

HPTN 084: Tips and Lessons Learned from 084 Sites

Questions regarding the safety assessments and clinical management of participants in HPTN 084 should be directed to the HPTN 084 Clinical Management Committee (084CMC@hptn.org).

General non-clinical questions and questions about Protocol Deviations should be directed to (084mgmt@hptn.org). Staff members from the HPTN LOC, HPTN Statistical and Data Management Center (SDMC), and HPTN Laboratory Center (LC) will receive the email. Emails with questions will be responded to by the most appropriate HPTN representative.

1. Missed Visits or Injections

- It has taken close to an hour for injectable product preparation; be sure to plan for any pharmacy-related delays for Injection Visits.
- Refer to your site's Pharmacy Establishment Plan (PEP) which outlines how the site Pharmacist of Record (PoR) will dispense study products- whether to a clinician, or directly to a participant. Both are acceptable so long as the clinician and participant remain BLINDED (unless unblinding has occurred for safety or pregnancy).
- Week 4 missed or late: Contact the CMC for guidance before you do anything!!! Participants who miss Week 4 must complete Week 4 procedures before moving to Week 5, regardless of the visit window. Week 4 is a mandatory visit, irrespective of the interval between Week 2 and Week 4 visit. The CMC will provide guidance on whether a transition to Step 2 may take place and, if so, under what circumstances.
- At the Week 5 visit, the date of visit should reflect the date of first injection. The date of the first injection resets the visit schedule from that point forward (i.e. Week 6 will always be one week after Week 5- even if Week 5 is early or late). Rave calculates the remaining Step 2 visits based off Visit Date (item 1a) on the V5.0 Week 5 Date of Visit CRF. Participants technically stay in Step 2 (regardless of visit schedule) until everyone switches to Step 3.
 - Please note, this is unique for Week 5/Visit 5.0, as typically Visit Date reflects the earliest date the participant was seen for a visit. Therefore, if any assessments were completed prior to the first injection, queries may open. Please respond to indicate that the data are correct as entered.
- Consider printing out the Schedule of Visits at Enrollment and again at Week 5 and giving it to participants, so they can plan for those visits and hopefully reduce missed visits.

2. Adherence

- Pill counts are only conducted at Weeks 2 and 4 (Oral Safety Visits). These pill counts are done to ensure adequate participant study product exposure before moving to injectable product. Pill counts are not formally reviewed for visits in Step 2 or Step 3.

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- Participants should be advised to bring open bottles to appointments, finish an open bottle before opening a new one, and should not combine or transfer pills between open bottles

3. Pregnancy/Contraception

- At the first positive pregnancy test, contact the CMC at 084cmc@hptn.org.
- If pregnancy is confirmed at 4 weeks, please ensure the procedures under SSP Section 9.15.6 Unblinding Procedures in the Event of Confirmed Pregnancy are followed.
 - Kindly note these procedures are different from those for *Emergency Unblinding for Medical Reasons* (SSP Section 9.15.1), which should occur rarely, if at all, during the study. Emergency unblinding discloses arm information to the IoR in Rave, which may be required in the setting of an urgent, potentially life-threatening clinical event. Pregnancy unblinding procedures limit information to direct treatment assignment for only the individual participant affected.
- Sites should also contact the CMC if a participant has a contraceptive coverage lapse (Refer to LoA #3)

4. CPK, Liver Function, other laboratory testing/ results

- Contact 084mgmt@hptn.org for questions about lab redraws.
- Sites can proceed with the Week 5 injection while awaiting the LDL result. Contact SDMC for any questions on eCRF completion. Try to have the participant come back within 72 hours for LDL testing (after the Week 5 visit).
- If there is a clinical indication for syphilis at the screening visit and syphilis testing is done at screening, it must be repeated at enrollment. STI positivity does not exclude enrollment. In fact, it demonstrates that the participant is high risk and a good candidate.
- If a woman is on her menses at the enrollment visit and a TV swab cannot be obtained, it should be collected as close to the enrollment visit as possible.
- The protocol inclusion and exclusion criteria were created with the goal of ensuring the safety of the participants. Therefore, laboratory values that are gradable but not exclusionary should be considered in the context of the overall health of the participant.
- A participant had a grade 2 platelets result of 81,000 at screening and the platelets were clumped/ reported as an inaccurate reflection of true platelet count.
 - This is a legitimate result from the instrument, but the lab should confirm the result on a slide review prior to releasing the result. Some instruments tend to have this happen (clumping) more frequently than others. A new draw had to be performed (Complete Blood Count or CBC). As a reminder the sites should make sure they are following appropriate mixing of the tubes when collecting as this could attribute to platelet clumping. In certain cases, another anticoagulant, citrate, may need to be used to determine just the platelet count.

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- Sites should be aware of low platelets at screening/enrollment because this may affect the ability to provide injections. Participants with plts <50,000 may not be able to receive injections.
- Low WBC or absolute differential values should be reviewed in the laboratory following standard procedures of slide review before release.
- Low calcium values should be confirmed by the laboratory. The laboratory should also check potassium levels to determine if there is EDTA contamination in the SST/Red top tube. If so the clinic should review their blood draw practices to ensure that collections follow appropriate blood draw sequence.
- The clinic should liaise with the laboratory for any concerns with particular lab results.
- A site received a query on entering both BUN and Urea, because either BUN or UREA is required to be reported but not both. Please refer to the CCGs for additional details on entry and query response for any test that was not done.
- Original lab reports that include PTID, DOB and sex can be stored in a participant's binder versus making certified copies of originals. Check that this is in line with your site SOPs.

