IMPAACT P1068s

P1060 SUBSTUDY COMPARING DIFFERENCES IN MALARIA PARASITEMIA BY REAL TIME QUANTITATIVE PCR IN HIV-INFECTED INFANTS AND CHILDREN ON PI-BASED HAART VERSUS NNRTI-BASED HAART

A Multicenter, US Domestic and International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

This file contains all documents related to Version 1.0 of IMPAACT P1068s, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #2, dated December 11, 2015
- Letter of Amendment #3, dated June 21, 2011
- Letter of Amendment #2, dated March 15, 2010 (Zambia only)
- Letter of Amendment #1, dated October 1, 2009
- Clarification Memorandum #1, dated September 3, 2009
- Protocol Version 1.0, dated June 4, 2008
Clarification Memorandum #2 for:
IMPAACT P1068s
P1060 SUBSTUDY COMPARING DIFFERENCES IN MALARIA PARASITEMIA BY REAL TIME QUANTITATIVE PCR IN HIV-INFECTED INFANTS AND CHILDREN ON PI-BASED HAART VERSUS NNRTI-BASED HAART

Clarification Memo Date: 11 December 2015

Summary and Rationale of Clarifications

This Clarification Memorandum (CM) updates the study roster.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this Clarification Memorandum (CM) is not required by the study sponsor prior to implementation. However, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The content of the CM does not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants. This CM should be maintained in each site’s essential documents file for IMPAACT P1068s.

Update of Protocol Team Roster

Contact information for the Protocol Chair has been updated as follows:

Charlotte Hobbs, M.D.
Pediatric Infectious Disease; Microbiology
University of Mississippi Medical Center
Batson’s Children’s Hospital
2500 North State Street
Jackson MS 39202
New York University School of Medicine
Department of Pediatrics
Division of Infectious Diseases
8 West, New Bellevue Avenue
550 First Avenue
New York, New York 10016
United States
Phone: (347) 306-0150
FAX: (212) 263-7806 (253) 399-0150
E-mail: hobbse01@med.nyu.edu chobbs@umc.edu

Patrick Duffy has been added as a Protocol Specialist and Erin Gabriel as a Protocol Statistician:

Patrick E. Duffy, M.D.
Laboratory of Malaria Immunology and Vaccinology
Division of Intramural Research
NIAID, NIH
5640 Fishers Lane
Twinbrook 1, Room 1111
Rockville MD 20852
Phone: (301) 443-4605
FAX: (301) 480-1962
E-mail: patrick.duffy@nih.gov

Erin E Gabriel
BRB NIAID
5601 Fishers Lane, Room 4D10
Rockville, MD 20852
Phone: (240) 669-5254
E-mail: erin.gabriel@nih.gov
TO: IMPAACT Principal Investigators and Study Coordinators

FROM: IMPAACT P1068s Protocol Team

DATE: June 21, 2011

RE: Letter of Amendment #3 for IMPAACT P1068s “P1060 SUBSTUDY COMPARING DIFFERENCES IN MALARIA PARASITEMIA BY REAL TIME QUANTITATIVE PCR IN HIV-INFECTED INFANTS AND CHILDREN ON PI-BASED HAART VERSUS NNRTI-BASED HAART”, Version 1.0 dated 06/04/08

THE FOLLOWING INFORMATION IMPACTS THE P1068s STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY ALSO IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

UPON RECEIVING FINAL IRB/EC AND ANY OTHER APPLICABLE REGULATORY ENTITY (RE) APPROVAL(S) FOR THIS LoA, SITES SHOULD IMPLEMENT THE LoA IMMEDIATELY. SITES ARE STILL REQUIRED TO SUBMIT A LoA REGISTRATION PACKET TO THE DAIDS PROTOCOL REGISTRATION OFFICE (PRO) AT THE REGULATORY SUPPORT CENTER (RSC). SITES WILL RECEIVE A REGISTRATION NOTIFICATION FOR THE LoA ONCE THE DAIDS PRO VERIFIES THAT ALL THE REQUIRED LoA REGISTRATION DOCUMENTS HAVE BEEN RECEIVED AND ARE COMPLETE. A LoA REGISTRATION NOTIFICATION FROM THE DAIDS PRO IS NOT REQUIRED PRIOR TO IMPLEMENTING THE LoA. A COPY OF THE LoA REGISTRATION NOTIFICATION ALONG WITH THIS LETTER AND ANY IRB/EC CORRESPONDENCE SHOULD BE RETAINED IN THE SITE’S REGULATORY FILES.

