STATISTICAL ANALYSIS PLAN

Protocol HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

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Version 4.0

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ABBREVIATION AND DEFINITIONS

ALT	Alanine Aminotransferase
ARV	Antiretroviral
AST	Aspartate Aminotransferase
CAB	Cabotegravir
CI	Confidence Interval
Cr	Creatinine Clearance
CRF	Case Report Form
csHT	cross-sex Hormone Therapy
DBS	Dried Blood Spots
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
exp	Exponential
GFR	Glomerular Filtration Rate
HBsAg+	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDU	Injection drug user
IM	Intramuscular
IoR	Investigator of Record
ITT	Intent to Treat
LFT	Liver Function Test
MSM	Men who have Sex with Men
NI	Non-Inferiority
OBSP	On Blinded Study Product
PEP	Post-Exposure Prophylaxis
PrEP	Pre-Exposure Prophylaxis
PT	Preferred Term
RR	Relative Risk
SAP	Statistical Analysis Plan
SDMC	Statistical and Data Management Center
SOC	System Organ Class
STD	Sexually Transmitted Disease
STIs	Sexually Transmitted Infections
TDF/FTC	Tenofovir Disoproxil Fumarate/Emtricitabine
TFV	Tenofovir
TFV-DP	Tenofovir Diphosphate
TGW	Transgender Women

1. INTRODUCTION

This statistical analysis plan (SAP) details the statistical procedures that address the primary study objectives specified in Version 3.0 of *Protocol HPTN 083: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men.* A brief description of secondary endpoint analyses is included. New versions of the SAP will be issued to document updates and changes in the plan. Any meaningful changes or additions to this SAP (e.g., in response to protocol amendments or violations of assumptions underlying pre-planned analyses), and the timing of such changes in relation to unblinding of statisticians performing the analyses, will be documented in a designated section of the SAP. Analysis plans for sub-studies not addressed in the protocol, and for secondary analyses not anticipated prior to study completion, and for exploratory analyses will be developed as separate documents.

Plans for formal interim analysis of trial data are outlined in Section 7.2. A more detailed plan is documented separately in HPTN 083 Interim Monitoring Guidelines. Any substantive modifications to analysis methods or type I error control made in response to DSMB reviews or changes in the protocol will be documented in subsequent versions of the SAP. In DSMB reviews, the HPTN Statistical and Data Management Center (SDMC) will routinely report on operational metrics (e.g., rates of recruitment, retention, study drug discontinuation). These reports are also routinely shared with the study sites to monitor operational performance based on these metrics. No aggregate reporting of HIV infection events or safety data are included in these routine reports to study sites, the format and schedule of which are not considered further in this SAP.

2. STUDY OBJECTIVES GENERAL DESIGN CONSIDERATIONS

2.1 Purpose

The purpose of this study is to evaluate the safety and efficacy of the injectable agent, cabotegravir (CAB LA), for pre-exposure prophylaxis (PrEP) in HIV-uninfected cisgender men and transgender women who have sex with men (MSM and TGW).

2.2 Design

Multi-site, double blind, two-arm, randomized (1:1), controlled non-inferiority trial of the efficacy of CAB LA compared to daily oral tenofovir disoproxyl fumarate (TDF)/emtricitabine (FTC) for HIV prevention.

2.3 Population

HIV-uninfected MSM and TGW at risk for acquiring HIV infection, ages 18 or older.

2.4 Study Size

Approximately 5000, 2500 per arm. Following DSMB review in November 2019 the sample size was increased from 4500 to 5000, as documented in the DSMB recommendations.

2.5 Study Duration

Approximately 5.5 years total, with individual participants being followed between 2.5 years (for the latest enrolling participants) to 4 years (for the earliest enrolling participants). Accrual will require approximately 130 weeks. In Step 1, participants will

receive oral tablets for 5 weeks. In Step 2, participants will receive injections (as a single injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral tablets. Step 2 will be continued until the required number endpoints is reached, or the maximum number of person years specified in the protocol is reached, whichever occurs first. Participants will all be simultaneously unblinded at the conclusion of Step 2. In Step 3, all participants on blinded study drug will receive open-label daily oral TDF/FTC for up to 48 weeks. Participants will therefore be followed for a maximum of four years, including up to three years on blinded study medication and 48 weeks on open-label daily oral TDF/FTC. All participants will be transitioned to locally-available HIV prevention services, including services for PrEP, if available, at the end of their participation in the study.

2.6 Study Regimen and Follow-up

Once randomized to one of two arms, participants will move through the following steps (active drugs are shown in bold text):

Step 1:

Arm A – **Daily oral CAB** (30 mg tablets) and oral TDF/FTC placebo for five weeks

Arm B – **Daily oral TDF/FTC** (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for five weeks

A participant that becomes HIV-infected during Step 1 of the study will permanently discontinue study product, be terminated from the study, and referred for HIV-related care. Individuals who discontinue study participation after receiving oral product in Step 1, but do not receive any study product in Step 2 will be followed annually with HIV testing for a maximum of three years from enrollment.

Step 2:

Arm A – **CAB LA** (600 mg as a single intramuscular [IM] injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral TDF/FTC placebo.
Arm B – **Daily oral TDF/FTC** (300/200 mg fixed-dose combination tablets) and IM placebo at two time points 4 weeks apart and every 8 weeks thereafter (matching vehicle, identical volume as active injectable product in Arm A).

For individual participants 8 weekly injections/pills will continue until three years of follow-up is complete, to Week 153, with the last injection provided and the last blinded oral study product dispensed at Week 145. Participants who prematurely discontinue blinded study products during Step 2 (having received at least one injection) for any reason other than HIV infection will transition to Step 3 early.

This step will continue until (a) the maximum number of endpoints have been observed or (b) the maximum number of person years specified in the protocol is observed, whichever occurs first.

A participant who becomes HIV-infected during Step 2 of the study will permanently discontinue study product, be placed on immediate suppressive ART, and will be followed at quarterly intervals for 52 weeks after their last injection prior to diagnosis of HIV in order to test for safety parameters, as well

as CD4 cell count and HIV viral load. After 52 weeks, they will be terminated from the study and transitioned to continued HIV-related care.

Step 3:

Both arms: **Open-label daily oral TDF/FTC** no later than 8 weeks after the last injection (in order to provide ongoing HIV prophylactic coverage to high risk individuals), for up to 48 weeks. Participants will then transition to locally-available HIV prevention services, including services for PrEP, if available.

A participant with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the Clinical Management Committee (CMC).

3. Study Objectives

3.1 Primary Objectives

- To compare HIV incidence among participants randomized to oral CAB/CAB LA (oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2)
- To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC

3.2 Secondary Objectives

- To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC in Step 2
- To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC (Steps 1, 2, and 3 combined)
- To compare HIV incidence among participants randomized to CAB LA injections vs. oral TDF/FTC while taking open label TDF/FTC (Step 3 only, descriptive)
- To compare the change in risk of HIV acquisition between CAB and oral TDF/FTC strategies (Arm A and Arm B) as participants progress from Step 2 to Step 3 (i.e. post week 153)
- To compare HIV incidence among the subgroups of participants receiving oral CAB/CAB LA vs. oral TDF/FTC by region, age, race, ethnicity, baseline risk, and gender identity
- To compare changes in renal function, liver function, and bone mineral density (BMD) among participants receiving oral CAB/CAB LA vs. oral TDF/FTC
- To evaluate and compare rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs oral TDF/FTC
- To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC
- To compare changes in weight, blood pressure, and pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC

3.3 Tertiary Objectives

- To examine the association between levels of adherence and HIV incidence

- To compare and describe the rates, patterns, and correlates of adherence to CAB LA vs oral TDF/FTC, in aggregate and by psychosocial/demographic variables
- To estimate changes in sexual-risk behavior as measured by self-report and rates of incident gonorrhea, chlamydia, and syphilis in the study population
- To compare the resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa
- To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa

3.4 Exploratory Objectives

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or sexually transmitted infections (STIs); antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives
- To explore possible drug-drug interactions between cross-sex hormone therapy (csHT) and cabotegravir and TDF/FTC in a subset of TGW taking commonly prescribed cross-sex hormone therapy regimens

4. STATISTICAL CONSIDERATIONS

4.1 Randomization

Enrolled participants will be randomized to one of two study arms in a 1:1 ratio. Randomization will be stratified by study site, and a permuted blocks design will be used to ensure balanced treatment assignments within study site. Once a participant has been enrolled, the random-arm assignment will be automatically retrieved from the central server and provided to site pharmacist via the *Balance* module in the *Medidata Rave* web interface. Only the pharmacist will know which oral and injectable products are being dispensed.

4.2 Blinding

In this double-blind double-dummy design, both oral and injectable study products are blinded, and both oral and injectable products are administered to each participant.

Step 1: Blinded oral products

Arm A: Oral CAB tablets 30 mg, one tablet orally daily for five weeks, with or without food AND placebo for TDF/FTC tablets, one tablet orally daily for 5 weeks, with or without food

Arm B: TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally daily for five weeks, with or without food AND placebo for oral CAB tablet, orally daily for 5 weeks, with or without food

Step 2 – Blinded injections and blinded daily oral pills:

Arm A: CAB LA 600 mg administered as one 3 mL (600 mg) intramuscular IM injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter, AND placebo for TDF/FTC tablet, one tablet orally daily with or without food

Arm B: TDF/FTC 300 mg/200 mg fixed dost combination tablet, one tablet orally daily, with or without food AND placebo for CAB LA (Intralipid 20% fat emulsion infusion) administered as one 3mL intramuscular (IM) injection in the gluteal muscle as two time points 4 weeks apart and every 8 weeks thereafter

Study site staff and participants will be blinded to the random assignments, with the exception of the site Pharmacist of Record or their designee. Blinding will be maintained until the trial is completed or stopped, i.e., the trial is stopped early, or the required number of endpoints or person years has been met (with the exception of emergency unblinding). At a specified time directed by the HPTN SDMC, participants will be notified of their treatment assignment. In addition, as noted in Section 5.14.2, an Investigator can request unblinding to the HPTN SDMC in the event that a participant becomes infected with HIV during the study, and the SDMC will assist in directly providing the participant's primary health care provider the randomized arm assignment information per their SOP; the randomized assignment will not be provided to the site where the participant was enrolled and followed.

If, in the judgment of the site investigator of record (IoR), or in the judgment of the participant's medical provider and the site IoR, a medical event is of sufficient extreme severity that it requires the immediate unblinding of a participant, the site IoR may proceed with unblinding a participant. Emergency unblinding is expected to be extremely rare. It should only occur in the setting of a potentially life-threatening clinical event, and if knowing the participant's treatment assignment would affect decisions regarding the participant's immediate medical management. Both conditions must be satisfied. Study site pharmacists who prepare the study drugs are not blinded.

4.3 Sample size and Power

The sample size was computed assuming CAB LA is 25% more effective than TDF/FTC, for a non-inferiority margin of 1.23. Approximately 172 observed HIV-infections will provide 90% power to rule out a non-inferiority margin of HR=1.23, with one-sided type-I error alpha = 0.025. This non-inferiority margin is an M2 margin based on an inverse-variance weighted meta-analysis of three randomized controlled trials of TDF/FTC versus placebo in MSM: iPrex, iPERGAY, and PROUD(1-3). The M2 margin is defined as the reduced bound that is designed to preserve a clinically acceptable amount of the benefit provided by the active control (TDF/FTC). Setting M2 to be 50% of M1 (on the log scale in the case of hazard ratios) is considered to be conservative. M1 is defined as the lower limit of the 95% confidence interval around the placebo versus active-control HR estimate (1.51, based on the meta-analysis). Once the stated number of HIV-infections have been observed, non-inferiority will be established if the estimated CAB LA versus TDF/FTC hazard ratio point estimate is approximately 0.90 or less (indicating a 10% advantage of CAB LA over TDF/FTC), and superiority will be established if the hazard ratio point estimate is approximately 0.74 or less (indicating a 26% advantage of CAB LA over TDF/FTC). The power to detect superiority is 47%. Sample size was computed using RCTDesign package in R and confirmed in nQuery.