5. Data Management

- Medidata Rave can be challenging to learn but, with some practice, it is easy to use.
- A PTID should be generated and assigned when a participant signs the consent. In the event she doesn't return after the first visit, she is counted as a screen out.
- Details regarding the 45-day screening to enrollment window are in SSP Section 4.7.
- For participants who screen out/screen fail:
 - The only eCRFs that are required are the following: HIV Test Results, Plasma Storage, Screening Outcome, and VOICE Risk Score. These are all located in the Screening visit folder. Please do not enter any Enrollment visit eCRFs until eligibility is determined.
 - In the event lab data are entered at screening, please disregard queries on the lab eCRFs. Sex and age are required for grading, but the Demographics eCRF, which contains these fields, is not entered until enrollment.
- At screening and enrollment any abnormal labs are considered part of the participant's Medical History and are not considered AEs.
- Data should be updated directly in the entry field using the pencil icon and not reported in the query response box. Data entered in a query response will result in a re-query.
- For Lab eCRFs (Chemistry, Hematology, Fasting Lipids, and Liver Function) that 1) are missing lab ranges and therefore also missing calculated severity grade or 2) have errors with severity grade calculations: please select site name from the "Lab" drop-down menu at the top of the page to populate ranges and re-run calculations.
- On the Enrollment eCRF, check "Not applicable" for the Contraceptive Sub-study item regarding participant consent until this substudy is open and enrolling.

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- CASI tips:
 - Ensure up-to-date versions of designated browsers are being used, i.e. Chrome, Firefox, Edge, or Safari, to avoid issues with the display and translations. See SSP section 14.2. *Technical Requirements* for a full list of compatible browsers.
 - After participants complete the CASI and return tablets, staff must be careful not to click to go back into the participant's CASI session, where it would be possible to change responses accidentally. If the participant has not already done so, as outlined in SSP Section 14.3.6., please click to "Submit" the completed survey and close the session. If the participant has stopped the survey before completion, you may also close the web browser directly to exit the session from the current page. Data from all previously completed pages will already have been submitted to the server and saved. The SDMC has been alerted to this issue. In the meantime, site staff should take care to close and not accidentally access any CASI session data.

6. Other

- One site mentioned that good Community engagement is critical for recruitment.
- The initial dose of the Hep B vaccination must be given at Week 2. Subsequent doses may be given at different visits than indicated in this SOE, as long as sites follow manufacturer guideline timing. This is noted the footnote in protocol Appendix IB.
- In general, we want to avoid enrolling participants with underlying medical conditions and concomitant medications that can cause difficulty in deciding whether an adverse event should be attributed to the pre-existing condition or study product. The protocol eligibility criteria state the following: *"No medical condition that, in the opinion of the study investigator, would interfere with the conduct of the study"*. This leaves the determination regarding enrolment of participants with comorbid conditions to the discretion of the site investigator. Sites should not feel compelled to enroll a participant that they are unsure would be suitable.
- One site is conducting mock visits to make sure it has thought through everything before participants come in.
- Not all participants are computer literate, so it helps to assess this at the Screening visit. If needed, additional time can be allocated to computer education at the Enrollment visit.
- In cases where a participant requests withdrawal, encourage the participant to come in for a final visit to gain a better understanding of her reasons for withdrawal. Possible issues to explore with the participant include community or family beliefs about the study as well as pressure from partner(s) to withdraw from the study. You can also propose to her the option of transitioning to the annual HIV testing arm of the study if she prefers not to take study product but is willing to remain engaged in the study.
- Carefully pre-screening study candidates and then having a group discussion amongst site staff (perhaps a weekly meeting) about each potential participant is helpful to avoid enrolling

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participants who may not be retainable. If a participant meets all inclusion/ exclusion criteria but you feel that she will not be retainable, you may invoke the “Investigator’s decision” clause in the exclusion criteria. Be careful, though, as some difficult to retain participants may also be at highest risk. Contact the CMC if you have any doubts.

- One site has suggested that women who wish to be screened for the study first be HIV-tested (after providing consent). That way, women who are HIV-infected will not need to undergo all the additional screening procedures. You could also perform pre-screening, which may include HIV rapid testing outside of the parameters of the study and would not require the long study consent. Of course, you will STILL need to perform all HIV testing procedures required at Screening when that visit does occur, making sure to obtain consent first.
- Check the prohibited meds list as some antacids may contain prohibited medication. Always contact the CMC if you have any doubts.
- Split visit at enrollment: A participant came for enrollment and completed the procedures prior to enrollment including blood draw and CASI. It was found that she was not fasting and so was informed that she would have to come in again to have the fasting blood test. She misunderstood this to mean she should leave and so left without being randomized. In instances of split Enrollment visits, both HIV rapid tests and pregnancy tests are required to be conducted on the day of randomization (so these will likely be repeated). In this case, all labs should have been repeated when the participant returned, and the HIV RNA test blood draw/ result was required to match the strict “14 day” guidelines noted in the protocol.