This Letter of Amendment (LOA) serves to increase subject enrollment in the P1068s protocol as well as extend the length of time that all subjects will be followed to March 31st, 2016.

1. Enrollment will be expanded to allow all subjects who are currently being followed as part of Cohort I or Cohort II in the P1060 study (whether on or off the original randomized regimen), to be enrolled into the P1068s study.

   This change will affect the following sections of the protocol: Schema and Study Design (Section 3.0) and Statistical Considerations (Section 6.0).

2. The eligibility criteria (Sections 4.1 and 4.2) will remain the same.

3. At sites where subjects were taken off P1060 on March 31, 2011 and are still awaiting regulatory approval to resume P1060, eligible subjects co-enrolled in
P1068s can resume P1068s study visits at the time that IRB approval is obtained to allow continuation of P1060.

4. Subjects that are already enrolled in the study, as well as new enrollees, will be followed every 12 weeks (± 6 weeks) via specimen and data collection until March 31, 2016. Sites should collect specimens on all subjects as per the revised Schedule of Evaluations (Appendix I - displayed at the end of this document).

5. As a result of the extension of the protocol, subjects may now be in this sub-study for up to 7 years depending on when they enrolled in the study. As such, the consent form should be revised as follows:

HOW LONG WILL MY CHILD BE IN THIS SUBSTUDY?
Your child will be in this substudy up to 7 years, depending on when your child joins the study.

6. As a result of the extension of the protocol, subjects will undergo a change in the visit schedule (as described in bullet #3 above). As such, the consent form should be revised as follows:

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

During the Study:

“If your child is eligible for this substudy, your child will come back to the clinic within 30 days for an enrollment visit. Then your child will be seen at the clinic again in 2 weeks, then once a month for the first 4 months of the study. After this, your child will be seen at the clinic every 2 to 3 months until the end of the study. At each visit, study staff will ask questions about your child’s health, signs of malaria (fever, chills, upset stomach, and tiredness), and if your child has taken any anti-malaria medicines. One drop (about 1/15th teaspoon) of blood will be taken for special blood tests to check for malaria parasites. Another test will be done to check how many parasites are in your child’s body. After your child has been on the study for 48 weeks (about 1 year), your child will be seen at the clinic every 3 months until the study is over. After week 48 a little less than ½ a teaspoon (2 mL) of blood will be drawn once per year to look at how the cells that fight infection in your child’s body react to malaria and if the reaction is related to a gene that your child may have. Some of these samples will be sent to doctors in laboratories overseas who have special ways of looking at malaria infection in the body.”

Please contact the P1068s protocol team (actg.teamp1068s@fstrf.org ) with any questions concerning this correspondence. This information will be incorporated into the next protocol version when a new version is issued.
### APPENDIX I

**SCHEDULE OF EVALUATIONS**

<table>
<thead>
<tr>
<th>STUDY VISIT SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening¹</td>
</tr>
<tr>
<td><strong>: CLINICAL EVALUATIONS</strong></td>
</tr>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>History</td>
</tr>
<tr>
<td>Physical Exam²</td>
</tr>
<tr>
<td><strong>: LABORATORY EVALUATIONS</strong></td>
</tr>
<tr>
<td>Thin/Thick Smear³</td>
</tr>
<tr>
<td>Dried Blood Spots⁴</td>
</tr>
<tr>
<td>Stored Plasma / Cell Pellet⁵</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
</tr>
</tbody>
</table>

**NOTE:** Samples should be collected during intercurrent illness visits, and subjects should be encouraged to return to the IMPAACT clinic for all care whenever possible. If subjects are treated elsewhere for illness, clinicians should capture this information on CRFs.

**Footnotes:**

1. Screening evaluations must be completed within 30 days prior to study entry, exactly as per the primary study, P1060. In addition to history information obtained through P1060, history of sickle cell disease (this information collected only at baseline), use of cotrimoxazole prophylaxis, history of medications administered outside of the study clinic by other health care workers, and any home-based therapies (medications administered at home without prescription by study site clinician) for malaria will be collected.

