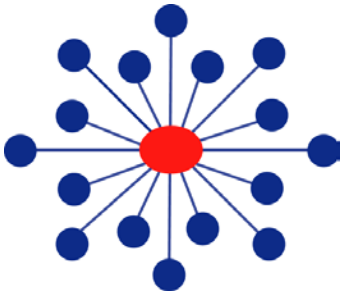

CTN-0049

Project HOPE -- Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users

Statistical Analysis Plan
Version 1.0

October 7, 2013

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1.0 STATISTICAL ANALYSES

1.1 Primary Outcome

The single primary objective of this trial is to discover whether there is a difference in the proportion achieving HIV viral suppression amongst the three study groups: (1) Patient Navigator, (2) Patient Navigator plus Contingency Management and (3) Treatment as Usual. There are three primary hypotheses, arm1 = arm2, arm1=arm3, and arm2=arm3. The family-wise error rate for these hypotheses is controlled to be no greater than .05.

The primary outcome variable is binary: presence of HIV viral suppression ($\leq$ 200 copies/ml) at the 12 month follow-up versus presence of viral load > 200 or death (all-cause mortality). Viral suppression is defined as a viral load $\leq$ 200 copies/ml rather than achieving a viral load "below the limit of detection of the assay" which, in this day, is usually < 50 copies/ml to avoid "blips" and episodes of low level viremia that are not uncommon, even among patients on stable antiretroviral therapy.

1.2 Protocol Violations

Protocol Violations will be summarized for each arm of the study. The number of participants with violations as well as frequencies and percents for the types of protocol violations will be presented.

1.3 Treatment Exposure

Treatment exposure will be summarized by arm and site, comparing the expected with observed number of Patient Navigator sessions attended (only among the two arms where participants randomized to Patient Navigator sessions).

1.4 Analysis of Participant Characteristics

Baseline demographic and clinical variables will be summarized for each arm of the study. Descriptive summaries of the distribution of continuous baseline variables will be presented with mean, median, minimum, maximum and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages. Since randomization is expected to produce balance at baseline among the three arms of the trial, statistical comparisons of treatment arms with respect to baseline characteristics should be more informal. If differences among treatment arms are suspected, statistical testing will be performed.

1.5 Participant Disposition

The visit completion status and the reason for early discontinuation of the study will be summarized by site and treatment arm with descriptive statistics. These include counts and percentages for each reason for discontinuation.

The number of randomizations and reasons for ineligibility will also be summarized.

1.6 Statistical Methods for Primary Analysis

The primary hypothesis test will compare the proportions achieving HIV viral suppression at 12 months across the three study groups. Death from any cause will be considered equivalent to non-suppression for the purposes of calculating this proportion. (Differences in outcome when deaths are categorized with respect to likelihood of being HIV and/or drug use related will be explored in a secondary analysis.) All treatment comparisons will be performed under the Intent-to-Treat (ITT) criterion in the sense that participants will be analyzed in the arm to which they were randomized, regardless of subsequent events. However, participants who are lost to follow-up before 6 months will not contribute to the primary analysis. A Generalized Estimating

Equations (GEE) model will be employed (Zeger & Liang, 1986) with a binomial distribution and logit link as implemented in SAS. The GEE model will include both 6-month and 12-month HIV viral suppression status. However, the primary test of the hypothesis will be based on contrasts involving the 12-month proportions only. This model gains statistical power by pooling the error term across the two follow-up times and is closer to an ITT approach than would be the analysis of 12-month events only. It does not impute data that are missing at month 12 with the exception of death, which will be considered equivalent to non-suppression. Any potential correlation between patients within a site will be controlled by estimating a fixed effect for site in this model.

A simple closed-testing procedure (Westfall, Tobias, Rom, Wolfinger, & Hochberg, 1999) will be used to control family-wide type I error at 0.05 while still allowing all three pairwise comparisons between arms. Specifically, let P(123) be the (two-sided) p-value of the contrast testing equality among all three arms, while P(12), P(13), and P(23) are the (two-sided) p-values for arms 1&2, 1&3, and 2&3, respectively. Then, let the adjusted p-value for the (1,2) comparison be

$$P^*(12) = \max[P(123), P(12)]$$

and similarly for the other pairwise comparisons. Tests of pairwise equality will be performed by comparing P*(12), P*(13), and P*(23) to the 0.05 level of significance.