5. BLINDED REVIEW OF HIV ENDPOINTS AND PROTOCOL VIOLATIONS

5.1 Blinded determination of HIV endpoints.

A blinded special endpoint adjudication committee (SEAC) is responsible for determining the HIV primary endpoints of the study, i.e. HIV infections occurring after enrollment and during primary analysis follow-up

Prior to each DSMB interim monitoring efficacy review, and prior to unblinding of the final analysis,), the SEAC will engage in a blinded review of all cases with positive/reactive HIV test results to adjudicate study endpoints. The review will make blinded decisions about the confirmation and timing of HIV infection and adjudicate any unexpected issues in the data affecting the primary efficacy endpoints. Data, algorithms and processes for SEAC review are documented in *Terms of reference for HPTN 083 SEAC* and summarized here.

Site testing typically first identifies participants with a reactive HIV test. The HPTN 083 seroconverter alias assist the site in managing the care of potential seroconverters, including additional testing, study drug hold etc. Subsequent testing at the LC, incorporating results from visits before, at and after visits with a reactive test are used to confirm HIV status of each participant with a reactive test.

Endpoint review will make final decisions on all cases of HIV acquisition and data related to the timing of HIV infection. Particular attention will be focused on the following:

1. All cases designated as infected at enrollment.
2. All cases where infection occurred at a visit prior to detection of infection by the site. In particular, this would include review of infections first detected in Step 3 that are subsequently determined to have occurred in Step 2.
3. All cases where site testing did not follow the HIV testing algorithm for determining infection for any reason.
4. Any other unusual cases determined by the LC, stat center or seroconverter alias.

5.2 Classification of protocol deviations

All protocol deviations will be reported and reviewed on a regular basis, and each case will be managed clinically and with regard to ongoing product administration by the CMC and DAIDS MOs during the course of the trial. Certain serious protocol deviations, identified during the blinded review, may warrant the exclusion of participants from the mITT and/or Per-Protocol analysis. Generally, exclusions from the mITT analysis are expected to be limited to participants deemed inappropriately enrolled and resulting in termination from the study. Any exclusion must be carefully adjudicated and scientifically justified prior to breaking the blind. The following list may be updated to reflect unanticipated protocol violations at the time of blinded review.

Protocol Violations
Potentially exclusionary from ITT analyses: Under 18 at enrollment Not male at birth IDU at enrollment ICF violations

Potentially exclusionary from the per-protocol analyses:

- HCV positive at enrollment
- Lab abnormality or relevant medical condition at enrollment
- Prior participation in HIV vaccine trial
- Incorrect study product received*
- Prohibited concomitant medicine use*
- Buttock implant*
- Did not meet sexual risk criteria
- HBsAg+
- History of liver disease
- Coagulopathy
- Allergy to components
- History of seizure
- Missed HIV testing elements
- Missed safety elements (e.g., LFTs, Cr)
- Incorrect/inappropriate amount of study product dispensed*
- Inadequate adherence for progression to step 2
- Injection administration/product dispensation prior to appropriate lab results available*
- Outside protocol TDF/FTC use during protocol (outside PEP)*

*Potential partial exclusion. Exclude (censor) from analyses at the time of the deviation

Minor – not exclusionary:

- Co-enrollment in another study without permission
- Clinically significant CV disease
- Inflammatory skin condition without CMC approval
- Tattoo on buttock without CMC approval
- Visits out of window without with/without CMC approval
- Missed labs/assessments on-study (except HIV testing, LFTs, Cr)
- Non-fasting lipids
- Missed STD testing
- Missed/incorrect f/u for laboratory or clinical AEs
- ECG parameter violations

6. ANALYSIS POPULATIONS

6.1 Intent to Treat (ITT) Population

All participants who were randomized, excluding those who were inappropriately enrolled

6.2 Modified ITT (mITT) Population (Primary Efficacy)

The ITT population, excluding those who were found to be HIV infected at randomization.

Analysis period: Primary analysis follow-up data will include study time through the completion of the blinded injection phase of study follow-up (i.e. Week 153 or the study-wide transition to

Step 3, or end of the blinded phase of the study, whichever occurs first). Inclusion/exclusion of visits are detailed in Appendix A.

6.3 Per-Protocol (PP) Population

The mITT population excluding all participants with protocol violations that were judged to be exclusionary from the per-protocol population.

6.4 Injection (Step 2) Efficacy Population

The mITT population who receive at least one injection and are uninfected at the time of the first injection.

Analysis period: Follow-up time will include primary analysis study time from the time of the first injection through the completion of the blinded injection phase of study follow-up.

6.5 Step 3 Population

All mITT participants who are uninfected at the start of Step 3 follow-up, (i.e. the Week 153/ study-wide transition to Step 3).

6.6 Safety Population (Primary Safety)

All ITT participants who received any oral or injectable product. All safety events occurring on study will be reported.

Step 1 adverse events will include all adverse events occurring until the first injection date, or 120 days post randomization, whichever comes first.

6.7 Injection Step 2 Safety Population

All Safety Population participants who receive at least one injection.

Step 2 safety will include all adverse events occurring from the first injection date through 48 weeks after the last injection.

6.8 Longitudinal Pharmacokinetic CAB Concentration Population

A longitudinal evaluation of CAB PK in the CAB arm will be conducted in 200 participants who received all injections up through week 57, selected with the following regional distribution

- 5% US sites Non-African American (10 participants)
- 5% US sites African American (10 participants)
- 40% Asia (80 participants; 50% TGW using gender affirming hormonal therapy/cross-sex hormonal therapy)
- 40% Latin America (80 participants, 50% TGW using gender affirming hormonal therapy/cross-sex hormonal therapy)
- 10% Africa (20 participants)

This population will be used for the CAB concentration listing and to enhance the population represented in the global modelling of CAB-LA PK.

6.9 TDF-FTC Adherence Population

Cohort of approximately 400 participants randomly selected at baseline from the oral TDF/FTC arm.

6.10 Seroconverter Population

All ITT participants who are identified to be HIV infected following randomization.

6.11 Primary Seroconverter Population

All ITT participants who are HIV-uninfected at randomization and acquire HIV infection during primary analysis follow-up.

6.12 Enrollment Seroconverter Population

All ITT participants who were determined to be HIV-infected at randomization

6.13 Subgroups

Important participant subgroups are

- Region: USA, Latin America, Asia, Africa
- Age:<30 vs ≥30 years old
- Race/Ethnicity: US Black vs non-Black; Hispanic (Yes/No)
- Baseline risk:
  - ≤/> median number of sexual partners
  - ≤/> median report of condomless receptive anal sex
- Gender identity: MSM/TGW.
- Detailed definitions of subgroups are given in Appendix B

7. STATISTICAL ANALYSES

7.1 General analysis considerations

Summary statistics

Summary statistics for categorical variables will include frequency and percentage. For continuous variables, number of subjects with non-missing value (n), mean, median, Q1, Q3, standard deviation (SD), minimum (min), and maximum (max) will be reported. Baseline is defined as Visit 2.0 (Enrollment). All summaries and analyses will be presented by treatment group. Any deviations from the original statistical plan will be described in the final report.

Visit Windows

All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. In data listings, the relative day, of all dates will be presented e.g. from date of randomization, or date of last injection.

7.2 Interim Analyses and Data Monitoring Committee

A summary of the planned approach to interim monitoring is given here. Detailed guidance for early stopping is contained in a separate document: HPTN 083 Monitoring Guidelines.

7.2.1 Interim Monitoring of drug levels

Population: TDF/FTC Adherence Population

Plasma and DBS samples from the TDF/FTC ADHERENCE cohort will be assessed for TFV and TFV-DP concentrations throughout the trial. These data will not be available to the protocol team. Data on TDF/FTC adherence, as measured by plasma and DBS concentrations, will be presented to the DSMB in each DSMB report. This will allow the DSMB to monitor the adherence to oral PrEP and assess the likelihood of reduced HIV acquisition in the TDF/FTC arm. In the event the TDF/FTC adherence appears to be substantially lower than assumed in the protocol, the DSMB can evaluate potential communication with the protocol team leadership if it is thought that actions could be taken to improve adherence to the daily oral medication. The detectable plasma concentrations will be used to estimate the average adherence in the cohort and model, based on plasma concentration data reported from prior placebo randomized trials, the estimated efficacy of TDF/FTC in the cohort. Comparable efficacy data is not available for DBS, although data from DBS concentrations achieved in directly observed therapy studies will permit additional interpretation of the average adherence to TDF/FTC.

7.2.1 Interim Endpoint Analyses

Formal interim statistical analyses are planned for three time points during the trial, with analysis times corresponding to approximately when ¼, ½ and ¾ of the estimated maximum number of HIV infections have been observed. Interim analysis results will be provided to the DSMB at the scheduled DSMB meeting immediately following the time each interim number of events have been observed, or at other time requested by the protocol team or DSMB. The DSMB will receive updated numbers of infections observed at each DSMB meeting.

Population: mITT

Analysis: This analysis will mimic the first objective in the primary analysis with the exception that the interim estimated hazard ratio will be compared to the pre-specified group-sequential stopping boundaries instead of to the non-inferiority margin. It was initially planned to monitor the trial early for early stopping based on the interim monitoring boundary for superiority, or early evidence that oral CAB/CAB LA is definitively less effective than oral TDF/FTC. In light of the disruption to the dispensing of study drug caused by COVID-19 beginning in Mar 2020, the interim monitoring guidance was changed to recommend early stopping based on the non-inferiority boundary, i.e. to recommend stopping based on crossing the O'Brien-Fleming boundary for non-inferiority.

The primary endpoint will be time to detection of HIV infection (time from randomization to midpoint between last HIV negative and first detection). HIV infection status will be assumed to be negative at all missing visits, if any, prior to the first reactive/positive HIV test. In accordance with intention-to-treat principles all participants will be classified into the study arm to which they were randomized. For study participants who do not acquire HIV infection, study time will be censored at the most recent HIV test, as specified in Appendix C. Censoring will be treated as uninformative. A Cox-regression model will be used to estimate the hazard ratio comparing the risk of HIV infection in Arm A (oral CAB/CAB LA) to Arm B (TDF/FTC), and the estimated hazard ratio will be compared to the O'Brien Fleming boundaries for non-inferiority and harm. Boundaries will be estimated based on the faction of observed information calculated based on the planned study design of a maximum of 172 events.

ON BLINDED STUDY PRODUCT Analysis

To support the non-inferiority hypothesis, a supportive analysis will be presented using the OBSP censoring in the Injection (Step 2) Efficacy population (see Section 7.3.4), where study follow-up is censored when a participant does not receive blinded injection study product on time.

7.3 Efficacy Analyses

7.3.1 Study Hypothesis

The statistical hypotheses being tested in this double-blind double-dummy non-inferiority trial are:

Ho: HR (CAB-LA vs FTC/TDF) = 1.23

Ha: HR (CAB-LA vs FTC/TDF) < 1.23

7.3.2 Primary Endpoint

The primary endpoint is HIV-infection occurring after study enrollment. (See Section 5.1) The time to HIV infection will be calculated as the time from randomization to the mid-point between first visit where HIV infection was present and the most recent prior visit where HIV infection was not detectable.

7.3.3 Primary Analyses

Objective: To compare HIV incidence among participants randomized to oral CAB/CAB LA (oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2)

Population: mITT

Censoring time: Study time is censored at the completion of the blinded injection phase of study follow-up (i.e. Week 153 or the study-wide transition to Step 3, or end of the blinded phase of the study, whichever occurs first).

Descriptive analysis: The number of participants, number of infections and cumulative person years will be presented by arm and overall. Incidence rates in each group will be calculated as the number of HIV infections divided by the total observed person time. Confidence intervals will be computed assuming infections are distributed according to a Poisson distribution. A Kaplan Meier plot will be used to display the cumulative rates of acquired HIV-infections by arm (i.e. 1 – KM(t))). Cumulative incidence rates of HIV detection at 12, 24, and 36 months will be reported from the Kaplan Meier plot by study arm and overall, with 95% confidence intervals calculated from the pointwise standard errors, assuming an asymptotic Normal distribution. Participants who are randomized and receive study product but are later determined to have been infected at enrollment are not included in this analysis and will be reported separately.

Statistical Analysis: In accordance with intention-to-treat (ITT) principles all eligible participants not infected at enrollment are included, classified according to randomized study arm. The primary mITT population includes primary analysis time for participants who stop injections early and could have subsequently initiated open label TDF/FTC. Person time in primary analysis is the time from enrollment to the first of (a) midpoint of interval where HIV infection was detected, (b) the last HIV test included in the primary analysis period. For study participants who do not acquire HIV infection, study time will be censored at the last HIV test in primary analysis follow-up. Details of the censoring for

the primary analysis follow-up are in Appendix C. Censoring will be treated as uninformative.

