IMPAACT 2002

Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

Manual of Procedures

Version 1.1
28 January 2017

Table of Contents

SUMMARY OF CHANGES

28 January 2017	**Version 1.0 to 1.1**
Section 8.0	**In accordance with protocol Section 6.9.2., sites are advised to store residual samples on-site until the end of study upon which samples will be shipped to the appropriate repository as per the LPC.**

1.0 Study Overview

IMPAACT 2002 is a multi-site, two-arm, cluster-randomized study to examine if a Health and Wellness Cognitive Behavioral Therapy and Medication Management (COMB-R) intervention for depression demonstrates improved outcomes for HIV-infected youth in the United States.

Study Population: HIV-infected youth, ages 12 to 24 years, diagnosed with nonpsychotic depression

Sample Size: Approximately 14 sites will be randomized to one of two study arms. A total of 156 participants will be enrolled to achieve at least 140 evaluable for primary study outcomes. The sample size may be increased to achieve a sufficient number of evaluable participants, if the percentage of non evaluable participants or the intracluster correlation coefficient turn out to be higher than assumed for the sample size calculations.

Study Intervention: Sites will be assigned to provide either COMB-R or Enhanced Standard of Care (ESC) to enrolled participants for 24 weeks.

Study Duration: Approximately 36 months total; accrual is expected to require approximately 24 months and each enrolled participant is expected to complete approximately 48 weeks of follow-up.

2.0 Preparing for the Study

This study will be conducted at the following IMPAACT clinical research sites (CRSs), which were selected by the Protocol Team based on review and approval of site selection materials. A copy of the approved site selection materials should be maintained in each site's study-specific essential document files.

CRS 3801	Baylor/Texas Children's Hospital CRS
CRS 4001	Lurie Children's Hospital
CRS 4601	UCSD Mother-Child-Adolescent HIV Program
CRS 5013	Jacobi Medical Center
CRS 5030	Emory University School of Medicine
CRS 5040	Stony Brook University Medical Center
CRS 5048	University of Southern California Medical Center
CRS 5052	University of Colorado Denver
CRS 5055	Children's Diagnostic and Treatment Center, Ft. Lauderdale
CRS 5083	Rush University Medical Center
CRS 5092	Johns Hopkins University School of Medicine
CRS 5112	David Geffen School of Medicine at UCLA
CRS 5114	Bronx-Lebanon Hospital Center
CRS 6501	St. Jude Children's Research Hospital

2.1 Investigator Responsibilities

At each site, this study must be conducted in accordance with the United States (U.S.) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP). The Division of AIDS (DAIDS) policies on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following website and must be followed throughout implementation of IMPAACT 2002:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

This study also must be conducted in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all of the above-listed regulations, policies, and guidelines should be maintained in on-site essential document files.

The Investigator of Record (IoR) at each site must sign a DAIDS Investigator of Record Form to formally indicate his or her agreement to conduct the study in accordance with the protocol and all applicable regulations, policies, and guidelines. The obligations and responsibilities assumed by the IoR when signing this form are listed on the form, which is available on the DAIDS Regulatory Support Center (RSC) website:

http://rcc.tech-res.com/clinical-research-sites/protocol-registration

IoRs may delegate their obligations and responsibilities for conducting this study to other study staff; however, delegation does not relieve the IoR of his or her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout the period of study implementation.

Consistent with the regulations, guidelines, and policies cited above, the IoR at each site must obtain all applicable ethical review approvals prior to study initiation; the IoR must also maintain these approvals in good standing throughout the period of study implementation. With regard to institutional review boards and ethics committees (IRBs/ECs), further guidance on initial and continuing review requirements is available in 45 CFR 46 and the ICH GCP guidance, as well as on the website of the U.S. Office for Human Research Protections (OHRP):

http://www.hhs.gov/ohrp/

All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their IRBs/ECs and to request that IRBs/ECs note the effective and expiry dates of all approvals. Because IMPAACT 2002 involves adolescent participants, IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to adolescents and assess the justification for their inclusion in the study (see protocol Section 12.4 and 12.5). As part of this assessment, IRB/ECs must assess the level of risk to children in the following categories:

§46.404	Research not involving greater than minimal risk
§46.405	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
§46.406	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
§46.407	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

The risk category assessed by the IRBs/ECs then determines the informed consent requirements for participation of children in the study. Specifically, per 45 CFR 46.408 (b), "the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child."

A participant at a site that requires parental/guardian permission may enroll in the study as a minor, but may reach the legal age of consent during study follow-up. In this case, they will sign the assent form upon screening and will later sign the consent form once they reach legal age, at their next scheduled visit. A participant at a site that obtained a waiver for parental permission, may enroll in the study as a minor and sign the participant informed consent form without a separate parental consent.

IRBs/ECs should document their risk determination, and study sites should adapt the signature pages of their informed consent forms as needed to accommodate the parental consent requirements associated with the IRBs'/ECs' determination. In the absence of a clearly documented determination from the IRBs/ECs, the most conservative approach specified in the regulations should be followed.

