cognitive behavioral therapy or TI-CBT. An older peer will be available during the discussion group, but the conversation will be guided by the youths in the group.**
- **Both groups will consist of about 8 youth participants, ages 15-19 years living with HIV.**
- **The group a youth is assigned to is decided by chance. Neither the youth nor site staff will choose the group a youth is assigned.**
- **Each group will attend six, two-hour sessions over eight weeks. A final two-hour session will take place six months later.**
- **In both groups, youth participants will complete questionnaires about their mental health. Blood and hair samples will also be taken at the beginning and end of the study to look at the amount of virus and ART medication in the body.**
- **There may be no benefit to participating in the study.**
- **There are possible risks to participating in the study. One possible risk is that some topics discussed during the group sessions may make you feel uncomfortable, embarrassed, or upset.**
- **The decision to participate is voluntary (your choice). Your decision will have no effect on the services you would normally receive.**

— Under #3, the paragraph below is added.

[Sites that have opted out of collection of gender identity data should remove this paragraph; sites may also modify the explanation of gender identity to reflect locally applicable gender options and descriptions.] We will ask [you/your] youth about their gender identity. Gender identity is the internal sense people have of whether they are male, female, gender non-binary, or something else. A person's gender identity may be different from their sex at assigned birth. We will ask you/your youth about their gender identity in private.

— Under #12, the below text is modified.

All people who take part in the group session are asked respect the privacy of others in the group. However, it is possible that people in the group could talk about the group with others, **including a parent or guardian**. If this happens, others could find out that [you/your youth] took part in a group. [You/Your youth] could be treated badly or unfairly. [You/Your youth] could feel stress or embarrassment.

— Under #16, the below text is added

Your/your youth] study information may be disclosed to other authorities if required by law. [Sites may add more specific detail here describing local laws that may be applicable]

32. Appendix VII, Sample Informed Consent Form for Caregivers in Randomized Trial, under Introduction, the text below is added.

Here is some important information about the study:

- **This study will look at the effects of group-based counseling sessions led by study staff on the mental health of youth living with HIV and adherence to their medication.**
- **If youth agree, their caregiver will also participate in separate group sessions, along with other caregivers.**
- **There are two groups that caregivers may be placed in. In the first group, caregivers will attend group sessions led by study staff. The staff who leads the session will follow a type of therapy called trauma-informed cognitive behavioral therapy, or TI-CBT. The sessions will discuss topics such as HIV knowledge, stigma, and how to support youth living with HIV in taking their medication.**
- **In the second group, caregivers will attend discussion groups a study staff will be present. The staff leader will be trained in leading group discussions. The discussion topics will be picked by the caregivers.**
- **Caregivers will be placed in the same type of group session as their youth.**
- **Each group will contain about 8 caregivers.**
- **In both groups, caregivers will attend two, 2 hours sessions on two separate weeks and within the time that youth groups are taking place. A final two hour session will take place six months later and exit visit at 12 months.**
- **There may be no benefit to participating in the study**
- **There are possible risks to participating in the study. One possible risk is that some topics discussed during the group sessions may make you feel uncomfortable, embarrassed, or upset.**
- **The decision to participate is voluntary (your choice). Your decision on participation in the study will have no effect on the services you or your youth would normally receive.**

33. Appendix IX, Operational Guidance for Study Implementation at Sites Experiencing Operational Disruptions Due to COVID-19, is added.