A Cox-regression model, stratified by region, with study arm as the only covariate will be used to estimate HR_{ITT}: the hazard ratio comparing the risk of HIV infection in Arm A (oral CAB/CAB LA) to Arm B (oral TDF/FTC) and generate the 95% Wald-based confidence interval. The upper bound of the 95% confidence interval will be compared to the pre-specified non-inferiority margin of 1.23, with an upper 95% confidence bound less than 1.23 indicating non-inferiority.

Interpretation of the primary ITT analysis when H_0 is not rejected

In a scenario where the primary ITT analysis just fails to show non-inferiority, that is, the upper confidence limit on the hazard ratio is larger than the NI margin by a small amount, consideration will be given to determining whether CAB LA may provide important levels of benefit as compared to placebo. According to the FDA guidance document on NI trials(4):

Failure to exclude inferiority relative to M1 means there is no assurance of any effect. Just as it would be unusual to accept a placebo-controlled study as positive (i.e., a finding of superiority) with $p > 0.05$, it would be unusual to accept an NI study as positive (i.e., a finding of non-inferiority) where the upper bound of the 95% confidence interval was > M1. On the other hand, failing to exclude M2 by a small amount may be acceptable, as the small amount would not suggest the absence of an effect of the drug.

Provided that adherence to TDF/FTC is approximately as expected (57.5%) or higher, if HR_{ITT} is not shown to be conclusively less than the pre-defined (M2) margin 1.23, but clearly and definitively rules out the M1 margin (1.51), it may be appropriate to discuss whether the trial results are consistent with CAB LA providing clinically important protection superior to placebo.

Recomputation of the NI margin when TDF/FTC adherence is lower or higher than assumed

Of key importance in a non-inferiority trial is the assumption that the active-control therapy (oral TDF/FTC in our case) will be as effective as it was in the prior trials used to construct the NI margin. This is referred to as the constancy assumption. Although it is impossible to know with certainty whether the constancy assumption is true, if there exist strong, measurable predictors of effectiveness it may be possible to determine the degree to which the constancy assumption is not true. In the case of oral TDF/FTC it has been shown that drug adherence is a powerful predictor of effectiveness. In order to assess adherence, a random sample of participants in the TDF/FTC arm (the “TDF/FTC Adherence Cohort”, described below) will be selected for laboratory testing of drug levels in plasma. As per section 7.4 in the protocol, if observed adherence rates are substantially outside the range of what was projected for the trial, i.e. adherence is lower than 50% or higher than 65%, the NI margin will be recomputed based on the methods described by Hanscom et al. (2017), and used to help gauge the potential prevention efficacy of CAB LA. The recomputed margin will not replace the pre-specified primary analysis margin or change the conclusion of the primary analysis, but may provide valuable information with respect to determining the prevention effectiveness of CAB LA.

TDF/FTC Adherence Cohort: A sample of 400 participants in the active TDF/FTC arm will be selected at random during the enrollment period and available plasma samples from selected visits (weeks 4, 9, 33, 57, 81, 105, 129, 153, 177) will be assessed for the

presence of TDF/FTC and associated metabolites. The TDF/FTC adherence cohort will be selected to ensure uniform representation over the course of the enrollment period. Random selection of this cohort will be stratified by geographic region (Latin America, Asia, United States, and Africa), and proportionally representative. Average, study-wide adherence will be computed as the overall proportion of all tested samples where TFV is detected in plasma (i.e. concentrations greater than 0.31 ng/ml).

Adapted NI Margin: The adapted NI margin will be based on the estimated TDF/FTC effectiveness given the observed adherence to TDF/FTC in the study cohort. Adherence to TDF/FTC is assessed as the proportion of tested samples in the adherence cohort who have detectable TFV in plasma. This is estimated using the meta-analysis regression equation derived from all prior randomized placebo controlled trials of oral TDF/FTC (5):

Relative Risk (TDF/FTC vs Placebo) = exp(0.735 - 2.439 x adherence)

The corresponding lower 95% confidence limit for this estimated relative risk becomes the revised M1 margin, which we will refer to as M1*. The adapted NI margin is then computed so as to assure that at least half of the observed TDF/FTC benefit is preserved by CAB, and in addition that the margin requires CAB to be at least 15% more effective than placebo. This is accomplished by setting the margin as follows:

Adapted NI Margin = Min(Sqrt(M1*), 0.85 x M1*),

where Sqrt(M1*) represents the point at which half of the observed TDF/FTC benefit is preserved, and 0.85 x M1* represents a 15% improvement over placebo. Note that if TDF/FTC adherence is so low that M1* is less than or equal to 1.17, the adapted NI margin will be less than 1.0, indicating that super superiority is required to assure that CAB is at least 15% more effective than placebo.

7.3.4 Supportive analyses of the primary efficacy results while on blinded study product

In a non-inferiority trial, where all participants are on active treatment, the ITT analysis can be anti-conservative if adherence to either regimen is poor. The efficacy analysis restricted to time while on blinded study product (OBSP) will be a supportive analysis conducted to verify consistency with the ITT analysis, and understand the potential mechanisms for lack of consistency if that occurs. If the ITT and OBSP results are discrepant, possible reasons for the discrepancy will be carefully explored. For example,

1) If the experimental therapy is as biologically effective as the active control, but adherence is low in the active control arm, the ITT analysis would likely show that the experimental therapy was superior to the control ($HR_{ITT} < 1.0$, a non-conservative result), while the OBSP analysis would be expected to show equal effectiveness ($HR_{OBSP} = 1.0$).
2) If the experimental drug is biologically inferior, and adherence to active control was low, the ITT relative effectiveness HR_{ITT} would be expected to be closer to 1 ($HR_{ITT} < HR_{OBSP}$) than the OBSP relative effectiveness ($HR_{OBSP} > 1.0$).
3) If the experimental drug is truly superior and active control arm adherence in the experimental arm was moderate, both analyses would be expected to show superiority, but the ITT effectiveness would be expected to be stronger than the OBSP analysis ($HR_{ITT} < HR_{OBSP} < 1.0$).

It is worth noting that the expected differences between HR_{ITT} and HR_{OBSP} are quite different in this trial than in a typical non-interiority trial. In this trial the experimental

therapy is given by clinician-administered injection and therefore adherence is expected to be high. The active-control therapy, on the other hand, is given by self-administered oral tablets and hence adherence could be low. This could lead to substantial differences in adherence between treatment arms, which could lead to the results described above. In a typical non-inferiority trial both treatments are administered using the identical method, and hence any lack of adherence will affect both study arms equally. In general, this means that HR_{ITT} is expected to be closer to 1.0 than HR_{OBSP}, regardless of whether the experimental therapy is more or less effective than the active control.

Population: Injection Step 2 Efficacy population

Censoring time: For ON BLINDED STUDY PRODUCT (OBSP) analysis, study time is censored at the first time during the blinded injection phase of study follow-up when study injections are not received on the protocol schedule for any reason. Details of the OBSP censoring definitions are given in Appendix C.

Descriptive analysis: Same as the primary analysis, with participants, HIV infections and follow-up time restricted to the dataset.

Statistical Analysis:

The intent of this analysis is to assess relative effectiveness during the study time after randomization when the participant remained consistently on blinded injectable product. All participants who received an injection are included, with study time up to the first time the blinded injection is not given on time for any reason.

Censoring will be treated as uninformative. A Cox-regression model, stratified by region, with study arm as the only covariate will be used to estimate the hazard ratio comparing the risk of HIV infection in Arm A (oral CAB/CAB LA) to Arm B (oral TDF/FTC) and generate the 95% Wald-based confidence interval. The relative OBSP effectiveness, together with available lab-based assessments of adherence to TDF/FTC during OBSP time on study, will be used to interpret the analysis. If substantial differences in HIV incidence are observed between MSM and TGW, consideration will be given to stratifying the Cox regression model by gender identification.

7.3.5 Per-protocol Analysis of Primary Outcome

A per-protocol analysis, excluding participants with exclusionary protocol violations, will be conducted if the number of participants affected exceeds 2% of the enrolled population.

Population: Per Protocol

This analysis will be identical to the mITT analysis specified in section 7.3.3

7.3.6 All Follow-Up, Primary Outcome

An analysis of all participants in the mITT cohort, including all follow-up data through the end of the study.

7.4 Safety Analyses

Objective: To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC

7.4.1 Adverse Events

Adverse events: Primary

Population: Primary Safety

Descriptive: AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class and within preferred term category by severity (grade). For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity. Adverse events reported with an onset date prior to the start of treatment will not be considered in the safety analyses. The time windows for consideration of adverse events with onset dates after the discontinuation of treatment are described below (adverse events on Step 1 and Step 2). All adverse events with onset dates within these constraints are considered to be treatment emergent adverse events.

Statistical analysis: Formal statistical comparison of number of safety events across arms is not planned for all events since interpretation of differences must rely heavily upon clinical judgment. Where formal statistical testing is considered necessary to guide judgement of observed differences for any single event or collection of events, differences in events Grade 2 and higher will be assessed. The event rate and 95% confidence interval for each treatment arm will be calculated based on an exact Poisson model, and event rates will be compared between treatment arms using an exact Poisson test.

Adverse events on blinded study drug product

Objective: To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC while on blinded study drug

Population: Primary Safety

Censoring: For participants who never receive an injection, AEs are censored at the earliest of 1 day after the date of termination or investigational product discontinuation or 120 days after randomization. For participants who receive an injection, AEs are censored at earliest of: open label TDF/FTC first dispensed, 6 weeks after injection if only one injection is given or 10 weeks after the last injection received if 2 or more injections are given. If a termination or product discontinuation occurs, Reported AEs will be excluded if they occur after the censoring time. Details of the OBSP safety censoring definitions are given in Appendix C.

Descriptive and statistical analyses will be as described for Primary Safety above.

Adverse events in Step 1

Objective: To compare the safety of oral CAB vs. oral TDF/FTC in Step 1

Population: Primary Safety

Censoring: For participants who never received an injection AEs are censored at the first of 1 day after the date of termination or investigational product discontinuation or 120 days after randomization. For participants who receive an injection, AEs are censored at date of first injection. Reported AEs will be excluded if they occur after the censoring time.

Descriptive and statistical analyses will be as described for Primary Safety above.

Adverse events Step 2 only

Objective: To compare the safety of CAB LA vs. oral TDF/FTC while on blinded injectable study drug

Population: Step 2 safety

Censoring: AEs are censored at 6 weeks after the first infection if only one injection is given, or 10 weeks after the time of the last blinded injection if 2 or more injections are given. Details of the OBSP Safety censoring definitions are given in Appendix C. Reported AEs will be excluded if they occur before the first injection or after the OBSP Safety censoring time.

Descriptive and Statistical Analysis will be performed as described for Primary safety above.

7.4.2 Laboratory evaluations

Population: Primary Safety

Descriptive: Laboratory findings for CBC, chemistries (urea, creatinine, CPK, glucose, calcium, phosphorous, amylase, lipase), liver function (AST, ALT, total bilirubin, alkaline phosphatase) and fasting lipid profile (total cholesterol, triglycerides, HDL, LDL) will be reported by grade, as defined in the "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events". The proportion of laboratory findings qualifying as Grade 2 or above will be presented. Laboratory values will be reported by arm as median, 1st and 3rd quartiles, min and max, and (at follow-up visits) as median, 1st and 3rd quartile change from baseline (see below). Summaries involving values and changes from baseline at scheduled visit time points will consider values from scheduled visits only, and in the case of missing values, results will not be carried forward from interim (unscheduled) visits. For summaries and analyses involving changes in laboratory values over time or maximum change from baseline (e.g. shift tables), values from interim (unscheduled) visits will also be considered.

Formal comparisons of laboratory values will be conducted as follows:

1) Absolute values: A mixed-effects model with participant as the random effect and site and arm as fixed effects will be used to assess overall differences in each laboratory outcome by arm. A continuous time (elapsed study time) term and an interaction term with study arm will be added to model time trends in laboratory values that may emerge with continuous exposure to study drug. Only post baseline visits will be included.

2) Change from baseline. A fixed effect model with site and arm as covariates will be used to assess overall in change from baseline value for each laboratory outcome by arm. A continuous time (elapsed study time) term interaction with study arm will be added to model differences in laboratory values that may emerge with continuous exposure to study drug.

Laboratory evaluations while on blinded study drug

Population: Primary Safety

Censoring: Lab assessments are censored at 120 days after enrollment for participant who never receive an injection; at open label FTC/TDF first dispensed, or 10 weeks after

the last injection (6 weeks if only one injection is given), whichever occurs first, otherwise. Laboratory evaluations will be excluded if they occur after the censoring time.

