### SCREENING BLOCKS AND RANDOMIZATION PROCEDURES

*Note:* The primary purpose of Letter of Amendment (LoA) #1 was to modify the procedures for the screening and enrollment process, specifically to remove the requirement that sites approach participants in a randomly assigned order. FAQs have been updated to reflect the current screening procedures, under Protocol V1.0, with LoA #1 and Clarification Memoranda #1-2, dated 19 August 2016.

### SCHEDULE OF EVALUATIONS

1. **For the COMB-R sites,** per the MM Manual, treatment decisions are based on response to treatment, and are determined by QIDS-C score. The SOE and the CRF Schedule do not list QIDS-C evaluation as required under the interim visit column. When is the QIDS-C required?

   The MM Manual was not updated in this area. The QIDS-C is *not* required after the initial baseline assessment and treatment thereafter is based on the QIDS-SR not the QIDS-C.

   Currently, there are no plans to update the manuals. If there are discrepancies between the protocol and the manuals, please follow the protocol. If the situation is unclear, please query the core protocol team ([IMPAACT.core2002@fstrf.org](mailto:IMPAACT.core2002@fstrf.org)).

2. **For the COMB-R sites,** per the SOEs, the QIDS-SR is only required when the participant meets with the site prescriber; however, per the CRF schedule the QIDS-SR form is required at every interim visit. When should the QIDS-SR be conducted?

   The QIDS-SR should be conducted at *every MM interim visit* and at the scheduled 6- and 12-week interim visits.

3. **For the COMB-R sites,** the QIDS-SR did not warrant concern during an interim visit with a participant; however, based on clinical observation and judgment of the CBT therapist, presenting clinical symptoms appeared much more severe than as indicated by the QIDS-SR. Based on the CBT therapist’s concern, the participant was evaluated by the MM prescriber. QIDS-C was administered per the MM Manual and the participant scored significantly higher. MM evaluation was incorporated into the interim visit and participant’s medication dose was maximized as per treatment algorithm. How should sites document this in terms of the CRFs? Should the QIDS-C form be reported for this visit?

   The therapist was correct to use clinical judgement since the QIDS-SR did not match with what was observed in the session and asking for MM evaluation was appropriate. The MM form for the interim visit should be completed. The protocol does not require the QIDS-C at subsequent visits (as it is only required at the initial study visit); however, conducting it is not a deviation and does not need to be reported on the CRFs.

4. **For the COMB-R sites,** if a participant has a separate appointment for medication management (MM) is that considered an interim visit? Or is it only an interim visit if the participant also has psychotherapy at the same visit?

   If the visit is not part of Week 1 or Week 6 (for example, if the visit is conducted at Week 3) then it should be documented as an interim visit, even if it is only medication management. Psychotherapy does not have to be conducted at the same time as MM.
5. **For the COMB-R sites, can therapists continue to use the CBT manual with participants after they complete their Week 24 visit?**

It is fine for therapists to use any of the CBT modules/sessions after Week 24. The therapists were trained in the entire manual, so they and their patients should continue to have access to it. For example, if a patient presented with new onset of suicidality after 24 weeks, those guidelines would be appropriate, even if they had not been used in the first 24 weeks.

This is similar to the use of the Med Management Algorithm. If a patient's symptoms increase or fail to improve at Stage 2 after 24 weeks, we would not want the clinician to keep the patient at Stage 2, rather than moving to Stage 3. And we would not want them to ignore the clinical guidelines that inform these stages.

But, clinicians are also free to ignore the guideline and CBT sessions after 24 weeks. The choice is theirs.

6. **What process should sites follow if we need to request a visit outside the window?**

Generally, protocol teams do not grant permission to conduct a visit outside of the protocol-specified window. If it is necessary to conduct or complete a study visit outside of the visit window, the team encourages you to conduct the visit as soon as possible and document why this occurred.

For any study visits or procedures conducted outside of the protocol-specified window for a given visit, sites must provide a description of the deviation, document the reasons why it occurred, and any corrective and preventative actions taken in the participant’s study chart and the site’s study specific deviation log. The protocol team’s response to any messages regarding the deviation should continue to be included in the documentation.

Additional guidance on protocol deviations, including the policy requirements for protocol deviations considered reportable by the IMPAACT Network can be found here: [http://impaactnetwork.org/DocFiles/MOP/ProtDevs_08MAR17.pdf](http://impaactnetwork.org/DocFiles/MOP/ProtDevs_08MAR17.pdf).