1.6.1 Covariates including Site

Randomization should ensure that the distributions of characteristics across our 3 groups are similar at baseline. Thus, the analysis is straightforward, and the primary analysis of association of the particular contrasts of group on the particular outcome will not need to control for covariates, with the exception of an indicator of baseline CD4 count (greater than 350 cells/uL), an indicator of detectable viral load at baseline, and site of recruitment. Site will be included as a covariate because there is the possibility that participants within a site will be more alike than will be participants from different sites. If ignored, this would violate an assumption of the simple model that all observed participants are independent of each other. Inclusion of site as a covariate will correct the model for any dependence in observations within a site, and baseline viral load and CD4 count may prove important predictors. As noted, randomization should control for all other participant level covariates. Nevertheless, to assess the effects of and control for any unintended impact of group differentials across the range of covariates, in a second sensitivity analysis, the simple analysis listed above will be extended to additionally control for age at baseline, race and ethnicity, gender, and primary type of drug use (injection drug use vs. non-injection drug use, and opiate vs. non-opiate, stimulant vs. non-stimulant). The significance levels for any of these covariates will be reported, but will not affect the conclusions of the primary analysis. As listed below, the effects of these variables on viral suppression will be explored more fully in the secondary aims. We will also assess the interaction of each of these covariates with treatment group as they affect the primary outcomes. If statistically significant, the results of these analyses will not affect the p-value of the primary analyses, but may affect our interpretation. However, the results will be reported in the secondary analyses sections.

1.6.2 SAS Code for Primary Analysis

SAS code suitable for performing the primary analysis follows. In this code, it is assumed that non-suppression and death from any cause have been lumped together as outcomes. The p-values from the four contrasts will be used in the closed testing.

```
proc genmod data = all;
        class arm time patid site vloadbase cd4base;
        model outcome = vloadbase cd4base site arm time time * arm / dist = bin;
```

```
repeated subject = patid / type = exch;
contrast "TAU NAV" arm 1 -1 0 time * arm 0 1 0 -1 0 0;
contrast "TAU NAVCM" arm 1 0 -1 time * arm 0 1 0 0 0 -1;
contrast "NAV NAVCM" arm 0 1 -1 time * arm 0 0 0 1 0 -1;
contrast "TAU NAV NAVCM" arm 1 -1 0  time * arm 0 1 0 -1 0 0,
        arm 1 0 -1 time * arm 0 1 0 0 0 -1;
run;
```

1.7 Rationale for Sample Size and Statistical Power

Power calculations were based on a simulation of several scenarios, with 5000 iterations per scenario. In each iteration, 266 virally unsuppressed participants were recruited to each of three treatment groups, after which death and dropout rates, and rates of suppression before and after 6 months, were imposed so as to result in proportions of simulated participants dead, lost, suppressed, and unsuppressed at both 6 and 12 months as indicated below. These rates characterized the scenario. (Note that the rates dictate the probabilities of joint occurrences of outcomes at 6 and 12 months, but it is possible for more than one set of rates to produce the same set of 6-month and 12-month margins.)

Once these data were simulated, they were subjected to a Generalized Estimating Equation (GEE) analysis in which dropouts were ignored and dead participants were combined with unsuppressed participants. More specifically, the GEE regressed state (suppressed versus unsuppressed or dead) on time (6 months, 12 months), treatment group (Patient Navigator = PN, Contingency Management + Patient Navigator = CM, Treatment as usual = TAU) site (1-10) and the time by treatment group interaction using a binomial link. The outcome of interest was the proportion suppressed (versus unsuppressed or dead) in each arm at 12 months, but the analysis incorporated 6-month data so that the 6-month/12-month correlation could in part offset loss to follow-up between 6 and 12 months. Contrasts were used to obtain p-values for the hypotheses CM=PN=TAU, CM=PN, CM=TAU, and PN=TAU with respect to the outcome of interest.

These p-values were combined together using the closed-testing methodology explained in Section 1.6. Note was taken of which of the pairwise hypotheses were rejected (alpha = 0.05, two-tailed), and which accepted according to the Closed testing algorithm in each iteration. Finally, the power for the tests of the various hypotheses was estimated as the proportion of the 5000 iterations in which each hypothesis was rejected.