Descriptive and Statistical Analysis as described for Laboratory Evaluations above.

7.4.3 Time to study-product discontinuation

Population: mITT

Descriptive: The number and proportion of study participants who discontinue study product will be tabulated by time on study. A Kaplan Meier-type plot of time to first discontinuation will depict the proportion of participants with product discontinuation after randomization, by arm. Competing risk methods will be used to describe the proportion of discontinuation occurring due to safety concern, participant refusal, loss to follow-up or other reasons.

Analysis:

Discontinuation for safety: For the purposes of this analysis, study-product discontinuation for safety is defined as a clinical discontinuation prescribed by site clinicians, site staff, or the study CMC for reasons related to participant safety. For study participants who discontinue study medication on their own, or who are discontinued for reasons other than safety, discontinuation events will be treated as competing risks. A competing-risks model (6), stratified by region with study arm as the only covariate will be used to estimate the relative risk comparing the risk of safety discontinuation in Arm A (oral CAB/CAB LA) to Arm B (oral TDF/FTC) and generate the 95% Wald-based confidence interval. Non-safety related discontinuations will be treated as competing-risk events.

Discontinuation for any reason: For the purposes of this analysis, discontinuation of blinded study product for any reason, including loss to follow-up, will be included as an event. A Cox proportional hazard model, stratified by region with study arm as the only covariate will be used to estimate the relative risk comparing the risk of study product discontinuation in Arm A (oral CAB/CAB LA) to Arm B (oral TDF/FTC) and generate the 95% Wald-based confidence interval.

Details of definitions for safety and other reasons are given in Appendix D.

7.5 Secondary Analyses

7.5.1 Objective: To compare HIV incidence among participants randomized to CAB LA injections vs. oral TDF/FTC in Step 2 only

Population: STEP 2 Efficacy

Descriptive analyses: These parallel the descriptive analyses described in 7.3.3.

Statistical Analysis: This analysis exactly parallels the Primary ITT analysis, but includes only participants who receive an injection, with Time 0 starting at the time of the first injection (first active injection for the CAB LA arm or first placebo injection for the TDF/FTC arm). The statistical hypothesis being tested for Step 2 remains the same as the primary analysis. A sensitivity analysis using on blinded study product censoring time will follow the same plan as the primary analyses.

7.5.2 Objective: To compare HIV incidence among participants randomized to CAB LA injections vs. oral TDF/FTC (Steps 1, 2, and 3 combined)

Population: mITT

Descriptive analyses: These parallel the descriptive analyses in 7.3.3.

Censoring time: First of HIV seroconversion date or last HIV test conducted on study.

Statistical Analysis: This analysis will exactly parallel the Primary ITT analysis, but include all available study follow-up. No formal hypothesis test is proposed for this analysis, as similar infection rates are expected between both arms during Step 3 which could decrease incidence-rate differences between treatment arms.

7.5.3 Objective: To compare HIV incidence among participants randomized to CAB LA injections vs. oral TDF/FTC while taking open label TDF/FTC (Step 3 only, descriptive)

Population: STEP 3 Efficacy

Descriptive analyses: These parallel the descriptive analyses in 7.3.3

Statistical Analysis: This analysis will parallel the Primary analysis, but restricted to the study follow-up in after Week 153 (Step 3), with Time 0 set to the beginning of Step 3. Similar infection rates are expected between both arms during Step 3, although because of limited follow-up time the analysis is not powered to establish equivalence.

7.5.4 Objective: To compare the change in risk of HIV acquisition between CAB and oral TDF/FTC strategies (Arm A and Arm B) as participants progress from Step 2 to Step 3

Population: mITT

Analysis: Analysis of this objective will be descriptive, based on HIV incidence rates observed by study step. Study-arm specific incidence rates will be computed separately for Step 2 and Step 3, along with 95% confidence intervals. Definitions of Step 2 and Step 3 study time will follow the definitions used in the STEP2 and STEP 3 population.

7.5.5 Objective: To compare HIV incidence among the subgroups of participants randomized to oral CAB/CAB LA vs. oral TDF/FTC by region, age, race, ethnicity, baseline risk, and gender identity

Population: mITT

Subgroup Definitions:

Region: USA/Latin America/Asia and Africa

Age: <30/≥30 years old

Race/Ethnicity: Black/Hispanic/White/Other

Baseline risk:

</> median number of sexual partners

</> median report of condomless receptive anal sex

Gender identity: MSM/TGW

Descriptive analyses: These parallel the descriptive analyses described in Section7.3.3, presented for each of the subgroups defined above.

Analysis: The analysis will parallel the primary analysis, with hazard ratios estimated and reported within each subgroup defined by these baseline covariates. Formal tests of subgroup-by-arm interaction will be used to assess for the presence of effect

modification. On blinded study product analyses, if conducted, will parallel those described for the primary outcome analysis.

7.5.6 Objective: To compare changes in renal function, liver function, and bone mineral density (BMD) among participants receiving oral CAB/CAB LA vs. oral TDF/FTC

Population: Primary Safety

Endpoints:

- Serum creatinine
- Creatinine clearance (estimated GFR by Cockcroft gault equation)
- ALT
- AST
- Alk Phosphate
- Total bilirubin
- Bone Mineral Density parameters Z-score at hip and spine

Descriptive analysis: As previously described in Section 7.4.2, Laboratory values will be reported by arm as median, 1st and 3rd quartiles, min and max, and (at scheduled follow-up visits) median, 1st and 3rd quartile change from baseline.

Statistical Analysis: Each outcome measure will be assessed in two separate models. For each outcome variable all non-missing values will be modeled using mixed-effects regression for correlated data with participant as a random effect. In Model 1 the outcome measure will be change from baseline, and the model will include fixed effects for site and treatment arm; a treatment arm by study time interaction will be used. In Model 2 the outcome measure will be absolute levels of the lab measurement (vs change from baseline) and the model will include fixed effects for site, treatment arm, time (continuous, days from enrollment), and treatment arm by time interaction. Model 2 will assess any difference in time trend between the treatment arms. Log transformations will be used for lab values that show strongly skewed distributions. Non-linear terms for time will be considered if the time trends appear to be non-linear.

7.5.7 Objective: To evaluate and compare rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs oral TDF/FTC

Population: SEROCONVERTERS

Descriptive analysis: The number of participants with HIV drug resistance at the first HIV positive visit will be identified by the presence of mutations known to be associated with CAB (including T66I, E92Q/M, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H, T97I/A, G140S, and a 5AA duplication at 232), and associated with TDF/FTC (including K65R, K70E, M184V/I) and non-study drugs (all others). Samples from subsequent study visits may also be analyzed, and summaries of resistance and drug concentrations at the visit will be reported. Resistance will be reported separately for those infected prior to enrollment, and during primary analysis follow-up, compared to Step 3.

Statistical Analysis: Proportion of seroconverter participants who have drug-resistance mutations associated with CAB or TDF/FTC at the first HIV positive visit, will be compared between study arms using chi-squared tests (or exact binomial tests when sample size is small). Similar data from subsequent study visits may also be analyzed.

7.5.8 Objective: To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC

Population: mITT

Outcomes:

Primary preference outcome: Responses to whether participants prefer injections over oral tablets (Yes/No)

Primary acceptability outcome: Responses to whether participants feel that the injections/oral tablets are satisfactory (6 point Likert scale).

An additional set of questions are asked about the reasons for medication preference. An additional 12 satisfaction questions are asked for each medication (6 point Likert scale).

Descriptive analysis: Responses to each preference and satisfaction question overall and at each time period will be tabulated and compared across assigned treatment groups.

Statistical Analysis:

Chi-square tests and Fisher-exact tests will be used as appropriate, with Likert-scale date converted to binary variables according to distributions within the observed response levels (e.g. at the median response). Time trends will also be evaluated. Inference for differences by arm and trends in time will be analyzed using logistic regression models with GEE estimation to account for intra-participant correlation. Each model will contain four terms: (1) region, (2) time, (3) randomized study arm, and (4) time by arm interaction. Time will be entered into the model as a continuous variable scaled in years. A secondary analysis will evaluate non-linear time trends by entering the time variable into the model as a categorical factor.

7.5.9 Objective: To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC

Population: Primary Safety

Outcomes:

- Weight,
- BMI
- Blood pressure,
- Pulse,
- Fasting glucose,
- Fasting lipids

Statistical Analysis:

Change from baseline (enrollment) for each outcome will be computed at each follow-up visit where these measures are collected. The mean changes will be plotted over time by treatment arm. A linear mixed model will be fit with categorical intervals for time in study, treatment and time by treatment interaction to evaluate time trends in each arm and the association between treatment and biological measures. Categorical models will also be used to assess changes over time in BMI category, proportion of participants with 5% or more weight change, and occurrence of new diabetes diagnoses. Differences in time trends and treatment effects will be explored for demographic and clinical subgroups, including race/ethnicity, age, baseline smoking status, baseline BMI, and baseline weight.

8. MISSING DATA AND IMPUTATIONS

Data may be missing due to participant dropout, participant nonresponse, missed visits or failures in data collection. In general, the last category (failures in data collection) is quite rare in HPTN trials. Further, it is common to assume that such data are missing completely at random (MCAR) (7) and so will not bias results. However, participant dropout and/or nonresponse are unlikely to be MCAR and so attention must be paid to the potential for bias if there are high levels of missing data for these reasons. Here we discuss the approaches we will take for analyses in the presence of missing data.

For the primary endpoints, HIV infections, safety events, and other biological endpoints, the primary cause of missing data is missed visits and participant dropout. Historically, HPTN trials have had good retention of participants and we expect that to be the case for this trial. Therefore, analyses will be conducted assuming uninformative censoring. If loss-to-follow-up is low and similar between the arms we will not conduct any additional sensitivity analyses. However, if loss-to-follow-up is greater than 20% or meaningfully different between arms (>5%-points), then we will investigate the sensitivity of the results to assumptions about the missing data. Specifically, we will use inverse probability-of-censoring weights to adjust for loss-to-follow-up (8) and compare the adjusted treatment effect to the unadjusted treatment effect. In addition, we will perform a tipping-point analysis whereby we will determine the difference from the observed treatment arm effect (either higher or lower than observed) that would have to exist in the missing data to meaningfully change our interpretation of the results. We will also estimate the difference in treatment-arm effect that would be observed if all participants who are lost-to-follow-up are assumed to have stopped taking PrEP.

Behavioral and self-reported endpoints (e.g. acceptability) may also be subject to participant nonresponse. The analyses described below are based on a complete case approach. However, if non-response is high (>15%) or differential between arms (> 5%-points) then we will perform sensitivity analyses using multiple imputation. Baseline data will be used to develop the imputation model and standard errors will be adjusted using Rubin's method (9). Both complete case and multiple imputation results will be reported.

8.1 Missing Start and Stop Dates for Prior and Concomitant Medication, and Medical History

Start date:

1. If start date is completely missing, start date will not be imputed.
2. If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
3. If year and month are present and day is missing, set day to the 1st day of month.

Stop date:

1. If end date is completely missing, end date will not be imputed.
2. If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31st.
3. If year and month are present and day is missing, set day to the last day of month.

8.2 Missing Start and Stop Dates for Adverse Events

Start date:

1. If start date is completely missing, start date is set to date of first dose.
2. If (year is present, and month and day are missing) or (year and day are present and month is missing):
    a. If year = year of first dose, then set month and day to month and day of first dose.
    b. If year < year of first dose, then set month and day to December 31st.
    c. If year > year of first dose, then set month and day to January 1st.
3. If month and year are present and day is missing:
    a. If year = year of first dose and
        i. If month = month of first dose, then set day to day of first dose date.
        ii. If month < month of first dose, then set day to last day of month.
        iii. If month > month of first dose, then set day to 1st day of month.
    b. If year < year of first dose, then set day to last day of month.
    c. If year > year of first dose, then set day to 1st day of month.

Stop date:

If the outcome of the AE was ongoing or unknown, then the rules outlined below will not be applied.

1. If stop date is completely missing, stop date is set to date of study discontinuation.
2. If (year is present, and month and day are missing) or (year and day are present, and month is missing):
    a. If year = year of study discontinuation, then set month and day to month and day of study discontinuation.
    b. If year < year of study discontinuation, then set month and day to December 31st.
    c. If year > year of study discontinuation, then set month and day to December 31st.
    d. If date created from imputation is after study discontinuation, date of discontinuation will be used
3. If month and year are present and day is missing:
    a. If year = year of study discontinuation and
    b. If month = month of study discontinuation, then set day to day of study discontinuation date.
        i. If month < month of study discontinuation, then set day to last day of month.
        ii. If month > month of study discontinuation, then set day to last day of month.
        iii. If year < year of study discontinuation, then set day to last day of month.
    c. If year > year of study discontinuation, then set day to last day of month.