7. **We currently have a participant within the 24wk visit. Due to the participant’s schedule, it will not be possible to complete all visit activities on the same day. Could we draw 24-week lab this week, and complete the remaining components of the visit next week (both weeks are within window for the 24wk visit)?**

Per Section 6 of the protocol, all procedures specified to be performed at scheduled visits should ideally be performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day within the allowable visit window. So, if it is not possible to conduct all procedures on the same day, as long as the lab draw and other visit procedures occur within the +/- 14 day allowable window for the Week 24 visit, you are allowed to split the Week 24 visit and conduct these procedures on different days. Please contact the Protocol Data Manager, Chelsea Krotje (krotje@fstrf.org) for any questions related to completing the CRFs for a split visit.
8. For the “collect/review locator information” on the Schedule of Evaluations (SOE), there is no corresponding CRF. How should this be documented?

Per protocol, the locator information for each participant should be reviewed at each study visit to confirm that it is accurate and up-to-date. This information should be documented in the participant’s files, consistent with your site’s SOPs. Additionally, CRF Update Memo #1 (dated 22 May 2017) added an optional Sensitive Data (F0101) Form which sites may use.

9. What if a participant consented more than 30 days before completing screening procedures and enrolling into the study?

Per protocol Section 6.1, while screening procedures must be completed within 30 days of enrollment, it is not explicitly stated that consent must also occur within this 30-day period. In general, we would defer to sites to follow your local IRB procedures regarding provision of consent, which may include the circumstances in which re-consent would be required. Unless the protocol specifies otherwise, informed consent is generally not expected to be repeated within six months of initial signing. Prior to enrollment, the site staff will confirm consent verbally – and if needed can review the elements of consent before enrollment.

10. During our Screening/Enrollment visit, the therapist administered the QIDS-C. However, the Medication Management Manual (MM Manual) describes the administration of the QIDS-C being performed by the prescribing clinician. Is it acceptable for the therapist to administer the QIDS-C?

Per protocol Section 5.3.1, a licensed mental health clinician must complete the QIDS-C at Screening.

11. During the Screening/Enrollment visit, we realized we would not be seeing any of the responses to the ASSIST which was administered via ACASI. Should sites be assessing substance abuse risks using our own clinical tools rather than administering another ASSIST to perform this type of assessment?

Yes, sites should assess substance use as per your usual clinical procedures.

12. If the QIDS-SR score and presenting clinical symptoms are not a concern during an interim visit, do sites need to proceed with the medical monitoring visit?

No, if the QIDS-SR and clinical symptoms do not indicate a need, the medical monitoring does not need to be conducted at interim visits; however, it does need to be conducted at Weeks 6, 12 and 24, regardless of the QIDS-SR score and clinical symptoms.

13. For ESC sites, what counts as an interim visit? For example, most of our participants will be on a weekly therapy schedule for their depression. Should every weekly visit be conducted as an interim visit, if it is between study visits? If a participant has reached Week 24 and we continue to meet with them beyond this point, are those visits considered interim visits?

Yes, if participants come in for therapy any weeks between 1, 6, 12, and 24, those visits are considered interim visits. After Week 24, only Week 36 and 48 are considered study visits; any other visits are considered interim visits.
14. The ESC Therapist Checklist (QLW0285) does not appear on the Schedule of Evaluations for Week 36 and 48; but it does appear in Table 4 of the Protocol (Section 5.3 Study Evaluation and Measures). When should the ESC Therapist Checklist be submitted?

As per the SoE, the ESC Therapist Checklist should only be completed at Weeks 1, 6, 12, 24; it is not required at the Week 36 and 48 study visits.

**INCLUSION AND EXCLUSION CRITERIA**

15. A participant recently reported she is pregnant. We reviewed inclusion and exclusion criteria in IMPAACT 2002 protocol and pregnancy is not listed as an exclusion criterion. Is this participant still eligible for the study?

Pregnancy is not an exclusion criterion for IMPAACT 2002; as long as this participant meets all other inclusion and exclusion criteria, she is considered eligible.

16. A participant is getting therapy outside of the study. Is this person ineligible because they are receiving therapy from a non-study therapist?

It would depend on the therapy. If it is a support group that meets once a month, that could be allowed because it is different from being in treatment. But if the participant is in therapy that would meet any of the CBT checklist items, then they would be ineligible unless they are willing to switch to a study therapist. Please contact the protocol team ([IMPAACT.core2002@fstrf.org](mailto:IMPAACT.core2002@fstrf.org)) if it is unclear.