Complete documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. All submission letters should list the date of the submission, the contents of the submission, and the version number and/or version date of each document submitted.

2.2 Protocol Registration

The IMPAACT Operations Center will notify the DAIDS Protocol Registration Office (PRO) that sites with SIPs and Site Applications approved by the Protocol Team are permitted to submit for protocol registration for the study. After all required IRB/EC approvals are obtained, site staff are then responsible for submitting documentation of the approvals and other required documentation to the PRO.

Further information on the protocol registration process can be found in the *DAIDS Protocol Registration Manual*. Upon confirming receipt of all required documentation, the PRO will issue a registration notification that indicates successful completion of the process. Site staff are responsible for maintaining documentation of all submissions for the study, along with all associated approvals/notifications and other correspondence from the PRO.

2.3 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals as described in Section 2.2 above. Each site must also complete study-specific activation procedures specified by the Protocol Team. To help ensure site readiness for study initiation, the Protocol Team has specified a set of study activation requirements that must be met in order to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2002 Site-Specific Study Activation Checklist, which are provided to each of the participating sites and include sign-off on laboratory and data management readiness and completion of study-specific training.

Any questions related to the study activation process should be directed to the IMPAACT Operations Center. On a site-by-site basis, when all activation requirements have been met, the Operations Center will issue a site-specific study activation notice. At each site, no study procedures may be performed prior to receipt of the activation notice.

3.0 Study Resources

This section specifies the resources available to IMPAACT 2002 study site staff, including study-related communication and informational resources, the Data Management Center IMPAACT Portal, and other essential documents.

3.1 Study-Related Information and Communication

All IMPAACT 2002 visits and procedures must be conducted in accordance with the study protocol. The purpose of this Manual of Procedures (MOP) is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center of any such inconsistencies.

The Protocol Team has developed study-specific contacts for various types of issues and questions, as shown in Figure 3-1. For issues and questions directed to the study team, a response from the appropriate team member can generally be expected within 24 hours.

- ***General questions:*** Questions related to protocol interpretation or study implementation, including administrative, ethical, regulatory, counseling, data, and laboratory operations should be emailed to the IMPAACT 2002 Protocol Team as listed in Figure 3-1. Any questions that are not answered by the protocol or this document should also be emailed to the IMPAACT 2002 Protocol Team.

- ***Clinical and toxicity management questions and notifications:*** Questions concerning clinical management of study participants and adverse experiences should be emailed to the Core Team as listed in Figure 3-1. Additional detail is listed in Figures 3-2.

- ***Study implementation questions***: Questions related to participant eligibility, co-enrollment, potential enrollment of an ineligible participant, and/or deviation from other protocol requirements for screening and enrollment should also be directed to the IMPAACT 2002 Core Team as listed in Figure 3-1.

- ***Other types of questions*** should be managed as listed in Figure 3-1.

Figure 3-1
IMPAACT 2001 Study-Related Communications

Topic	Contact
Adding site staff to protocol email group **(IMPAACT.PROT2002@fstrf.org)**	**User Support** **user.support@fstrf.org** *(include "IMPAACT 2002" in the subject line of the message)*
Any aspect of protocol interpretation or study implementation not listed below	**IMPAACT 2002 Protocol Team** **impaact.team2002@fstrf.org** *for triage to other team members as needed*
Clinical management issues	**IMPAACT 2002 Core Team** **impaact.core2002@fstrf.org**
Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment	**IMPAACT 2002 Core Team** **impaact.core2002@fstrf.org**
Co-enrollment	**IMPAACT 2002 Core Team** **impaact.core2002@fstrf.org**
Data management computer and screen problems	**User Support (FSTRF)** **user.support@fstrf.org** *or by phone: +716-834-0900 x7302*
Subject Enrollment System	**DMC Randomization Support Office** **rando.support@fstrf.org** *or by phone: +716-834-0900 x7301*
Expedited Adverse Event (EAE) Reporting	**DAIDS RSC Safety Office** **DAIDSRSCSafetyOffice@tech-res.com** *or by phone: 800-537-9979 or +301-897-1709* *or by fax: 800-275-7619 or +301-8977-1710*
DAIDS Adverse Experience Reporting System (DAERS)	**CRMSsupport@niaid.nih.gov** *(questions also may be submitted from within the DAERS application)*

The IMPAACT 2002 Core Team is composed of study team members who have been designated to receive and reply to clinical management questions and notifications. When submitting clinical and management questions to the 2002 Core Team, please address each of the points listed in Figure 3-2, to help ensure that Core Team members have adequate information to respond in a timely manner. The responding Core Team member will reply to your question or notification by return email. All persons copied on the original question or notification will be copied on the reply.

Replies can generally be expected within 24 hours. When it may not be possible to provide a complete response within 24 hours, the person who submitted the question or notification will be provided with an interim response and informed that more time is needed to provide a complete response.