9. MONITORING REPORTS

9.1 Performance Metric Reports

Real-time performance metric reports will be available to the protocol team. The content of these reports will be developed by the protocol team and will generally include the following information, overall and by site:

Open Reports for the protocol team

1. Accrual
2. Demographics
3. Rates of progression from Step 1 to Step 2
4. Retention
5. Rates of continuation on study medications
6. Data completeness and timeliness

9.2 SMC Reports

Monitoring reports will be provided to the HPTN Study Monitoring Committee (SMC) approximately every six months (see HPTN SMC Charter). The content of these reports will be developed by the protocol team, but will generally include the following information, overall and by site:

Open Report

1. Screening
2. Accrual
3. Baseline demographic characteristics of enrolled participants
4. Baseline self-reported HIV risk behavior
5. Disposition
6. Retention (Step 1, Step 2, Step 3 separately)
7. Adherence to injection regimen, receipt of oral pills
8. Lost-to-follow-up, Withdrawal, Termination, Product Holds, Death (excluding those attributed to potential HIV infection)
9. Protocol deviations
10. DMQ and Lab Center report

Closed Report

1. HIV incidence rate by region, aggregated over study arm.

9.3 DSMB Reports

Monitoring reports will be provided to the DSMB approximately every six months or as requested by the DSMB. DSMB review will occur at a minimum once per year. At any DSMB meeting, or at any time between regularly scheduled meetings, the DSMB may alter the reporting schedule and request an additional meeting and/or report or request a

change to the meeting schedule. The contents of the DSMB reports will be detailed elsewhere (see DSMB Report Table of Contents), but will generally include the following:

Open Report:

1. All tables and figures in the SMC report.

Medical Officer Report

1. Grade 3 and above adverse events, aggregated by arm
2. SAEs, aggregated by arm
3. Injection Site Reactions, aggregated by arm

Closed report

1. Interim TDF/FTC adherence monitoring results
2. Adverse events and Injection Site Reactions, by arm
3. Summary of the primary outcome data (HIV incidence) by arm
4. At formal interim monitoring review, Interim Endpoint Analysis of the primary ITT outcomes, including pre-planned group-sequential stopping boundaries.
5. OBSP analyses of the primary outcomes
6. Descriptive tables of the timing of infections relative to injections for HIV infections in the CAB arm.

9.4 Clinical Study Report

The tables described below will be included in the CSR. Additional tables and analyses may be included, at the discretion of the protocol team or sponsor, e.g., depending on the availability of additional laboratory evaluations. All reports and analyses will be presented by study arm.

1. Participant Disposition
2. Screening Status
3. Study Populations Summary
4. Subject Status and Accountability
5. Protocol Deviations
6. Demographic and Baseline Variables
7. Concurrent Illnesses and Medical Conditions
8. Prior and Concurrent Medications
9. Adherence to Blinded Study Medication
10. Exposure to Blinded Study Medication and Needle Size Summaries
11. Sexually Transmitted Infection Summaries
12. Safety

Adverse events (including injection site reactions) will be summarized in the following reports:

- Overall Summaries of AEs
- Incidences of AEs
- Severity of AEs
- Relationship of the AEs to the Randomized Treatment
- Serious Adverse Events
- Adverse Events Leading to Drug Withdrawal
- Adverse Events with Study Steps
- Overall Summary of Adverse Events of Special Interest

Note: Adverse Events of Special Interest will be detailed separately in an Integrated Summary of Safety (ISS)

13. Safety Laboratory Data: Summaries and shift tables: Hematology, Renal Function, Liver Function, Lipid Profiles, Urinalysis, Other Clinical Chemistry, Laboratories Meeting Stopping Criteria
14. Vital Signs, including weight, BMI, BP, pulse, fasting glucose/lipids

    Note: Descriptive statistics only; no formal statistical comparisons included in the CSR
15. Efficacy Analyses and Summaries
16. Self-Reported Risk Behaviors

    Note: Descriptive statistics only; no formal statistical comparisons included in the CSR
17. Satisfaction, Attitudes, and Preferences Assessments

    Note: Descriptive statistics only; no formal statistical comparisons included in the CSR
18. FTC/TDF PK assessments of the adherence cohort (Plasma, DBS)

    Note: Descriptive statistics only; no formal statistical comparisons included in the CSR

    Cabotegravir PK assessments in a subpopulation

    Note: Descriptive statistics only; no formal statistical comparisons included in the CSR
19. PK assessments of seroconverters

    Note: Descriptive statistics only; no formal statistical comparisons included in the CSR
20. Resistance assessment of seroconverters

    Note: Descriptive statistics only; no formal statistical comparisons included in the CSR
21. Planned/Unplanned Participant Unblinding Events

10. Revisions of the SAP

10.1. Changes in version 2.0 of the SAP

Revisions prompted by changes in Version 2.0 and 3.0 of the protocol

- Change from open ended follow-up to maximum follow-up of 3 years per person.
- Increase of sample size from 4500 to 5000 participants

Revisions prompted by results external to the protocol

- Addition of new objective: To compare changes in weight, blood pressure, pulse, fasting glucose and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC
- Removal of the upper limit of 1.23 for the non-inferiority margin in the sensitivity analysis adapted to the FTC/TDF adherence observed in the study cohort.
- Two separate As treated analyses replaced by a single On Blinded Study Product analysis. This reduces and simplifies the number of sensitivity analyses proposed for the study.
- Change in emphasis of analysis recomputing the NI margin from sensitivity analysis to a supportive analysis.

Revisions related to alignment with the SAP template adopted by SCHARP

- Added signature page
- Addition of Sections on sample size and power, randomization, blinding
- Addition of pre-defined subgroups
- General rearrangement of sections and renumbering.
- Addition of section describing treatment of missing data

Revisions related to study data collection and/or conduct

- On study drug definition changed to align with injection delivery for both arms. Data about availability of pills in participants assigned to the FTC/TDF arms is too incomplete to accurately characterize potential adherence. In addition, the use of the same metric in both arms will likely reduce ascertainment bias.
- Removal of ongoing assessment of CAB concentration within seroconverters, to reduce the risk of inadvertent release of information about relative efficacy.
- Change study time contributed for seroconverters from time HIV infection detected to midpoint of interval in which seroconversion detected. This is to lessen the impact of different study schedules.

Revisions related to sponsor/DSMB requests

- Clarification of the information reported in Open, Medical Officer and Closed reports
- Clarification of the information reviewed by the HPTN SMC

10.2 Changes in version 3.0 of the SAP

Version 3.0 was prepared following the decision to unblind the study results following the May 14 2020 review. The unblinded statistician continued to not have access to individual level data.

Revisions to Safety

The safety population was revised to include safety observed in the oral lead-in (Section 6.6), and definitions of Step 1 and Step 2 safety populations.

Revision to interim monitoring

Interim monitoring guidance to stop for efficacy revised to stop for evidence of non-inferiority, i.e. monitoring against the trial null hypothesis H0: HR (CAB vs FTC/TDF) > 1.23. (Section 7.2.2)

Reorganization of sections and new sections

- Added Abbreviation and Definition Section
- Reorganized existing text into a new Section 4 Statistical Considerations which includes Randomization, Blinding & Sample Size and Power for the Study.
- Changed the Name of Section 4 (now section 5) Blinded Review of HIV and Protocol Exclusion to Blinded Review of HIV and Protocol Violations
- Changed the name of Section 5 (now section 6) from General Data Analysis Considerations to Analysis Population.
    - Added definition of STEP 1 population
- Reorganized existing text into a new Section 7 Statistical Analyses which includes Interim Analyses (previously Section 5), Efficacy Analyses (previously Section 8), Safety Analyses (previously Section 9) and Secondary Analyses (previously Section 10)
- Added a new Section 8 Missing Data and Imputation
- In Section 9 Monitoring Reports Added description of Clinical Study Report.

10.3 Changes in version 4.0 of the SAP

Version 4.0 was prepared during the planning process for the Clinical Study Report. The unblinded statistician continued to have no access to individual level data.

Analysis Populations

- Populations were renamed or clarified: ITT renamed mITT; Step 1 and 2 Safety, Step 2 Efficacy, Seroconverter populations.
- Populations were added: ITT; Longitudinal Pharmacology for cabotegravir.
- Populations were deleted: Step 1 Efficacy, All Follow-up.
- Populations were respecified as censoring schemes: On blinded study product.

Analysis Details and Clarifications

- Clarifications and additional details were added throughout the Statistical Analysis section. These included:
    - definitions of AE onset windows and censoring times added to safety analyses;
    - details added regarding analyses of change from baseline laboratory values;
    - references to “South America” changed to “Latin America”;
    - clarification to stop-date imputation algorithm;
- Appendices were added to provide detail for visit windowing, key subpopulations, efficacy analysis details, censoring and OBSP specifications, study drug discontinuation analysis, and a listing of adverse events of special interest (AESI).

Reports

- Updates were made to the Clinical Study Report contents

CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
2.0	April 17, 2020	All Sections	Update to ensure sections are in compliance with SCHARP SAP template. Substantive reviews as a result of changes detailed in Section 10.1.
3.0	July 01, 2020	Sections 5.1.2 and 6.2	Updated to reflect the change to interim monitoring based on non-inferiority margins (in revised Interim Monitoring Guidance v 2.0 (08May2020). Updated to included oral lead-in in safety population. Minor updates and reorganization as detailed in Section 15.7.
4.0	October 02, 2020	Throughout Sections 6 and 7; 9.3; Appendices	Clarifications and updates to Analysis Populations and subgroups. Additional details in definitions of censoring. Other updates as detailed in Section 10.3

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Appendix A Visit windows

HPTN 083 Visit Codes, Target Days, and Visit Windows

Week	Visit Code	Target day	Target visit window (±varies days)	Allowable visit window (± varies days)	Allowable visit window
Screening	1.0	--	--		
Step 1					
Day 0/Enrollment	2.0	0	(0 , 3)	+6	(0 , 6)
Week 2	3.0	14	(11 , 17)	-7 / +6	(7, 20)
Week 4	4.0	28	(25 , 31)	-7 / +3	(21, 31)
Step 2					
Week 5	5.0	35	(32 , 38)	-3 / +3	(32 , 38)
Week 6	6.0	42	(39 , 45)	-3 / +10	(39 , 52)
Week 9	7.0	63	(60 , 66)	-10 / +3	(53 , 66)
Week 10	8.0	70	(67 , 73)	-3 / +24	(67 , 94)
Week 17	9.0	119	(112 , 126)	-24 / +7	(95 , 126)
Week 19	10.0	133	(127 , 140)	-6 / +20	(127,153)
Week 25	11.0	175	(168 , 182)	-21 / +7	(154 ,182)
Week 27	12.0	189	(183 , 196)	-6 / +20	(183 , 209)
Week 33	13.0	231	(224 , 238)	-21 / +7	(210 , 238)
Week 35	14.0	245	(239 , 252)	-6 / +20	(239 , 265)
Week 41	15.0	287	(280 , 294)	-21 / +7	(266 , 294)
Week 43	16.0	301	(295 , 308)	-6 / +20	(295 , 321)
Week 49	17.0	343	(336 , 350)	-21 / +7	(322 , 350)
Week 51	18.0	357	(351 , 364)	-6 / +20	(351 , 377)
Week 57	19.0	399	(392 , 406)	-21 / +7	(378 , 406)
Week 59	20.0	413	(407 , 420)	-6 / +20	(407 , 433)
Week 65	21.0	455	(448 , 462)	-21 / +7	(434 , 462)
Week 67	22.0	469	(463 , 476)	-6 / +20	(463 , 489)
Week 73	23.0	511	(504 , 518)	-21 / +7	(490 , 518)
Week 75	24.0	525	(519 , 532)	-6 / +20	(519 , 545)
Week 81	25.0	567	(560 , 574)	-21 / +7	(546 , 574)
Week 83	26.0	581	(575 , 588)	-6 / +20	(575 , 601)
Week 89	27.0	623	(616 , 630)	-21 / +7	(602 , 630)
Week 91	28.0	637	(631 , 644)	-6 / +20	(631 , 657)
Week 97	29.0	679	(672 , 686)	-21 / +7	(658 , 686)
Week 99	30.0	693	(687 , 700)	-6 / +20	(687 , 713)
Week 105	31.0	735	(728 , 742)	-21 / +7	(714 , 742)
Week 107	32.0	749	(743 , 756)	-6 / +20	(743 , 769)
Week 113	33.0	791	(784 , 798)	-21 / +7	(770 , 798)
Week 115	34.0	805	(799 , 812)	-6 / +20	(799 , 825)
Week 121	35.0	847	(840 , 854)	-21 / +7	(826 , 854)
Week 123	36.0	861	(855 , 868)	-6 / +20	(855 , 881)
Week 129	37.0	903	(896 , 910)	-21 / +7	(882 , 910)
Week 131	38.0	917	(911 , 924)	-6 / +20	(911 , 937)
Week 137	39.0	959	(952 , 966)	-21 / +7	(938 , 966)
Week 139	40.0	973	(967 , 980)	-6 / +20	(967 , 993)
Week 145	41.0	1015	(1008, 1022)	-21 / +7	(994 , 1022)
Week 147	42.0	1029	(1023 , 1036)	-6 / +20	(1023 , 1049)
Week 153	43.0	1071	(1064, 1078)	-21 / +7	(1050 , 1078)
Week 155	44.0	1085	(1079 , 1092)	-6 / +20	(1079 , 1105)
Week 161	45.0	1127	(1120 , 1134)	-21 / +7	(1106 , 1134)
Week 163	46.0	1141	(1135 , 1148)	-6 / +20	(1135 , 1161)
Week 169	47.0	1183	(1176 , 1190)	-21 / +7	(1162 , 1190)
Week 171	48.0	1197	(1191 , 1204)	-6 / +20	(1191 , 1217)
Week 177	49.0	1239	(1232 , 1246)	-21 / +7	(1218 , 1246)
Week 179	50.0	1253	(1247 , 1260)	-6 / +20	(1247 , 1273)
Week 185	51.0	1295	(1288 , 1302)	-21 / +7	(1274 , 1302)
Week 187	52.0	1309	(1303 , 1316)	-6 / +20	(1303 , 1329)
Step 3					