17. A patient reported being diagnosed with bipolar (which is exclusionary), though the site psychiatrist is questioning that diagnosis and whether it was accurate. If the site psychiatrist does not confirm the bipolar diagnosis, could this patient be considered eligible?

If your site psychiatrist does not feel that the diagnosis is accurate, then you can approach and screen the patient. Further clinical screening at the time of the QIDS-C administration will determine whether the bipolar diagnosis is accurate. If the patient is subsequently enrolled, then the response for #21 "Does the participant have a known or self-reported history of any psychotic disorder and/or bipolar disorder" in the eligibility checklist in the Subject Enrollment System would be "No" since you determined the patient does not meet the criteria for bipolar.

18. Does only the clinician’s QIDS score determine participant eligibility?

Yes, per inclusion criterion 4.1.6 the clinician’s QIDS score (via Quick Inventory of Depressive Symptomatology – Clinician) determines participant eligibility and the participant completes the QIDS-SR via ACASI at Baseline.
19. Question 29 on the eligibility checklist asks for the subject's viral suppression status, with answers of “suppressed,” “non-suppressed” and “unknown.” If the status is unknown, they are considered ineligible, even though this is not an exclusion criterion. For instance, we have a potential enrollee, who hasn't had a VL done since Oct 2016, at which time they were non-suppressed. At that time, they were initiated ARV therapy, and so could very well be suppressed now, but we won't know this until we do the enrollment VL. So, how should we classify this participant? We think it should be unknown, but that makes her ineligible. If we say non-suppressed, based on the last VL, what if this is contradicted by entry VL?

The participant should be classified as non-suppressed, since that was the last documented viral load. If a later viral load has a different result, then that data is entered at that assessment point but does not influence eligibility.

20. A patient joined our site already on antiretroviral therapy and has only had one instance of a detectable viral load at our site. We are not sure we will be able to get the confirmation of the first diagnostic test and therefore may not have access to two samples to confirm HIV-1 infection. Can we enroll the patient if we do not have two tests that document HIV infection?

Per protocol Section 4.1, to be eligible for study participation, all participants must have confirmation of HIV-1 infection based on testing of two samples (whole blood, serum, or plasma) collected at different time points, as outlined in inclusion criterion 4.1.3 For tests performed in other settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available. In the absence of such documentation, confirmatory testing may be conducted as part of screening, as specified in protocol Section 6.1.
21. Protocol inclusion criterion (4.1.2) states: “Receiving mental health or HIV-related care at participating U.S. IMPAACT sites.” Does case management for HIV positive women, youth, children, and infants count toward HIV-related care?

Yes, case management would count toward HIV-related care.

22. What type of documentation is needed to document eligibility for the depression diagnosis?

Depression diagnosis as determined by the site investigator (or designee) based on participant self-report and/or available medical records would be acceptable to assess participant eligibility for screening per inclusion criterion 4.1.5 (“Per clinician assessment, primary diagnosis of nonpsychotic depression, including Major Depressive Disorder, Depression NOS, or Dysthymia, as defined by DSM-IV or DSM-V criteria.”). The QIDS-C, administered by a licensed mental health clinician at screening, will serve as the depression severity rating for eligibility for the study.

TRAINING

23. Where can we access study training materials?

All participating site staff were required to take place in both the General IMPAACT 2002 Study Startup Training and Arm-Specific Training held in December 2016. The materials from the General Startup Training can be found on the IMPAACT 2002 webpage: http://impaactnetwork.org/studies/IMPAACT2002.asp.

Arm-specific training for COMB-R and ESC sites consisted of webinar trainings for both Site Therapists and Licensed Prescribers. We are happy to provide the slides from this training upon request. Please contact Kate Lypen (klypen@fhi360.org) or Sarah Buisson (SBuisson@fhi360.org).

For any new site staff who will be joining IMPAACT 2002, please provide written confirmation that they have reviewed the training materials and request that they send any questions to the protocol team.

24. For ESC sites, does the person providing therapy need to be a licensed provider, or could they be a social worker with a lot of experience providing therapy to HIV-infected depressed youth?

We have two individuals at our clinic who provide regular therapeutic care and who have logged the number of hours required for a license, but have not yet received the actual license.