2. Physical exam should include height, weight, head circumference, and vital signs.

3. Giemsa-stained thick and thin smears, each requiring approximately 25 µl of blood (a total of 50 µl) will be performed (see Appendices III and IV). This can be done directly from a heel or finger stick or from an EDTA-anticoagulated venous drawn specimen.
4. Collect 250 μL of heel stick/finger stick blood or venous drawn, heparin-free, EDTA-anticoagulated blood to fill five spots on 1 Whatman Protein Saver card (CAT No 10534612) (50 μL per spot, 5 spots per card; 250 μl total) to be preserved for RTQ PCR. See Appendix III for details. This DBS collection is in addition to the required Whatman Protein Saver cards that are required within P1060.

5. Stored plasma/cell pellet (2 mL) will be used for immunologic assays. If inadequate blood is drawn for P1068s, subjects will not be asked to come back for another blood draw.
TO: IMPAACT Principal Investigators and Study Coordinators at the George Clinic, Lusaka, Zambia

FROM: IMPAACT P1068s Protocol Team

DATE: March 15, 2010

RE: Letter of Amendment #2 for IMPAACT P1068s “P1060 SUBSTUDY COMPARING DIFFERENCES IN MALARIA PARASITEMIA BY REAL TIME QUANTITATIVE PCR IN HIV-INFECTED INFANTS AND CHILDREN ON PI-BASED HAART VERSUS NNRTI-BASED HAART”, Version 1.0 dated 6/4/08

This Letter of Amendment (LOA) serves to remove the requirement for specimens to be shipped out of Zambia for study testing and will allow on-site specimen testing as an alternative. This LOA is specific for the Lusaka, Zambia clinical site only and does not impact specimen shipping requirements for Uganda or Malawi sites.

1. APPENDIX III – Preparation of Dried Blood Spots

   Unless otherwise instructed all specimens (dried blood spots, cell pellet and plasma specimens) should be stored locally on-site until ready for testing, which may also be performed on-site if possible.

   If instructed by the protocol team, and only upon approval from national and local approval bodies, dried blood spots and cell pellet and plasma specimen shipments should be shipped per the protocol.
2. APPENDIX IV – Preparation of Thick and Thin Smears

Unless otherwise instructed all specimens (dried blood spots, cell pellet and plasma specimens) should be stored locally on-site until ready for testing, which may also be performed on-site if possible.

If instructed by the protocol team, and only upon approval from national and local approval bodies, dried blood spots and cell pellet and plasma specimen shipments should be shipped per the protocol.

3. APPENDIX V – Informed Consent

The following additional text (indicated in bold below) should be added to the site informed consent form:

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?
Some of these samples will be sent to doctors in laboratories locally or overseas who have special ways of looking at malaria infection in the body.

STORED SPECIMENS
Some of the samples that are taken for this sub study will be kept in laboratories locally or overseas where they will be kept in a locked area and labeled with patient identification numbers, and not patient names.

Please contact the P1068s Protocol Team (actg.teamp1068s@fstrf.org) with any questions concerning this correspondence. This information will be incorporated into the next protocol version when a new version is issued.
TO: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1068s

FROM: IMPAACT P1068s Protocol Team

DATE: October 1, 2009.

RE: Letter of Amendment #1 for IMPAACT P1068s “P1060 SUBSTUDY COMPARING DIFFERENCES IN MALARIA PARASITEMIA BY REAL TIME QUANTITATIVE PCR IN HIV-INFECTED INFANTS AND CHILDREN ON PI-BASED HAART VERSUS NNRTI-BASED HAART”, Version 1.0 dated 6/4/08

This information supercedes information contained in IMPAACT P1068s, Version 1.0 dated 6/4/08.

The following information impacts the IMPAACT P1068s substudy and must be forwarded to your institutional review board (IRB) / ethics committee (EC) as soon as possible for their review. This letter of amendment must be approved by your IRB/EC before implementation.

The following information may impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Please file this letter and any IRB/EC correspondence in your regulatory file and other pertinent files. You are not required to submit these documents to the protocol registration office unless the changes result in changes to the informed consent at your site.