Day 0 (Step 3 only)	53.0	<8 weeks from last injection	(0 , 14)	+42	(0 , 42)
Week 12	54.0	84	70, 98	-41 / +42	(43 , 126)
Week 24	55.0	168	154, 182	-41 / +42	(127 , 210)
Week 36	56.0	252	238, 266	-41 / +42	(211 , 294)
Week 48	57.0	336	322, 350	-41 / +42	(295 , 378)

Appendix B Definition of subgroups

- Region: USA, Latin America, Asia, Africa as defined in Appendix E
- Age: 30 vs ≥30 years old
- Race/Ethnicity:
    - For US sites only: Black vs not Black.

      Black is defined as Black or African American (AA) or Mixed Race, including Black/AA, or Other that includes free text including any of these terms. Non-Black is any other designation that is not missing.
    - Hispanic vs. Non-Hispanic Directly from CRF asking whether participant considers him/herself to be Latino/a or of Hispanic origin
- Baseline risk:
    - ≤/> median number of sexual partners
    - ≤/> median report of condomless receptive anal sex
- Gender identity: MSM, TGW, and prefer not to answer.
- TGW includes participants who self−identify at enrollment as female, transgender male, transgender female, gender queer, transvestite, gender variant, gender non−conforming, or gender fluid or Other, where the free text or any other mentioned above. Participants who self-identify as gay, bisexual, homosexual are included in the MSM category.

Appendix C Details of Efficacy Analysis Definitions

Population Definition:

Modified ITT

- Participant is randomized
- Participant is HIV un-infected at randomization (determined by EAC)
- Participant does not have a major enrollment violation – TBD by independent adjudication

Note: Only participants with at least one follow-up visit (of any type, including safety and interim visits) with HIV status determined after enrollment will contribute study time to the efficacy analysis.

Censoring for primary efficacy analysis:

- If the study is stopped early, all data from the enrollment visit through the end of blinded injection visits will be included
- If no study-wide transition to Step 3 occurred, all data from the enrollment visit through 3 years plus one month (153*7+30=1101 days) will be considered.
- If study wide transition to Step 3 occurred
  - For participants who have been enrolled more than three years (153 weeks) prior to study-wide transition to Step 3, all data from enrollment through 1101 days will be considered
  - For participants who have been enrolled fewer than three years prior to study-wide transition to Step 3 and are on blinded study product, all the data from enrollment visit through the next scheduled injection visit in their Step 2 schedule after the Step 3 transition date plus one month (30 days) will be considered.
  - For participants who have been enrolled fewer than three years prior to study-wide transition to Step 3 who are not on blinded study product, all the data from enrollment visit through the Step 3 transition date plus one month (30 days) will be considered.

Calculation of study time:

- If HIV infected, study time will be calculated as the number of days between enrollment and the mid-point between first visit where HIV infection was detected and the most recent prior visit where HIV infection was not detectable, as determined by the EAC.
- If HIV un-infected, study time will be calculated as the number of days between enrollment and the last visit with HIV status at or before the censoring time.

Primary endpoint:

- Only infections that are confirmed by the EAC and detected within the analysis timeframe at the time of the final primary analysis adjudication (date of first positive visit as determined by the EAC within the analysis timeframe) will be considered. Infections that are not confirmed by the EAC or that occur out of the analysis timeframe will not be included as primary endpoints.

Censoring for on blinded study product (OBSP) efficacy analysis

Participants will be censored the first time an injection is delayed, defined as follows:

- **Last non-delayed injection:** The earliest of an injection whose subsequent injection is delayed for the first time (i.e. given >6 weeks after the Week 5 injection or >10 weeks after any other injection) or the last injection before a termination or a permanent product discontinuation
- For participants with a delayed injection, follow-up time will be censored at the last visit with HIV status determined up through 6 weeks after the Week 5 injection, if that is the last non-delayed injection, or 10 weeks after the last non-delayed injection for subsequent injections.
- For participants with no delayed injections, analysis time defined as for primary efficacy analysis

Censoring for OBSP Safety analyses

For a participant who never receives an injection, AEs will be censored when the onset date falls after the earliest of 120 days after randomization or at the termination or permanent product discontinuation date +1.
For participants who receive an injection, adverse event follow-up will be censored after the last injection regardless of any delays in injections. If only one injection is given, the participants safety events will be censored at 6 weeks after the injection, or 10 weeks after the last injection if more than one injection is given.

Interim Analysis (mITT and OBSP) specification

Interim analysis procedures will follow the primary analysis definitions above with the exception that the analysis timeframe will be truncated at the interim-analysis data cut date, as follows.

Interim mITT analysis

- For participants who have been enrolled at least 1101 days at the time of data cut, all data from enrollment through 1101 days will be considered
- For participants who have been enrolled fewer than 1101 days at the time of data cut, all available data from the enrollment visit through the data cut date will be considered.

Interim OBSP analysis

- If there is an injection delay prior to the data cut, all data up to the last visit with HIV status determined that occurred prior to the data cut date and within 6/10 weeks for the first/subsequent injection of the last non-delayed injection will be considered.
- If there is no injection delay prior to the data cut point, data included as for the ITT analysis

Appendix D Study drug discontinuation analysis due to safety

Definition of Censoring used in analysis of discontinuations due to safety

- Discontinuations due to death, investigator decision and HIV−infection are censored.
- Participants who exit the study at a scheduled exit visit or at the end of the study are also censored.
- Loss to follow-up is treated as a competing event in this analysis: Participants remaining on study product (I.e. in Step 1 or 2) are considered lost to follow-up if

  (1) participant did not move to step 2 within 60 days of enrollment and has not returned;

  (2) participant did not receive any injection within 180 days since last injection and has not returned.
- Permanent discontinuation and/or termination due to participant refusal are treated as a competing events, and include: participant unwilling or unable to comply study procedures, injection intolerance, other participant request, or refuse further participation.

The Safety events of interest are:

- Permanent discontinuation due to safety concerns including: clinical/laboratory AE, ISR, CMC recommendation and other clinical reason.

Appendix E Definitions of Regions for Study Sites

CRS ID	Region	State/Country	Site Name
31788	US	Alabama	Alabama CRS
31957	Latin America	Argentina	FundaciÂ¢n Huâ€šsped CRS
31968	Latin America	Argentina	Hospital JM Ramos Mejia
12101	Latin America	Brazil - Rio	Instituto de Pesquisa Clinica Evandro Chagas (IPEC) CRS
12201	Latin America	Brazil - Porto Alegre	Hospital Nossa Senhora da Conceiâ€¡ao CRS
31517	Latin America	Brazil - Sao Paulo	University of Sao Paulo CRS
31954	Latin America	Brazil - Sao Paulo	Centro Referencia e Treinamento DST/AIDS CRS
601	US	California	UCLA CARE Center CRS
30305	US	California	Bridge HIV CRS
31607	US	California	UCLA Vine Street Clinic CRS
31608	US	California	George Washington University CRS
31967	US	California	East Bay AIDS Center (EBAC) CRS
31961	US	Colorado	Children's Hospital Colorado CRS
5802	US	Georgia	Ponce de Leon Center CRS
31440	US	Georgia	Hope Clinic of the Emory Vaccine Center CRS
30347	US	Illinois	UIC Project WISH CRS
31958	US	Illinois	Adolescent and Young Adult Research at the CORE Center (AYAR at CORE)
31959	US	Louisiana	New Orleans Adolescent Trials Unit CRS
201	US	Maryland	Johns Hopkins University CRS
31785	US	Massachusetts	Fenway Health (FH) CRS
2101	US	Missouri	Washington University Therapeutics (WT) CRS
31786	US	New Jersey	New Jersey Medical School Clinical Research Center CRS
7804	US	New York	Weill Cornell Chelsea CRS
30261	US	New York	Bronx Prevention Research Center CRS
30276	US	New York	Harlem Prevention Center CRS
31801	US	New York	New York Blood Center CRS
3201	US	North Carolina	Chapel Hill CRS
3203	US	North Carolina	Greensboro CRS
2301	US	Ohio	Ohio State University CRS
2401	US	Ohio	Cincinnati Clinical Research Site
30310	US	Pennsylvania	Penn Prevention CRS
11301	Latin America	Peru	Barranco CRS
11302	Latin America	Peru	San Miguel CRS
30259	Latin America	Peru	Asociacion Civil Selva Amazonica (ACSA) CRS
31909	Latin America	Peru	Via Libre CRS
31970	Latin America	Peru	Centro de Investigaciones Tecnologicas, Biomedicas y Medioambientales (CITBM) CRS
31708	Africa	South Africa	Groote Schuur HIV CRS
6501	US	Tennessee	St. Jude Children's Research Hospital CRS
31473	US	Texas	Houston AIDS Research Team CRS
31458	Asia	Thailand	CMU HIV Prevention CRS
31681	Asia	Thailand	Silom Community Clinic CRS
31802	Asia	Thailand	Thai Red Cross AIDS Research Centre (TRC-ARC) CRS
31969	Asia	Vietnam	Yen Hoa Health Clinic

Appendix F: Adverse Events of Special Interest

Hepatotoxicity (Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions)

PT	PT Code
Acquired hepatocerebral degeneration	10080860
Acute hepatic failure	10000804
Acute on chronic liver failure	10077305
Acute yellow liver atrophy	10070815
Ascites	10003445
Asterixis	10003547
Bacterascites	10068547
Biliary cirrhosis	10004659
Biliary fibrosis	10004664
Cardiohepatic syndrome	10082480
Cholestatic liver injury	10067969
Chronic hepatic failure	10057573
Coma hepatic	10010075
Cryptogenic cirrhosis	10063075
Diabetic hepatopathy	10071265
Drug-induced liver injury	10072268
Duodenal varices	10051010
Gallbladder varices	10072319
Gastric variceal injection	10076237
Gastric variceal ligation	10076238
Gastric varices	10051012
Gastric varices haemorrhage	10057572
Gastrooesophageal variceal haemorrhage prophylaxis	10066597
Hepatectomy	10061997
Hepatic atrophy	10019637
Hepatic calcification	10065274
Hepatic cirrhosis	10019641
Hepatic encephalopathy	10019660
Hepatic encephalopathy prophylaxis	10066599
Hepatic failure	10019663
Hepatic fibrosis	10019668
Hepatic hydrothorax	10067365
Hepatic infiltration eosinophilic	10064668
Hepatic lesion	10061998
Hepatic necrosis	10019692
Hepatic steato-fibrosis	10077215
Hepatic steatosis	10019708
Hepatitis fulminant	10019772
Hepatobiliary disease	10062000
Hepatocellular foamy cell syndrome	10053244
Hepatocellular injury	10019837
Hepatopulmonary syndrome	10052274
Hepatorenal failure	10019845
Hepatorenal syndrome	10019846
Hepatotoxicity	10019851
Immune-mediated cholangitis	10083406
Immune-mediated hepatic disorder	10083521
Intestinal varices	10071502
Intestinal varices haemorrhage	10078058
Liver dialysis	10076640
Liver disorder	10024670
Liver injury	10067125
Liver operation	10062040