The scenarios were defined by the following parametric values, which varied from treatment group to treatment group:

- M6 = target suppressed proportion at 6 months (assuming no death or dropout)
- M12 = target suppressed proportion at 12 months (assuming no death or dropout)
- S = Probability that a participant will be suppressed at 12 months, given he was suppressed at 6 months
- U = Probability that a participant will be unsuppressed at 12 months, given that he was unsuppressed at 6 months
- E = quarterly probability of death for a suppressed participant
- F = quarterly probability of death for an unsuppressed participant
- G = quarterly dropout probability for a suppressed participant
- H = quarterly dropout probability for an unsuppressed participant

Four scenarios (A-D) were investigated, with parametric values given by the table below:

Scenario	Group	M6	M12	S	U	E	F	G	H
A	TAU	0.18	0.16	0.95	0.99	0.02	0.05	0.04	0.04
A	PN	0.375	0.26	0.85	0.99	0.02	0.05	0.04	0.04
A	CM	0.55	0.4	0.85	0.98	0.02	0.05	0.04	0.04
B	TAU	0.175	0.16	0.98	0.99	0.015	0.03	0.03	0.03
B	PN	0.33	0.24	0.94	0.98	0.015	0.03	0.03	0.03
B	CM	0.49	0.44	0.96	0.98	0.015	0.03	0.03	0.03
C	TAU	0.175	0.16	0.98	0.99	0.02	0.05	0.04	0.04
C	PN	0.33	0.24	0.94	0.98	0.02	0.05	0.04	0.04
C	CM	0.49	0.44	0.96	0.98	0.02	0.05	0.04	0.04
D	TAU	0.18	0.16	0.95	0.99	0.015	0.03	0.03	0.03
D	PN	0.375	0.26	0.85	0.99	0.015	0.03	0.03	0.03
D	CM	0.55	0.4	0.85	0.98	0.015	0.03	0.03	0.03

The numerical values of the parameters selected in scenarios A-D were chosen to match prior experience of the investigators and data from the literature. Out of care HIV-infected individuals who are admitted to the hospital will have very low rates of viral suppression, in the range of 10-15%. From clinical discussions amongst the research team it was decided that a 10% to 12% increase (i.e., moving from 15% to 25% or 15% to 27%) is a minimally clinically meaningful change. We therefore aimed power determination at uncovering around a 12% pair-wise difference between intervention conditions. From an ongoing study of Metsch and del Rio, a 12-15% death rate seemed to be likely in this cohort. Finally, since all participants are heavy drug and/or alcohol users it is appropriate to account for 10-15% attrition (in addition to the deaths) in these calculations even though, the research team has a history of achieving high rates of follow-up.

Power results are given in the following table, along with the parametric value of M12 and simulated resulting proportions of death, attrition, and suppression ignoring dropouts. Across each of the 4 scenarios, there is 87% power or greater to reject any of the 3 pair-wise comparisons under the assumptions set forth and a sample size of 266 study participants per treatment group.

	12-Month Statistics (percent)														
Scenario	Observed Attrition			Observed Death			Target Suppression(M12)			Realized Suppression			Power		
	TAU	PN	CM	TAU	PN	CM	TAU	PN	CM	TAU	PN	CM	TAU vs PN	PN vs CM	TAU vs CM
A	14	14	14	16	15	14	16	26	40	16	29	42	93	87	100
B	11	11	11	10	10	9	16	24	44	17	30	44	94	92	100
C	14	14	14	16	15	14	16	24	44	16	28	42	93	89	100
D	11	11	11	10	10	9	16	26	40	16	30	44	94	89	100

* Realized Suppression Outcome = suppressed / (suppressed + unsuppressed + dead)

1.8 Interim Analyses

If recruitment goes as planned, which originally was to enroll 800 participants over a 10 month period (80 participants/month), no interim efficacy or futility analyses will be done, as recruitment will be completed before any participants will have reached 12 months of follow-up, the period at which the primary outcome is measured. However, if the recruitment period becomes protracted to a point where, over a 26-month period, the number enrolled is 23.5 participants per month or slower (i.e., about 600 participants or fewer at 26 months), we will perform efficacy and futility analyses for DSMB and NIDA review. For these analyses, a two-sided, symmetric O'Brien-Fleming (1979) type boundary using the flexible Lan-DeMets (1983) procedure will be implemented for group sequential testing for efficacy, and a conditional power analysis (Jennison & Turnbull, 2000) will be implemented for futility. The threshold of 23.5 participants per month over 26 months was selected because this corresponds to an approximate point in time when 288 participants (approximately 40% of the targeted sample size after accounting for 10% attrition) will be available for 12-month outcome analysis, and approximately 600 of the targeted participants will have been enrolled (achieving 75% of the targeted sample size). Therefore, if a conclusion is reached based on efficacy or futility to stop the trial early, approximately 200 participants would not need to be enrolled into the trial. If the recruitment rate is higher than 23.5 participants per month at 26 months, i.e., if recruitment is expected to take less than 34 months, no interim analyses will be performed. Further, there is no scenario for which sample size re-estimation will be necessary. In addition, safety interim looks will be performed (without formal statistical testing) at the regular DSMB meetings or at unscheduled times per the DSMB's request.