Figure 3-2
IMPAACT 2002 Core Team Communications

Questions for IMPAACT 2002 Core Team: Please copy and paste this listing into the body of your email message to impaact.core2002@fstrf.org to help ensure that all required information is included. Include the protocol number and PID in the subject line of your email.

1. Site name and number:
2. ESC or COMB-R site:
3. Name of person submitting query:
4. PID(s):
5. Reason for query (choose one):
    a. Consultation on eligibility or enrollment (describe in case description)
    b. Consultation on AE (specify severity grade in case description)
    c. Other (specify in case description)
6. Age of participant:
7. Current week on study:
8. Case description and question or notification for Core Team:

Print and file a copy of the email exchange in the participant's study chart.

3.2 Data Management Center IMPAACT Portal

The IMPAACT Portal of the DMC website provides information, documents and tools to assist site staff with the data management aspect of conducting IMPAACT protocols. The documents and tools that can be found in the Portal are Case Report Forms (CRFs), Annotated CRFs, CRF appendices, data collection forms schedules, Forms Manual, calculator utilities, quality assurance (QA) tools, Participant Calendar and study-specific messages. The Subject Enrollment System, Order Entry System, and Forms Management Utility can also be accessed on the Portal.

Site staff members apply for access to the Portal by submitting a registration form located on the Frontier Science and Technology Research Foundation (FSTRF) home page. All requests for Portal access are subject to review and verification by User Support before processing. The site leader or site coordinator will be contacted by the DMC to ensure legitimate affiliation of the applicant. To request for DMC IMPAACT Portal access complete the form located at:

https://www.fstrf.org/apps/cfmx/apps/common/register/index.cfm

Confirmation of registration will be sent via email from User Support.

The portal can be accessed from the FSTRF home page at **https://www.fstrf.org/**. Click on the "Portal Login" on the top right of the page to log-in. Enter your username (format: lastname.firstname) and the password that you set up when your registered for DMC web access.

For clinical user support, send an email message to **impaact.support@fstrf.org** or call +1 (716) 834-0900 x 7302. If you experience problems, or have questions about the IMPAACT portal in the FSTRF website, please contact the Webmaster at **webmaster@fstrf.org** and include a detailed description of your question or the problem you encountered.

3.3 Case Report Form (CRF) Completion and Data Entry

The DMC has developed a Forms Manual to assist site staff in the accurate completion of Case Report Forms (CRFs) used for DAIDS-sponsored Clinical Trials. The Forms Manual is located in the DMC IMPAACT Portal under the Case Report Forms heading.

The manual outlines standards and guidelines which, when followed, will result in fewer queries, shorter delinquency lists, and most important, straightforward and timely analyses. The manual includes sections that cover topics such as the CRF notebook, reporting data, understanding forms, forms components and conventions, submitting data, data collection formats and participant status categories.

To obtain the most current version of the CRF appendix, please refer to the IMPAACT Portal of the DMC website:

https://www.fstrf.org/apps/cfmx/apps/common/Portal/index.cfm

3.4 Study Web Page

A variety of IMPAACT 2002 study-related materials and information can be found on the study-specific page of the IMPAACT Network website:

http://impaactnetwork.org/studies/IMPAACT2002.asp

Resources available on this site include:

- Current version of the protocol
- Study contacts
- Current study implementation materials, including the Laboratory Processing Chart (LPC)
- Study training materials
- Arm-specific materials, including CBT and MM manuals (for COMB-R sites)

3.5 Source Documentation and Essential Documents

All sites must comply with the DAIDS policy on Requirements for Source Documentation and Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials. Refer to the detailed operational guidance provided in Appendix I of this policy. Both the policy and the appendix can be found via the "Labs and Scientific Resources" page of the DAIDS Clinical Research Policies website:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

Links directly to the documents are as follows:

Source Documentation Requirements:

https://www.niaid.nih.gov/sites/default/files/documents/daids-essentialdocpolicy.pdf

Essential Documents Recordkeeping Requirements:

https://www.niaid.nih.gov/sites/default/files/documents/essentialdocappndx.pdf

4.0 Informed Consent and Assent

Obtaining informed consent is a process by which an individual voluntarily expresses his/her willingness to participate in research, and/or his/her child's participation, after having been informed of all aspects of the research that are relevant to their decision. Both the informed consent and assent process is rooted in the ethical principle of respect for persons and involves information exchange, assurance of comprehension, determination of voluntariness, and appropriate documentation. Each of these aspects of the informed consent process is described in greater detail below. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) *Consolidated Guidance for Good Clinical Practice* (GCP) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further information.

U.S. regulations (45 CFR 46) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and by delegation all study staff involved in the informed consent process, to deliver all required information to consenters.