This Letter of Amendment (LOA) serves to remove the requirement for concurrent enrollment in P1068s and P1060. These changes will affect the following sections:

- Section 3.0 - Study Design
- Section 4.11 - Inclusion Criteria
- Section 4.3 - Enrollment Guidelines
- Section 4.4 - Co-enrollment Guidelines
- Section 6.4 - Sample Size and Accrual

1. The inclusion criteria is being expanded to allow ANY subject who was enrolled into IMPAACT P1060 after April 20, 2009 (the date of closure of Cohort I for P1060) to be co-enrolled in P1068s. Subjects will ONLY be enrolled into Cohort II (NVP-unexposed infants/children). This will allow retrospective enrollment of subjects who meet all of the following criteria:

   - Subjects have enrolled in P1060 from April 20, 2009 onwards
   - Subjects are currently on study, AND
   - Subject previously consented to specimen storage as part of P1060 (see item #2 below).
2. If a site enrolls a subject in P1068s, data from the subject’s medical record or P1060 case report forms will be collected retrospectively. “Left-over” Dried Blood Spot (DBS) samples collected for resistance testing in P1060 will be used for laboratory tests in P1068s, therefore only subject’s who have previously consented to specimen storage in P1060, will be able to enroll in P1068s.

3. Subjects who enroll in P1068s and were enrolled in P1060 after April 20, 2009, should start evaluations and specimen collections for P1068s as if they had been enrolled on P1068s at the time they enrolled in P1060. For example, if the subject is currently on a Week 4 visit in P1060, and is co-enrolled in P1068s at that visit, the subject should start P1068s at the Week 4 visit according to the P1068s Schedule of Evaluations (Appendix I).

4. Sites should make every attempt to retrospectively collect all CRFs from all study visits from the time of P1060 enrollment through to the time of P1068s co-enrollment. In the above example, the subject would start P1068s at the Week 4 visit and so the site should try to complete the enrollment through Week 4 CRFs.

5. Sample size and primary and secondary objectives will remain the same. Since Cohort I is now closed, none of the P1068s subjects will enroll into this cohort. Cohort II is the only cohort open to enrollment and so will consist of 140 NVP-unexposed infants/children as described below:

- NVP-based HAART regimen (Group 3): 70
- LPV/r-based HAART regimen (Group 4): 70

6. APPENDIX II - INFORMED CONSENT FORM

The following additional text (indicated in bold below) should be added to the site informed consent form:

INTRODUCTION
To take part in this substudy, your child must be or have been in the P1060 study too.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If your child is already enrolled in IMPAACT P1060, “Phase II, Parallel, Randomized, Clinical Trials Comparing the Responses To Initiation of NNRTI-Based Antiretroviral Therapy in HIV-Infected Infants Who Have and Have Not Previously Received Single Dose Nevirapine for Prevention of Mother-To-Child HIV Transmission,” and you decide to participate in this trial also, we may review data and perform testing on specimens already collected as part of the first study (P1060).

Participating in this substudy may increase your child’s regularly scheduled visits by about 15 minutes. Your child will need to come to clinic about every
2-8 weeks as a part of this sub-study, depending on how long your child has been in the main study (P1060). At these visits, your child will have a physical exam, medical history and have a drop of blood (about 1/15th of a teaspoon) taken. At some of the study visits, your child will…….

The following paragraph should be removed from the consent form:

“If your child must stop taking the medication that is required for the main study (P1060) and is being monitored in the main study (P1060) your child may continue to take part in the main substudy.”

HOW LONG WILL MY CHILD BE IN THIS SUBSTUDY?

Your child may be enrolling in P1060 today or may already have been enrolled in P1060. If your child is already enrolled in P1060, how often your child will be followed in P1068s will depend on how long your child has been in P1060. Your child will be in this substudy between 6 months and 1 year, depending on when your child joins the study.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS SUBSTUDY EARLY?