Liver transplant	10024714
Lupoid hepatic cirrhosis	10025129
Minimal hepatic encephalopathy	10076204
Mixed liver injury	10066758
Nodular regenerative hyperplasia	10051081
Nonalcoholic fatty liver disease	10082249
Non-alcoholic steatohepatitis	10053219
Non-cirrhotic portal hypertension	10077259
Oedema due to hepatic disease	10049631
Oesophageal varices haemorrhage	10030210
Peripancreatic varices	10073215
Portal fibrosis	10074726
Portal hypertension	10036200
Portal hypertensive colopathy	10079446
Portal hypertensive enteropathy	10068923
Portal hypertensive gastropathy	10050897
Portal vein cavernous transformation	10073979
Portal vein dilatation	10073209
Portopulmonary hypertension	10067281
Primary biliary cholangitis	10080429
Regenerative siderotic hepatic nodule	10080679
Renal and liver transplant	10052279
Retrograde portal vein flow	10067338
Reye's syndrome	10039012
Reynold's syndrome	10070953
Splenic varices	10067823
Splenic varices haemorrhage	10068662
Steatohepatitis	10076331
Subacute hepatic failure	10056956
Sugiura procedure	10083010
Varices oesophageal	10056091
Varicose veins of abdominal wall	10072284
White nipple sign	10078438

Hepatotoxicity Continued (Hepatitis, non-infectious)

PT	PT Code
Acute graft versus host disease in liver	10066263
Allergic hepatitis	10071198
Alloimmune hepatitis	10080576
Autoimmune hepatitis	10003827
Chronic graft versus host disease in liver	10072160
Chronic hepatitis	10008909
Graft versus host disease in liver	10064676
Hepatitis	10019717
Hepatitis acute	10019727
Hepatitis cholestatic	10019754
Hepatitis chronic active	10019755
Hepatitis chronic persistent	10019759
Hepatitis fulminant	10019772
Hepatitis toxic	10019795
Immune-mediated hepatitis	10078962
Ischaemic hepatitis	10023025
Lupus hepatitis	10067737

Non-alcoholic steatohepatitis	10053219
Radiation hepatitis	10051015
Steatohepatitis	10076331

Hyperglycaemia

PT	PT Code
Acquired lipoatrophic diabetes	10073667
Blood 1,5-anhydroglucitol decreased	10065367
Blood glucose increased	10005557
Diabetes complicating pregnancy	10012596
Diabetes mellitus	10012601
Diabetes mellitus inadequate control	10012607
Diabetes with hyperosmolarity	10012631
Diabetic arteritis	10077357
Diabetic coma	10012650
Diabetic coronary microangiopathy	10080788
Diabetic hepatopathy	10071265
Diabetic hyperglycaemic coma	10012668
Diabetic hyperosmolar coma	10012669
Diabetic ketoacidosis	10012671
Diabetic ketoacidotic hyperglycaemic coma	10012672
Diabetic ketosis	10012673
Diabetic metabolic decompensation	10074309
Diabetic wound	10081558
Euglycaemic diabetic ketoacidosis	10080061
Fructosamine increased	10017395
Fulminant type 1 diabetes mellitus	10072628
Gestational diabetes	10018209
Glucose tolerance impaired	10018429
Glucose tolerance impaired in pregnancy	10018430
Glucose urine present	10018478
Glycated albumin increased	10082836
Glycosuria	10018473
Glycosuria during pregnancy	10018475
Glycosylated haemoglobin abnormal	10018481
Glycosylated haemoglobin increased	10018484
Hyperglycaemia	10020635
Hyperglycaemic hyperosmolar nonketotic syndrome	10063554
Hyperglycaemic seizure	10071394
Hyperglycaemic unconsciousness	10071286
Impaired fasting glucose	10056997
Insulin resistance	10022489
Insulin resistant diabetes	10022491
Insulin-requiring type 2 diabetes mellitus	10053247
Ketoacidosis	10023379
Ketonuria	10023388
Ketosis	10023391
Ketosis-prone diabetes mellitus	10023392
Latent autoimmune diabetes in adults	10066389
Monogenic diabetes	10075980
Neonatal diabetes mellitus	10028933
New onset diabetes after transplantation	10082630
Pancreatogenous diabetes	10033660
Steroid diabetes	10081755
Type 1 diabetes mellitus	10067584
Type 2 diabetes mellitus	10067585
Type 3 diabetes mellitus	10072659
Urine ketone body present	10057597

Hypersensitivity Reactions

PT	PT Code
Drug reaction with eosinophilia and systemic symptoms	10073508
Pseudolymphoma	10037127
Drug hypersensitivity	10013700
Hypersensitivity	10020751
Type IV Hypersensitivity reaction	10053613
Eosinophillia	10014950
Eye swelling	10015967
Eyelid oedema	10015993
Lip swelling	10024570
Angioedema	10002424
Circumoral oedema	10052250
Face oedema	10016029
Idiopathic angioedema	10073257
Lip oedema	10024558
Mouth swelling	10075203
Oedema mouth	10030110
Periorbital oedema	10034545
Swelling face	10042682
Periorbital swelling	10056647
Swelling of eyelid	10042690

Rash

PT	PT Code
Acute generalised exanthematous pustulosis	10048799
Bullous haemorrhagic dermatosis	10083809
Cutaneous vasculitis	10011686
Dermatitis bullous	10012441
Dermatitis exfoliative	10012455
Dermatitis exfoliative generalised	10012456
Drug reaction with eosinophilia and systemic symptoms	10073508
Epidermal necrosis	10059284
Erythema multiforme	10015218
Erythrodermic atopic dermatitis	10082985
Exfoliative rash	10064579
Oculomucocutaneous syndrome	10030081
SJS-TEN overlap	10083164
Skin necrosis	10040893
Stevens-Johnson syndrome	10042033
Target skin lesion	10081998
Toxic epidermal necrolysis	10044223
Toxic skin eruption	10057970
Eyelid rash	10074620
Genital rash	10018175
Mucocutaneous rash	10056671
Nodular rash	10075807
Rash macular	10037867
Rash maculo-papular	10037868
Rash maculovesicular	10050004
Rash morbilliform	10037870
Rash popular	10037876

Rash rubelliform	10057984
Rash scarlatiniform	10037890
Rash vesicular	10037898
Rash pruritic	10037884
Rash follicular	10037857
Rash pustular	10037888
Drug eruption	10013687

Suicide/self-injury

PT	PT Code
Assisted suicide	10079105
Columbia suicide severity rating scale abnormal	10075616
Completed suicide	10010144
Depression suicidal	10012397
Intentional overdose	10022523
Intentional self-injury	10022524
Poisoning deliberate	10036000
Self-injurious ideation	10051154
Suicidal behaviour	10065604
Suicidal ideation	10042458
Suicide attempt	10042464
Suicide threat	10077417
Suspected suicide	10082458
Suspected suicide attempt	10081704

Depression (Exclude suicide and self-injury)

PT	PT Code
Activation syndrome	10066817
Adjustment disorder with depressed mood	10001297
Adjustment disorder with mixed anxiety and depressed mood	10001299
Agitated depression	10001496
Anhedonia	10002511
Antidepressant therapy	10054976
Childhood depression	10068631
Decreased interest	10011971
Depressed mood	10012374
Depression	10012378
Depression postoperative	10012390
Depressive symptom	10054089
Dysphoria	10013954
Electroconvulsive therapy	10014404
Feeling guilty	10049708
Feeling of despair	10016344
Feelings of worthlessness	10016374
Helplessness	10077169
Major depression	10057840
Menopausal depression	10067371
Mixed anxiety and depressive disorder	10080836
Perinatal depression	10078366
Persistent depressive disorder	10077804
Post stroke depression	10070606
Postictal depression	10071324

Bipolar Disorder

PT	PT Code
Bipolar I disorder	10004939
Bipolar II disorder	10004940
Bipolar disorder	10057667
Cyclothymic disorder	10011724
Hypomania	10021030

Mania	10026749

Psychosis and Psychotic disorders

PT	PT Code
Acute psychosis	10001022
Alcoholic psychosis	10001632
Alice in wonderland syndrome	10001666
Brief psychotic disorder with marked stressors	10048549
Brief psychotic disorder without marked stressors	10056395
Brief psychotic disorder, with postpartum onset	10006362
Charles Bonnet syndrome	10063354
Childhood psychosis	10061040
Clang associations	10009232
Cotard's syndrome	10059591
Delusion	10012239
Delusion of grandeur	10012241
Delusion of parasitosis	10012242
Delusion of reference	10012244
Delusion of replacement	10012245
Delusion of theft	10084030
Delusional disorder, erotomanic type	10012249
Delusional disorder, grandiose type	10012250
Delusional disorder, jealous type	10012251
Delusional disorder, mixed type	10012252
Delusional disorder, persecutory type	10053195
Delusional disorder, somatic type	10012254
Delusional disorder, unspecified type	10012255
Delusional perception	10012258
Dementia of the Alzheimer's type, with delusions	10012295
Depressive delusion	10063033
Derailment	10012411
Epileptic psychosis	10059232
Erotomanic delusion	10015134
Flight of ideas	10016777
Hallucination	10019063
Hallucination, auditory	10019070
Hallucination, gustatory	10019071
Hallucination, olfactory	10019072
Hallucination, synaesthetic	10062824
Hallucination, tactile	10019074
Hallucination, visual	10019075
Hallucinations, mixed	10019079
Hypnagogic hallucination	10020927
Hypnopompic hallucination	10020928
Hysterical psychosis	10062645
Ideas of reference	10021212
Illusion	10021403
Jealous delusion	10023164
Loose associations	10024825
Mixed delusion	10076429
Neologism	10028916
Neuroleptic-induced deficit syndrome	10075295
Paranoia	10033864
Paranoid personality disorder	10033869
Parkinson's disease psychosis	10074835
Paroxysmal perceptual alteration	10063117
Persecutory delusion	10034702
Postictal psychosis	10070669
Post-injection delirium sedation syndrome	10072851

Posturing	10036437
Psychosis postoperative	10065617
Psychotic behaviour	10037249
Psychotic disorder	10061920
Psychotic disorder due to a general medical condition	10061921
Reactive psychosis	10053632
Rebound psychosis	10074833
Schizoaffective disorder	10039621
Schizoaffective disorder bipolar type	10068889
Schizoaffective disorder depressive type	10068890
Schizophrenia	10039626
Schizophreniform disorder	10039647
Schizotypal personality disorder	10039651
Senile psychosis	10039987
Shared psychotic disorder	10040535
Somatic delusion	10041317
Somatic hallucination	10062684
Substance-induced psychotic disorder	10072388
Tangentiality	10043114
Thought blocking	10043495
Thought broadcasting	10052214
Thought insertion	10043496
Thought withdrawal	10043497
Transient psychosis	10056326
Waxy flexibility	10047853

Mood Disorders

PT	PT Code
Affect lability	10054196
Affective ambivalence	10077173
Affective disorder	10001443
Alexithymia	10077719
Anger	10002368
Apathy	10002942
Blunted affect	10005885
Boredom	10048909
Constricted affect	10010778
Crying	10011469
Diencephalic syndrome of infancy	10012774
Dysphoria	10013954
Emotional disorder	10014551
Emotional distress	10049119
Emotional poverty	10014557
Euphoric mood	10015535
Flat affect	10016759
Frustration tolerance decreased	10077753
Inappropriate affect	10021588
Irritability	10022998
Laziness	10051602
Lethargy	10024264
Listless	10024642
Moaning	10027783
Mood altered	10027940
Mood disorder due to a general medical condition	10027944
Mood swings	10027951
Morose	10027977
Neuroleptic-induced deficit syndrome	10075295
Premenstrual dysphoric disorder	10051537
Premenstrual syndrome	10036618