The template informed consent form included in the protocol meets all required regulations. Based on the reviews completed as part of the IMPAACT 2002 protocol development, there is adequate assurance that once a site-specific study activation notice has been issued, a site's informed consent forms (ICFs) include all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consenter/assenter
- Assure that informed consent/assent is obtained in a setting free of coercion and undue influence
- Confirm that the consenter/assenter comprehends the information
- Document the process

Further guidance related to each of these requirements is provided in Sections 4.1.-4.3 below. Each site must have on file a study-specific SOP for obtaining informed consent/assent that addresses all aspects of the process consistent with all applicable regulations, DAIDS policies and procedures, and protocol specifications. All sites must follow their SOPs consistently for all IMPAACT 2002 informed consent processes.

4.1 Deliver all Required Information in a Manner that is Understandable to the Consenter

It is important that the consenter must not be asked to agree to take part in the study, or to sign or make their mark on the ICF, until they fully understand the study. Study staff are responsible for ensuring that each consenter understands all aspects of study participation before signing or marking the ICF.

Begin the informed consent process by providing the consenter with a copy of the ICF to read. Also provide them with any other informational materials developed to complement the ICF. After the consenter has read the materials (or had them read to him/her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, you may note the main points described in each paragraph of the ICF and ask if the consenter has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the consenter, and discuss these thoroughly. Take as much time as needed to address each question or concern.

As per the inclusion criteria, the participant must be fluent in written and spoken English, however, if the participant's consenter is not literate, an impartial literate witness must be present during the entire informed consent process. As part of the documentation steps detailed below, the witness will be asked to sign and date the ICF to attest that the information in the ICF was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. ICH-E6 identifies an "impartial" witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The IMPAACT Operations Center has previously received guidance from the U.S. Food and Drug Administration's GCP office stating that the witness need not be "totally unaffiliated with the study. It may be possible, for example, to designate a "subject advocate" who would be available at each site …" Sites with questions about who may serve as an impartial witness are encouraged to consult with their IRBs/ECs on possible options.

4.2 Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also describe the alternatives to study participation and emphasize that the availability of medical care and other services routinely obtained from the study site institution will not be affected by the consenter's decision whether or not to take part in the study. Encourage the consenter to take as much time as he/she needs — and to talk about study participation with others if he/she chooses — before making a decision.

If a participant is required to have parental consent, the parent and participant can consent in the same room together or consent can be done separately, if the consenter is concerned with coercion. Both the participant and the parent must have signed the consent form before any screening procedures begin.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the consenter, with emphasis on the fact that the witness is there as a protection for the consenter, not as an agent of the study per se.

4.3 Document the Process

U.S. regulations require that informed consent be documented through the use of a written informed consent form approved by the IRB/EC and signed and dated by the consenter and the consenter's legally authorized representative, if required.

To fulfill this requirement, all signature and date blocks on the ICF should be completed in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a consenter's full surname, and it is strongly recommended that initials not be used in place of a consenter's full first name. However, if a consenter commonly signs her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

If a participant's parent/guardian is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. The consenter's printed name, signature, and signature date blocks on the ICF should be completed as described in the section appendix.

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. Study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets similar to the examples provided in the section appendix. Sites choosing to use coversheets should identify the coversheets as source documents in their study-specific SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consenter. All informed consent documentation must be maintained on file in participant study records.

In addition to completing the documentation requirements of the ICF itself, each informed consent process should be documented in a signed and dated chart note. The note should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Regulations require that consenters be given a signed copy of their ICF. If a consenter opts not to receive a copy, this should be documented and the consenter should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF.

5.0 Protocol Implementation

5.1 Recruitment

At each site, recruitment of potential study participants may begin after a site-specific study activation notice has been issued. It is expected that sites will identify potentially eligible participants from site-related healthcare centers where children are routinely receiving mental health or HIV-related care.

5.2 Pre-Screening Process

Prior to screening and enrollment, the sites create a list of all potentially eligible youth at their site. Sites should consider youth with or without a history of depression, with or without a history of mental health treatment, and those currently in mental health treatment; provided they are thought to meet study eligibility criteria. Sites will complete a Screening Log for each potentially eligible participant. The Statistical Data Management Center (SDMC) will retrieve the lists of potential participants entered, and randomly order all of the screening numbers within each site into blocks. The DMC will notify sites that this process has been completed and that they can begin screening and enrollment. Refer to protocol Section 4.4 for additional detail regarding this pre-screening process.

5.3 Screening and Enrollment

Sites may approach anyone from the first block of screening numbers. Potential participants from subsequent blocks may not be approached until all of the potential participants from the previous block are enrolled or have been approached, but will not enroll in the study for any reason. Per the DAIDS policy for Essential Documents, study sites are required to document screening (including screening failures) and enrollment activity on screening and enrollment logs. Screening and enrollment/randomization logs may be separate or combined. If a potential participant is interested in the study, they will undergo the informed consent/assent process and will be assigned a participant identification number (PID). An enrolled participant is defined as having signed the study consent. Logs should include the following information:

- Initials of all patients screened for each study
- PID
- Date screened

When a patient is enrolled into IMPAACT 2002, the screening number, in addition to the eligibility criteria, will be entered into the data base. Enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID).