A therapist without a license is acceptable as long as the therapist is currently providing psychotherapy at your clinic, is licensure eligible (meaning has a clinical degree, acquired experience hours) and has access to supervision by a licensed mental health professional at the site. Please contact the protocol team (IMPAACT.core2002@fstrf.org) regarding training requirements for staff.

SOURCE DOCUMENTATION

25. Regarding source documentation for pregnancy, are specific labs required to determine participant is currently not pregnant or can we use participant’s self-report (no suspicion of pregnancy) if labs are not available.

Sites may conduct pregnancy testing as indicated per standard of care; however, pregnancy testing is not required per protocol. Participant self-report may be utilized for source documentation.
## 26. What should sites be doing for source documentation that ACASI was administered?

The SVW0289 Study Event Tracking form asks if the ACASI was administered. Complete that question on the tracking form and include a note in the patient’s chart documenting that the ACASI was administered to provide source documentation.

## 27. At ESC sites, how should the site mental health clinician document counseling sessions?

Sites should document whatever information they need to for their clinical record as they would normally do, and the therapist should complete the ESC Therapy Checklist.

## DATA COLLECTION AND CASE REPORT FORM CONSIDERATIONS

### 28. For COMB-R sites, how should the CBT adherence checklist be completed if a client was present, agreed to start the session but very soon after asked to stop and go back home? Should the therapist check that the participant refused, or check the skills that were used?

Check the skills that were used and those completed. Indicate that the session ended early due to the patient asking to discontinue the session. If the participant returns, you can complete the rest of the content for that session.

### 29. For the COMB-R sites, the CBT session was conducted as a family session and no individual session was conducted with the participant. The CRF form QLW0280 does not accept a value of zero for the individual session. What values should sites enter in the CRF form?

If the session was conducted completely as a family session, sites should override the warning in eData and submit a response in Resolve when they receive their next update report, this report will contain a list of warnings to address. Once the site’s response is submitted in Resolve, the Protocol Data Manager will be notified to review and approve the site’s response.

### 30. For the COMB-R sites, the CBT Adherence Checklist (QLW0280) asks about the length of the individual session and total length of the visit. What should be included in the total length of visit? For example, should the time to complete the QIDS-SR be included in the time for the individual session or in the total length of the visit? If the participant also saw the Prescriber for medical management, should that time be included in the total length of visit?

The length of session should reflect the length of the **CBT session**. Please exclude the MM session and the time it took to complete the QIDS-SR. Question #4 “total duration of visit” on this form was removed in CRF Update Memo #2 (dated 4 August 2017).
31. For COMB-R sites, for the QIDS-SR CRF form QLW0277:

- Does the CBT clinician need to ask the QIDS-SR questions during the interim visits (face-to-face-interview) or does the participant need to complete the questionnaire on his/her own?

  The clinician does not complete the QIDS-SR; the participant should. The only interim visits in which needs to be completed are the MM visits, not the CBT visits.

- If the participant must complete the questionnaire on their own, can the clinician help participants if they have any questions, or if they prefer can clinician read the questions to them?

  If the participant has difficulty with comprehension, their questions about a word or phrase can be answered. If it is anything else, they should be encouraged to "give it your best guess.”

- Does the clinician sign the CRF as source documentation?

  Source documentation is site specific. Please consult your site’s SOPs.

32. For the COMB-R sites, after enrollment into the CBT arm, a participant has been completely non-adherent with study visits. The participant called this morning to say that she is ready to start coming and asked if she could be seen today. We are technically in Week 3 for this participant and have missed the Week 1 visit window by 5 days. Under which week should this visit to be performed?

  The best thing to do will be to conduct all of the week one activities when that participant comes in. For the data, key this as the Week 1 visit given that you will be keying the expected Week 1 CRFs. This will prevent the need to exempt the Week 1 forms in delinquency, as well. If you receive any warnings in your upd8 report, please just submit a response in Resolve and the Protocol Data Manager will address.

33. For the COMB-R sites, a mental health (psychotherapy) counseling session and a Medication Management session usually occur on the same day for the same visit. However, due to research participant and medication management clinician availability, the medication management portion of the visit is sometimes scheduled on the day prior to or after the mental health counseling session. Is this ok to do? Which date should be used when submitting data via E-data?