Screaming	10039740
Seasonal affective disorder	10039775
Steroid withdrawal syndrome	10042028
Substance-induced mood disorder	10072387

Anxiety

PT	PT Code
Acrophobia	10000605
Activation syndrome	10066817
Acute stress disorder	10001084
Aerophobia	10080300
Agitation	10001497
Agitation postoperative	10049989
Agoraphobia	10001502
Akathisia	10001540
Algophobia	10078056
Animal phobia	10002518
Anniversary reaction	10074066
Anticipatory anxiety	10002758
Anxiety	10002855
Anxiety disorder	10057666
Anxiety disorder due to a general medical condition	10002859
Arachnophobia	10051408
Astraphobia	10078372
Autophobia	10071070
Body dysmorphic disorder	10052793
Burnout syndrome	10065369
Catastrophic reaction	10082329
Cibophobia	10082413
Claustrophobia	10009244
Compulsions	10010219
Compulsive cheek biting	10076510
Compulsive handwashing	10071263
Compulsive hoarding	10068007
Compulsive lip biting	10066241
Compulsive shopping	10067948
Cryophobia	10082662
Dermatillomania	10065701
Dysmorphophobia	10049096
Emetophobia	10070637
Fear	10016275
Fear of animals	10016276
Fear of closed spaces	10016277
Fear of crowded places	10050365
Fear of death	10066392
Fear of disease	10016278
Fear of eating	10050366
Fear of falling	10048744
Fear of injection	10073753
Fear of open spaces	10016279
Fear of pregnancy	10067035
Fear of weight gain	10016280
Fear-related avoidance of activities	10080136
Generalised anxiety disorder	10018075
Glossophobia	10080077
Haemophobia	10073458
Haphephobia	10067580

Herpetophobia	10081809
Hydrophobia	10053317
Hyperarousal	10080831
Immunisation anxiety related reaction	10075205
Kinesiophobia	10078430
Limited symptom panic attack	10024511
Mysophobia	10078769
Nail picking	10066779
Nervousness	10029216
Neurosis	10029333
Noctiphobia	10057946
Nocturnal fear	10057948
Nosocomephobia	10083993
Nosophobia	10063546
Obsessive need for symmetry	10077179
Obsessive rumination	10056264
Obsessive thoughts	10029897
Obsessive-compulsive disorder	10029898
Obsessive-compulsive symptom	10077894
Ochlophobia	10050095
Osmophobia	10060765
Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection	10072147
Panic attack	10033664
Panic disorder	10033666
Panic reaction	10033670
Paruresis	10069024
Performance fear	10034432
Phagophobia	10050096
Pharmacophobia	10069423
Phobia	10034912
Phobia of driving	10056676
Phobia of exams	10034913
Phobic avoidance	10034918
Phonophobia	10054956
Photaugiaphobia	10064420
Postpartum anxiety	10082233
Postpartum neurosis	10036419
Postpartum stress disorder	10056394
Post-traumatic stress disorder	10036316
Procedural anxiety	10075204
Pseudoangina	10056610
Selective mutism	10039917
Separation anxiety disorder	10040045
Sitophobia	10080170
Social anxiety disorder	10041242
Social fear	10041247
Stress	10042209
Tension	10043268
Terminal agitation	10077416
Thanatophobia	10064723
Thermophobia	10075147
Trichotemnomania	10072752
Trichotillomania	10044629

Sleep Disorders

PT	PT Code
Abnormal dreams	10000125
Abnormal sleep-related event	10061613
Advanced sleep phase	10001423

Behavioural induced insufficient sleep syndrome	10081938
Behavioural insomnia of childhood	10072072
Breathing-related sleep disorder	10006344
Cataplexy	10007737
Central-alveolar hypoventilation	10007982
Circadian rhythm sleep disorder	10009191
Confusional arousal	10067494
Delayed sleep phase	10012209
Dyssomnia	10061827
Exploding head syndrome	10080684
Fatal familial insomnia	10072077
Hypersomnia	10020765
Hypersomnia related to another mental condition	10020767
Hypersomnia-bulimia syndrome	10053712
Hypnagogic hallucination	10020927
Hypnopompic hallucination	10020928
Hyposomnia	10067530
Initial insomnia	10022035
Insomnia	10022437
Insomnia related to another mental condition	10022443
Irregular sleep phase	10022995
Irregular sleep wake rhythm disorder	10080301
Loss of dreaming	10065085
Microsleep	10076954
Middle insomnia	10027590
Narcolepsy	10028713
Nightmare	10029412
Non-24-hour sleep-wake disorder	10078086
Parasomnia	10061910
Paradoxical insomnia	10083337
Periodic limb movement disorder	10064600
Pickwickian syndrome	10035004
Poor quality sleep	10062519
Rapid eye movement sleep behaviour disorder	10077299
Rapid eye movements sleep abnormal	10037841
Shift work disorder	10078088
Sleep apnoea syndrome	10040979
Sleep attacks	10040981
Sleep deficit	10080881
Sleep disorder	10040984
Sleep disorder due to a general medical condition	10063910
Sleep disorder due to general medical condition, hypersomnia type	10040985
Sleep disorder due to general medical condition, insomnia type	10040986
Sleep disorder due to general medical condition, mixed type	10040987
Sleep disorder due to general medical condition, parasomnia type	10040988
Sleep inertia	10067493
Sleep paralysis	10041002
Sleep sex	10067492
Sleep talking	10041009
Sleep terror	10041010
Sleep-related eating disorder	10067315
Somnambulism	10041347
Somnolence	10041349
Somnolence neonatal	10041350
Sopor	10058709
Stupor	10042264
Sleep deficit	10080881
Terminal insomnia	10068932
Upper airway resistance syndrome	10063968

Injection site Reactions

Use CRF terms for ISR.

Seizures/Convulsions

PT	PT Code
1p36 deletion syndrome	10082398
2-Hydroxyglutaric aciduria	10078971
Acquired epileptic aphasia	10052075
Acute encephalitis with refractory, repetitive partial seizures	10076948
Alcoholic seizure	10056347
Alpers disease	10083857
Aspartate-glutamate-transporter deficiency	10079140
Atonic seizures	10003628
Atypical benign partial epilepsy	10056699
Automatism epileptic	10003831
Autonomic seizure	10049612
Baltic myoclonic epilepsy	10054895
Benign familial neonatal convulsions	10067866
Benign rolandic epilepsy	10070530
Biotinidase deficiency	10071434
CEC syndrome	10083749
CDKL5 deficiency disorder	10083005
Change in seizure presentation	10075606
Clonic convulsion	10053398
Congenital bilateral perisylvian syndrome	10082716
Convulsion in childhood	10052391
Convulsions local	10010920
Convulsive threshold lowered	10010927
CSWS syndrome	10078827
Deja vu	10012177
Double cortex syndrome	10073490
Dreamy state	10013634
Drug withdrawal convulsions	10013752
Early infantile epileptic encephalopathy with burst-suppression	10071545
Eclampsia	10014129
Epilepsy	10015037
Epilepsy surgery	10079824
Epilepsy with myoclonic-atonic seizures	10081179
Epileptic aura	10015049
Epileptic psychosis	10059232
Febrile convulsion	10016284
Febrile infection-related epilepsy syndrome	10079438
Focal dyscognitive seizures	10079424
Frontal lobe epilepsy	10049424
Gelastic seizure	10082918
Generalised onset non-motor seizure	10083376
Generalised tonic-clonic seizure	10018100
Glucose transporter type 1 deficiency syndrome	10078727
GM2 gangliosidosis	10083933
Grey matter heterotopia	10082084
Hemimegalencephaly	10078100
Hyperglycaemic seizure	10071394
Hypocalcaemic seizure	10072456
Hypoglycaemic seizure	10048803
Hyponatraemic seizure	10073183
Idiopathic generalised epilepsy	10071081
Infantile spasms	10021750
Juvenile myoclonic epilepsy	10071082
Lafora's myoclonic epilepsy	10054030
Lennox-Gastaut syndrome	10048816

Migraine-triggered seizure	10076676
Molybdenum cofactor deficiency	10069687
Multiple subpial transection	10079825
Myoclonic epilepsy	10054859
Myoclonic epilepsy and ragged-red fibres	10069825
Neonatal epileptic seizure	10082068
Neonatal seizure	10082067
Partial seizures	10061334
Partial seizures with secondary generalisation	10056209
Petit mal epilepsy	10034759
Polymicrogyria	10073489
Post stroke epilepsy	10076982
Post stroke seizure	10076981
Postictal headache	10052470
Postictal paralysis	10052469
Postictal psychosis	10070669
Postictal state	10048727
Post-traumatic epilepsy	10036312
Schizencephaly	10073487
Seizure	10039906
Seizure anoxic	10039907
Seizure cluster	10071350
Seizure like phenomena	10071048
Severe myoclonic epilepsy of infancy	10073677
Simple partial seizures	10040703
Status epilepticus	10041962
Sudden unexplained death in epilepsy	10063894
Temporal lobe epilepsy	10043209
Tonic clonic movements	10051171
Tonic convulsion	10043994
Tonic posturing	10075125
Topectomy	10073488
Transient epileptic amnesia	10081728
Tuberous sclerosis complex	10080584
Uncinate fits	10045476
Confusional state	10010305
Loss of consciousness	10024855
Syncope	10042772
Sopor	10058709
Stupor	10042264
Altered state of consciousness	10050093
Depressed level of consciousness	10012373
Consciousness fluctuating	10050093

Weight Gain

PT	PT Code
Abdominal fat apron	10077983
Overweight	10033307
Abnormal weight gain	10000188
Central obesity	10065941
Obesity	10029883
Weight abnormal	10056814
Weight increased	10047899
Waist circumference increased	10064863
Body mass index abnormal	10074506
Body mass index increased	10005897
Fat tissue increased	10016251
Sarcopenic obesity	10083992

Rhabdomyolysis

PT	PT Code
Muscle necrosis	10028320
Myoglobin blood increased	10028625
Myoglobin blood present	10059888
Myoglobin urine present	10028631
Myoglobinaemia	10058735
Myoglobinuria	10028629
Myopathy	10028641
Myopathy toxic	10028648
Necrotising myositis	10074769
Rhabdomyolysis	10039020
Thyrotoxic myopathy	10081524
Myalgia	10028411
Myositis	10028653

Pancreatitis

PT	PT Code
Cullen's sign	10059029
Grey Turner's sign	10075426
Haemorrhagic necrotic pancreatitis	10076058
Hereditary pancreatitis	10056976
Immune-mediated pancreatitis	10083072
Ischaemic pancreatitis	10066127
Oedematous pancreatitis	10052400
Pancreatic abscess	10048984
Pancreatic cyst drainage	10082531
Pancreatic haemorrhage	10033625
Pancreatic necrosis	10058096
Pancreatic phlegmon	10056975
Pancreatic pseudoaneurysm	10081762
Pancreatic pseudocyst	10033635
Pancreatic pseudocyst drainage	10033636
Pancreatic pseudocyst haemorrhage	10083813
Pancreatic pseudocyst rupture	10083811
Pancreatitis	10033645
Pancreatitis acute	10033647
Pancreatitis haemorrhagic	10033650
Pancreatitis necrotising	10033654
Pancreatitis relapsing	10033657
Pancreatorenal syndrome	10056277

Impact on Creatinine

PT	PT Code
Acute kidney injury	10069339
Acute phosphate nephropathy	10069688
Anuria	10002847
Azotaemia	10003885
Continuous haemodiafiltration	10066338
Dialysis	10061105
Foetal renal impairment	10078987
Haemodialysis	10018875
Haemofiltration	10053090
Neonatal anuria	10049778
Nephropathy toxic	10029155
Oliguria	10030302
Peritoneal dialysis	10034660

Prerenal failure	10072370
Renal failure	10038435
Renal failure neonatal	10038447
Renal impairment	10062237
Renal impairment neonatal	10049776
Atypical haemolytic uraemic syndrome	10079840
Cardiorenal syndrome	10068230
Chronic kidney disease	10064848
Crush syndrome	10050702
Diabetic end stage renal disease	10012660
End stage renal disease	10077512
Haemolytic uraemic syndrome	10018932
Hepatorenal failure	10019845
Hepatorenal syndrome	10019846
Nail-patella syndrome	10063431
Pancreatorenal syndrome	10056277
Postoperative renal failure	10056675
Postrenal failure	10059345
Propofol infusion syndrome	10063181
Renal injury	10061481
Scleroderma renal crisis	10062553
Traumatic anuria	10044501