5.4 Obtaining a Screening Slot

For all potential participants, a Screening Log must be entered through the DMC Subject Enrollment System on the FSTRF Portal:

- Log into the FSTRF Portal: https://www.fstrf.org/apps/cfmx/apps/common/Portal/index.cfm.
- Click on the "IMPAACT" tab.
- Under the Systems header, click on "Subject Enrollment."
- Choose your institution from the Institution dropdown menu.
- Choose the "PS2001 Screening Checklist" from the Study dropdown menu.

For potential participants who have not provided informed consent and are ineligible or do not enroll in the study for any reason, a Screening Failure and Non-Enrollment Results Form (SCR0055) must be completed and keyed into the eData system on the FSTRF Portal. Once consented, if a participant is no longer able to participate in the study, an Off-Study Form (F1601) should be completed and keyed into the eData system on the FSTRF Portal.

5.5 Overview of Screening and Enrollment Visits

Figure 5-1
IMPAACT 2002 Screening Visit Procedures

SCREENING VISIT PROCEDURES
within 30 days prior to study entry

- Perform procedures specified in Section 6.1 of the protocol, including informed consent procedures
- Assess eligibility:
  - ⇒ If eligible, continue with enrollment and remaining procedures in Entry visit. If remaining entry visit procedures do not occur on same day, schedule entry visit within 30 days
  - ⇒ If not eligible, discontinue study procedures but complete documentation as listed below
- Document visit per site SOPs and DAIDS policies for source documentation
- Update screening and enrollment log
- Complete and submit required CRFs. If participant is found to be ineligible, or does not enroll for any reason, each site must also complete a Screening Failure and Non-Enrollment Results (SCR0055) case report form (CRF).

Figure 5-2
IMPAACT 2002 Entry Visit Procedures

ENTRY VISIT PROCEDURES
Within 30 days of screening

- Perform procedures specified in Section 6.1 of the protocol
- If the entry visit is conducted separately from the screening visit, obtain an updated medical and medication history, review available medical records and findings of all other screening evaluations to determine whether participant remains potentially eligible
  - ⇒ If eligible, continue
  - ⇒ If not eligible, discontinue study procedures but complete documentation as listed below
- Collect blood for CD4+ T-cell count, HIV-1 RNA and plasma storage; documented laboratory results from an external provider that is CLIA-certified may be utilized for IMPAACT 2002, if the sample(s) was collected within 14 days of study entry
- Administer baseline behavioral questionnaire, QIDS-SR and QIDS-C forms
- Schedule Week 1 visit; provide reminders for Week 1 visit; and provide site contact instructions. Note: Sites may conduct the Week 1 visit procedures on the same day as the Screen/Entry visit, if the participant and site staff have adequate time.
- Document visit per site SOPs and DAIDS policies for source documentation
- Update screening and enrollment log
- Complete and submit required CRFs

Ideally, screening and enrollment into the study will be conducted on one day, if the participant is willing and found to be eligible.

5.6 Screening Failures

If a subject consented for the study fails to meet all of the inclusion/exclusion criteria to participate in the study, or fails screening evaluations, the subject will be considered a screen failure. The reason for screen failure should be documented appropriately in the source documentation and Screening Failure and Non-Enrollment Results Form CRF must be entered into the DMC database. Ineligible participants may rescreen for study participation provided their initial reason for ineligibility has changed.

In addition, those participants listed on the pre-screening list who do not screen for the study or do not enroll for any reason may be subsequently assigned new screening numbers, and new potential participants will be assigned screening numbers as they are identified. The SDMC will regularly retrieve the lists of potential participants from sites as needed to achieve the target study enrollment.

5.7 Follow-up Visits and Procedures

Participants in this study will be scheduled to complete follow-up clinic visits at Weeks 1, 6, 12, 24, 36, and 48. In addition, participants in the COMB-R sites will be encouraged to return to the clinic for weekly therapy visits through Week 8, every other week through Week 16, and then monthly until Week 24. These visits are not mandatory, and will be considered and documented as interim visits. At these interim visits, study staff will conduct therapy utilizing the CBT manual, and provide medication management, utilizing the MM manual, as indicated. Participants in the ESC sites will likewise return to the clinic for interim visits, based on the clinical indication of the participant.

Further key points regarding the follow-up visit schedule are as follows:

- Target visit dates are counted from the day of study entry; day of entry = Day 0.
- Sites may conduct the 1-Week visit on the same day as the Screen/Entry visit, if there is adequate time to complete these visits.

5.8 Follow-up Visit Schedule

Participants in this study will be scheduled to complete follow-up clinic visits at Weeks 1, 6, 12, 24, 36, and 48. In addition, participants in the COMB-R sites will be encouraged to return to the clinic for weekly therapy visits through Week 8, every other week through Week 16, and then monthly until Week 24. These visits are not mandatory, and will be considered and documented as interim visits. At these interim visits, study staff will conduct therapy utilizing the CBT manual, and provide medication management, utilizing the MM manual, as indicated. Participants in the ESC sites will likewise return to the clinic for interim visits, based on the clinical indication of the participant.