  Yes, this is fine and expected to occur. Please use the date the visit actually occurred for all forms. Please key the ADM0040: Visit Status Report for each visit to document that two visits occurred
### 34. For the COMB-R sites, for the antiretroviral medication, on form CMW0047: When reporting the need to maximize dose, (e.g. participant was initiated on Lexapro 10mg, but after MM it was determined that participant will receive Lexapro 20mg), do we need to stop Lexapro (status 1) and re-start medication on the same form with a different status or a different reason for prescription?

Per CRF Update Memo #2 (dated 4 August 2017), the form was updated to include total daily dose and dose status for psychiatric non-antiretroviral concomitant medications. For medications where the dose has been changed, the resolution of the previous dose needs to be reported and then the starting of the “new” dose (i.e. the dose after the modification) needs to be reported in a separate line on the CMW0047 CRF.

### 35. For the COMB-R sites, when participants are coming in for their individual sessions, (e.g. during interim visits), and the QIDS-SR is being administered on paper should it be completed before or after the counseling session?

Sites should administer the QIDS-SR before the session, so that the clinician can see the scores.

### 36. For the COMB-R sites, how should missing components (i.e. “Prefer not to answer”) be scored for the QIDS-SR, on the QLW0277 form?

Missing values (i.e., “Prefer not to answer”) are coded as “8”. These numerical values should not be incorporated into the scoring algorithm. For components that are based on selecting the highest score of two or more “item” scores, if one of the items is missing (i.e. Prefer not to answer=8), select the highest score of the non-missing items. If all items are missing, consider the component score to be missing.

For computing the Total QIDS-SR Score: If one or two of the nine component scores are missing, the QIDS-SR can still be scored as follows.

- First, assign the missing components values equal to the average of the non-missing component scores.
- The Total QIDS Score is the sum of the nine components, after missing values have been replaced by the average of the non-missing component scores.

If more than two component scores are missing, the QIDS cannot be scored and the Total Score should be coded as missing. In this case, the Protocol Data Manager will instruct sites on how to enter missing values into e-Data for the relevant component and Total scores.

37. For the COMB-R sites, is there a “calculator utility” available for scoring the QIDS-SR?

Unfortunately, there is not a calculator utility available for scoring the QIDS-SR. The QIDS-SR Scoring Guidance is posted on the IMPAACT 2002 protocol-specific webpage: [http://impaactnetwork.org/studies/IMPAACT2002.asp](http://impaactnetwork.org/studies/IMPAACT2002.asp). If you have specific questions about how to score the QIDS-SR, you can reach out to our colleagues at SDAC, Miriam Chernoff (mchernoff@sdac.harvard.edu) and Shirley Traite (traite@sdac.harvard.edu), who prepared the scoring guidance document. Our Protocol Data Manager, Chelsea Krotje (krotje@fstrf.org), can also answer questions about the completion of the form QLW0277, as needed.

38. For the COMB-R sites, how should a situation in which a participant who was changed from Stage 0 to Stage 1 during study visit Week 1 follow-up be documented? This participant was prescribed medication for depression as per protocol; however, they reported that the medication was never started, and they are currently not taking the antidepressant nor are they planning on starting it. Should we change the Stage from 1 back to Stage 0? And how can we accurately report this scenario on the CRF - QLW0281-Medication Management Checklist?

The team would suggest keeping it at Stage 1, but at the next visit, if it is not clear that the patient will follow the recommendations, would switch back to Stage 0. The stage should reflect the agreed upon plan. On the Medication Management Checklist, the participant would be recorded at Stage 1 at Week1 because the medication was prescribed. At the subsequent visit, in which they report not taking the medication and not planning on taking it, they would be recorded at Stage 0. This would be indicated as a change in Stage (Question 4) and the reason (part a) would be #3 - “participant choice.”

39. For ESC sites, do we still complete form QLW0288 for medication management for a Week 24 visit if the participant is not taking medication for depression? Does the clinician do a medication management visit with him?

Yes, the prescribing clinician should still complete the form. If applicable, Question 1 can be answered even if the patient never takes medication. For example, the prescriber might have concluded that no medicine was indicated or might have felt it was warranted but there was some barrier to beginning it. Per CRF Update Memo #3 (dated 3 April 2018), QLW0288 was updated to include “not applicable” as a response option for both questions on the form.

A medication management visit should only be done if clinically indicated.

