SUMMARY OF CHANGES

INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

HPTN 071:

Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART):

A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa

Version 1.0 / 26 October 2012

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Final Version 3.0 / 16 November 2015

Non-IND Study

Information/Instructions to Study Sites from the Division of AIDS

Prior to implementing the changes in this amendment, HPTN 071 study sites will submit this Summary of Changes, Version 3.0 of the protocol, and new informed consent forms, to all relevant regulatory authorities and Institutional Review Boards (IRBs). Once approved by the relevant regulatory authorities and IRBs, the changes in this amendment should be implemented, including immediate use of new informed consent forms.

The amended protocol and revised informed consent forms must be registered with the DAIDS Protocol Registration Office after IRB approval is obtained; however, implementation of the changes, including use of new informed consent forms, should not wait for registration.

File this Summary of Changes, Version 3.0 of the protocol, corresponding site-specific informed consent forms, and all associated IRB correspondence in your essential document files for HPTN 071.

SUMMARY OF REVISIONS AND JUSTIFICATION

Summary of Revisions

This protocol amendment includes many revisions to version 2.0 of the protocol, some of which are minor or administrative in nature. The principal and most significant revision is the first item in the list below, provision of immediate access to ART.

- Describes provision for immediate access to ART in all three study arms, pending funding
- Remove reference to potential PMTCT survey due to lack of funding
- Version number and dates changed throughout
- Updates to protocol team roster

Protocol Team Roster

- Removed: Megan Baldwin, Peter Kim, Shauna Wolf
- Added: Erin Hughes
- Revisions: Lynda Emel's title, David Burns's address

Schema

- Reference to PMTCT survey removed.
- Footnote added to the description of the arms to explain the change in ART access from local guidelines (treatment eligibility based upon CD4 cell count or disease progression) to immediate eligibility in Arms B and C, pending funding.
- Minor wording changes in the secondary objectives regarding funding availability of some objectives.
- Reference to Cloetesville community revised to also include Idas Valley.

Overview of Study Design and Randomization Scheme

- Table and footnote revised to reference immediate access to ART in all three study arms, pending funding.

Section 1.1 – Background and Prior Research

- Reference added to describe recent research demonstrating personal health benefits for individuals who start ART early.

Section 1.2 – Rationale

- Description added of changes to ART eligibility with protocol version 3.0.

Section 1.2.3 – Anti-Retroviral Therapy (ART) for HIV Prevention

- Description added of the rationale for the original design of the three arms (access according to local guidelines in Arms B and C) and the rationale for the change to immediate access in all arms with the current protocol revisions.

Section 1.2.4 – Innovation

- Reference to timing of an article was deleted.
- References added that recent compelling research data (START study) shows that immediate ART confers substantial health benefit for HIV-infected patients irrespective of CD4 count and immediate ART is poised to rapidly become standard of care.
- Language was updated to better reflect how a universal test-and-treat approach can simplify delivery of care to HIV infected patients.
- Explanation added that analysis of study results is still expected to provide insight into the differential value of immediate ART since approximately two years of the intervention will have been implemented with Arm B and C clinics offering ART based upon CD4 cell count or disease progression.
- Note added that changes in ART offering will be incorporated into the statistical analysis plan.
- Reference to PMTCT study removed.
- Note added that the changes between Arms A and B are predicted to become very small due to immediate ART access in both arms however, changes between Arms A and C are expected to remain large because of the CHiPs activities.
- Note added that modeling projections will be adjusted in accordance with changes in the criteria for ART initiation, either through changes in local guideline or through this protocol amendment.

Section 2.2 – Secondary Objectives

- Minor wording changes in the secondary objectives regarding funding availability of some objectives.

Section 2.3 – Study Design

- Minor wording changes made to change the tense of the study description.
- Clarification added that Version 3.0 changes result in the offer of immediate ART in all three arms.
- "Approximately" added to the number of participants in the *Population Cohort*.
- Minor wording revisions made to the description of the *Population Cohort*.
- "If funded" removed from the description of the *Population Cross-Sectional Survey*.

Section 2.4 - Timing of Deployment of Intervention and Research Components

- Reference to PMTCT survey removed.
- Figure 2 was updated to reflect current expectations for study timelines.

Section 3.3 - Universal HIV Testing and Linkage to Care

- Language added to reference potential additional approaches to testing, to be determined at a later date by the study team.

Section 3.5 – Universal Treatment

- (Arm A) removed from the section header.
- Reference added to immediate access to ART in all arms with current protocol version.
- Reference to residency requirement for ART removed.
- Clarification added that linkage to care and adherence are critical in Arms A and B.
- Description of ART eligibility revised to explain timing and shift to immediate ART access.
- Clarification made that any patient starting ART immediately in any study clinic in any arm, will remain on treatment, even after the study ends.