Further key points regarding the follow-up visit schedule are as follows:

- Target visit dates are counted from the day of study entry; day of entry = Day 0.
- Sites may conduct the 1-Week visit on the same day as the Screen/Entry visit, if there is adequate time to complete these visits.

A listing of follow-up visit procedures for Week 1 is listed in Sections 6.2 of the protocol. Unless otherwise specified, all procedures should be performed at all visits. There is no specified ordering or required sequence for most procedures at most visits. If the 1-Week visit is conducted on the same day as the Screen/Entry Visit, then repeat procedures should not be done. The primary purpose of the 1-Week visit in this case would be to provide therapy and medication management

FOLLOW-UP VISIT PROCEDURES FOR WEEK 1
See Section 6.0 of the protocol for appropriate visit windows

- Perform procedures specified in Sections 6.2 of the protocol
- Administer QIDS-SR
- Obtain an updated medical and medication history
- Schedule Week 6 visit and/or interim visit; and provide site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Complete and submit required CRFs

COMB-R Sites Only:

- Sessions: CBT and MM
- Checklists: CBT Adherence Checklist, Medication Management Checklist

ESC Sites Only:

- Session: Psychotherapy (medication as indicated by symptoms)
- Checklist: Enhanced Standard of Care (ESC) Therapist Checklist

FOLLOW-UP VISIT PROCEDURES FOR WEEK 6 AND 12
See Section 6.0 of the protocol for appropriate visit windows

- Perform procedures specified in Sections 6.3 of the protocol
- Administer QIDS-SR and behavioral questionnaire (QIDS-SR by paper at COMB-R sites)
- Obtain an updated medical and medication history
- Schedule Week 12, 24 visit, or interim visit; and provide site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Complete and submit required CRFs

COMB-R Sites Only:

- Sessions: CBT and MM
- Checklists: CBT Adherence Checklist, Medication Management Checklist

ESC Sites Only:

- Session: Psychotherapy (medication as indicated by symptoms)
- Checklists: Enhanced Standard of Care (ESC) Therapist Checklist

FOLLOW-UP VISIT PROCEDURES FOR WEEK 24
See Section 6.0 of the protocol for appropriate visit windows

- Perform procedures specified in Sections 6.4 of the protocol
- Administer QIDS-SR and behavioral questionnaire
- Administer client satisfaction questionnaire
- Obtain an updated medical and medication history
- Schedule Week 36 visit; and provide site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Complete and submit required CRFs
- Collect blood for CD4+ T-cell count, HIV-1 RNA, and plasma storage

COMB-R Sites Only:

- Sessions: CBT and MM
- Checklists: COMB-R Site Prescribing Clinician Satisfaction Scale, COMB-R Site H&W CBT Clinician Satisfaction Scale, CBT Adherence Checklist, Medication Management Checklist

ESC Sites Only: • Session: Psychotherapy (medication as indicated by symptoms) • Checklists: ESC Site Counseling Clinician Satisfaction Scale, ESC Site Prescribing Clinician Satisfaction Scale, Enhanced Standard of Care (ESC) Therapist Checklist

FOLLOW-UP VISIT PROCEDURES FOR WEEK 36 AND 48 ***See Section 6.0 of the protocol for appropriate visit windows***
• Perform procedures specified in Sections 6.5 of the protocol • Administer QIDS-SR and behavioral questionnaire • Obtain an updated medical and medication history • Document visit per site SOPs and DAIDS policies for source documentation • *Week 48 only: Collect blood for CD4+ T-cell count, HIV-1 RNA, and plasma storage*
COMB-R Sites Only: • Sessions: Therapy and medication management as indicated • Checklists: None
ESC Sites Only: • Session: Psychotherapy and medication as indicated by symptoms • Checklists: None

INTERIM VISIT PROCEDURES ***See Section 6.6 of the protocol for appropriate visit windows***
• Perform procedures specified in Sections 6.5 of the protocol • AT COMB-R only administer QIDS-SR (by paper) • Obtain an updated medical and medication history • Document visit per site SOPs and DAIDS policies for source documentation
COMB-R Sites Only: • Sessions: CBT and MM (as indicated) • Checklists: CBT Adherence Checklist, Medication Management Checklist (for sessions given that visit)
ESC Sites Only: • Session: Psychotherapy or Medication if indicated Checklists: Enhanced Standard of Care (ESC) Therapist Checklist (if session given)

5.9 Accrual and Retention

The study involves two arms of HIV-infected youth ages 14-24 with depression: ARM 1: Health and Wellness Cognitive Behavioral Therapy and Medication Management (COMB-R) and ARM 2: Enhanced Standard of Care (ESC).

Approximately 156 HIV-infected youth are expected to be enrolled into the study to achieve 140 evaluable. Youth will be considered evaluable if the QIDS-SR data at both baseline and Week 24 were obtained.