40. Where can we access the Subject Enrollment System (SES) and what variables do we enter?

Once you are logged into the FSTRF System, there is a ‘Subject Enrollment’ link under the Systems column that will take you directly to the SES. Additional information on how to access the Data Management Center IMPAACT Portal, including the Subject Enrollment System, can be found in the IMPAACT 2002 Manual of Procedures: [http://impaactnetwork.org/DocFiles/IMPAACT2002/IMPAACT%202002%20MOP%20v1.1%2028JAN17.pdf](http://impaactnetwork.org/DocFiles/IMPAACT2002/IMPAACT%202002%20MOP%20v1.1%2028JAN17.pdf).
41. Do we need to submit signs/symptoms and diagnoses CRFs at each interim visit if there have been no changes to medical history but if there are ongoing issues?

While medical history should be reviewed/assessed at interim visits, if the participant has ongoing diagnoses and signs/symptoms grade 3 or higher, yes, the Diagnoses and Signs/Symptoms CRFs are required to be submitted. If the participant has ongoing diagnoses and signs/symptoms that are not grade 3 or higher (i.e. grade 2 or grade 1), the Diagnoses and Signs/Symptoms CRFs are not required to be submitted. The SVW0289 will only trigger delinquency to look for the additional CRFs if there are new, ongoing, or resolved diagnoses and signs/symptoms grade 3 or higher (Questions 4 and 5 on the SVW0289 CRF).

42. Do we need to submit the medications CRFs at each interim visit if there have been no changes but there are ongoing medications?

While medications should be reviewed/assessed at interim visits, if there have been no changes to the participant's medications, then the concomitant medications CRFs do not need to be submitted. The SVW0289 will only trigger delinquency to look for the additional CRFs if there are new or updated medications (Questions 6 and 7 on the SVW0289 CRF).

43. When completing the concomitant medications CRFs (PE0421, PE0412 for ESC Sites, and CMW0047 for COMB-R Sites), do we need to report only the changed medications or does the status of all medications at that visit need to be reported?

Whenever a concomitant medications CRF is completed, the status of all medications must be reported, not just the changes.

44. On form SVW0289- Study Event Tracking: Questions 4-7 (ex: Participant experienced any new, ongoing or resolved greater than Grade 3 at this visit or since the last visit? Experienced any new, ongoing or resolved diagnoses greater than Grade 3?). At entry, there are new diagnosis, symptoms, and medications that are recorded on the appropriate CRFs. This CRF however, asks specifically if there are grade 3 or above and to answer YES or NO. Do we answer NO and still continue to complete the diagnosis, symptoms and medication CRFs?

The following forms - PE6834 (Signs and Symptoms), PE6854 (Diagnoses), and PE0421 (Medications) - are required at Entry whether you answer “Yes” or “No” to questions #4-7 on the SWV0289 so that participant history may be obtained. Refer to the CRF Update Memo #1 (dated 22 May 2017) for further clarification. Also note per CRF Update Memo #4 (dated 12 September 2018), the PE6833 and PE6853 forms were replaced in the forms packet by the PE6834 and PE6854 CRFs.

45. For participants who complete Screening/Entry in the same visit and do not need to come back for a 1 Week Visit, would it be possible to create a new form that would allow sites to record this? Otherwise, sites will be required to contact the DMC to exempt them from the 1 Week form when these visits are combined.

The Visit Tracking (TRK0181) Form is required at Week 0 for all participants and is designed to capture whether the Week 0 and Week 1 visits were conducted separately (on different days) or as a combined (same day) visit. Refer to CRF update memo #1 (dated 22 May 2017) for additional information.
46. On Form PE0046- CDC Revised HIV Classification: If a participant’s CDC HIV classification improves from the most severe classification stage would you like that to be reflected on the CRF or should the most severe classification prevail? Also, is there a time-frame for current?

At Entry, sites would answer Q1 “1-Yes” and indicate the most severe stage the participant reached prior to entry. Q2 would be skipped at Entry and Q3 would be completed for the participant’s stage at the time of enrollment. Both stages (most severe and current) would be captured at the time of enrollment.

When this CRF is required after Entry (per the data collection forms schedules), sites will need to answer Q1 with “2-No” and indicate whether a change has occurred. If there has been a change in the participant’s CDC HIV Classification, sites should enter “1-Yes” for Question #2, and indicate the participant’s current CDC HIV Classification for Question #3. If no change has occurred, Q2 is the last question they will need to answer. “Current” in this situation indicates since the last time the CRF was keyed (i.e. at Week 24, this refers to everything since study entry; at Week 36, this refers to any changes since Week 24, etc.).