Section 3.5.1 – Choice of ART Regimen

- The restriction "(Arm A)" was removed from the section title.
- Language to specific ART regimen has been removed and replaced with reference to local standard regimen.

Section 3.6 - Treatment According to Local Guidelines (Arms B & C)

- Language revised to include changes in ART eligibility with Version 3.0 of the protocol.

Section 3.7 - Prevention of Mother-to-Child Transmission

- Reference to Arm A clinics removed.

Section 3.11 – Standard of Care

- Reference added to changes in ART eligibility in Arm C with Version 3.0 of the protocol.

Section 3.12.2 - Collaborations

- Table 1 updated to reflect changes to immediate ART eligibility in all study arms.

Section 5.1.1 – Sampling/Recruitment of *Population Cohort*

- Language about the randomization process was revised.

Section 5.4.1 –Evaluation of the Acceptability of the Intervention

- Description of additional research added that will evaluate acceptability of transition to immediate ART in Arms B and C.

Section 5.4.2 - Qualitative Longitudinal Study in Arms A and B – sub-set of *Case-Control Study 1*

- Minor changes done to more accurately reflect the timing of the study.
- Edit made on who will be carrying out the research.
- Description added of additional individuals who will be included in this research from Arm C due to the shift to immediate access to ART.

Section 5.4.3 – Ethnography and HIV Landscape

- Reference to participation in Arms A and C only has been removed.

Figure 1- Qualitative Activities in HPTN 071

- The figure has been changed to reflect that Ethnograhy of Combination Prevention will not be restricted to Arms A and C.

Section 5.6 - Proposed Additional Surveys

- Reference to PMTCT has been removed.

Section 5.7 - Comparative Table of Study Activities across All Study Arms

- Footnote added to describe changes in ART eligibility with Version 3.0 of the protocol.

Table 1- Study Activities across All Study Arms

- Reference to PMTCT survey has been removed.

Section 6.1- Safety Monitoring

- Language was added to indicate that data collected about drug adherence is self-reported.

Section 7.1.3 - Secondary Endpoints

- Community Viral Load testing noted to be subject to funding.

Section 7.3 – Statistical analysis

- Description revised taking into account shift to immediate ART access with changes to Version 3.0 of the protocol.

Section 7.5 – Mathematical Modeling

- Note added that the compartmental model used for this protocol will be updated regularly as the trial progresses to allow investigators, stakeholders and the Data Safety and Monitoring Board to assess revised projections.

Section 7.6 - Outcomes for Secondary Objectives

- Minor wording changes in the secondary objectives regarding funding availability of some objectives.

Section 8.4 – Fair Subject Selection

- Language was clarified to indicate restrictions on those under 18 initiating treatment outside of local guidelines apply to minors in any community, not just those in Arm A.

Section 8.5.1.1 – (Community Level) Benefits

- Language was updated to reflect that the control communities may receive additional benefit with the offer of immediate eligibility for ART.

Section 8.5.2.1 – (Individual Level) Benefits

- Language was modified to reflect recent evidence showing that early ART provides benefit to individuals with HIV infection.

Section 8.5.2.2 – (Individual Level) Risks

- This section was updated to indicate that ART guidelines are believed to be likely to change and that current evidence is that early treatment is beneficial.

Section 8.5.2.3 – Minimizing Risks to Individuals

- Language was modified to reflect the expansion of the offer of early ART by the study to arms other than Arm A.

Section 8.5.2.4 – Risk-Benefit Assessment at Individual Level

- Language was updated to reflect current evidence that early initiation of ART is beneficial to infected individuals.

Section 8.6.3 – Individual Consent

- Language was revised to reflect offering ART outside of guidelines to other arms besides Arm A.
- It was clarified that once local guidelines change it will not be necessary for the study team to obtain consent to initiate immediate ART.

Appendix V - Sample Informed Consent Form

- The title of this consent form was changed to reflect that it will no longer be used only in Arm A, but in all arms where immediate eligibility for ART is offered by the study, outside of routine local guidelines.
- In the "Purpose of the Research in the Communities" section, the description of the three study arms was updated to reflect the changes that will occur with the implementation of his amendment. A sentence was also added to make it clear why the research study is investigating early offer of ART as a way to reduce HIV incidence.
- In the "What will happen during this study" section, language was modified to be clearer about what treatment procedures will be different for a client who provides study consent. Previous language emphasizing the purpose of the research was removed. Also in this section, language was added to indicate that local guidelines are expected to change to immediate ART and the rationale for these changes was provided.

Appendix IX – Proposed PMTCT Survey

- This appendix was removed since multiple attempts to secure funding for this work were not successful, and the team is no longer pursuing this proposed survey.