The study doctor may need to take your child off the substudy early without your permission if:

- The substudy is cancelled by the National Institutes of Health (NIH), or the site’s Institutional Review Board (IRB) or Ethics Committee (EC), or other governmental agencies
- Your child is not able to attend the study visits as required by the substudy
- Taking part in the substudy may be harmful to your child
- The P1060 study is terminated

Please contact the P1068s Protocol Team (actg.teamp1068s@fstrf.org) with any questions concerning this correspondence. This information will be incorporated into the next protocol version when a new version is issued.
DATE: September 3, 2009

RE: CLARIFICATION MEMO #1 for P1068s Version 1.0

TO: IMPAACT Principal Investigators & Study Coordinators at Sites Participating in P1068s

FROM: P1068s Protocol Team

The following is a Clarification Memo for P1068s “P1060 Sub study – Comparing Differences in Malaria Parasitemia by Real Time Quantitative PCR in HIV-Infected Infants and Children on PI-Based HAART Versus NNRTI-Based HAART” Version 1.0, Dated June 4, 2008. The protocol can be obtained from the protocol specific web page of the IMPAACT Website (http://impaact.s-3.com). The username is: ‘impaact’ and the password is: ‘cure’ (all lower case). From the IMPAACT home page, click on ‘Protocol Specific Web Pages’, then select ‘P1068s’. The document is available under ‘Current Protocol Related Documents’.

This memo serves to clarify the following:

1. Please be advised that the Laboratory Contact and Shipping Instructions in Appendix III and the Laboratory Processing Chart (LPC) are incorrect. Please note the corrected address and instructions below:

   **LABORATORY CONTACT AND SHIPPING INSTRUCTIONS:**
   
   ALL dried blood spots, ALL thick and thin smears, and ALL cell pellet and plasma specimen shipments should be addressed to:

   Charlotte Hobbs, M.D. or William Borkowsky, M.D.
   New York University School of Medicine
   Department of Pediatrics
   Division of Infectious Diseases
   Pediatric Infectious Disease Laboratory
   8N16
   462 First Avenue
   New York, New York 10016
   United States
   Phone: (212) 562-3612, (212) 263-8971, (212) 263-6513
   FAX: (212) 263-7806

   Shipping notification should be sent PRIOR TO SHIPMENT to charlotte.hobbs@nyumc.org, with a copy to andre.Fidelia@nyumc.org, william.borkowsy@med.nyu.edu and charlottehobbs@gmail.com. Please ensure shipment is during the week so as not to arrive on a weekend or holiday.
2. The catalog number for the RNA Later reagent that is listed in the Laboratory Processing Chart (LPC) is incorrect. It should read AM7020 and not AM7929. This catalog number appears in the LPC at the following visits: Entry, Week 48, Every 48 weeks (+/- 6 weeks), early discontinuation and End of Study. The corrected text is shown below:

“Remove 0.3mL blood to 2mL tube containing 1.3mL RNA Later (Ambion, Cat.# AM7020 [www.ambion.com](http://www.ambion.com)) Mix thoroughly by inverting the tube several times, store at 4°C for up to one month or at -20°C for >30 days.”

3. Additional information is provided for details on DBS collection and storage which is described in Appendix III and in the Laboratory Processing Chart (LPC):

“Please see [http://www.hanc.info/labs/Pages/ACTGIMPAACTLabManual.aspx](http://www.hanc.info/labs/Pages/ACTGIMPAACTLabManual.aspx) for further details on DBS collection and storage, in addition to proper shipping procedures.”

4. Additional information is provided for details on thick and thin smear preparation which is described in Appendix I, footnote #3; Appendix IV and in the Laboratory Processing Chart (LPC):

“Please note that a heel or finger stick is the preferred method for preparation of thick and thin smears, wherever possible.

**Preparation of Giemsa Stain from Stock Solution**

- Tap water may NOT be used.
- The use of Triton is preferred, however if it cannot be obtained, it is not essential (Fisher catalog # AC32737-1000; [www.fishersci.com](http://www.fishersci.com)).
- Bottled water MAY be used as long as the pH is confirmed to be at 7.2.
- Buffer tablets that will adjust the solution to pH 7.2 are commercially available and may be used to aid in adjustment of pH, should this be necessary. Buffer tablets (VWR catalog # 363102W) are available from VWR: [http://at.vwr.com/app/Header?tmpl=/vwr_programs/clinical/haematology_buffers_products.htm](http://at.vwr.com/app/Header?tmpl=/vwr_programs/clinical/haematology_buffers_products.htm)

In summary, the use of bottled water (buffered to pH 7.2) with or without Triton is acceptable in the preparation of Giemsa stain from stock solution, for thick and thin smear staining.”

These changes will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1068s@fstrf.org with any questions about this correspondence.