Accrual is expected to be completed within 24 months, beginning on the date of the first participant enrollment at each site. Each site is expected to enroll a minimum of eight participants. There will be a cap of ten participants enrolled at any single site in the first year of accrual, and the study team will re-evaluate whether to have a cap for the second year of accrual. The study accrual plan, which lists monthly accrual projections for each site, will be updated and distributed to all sites at least monthly. Each study site should have a standard operating procedure (SOP) for participant accrual on file. All sites are

responsible for following these SOPs and for updating them if needed to meet site-specific accrual projections throughout the study accrual period.

For each site, accrual will begin after all required approvals are obtained and a site-specific study activation notice is issued by the IMPAACT Operations Center. Once accrual is initiated, the Data Management Center (DMC) will report the number of participants screened and enrolled at each site to the Protocol Team at least monthly.

Throughout the accrual period, the Protocol Team will review accrual and other performance data from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made after the IMPAACT Study Monitoring Committee (SMC) reviews of the study, which are expected annually.

5.10 Participant Withdrawal

Regardless of the reason for withdrawal, study personnel are responsible for identifying all participants who withdraw and documenting the reason and date of study termination.

- Parents/guardians may withdraw their child from the study at any time.
- Study personnel should attempt to collect final data from subjects who are withdrawn early.
- Study personnel will record the date and reason for withdrawal in the subject's source record, and on the subject case report form.
- In general, the investigator should not withdraw a subject unless that subject is lost to follow up or is noncompliant with the protocol.
- If the subject is withdrawn from the study drug due to an adverse event (AE), the subject should be followed by the clinical site until the AE resolves (per Schedule of Evaluations, Appendix I of protocol).

6.0 Health and Wellness Cognitive Behavioral Therapy Manual

Sites that are randomized to the Health and Wellness Cognitive Behavioral Therapy and Medication Management (COMB-R) arm of IMPAACT 2002 will follow the CBT Treatment Manual for ATN 080 (Kennard et. al., 2012). This manual can be found on the IMPAACT Network website.

7.0 Medication Management Manual

Sites that are randomized to the Health and Wellness Cognitive Behavioral Therapy and Medication Management (COMB-R) arm of IMPAACT 2002 will follow the Medication Management Manual for ATN 080 Version 2.0 (Emslie et. al., 2012) which can be found on the IMPAACT Network website.

8.0 Specimen Collection and Laboratory Considerations

This section contains instructions related to collection and processing of IMPAACT 2002 specimens. For detailed information on tests and specimens required for each visit, please refer to the IMPAACT 2002 Schedule of Evaluations (Appendix I) of the protocol and the and Laboratory Processing Chart (LPC).

Regardless of where tests are performed, personnel who collect specimens and/or perform assays must be trained in proper collection, handling, testing and associated QA/QC procedures prior to performing the tests for study purposes. Training documentation must be available for inspection at any time.

All laboratory activities should be conducted in accordance with accepted Good Clinical Laboratory Practice (GCLP), the IMPAACT and ACTG Network Laboratory Joint Laboratory Manual and site-specific Standard Operating Procedures (SOPs) for proper collection, processing, labeling, and transport of specimens. Transport of all specimens must comply with federal, state, local, IATA and ACTG/IMPAACT specimen shipping regulations. In accordance with protocol Section 6.9.2, sites are advised to store residual samples on-site until the end of study upon which samples will be shipped to the appropriate repository as per the LPC.

As the transmission of HIV and other blood-borne diseases can occur through contact with contaminated needles, blood and blood products, appropriate precautions should be employed by all personnel when drawing blood and handling clinical specimens for this study in both the clinical and laboratory setting, as recommended by the U.S. Centers for Disease Control and Prevention (US-CDC). All study staff should take appropriate precautions when collecting and handling biological specimens. Guidance on Universal Precautions/ Body Substance Isolation is available from the U.S. Centers for Disease Control and Prevention:

http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html

8.1 Laboratory Data Management System (LDMS)

The LDMS is to be used at all sites to track the collection, storage, and shipment of the laboratory specimens. Sites without an LDMS **must** send specimens to be processed at a local LDMS processing lab. All sites should upgrade to the most current version of the LDMS as soon as possible. Detailed instructions for use of the LDMS are available at:

http://www.fstrf.org/ldms

For supported label and printer options, refer to the product listing documents located on the LDMS Client Reference Guides page on the FSTRF Portal:

https://www.frontierscience.org/apps/cfmx/apps/common/Portal/index.cfm

Contact LDMS user support for further information.