47. On Form PE6834- Signs and Symptoms: Would you like all psychiatric symptoms associated with diagnosis of depression reported? This would include symptoms that are already captured by the QIDS-C.

As stated in the Safety Assessment and Reporting section (7.2) of the Protocol, “All pre-existing conditions, occurring within 30 days prior to enrollment and regardless of grade, will be recorded on case report forms as signs, symptoms, and diagnoses.” Please note that this includes signs and symptoms of psychiatric disorders, including depression. As stated in 7.3, “Grade 3 or higher signs and symptoms occurring after enrollment through study exit visit, which may or may not be related to the study counseling procedures, will be recorded on the relevant CRF.” Please note that this includes signs and symptoms of psychiatric disorders, if they are new or become more severe (e.g. Grade 3 symptom becoming Grade 4).

48. It is clear that any grade 3 symptoms should be reported after entry. However, for psychiatric symptoms, should sites use Table 6, cited in the protocol, or use the psychiatric symptom parameters on page 18 in the DAIDS Version 2.1 grading table (which differs from table 6 of the protocol)?

Table 6 in the protocol should be used to grade all signs and symptoms. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, can be used to provide additional information for grading of specific symptoms and/or conditions, such as insomnia. We recognize that the DAIDS grading table for psychiatric symptoms uses slightly different language than the description in Table 6; however, we believe that the interpretation and subsequent grading of psychiatric symptoms would be the same using either Table 6 or the DAIDS grading table.
49. **What adverse events should be reported via expedited reporting?**

Based on protocol Section 7.4.2, the only events for which expedited reporting is required (through the DAERS system) are: 1. Suicide attempts and 2. Psychological hospitalizations. The note in this section instructs sites to inform the protocol team, via email, if any other events occur that may cause harm to the participant or others, at the discretion of the site investigator. Sites should continue to report other events that are not necessarily a suicide attempt or psychological hospitalization in this manner, as they have been doing.

One specific example that was discussed on the team call was whether a Grade 4 pancreatitis should be reported through DAERS as an EAE. Per Section 7.4.2, sites are not required to report this as an EAE. This event would, however, be documented on the relevant CRFs, consistent with protocol Section 7.3.

50. **Are any questionnaires conducted on paper at any visit during the study?**

All *participant completed* questionnaires are conducted through the ACASI, with the exception of the QIDS-SR which is completed on paper at Weeks 1,6, 12, and interim visits for COMB-R sites only, and the QLW0283 (Sociodemographics questionnaire) which is completed on paper at Week 0.

51. **If we conduct Week 0 and Week 1 visits on the same day, which week should be selected for the ACASI?**

The ACASI should be entered as Week 0; will then skip to Week 6 and won’t enter anything from Week 1.

52. **Should participants complete ACASI assessments before or after counseling sessions?**

Either way is acceptable.

53. **Is there a way for sites to test the ACASI prior to implementation?**

Yes, please contact the Protocol Data Manager, Chelsea Krotje (krotje@fstrf.org), and she will provide you with a test link.

54. **How do sites know whether a participant has fully completed the ACASI questionnaires?**

The DMC downloads the ACASI data twice per month. If you would like to confirm that the ACASI questionnaires were completed for a particular visit, please contact the Protocol Data Manager, Chelsea Krotje (krotje@fstrf.org) to confirm whether or not the ACASI questionnaires were successfully submitted.

55. **On the SVW0289 tracking form, for the question about how many interim visits were scheduled and how many were kept, should sites record the number of visits between Visit A and Visit B, excluding the current visit?**

That is correct, do not include the current visit in this tally.
56. What forms are required for interim visits?

For COMB-R Sites
At Interim Visits **prior to** Week 24, the following forms are required:
- ADM0040: Visit Status Report
- QLW0280: CBT Adherence Checklist
- QLW0281: Medication Management Checklist
- SVW0289: IMPAACT 2002 Study Event Tracking

For ESC Sites:
At Interim Visits **prior to** Week 24, the following forms are required:
- ADM0040: Visit Status Report
- QLW0285: Enhanced Standard of Care (ESC) Therapist Checklist
- SVW0289: IMPAACT 2002 Study Event Tracking

For both COMB-R and ESC Sites, no forms are required for Interim Visits **after** Week 24 (sometimes referred to as “clinical visits”). All of the pertinent information from these visits should be entered on the CRFs at the Week 36 and Week 48 visit. Please refer to Forms Schedule for the form requirements for each visit. Note: If CRFs have already been submitted to the database for interim visits after Week 24, please do not delete these CRFs.