Questions about LDMS, shipping and storage for this protocol should be raised with the Laboratory Data Manager at FSTRF:

Kaitley Wozer
FSTRF
Phone: +1 (716) 834-0900, x7224
Email: wozer@fstrf.org

8.2 24-Hour LDMS User Support

Technical support is also available from LDMS User Support. Usual business hours from LDMS user support are 12 AM - 6:00 PM Eastern Time in the US (ET) Monday through Friday. During business hours, please contact LDMS User support as follows:

Email: Ldmshelp@fstrf.org
Phone: +1 (716) 834-0900, extension 7311
Fax: +1 (716) 898-7711

9.0 Expedited Adverse Event Reporting to DAIDS

This section presents information related to expedited adverse event reporting in IMPAACT 2002. Also refer to Section 7 of the IMPAACT 2002 protocol and the following resources:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Toxicity Table), Version 2.0, dated November 2014
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dated January 2010
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians

All of the above are available on the DAIDS RSC website:

http://rsc.tech-res.com/safetyandpharmacovigilance/

9.1 Selected Definitions

Key definitions associated with expedited adverse event reporting in IMPAACT 2002 are provided below. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for additional terms and definitions.

Adverse event (AE)

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the counseling procedures, whether or not related to the counseling procedures.

The above definition is applied to participants in IMPAACT 2002 beginning at entry into the study. Medical conditions, illnesses, problems, signs, symptoms, and findings identified before entry are considered pre-existing conditions. If a pre-existing condition worsens (increases in severity or frequency) after entry into the study, the worsened condition is considered an AE. If a pre-existing condition resolves after entry into the study but then recurs at a later date, the recurrence is considered an AE.

All reportable AEs occurring among participants enrolled in IMPAACT 2002 must be source documented in participant study charts, including the documented assessment of the Investigator of Record (IoR) or designee of the severity of the AE (see Section 7.3) and its relationship to counseling procedures (see Section 8.1).

Expedited AE (EAE)

An AE that meets protocol criteria for reporting in an expedited manner to the DAIDS Regulatory Support Center Safety Office.

9.2 AE Severity

The term severity refers to the intensity of an AE. All AEs occurring among participants enrolled in IMPAACT 2002 must be assessed for severity on the following scale according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, dated November 2014:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially Life-Threatening
- Grade 5 = Death

9.3 AEs that Meet Protocol Criteria for Expedited Reporting (EAEs)

For participants enrolled in IMPAACT 2002, the following types of events will be reported on an expedited basis for this study:

1. Suicide attempts
2. Psychological hospitalization

The EAE reporting period begins at the time of enrollment and continues through the Week 48 Visit.

9.4 AE Relationship Assessment

For purposes of ***EAE reporting***, the IoR or designee must report the relationship of EAEs to the counseling procedures according to the categories shown in Figure 9-2.

Figure 9-2
Relationship Assessment Categories for EAE Reporting

Relationship Category	Definition
Related	There is a reasonable possibility that the adverse event may be related to the study counseling procedures.
Not related	There is not a reasonable possibility that the adverse event may be related to the study counseling procedures.

9.5 EAE Reporting Procedures

All EAEs should be reported to the DAIDS RSC Safety Office using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Reporters and Study Physicians.

The process of EAE reporting via DAERS involves a designated "Study Reporter" creating an electronic EAE report and a designated "Study Physician" reviewing the EAE report, signing the EAE report with

an electronic signature, and submitting the EAE report to the DAIDS RSC Safety Office. If an EAE report is not completed and submitted within three reporting days of site awareness that an event meets EAE reporting criteria, an explanation must be entered in DAERS before the report can be submitted (see the Manual for Expedited Reporting of Adverse Events to DAIDS for the definition of reporting days).

DAERS also may be used to withdraw an EAE report that was submitted in error and to modify or update a previously submitted EAE report.

For all submitted EAE reports, updates must be submitted to report the final or stable outcome of the EAE, unless the original report provided a final or stable outcome. Updates also should be submitted if significant additional information becomes available after an EAE report is first submitted. Significant additional information may include, for example, an updated severity grade or relationship assessment, information on participant status after resumption of one or more study drugs, and/or newly available information on cause of death.

When updated EAE reports are submitted, it is NOT necessary to complete and submit another Event Evaluation CRF (PE6866) to the DMC. Only one PE6866 CRF should be completed and submitted for each event.

DAERS incorporates a report printing function that should be used to print all EAE reports — including modifications and updates — for filing in participant study records. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.

For questions about DAERS, email **DAIDS-ESSupport@niaid.nih.gov**. Questions also may be submitted from within the DAERS application itself.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC Safety Office. The EAE Form and form completion instructions are available on the DAIDS RSC web site; contact details for submission of EAE Forms are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS, which is also available on the DAIDS RSC web site.

Appendix I: Summary of Considerations for Obtaining Informed Consent from Illiterate Guardians of Participants

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and must be followed each time informed consent is obtained from an illiterate consenter. It is recommended that each site seek IRB/EC review and approval of these procedures.

- An impartial witness must be present during the entire informed consent process with an illiterate consenter. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter.

- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.

- Take care to minimize the perception of coercion due to the presence of the witness.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should print the consenter's name below the consenter's printed name line on the informed consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see figure below).

- The consenter should make their mark on the consenter's signature line.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should enter the date upon which the consenter made her mark on the informed consent form below the consenter's signature date line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see figure below).

- For more information, see Section 4.8 of the ICH GCP guidance and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*.