57. Can the study physician (PI) complete the Prescribing Clinician Satisfactory Scale if he did not prescribe drug to the study participant?

The clinician who saw the participant for Medication Management sessions at Weeks, 6, 12 and 24 should complete the form; this can be the site PI or anyone else who is able to prescribe medications and evaluated the participant at those weeks.

All personnel directly involved with IMPAACT 2002 at each site must be listed on the Study Staff Roster and Signature Log. This log was a required element of activation for each site and must be maintained with all other IMPAACT 2002 essential documents and updated whenever staffing information changes. As long as the Prescriber is listed on the staff roster and signature log and is indicated for appropriate roles and responsibilities, they may complete the Prescribing Clinician Satisfactory Scale. If this Prescriber is not listed, sites should update the roster accordingly.

58. How should we document when a particular medication has been prescribed but the participant has not yet taken it?

Sites should wait until the participant starts taking a medication before recording it on the CMW0047: Non-ARV Concomitant Medication CRF; however, we still want sites to indicate that a medication was prescribed at the visit it was prescribed. Therefore, sites should record the prescribed medication on the QLW0281-Medication Management Checklist form. For any medications that are documented as prescribed on the QLW0281 form but not recorded on CMW0047, this will prompt the DMC to query sites. Sites can respond that the participant has not yet started the medication and that will satisfy the query. No further action will be required from the site until the participant has started taking the medication. At that time, sites should report the medication on the CMW0047 CRF.
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>59. Is there a screening failure CRF that should be submitted and how is it different if you couldn't get consent?</strong></td>
<td>Yes; the Screening Failure and Non-Enrollment Results form (SCR0055). The first question on this form asks whether the participant provided consent, if the answer is “no,” the rest of the form is left blank.</td>
</tr>
<tr>
<td><strong>60. How can we complete the ACASI if the FSTRF Portal is not working?</strong></td>
<td>Below is the link to the ACASI survey. The survey runs independent of the FSTRF Portal so there should not be any issues with completing the ACASI even if the Portal is not working. If you have any questions you can contact the Protocol Data Manager, Chelsea Krotje (<a href="mailto:krotje@fstrf.org">krotje@fstrf.org</a>).</td>
</tr>
<tr>
<td><strong>61. Form CMW0047 (Non-Antiretroviral Concomitant Medications) questions ask to Specify Drug and to select the Category the drug is indicated for. Frequently our study participants are prescribed Bactrim DS and/or Azithromycin for OI prophylaxis due to low CD4 counts, and not for acute infection. What Category Option should be selected in this situation?</strong></td>
<td>Given that Bactrim and/or Azithromycin were prescribed for OI prophylaxis due to low CD4 counts and not for acute infection, Category 14 should be selected for this medication.</td>
</tr>
<tr>
<td><strong>62. Form SVW0289 (question 2) asks for the number of medical visits a participant has scheduled with a site prescribing clinician since their last study visit. Is this question referring to the number of appointments with a medical practitioner who is managing their psychiatric prescriptions, their HIV care or both?</strong></td>
<td>This question is referring to the number of appointments that the participant has scheduled since their last study visit with their medical practitioner who is managing their psychiatric prescriptions or is assessing the participant for possible use of such medications.</td>
</tr>
</tbody>
</table>
63. Is there a Protocol Signature Page for IMPAACT 2002?

DAIDS has recently instituted a new policy for use of Protocol Signature Pages (PSPs). To address this, a signature page for IMPAACT 2002 protocol V1.0, with LoA#1 and Clarification Memoranda #1-2, was included within the LoA document that was released to sites on 4 May 2018. The IMPAACT 2002 Investigator of Record at each site should have completed this page and submitted it to the DAIDS Protocol Registration Office (DAIDS PRO) as part of the LoA#1 submission. Refer to the email communication sent to sites for additional guidance for submitting the completed protocol signature page to DAIDS PRO.

64. What email should sites send IMPAACT 2002 related questions to?

Please follow the below guidance for queries:

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 (impaact.team2002@fstrf.org). Note: Any queries regarding participant management including those which may include case summaries and/or PID numbers should be sent to only the Core Team (as described below).

Clinical and toxicity management questions and notifications: Questions concerning clinical management of study participants and adverse experiences should be emailed to the IMPAACT 2002 Core Team (impaact.core2002@fstrf.org).

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 (impaact.core2002@fstrf.org).