1.9 Secondary Endpoints and Analyses

Secondary outcomes are divided into those related to HIV and those related to substance use. Note that the date of randomization is the time point from which all outcomes will be measured.

1.9.1 HIV Related Secondary Outcomes

The data associated with the HIV secondary outcomes include binary (Yes/No), count and continuously distributed data. In the following list of HIV secondary outcomes the expected distribution is in parenthesis:

a) Repeat primary analysis with the addition of a treatment interaction with viral suppression status at baseline (binary)

b) Viral suppression at 12 months or HIV-related deaths (binary, note that non-HIV related deaths would be classified as missing in this analysis)

c) Viral suppression at 6 months (binary)

d) CD4 Cell count (continuous at 6 and 12 months)

e) Engagement into care (visit constancy, a repeated binary at 3-month intervals)

f) HIV care visit attendance (count)

g) Medication Adherence (count)

h) Hospitalizations (count)

i) All cause mortality (binary)

1.9.2 Substance Use Related Secondary Outcomes

a) Substance use frequency (count and binary)

b) Substance Use Severity (continuous)

c) Self-reported treatment engagement (binary)

d) Self-reported number of drug treatment sessions (Count)

1.9.3 Mediators and Moderators of Outcomes

a) Viral Suppression Moderators: psychological distress (BSI), Housing instability, Food Insecurity Health literacy, HIV-related cognitive problems renal function and liver function.

b) Viral Suppression Mediators: Medication self-efficacy, Physician-Patient relationship social support and substance use.

c) CD4 Count Moderators: HCV status.

d) Drug Use Moderators: Readiness for drug treatment.

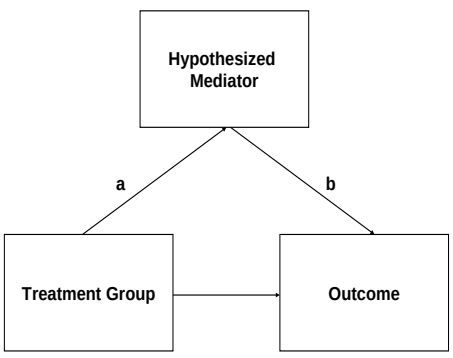
e) Drug Use Mediators: Readiness for drug treatment and social support.

1.10 Cost and Cost-Effectiveness Secondary Outcomes

Cost effectiveness analysis, which will not be performed by the DSC, is described separately in the protocol.

1.10.1 Tests of the Secondary Outcomes

Each of the stated secondary outcomes listed in Section 1.9 will be tested separately, using the closed testing procedures described for the primary outcome to control family-wide type I error. The statistical methods used will also mirror the methods used for the primary hypothesis. Those secondary outcomes that are binary will be tested as described for the primary hypothesis using a logistic regression; whereas those secondary outcomes that involve either continuous or ordinal variables will utilize the appropriate distribution and link function. Note that the exact method of analysis will depend on the realized distribution of the particular outcome in this trial for example, an expected count data variable may need to be modeled using a zero-inflated Poisson Regression rather than a Poisson regression if there are too many zero observations to fit the standard Poisson. If there is over-dispersion, a negative binomial (or zero-inflated negative binomial) regression may be appropriate. The hypothesized



moderator variables (for viral suppression: psychological distress, housing instability, food insecurity, health literacy, HIV-related cognitive function, renal function and liver function; and CD4 count. Drug Use moderator: readiness for treatment and HCV status) will be addressed in the same way that the covariates for the planned sensitivity analysis of the primary outcomes (site, age at baseline, race and ethnicity, gender, and primary type of drug use [IV vs. non-IV, opiate vs. non-opiate, and stimulant vs. non-stimulant], baseline level of viral load) will be addressed. Models will be estimated with main effects for these variables, a main effect for randomization group and an interaction between the particular variable and randomized group on the primary outcomes. For these analyses, the overall Type I error will not be controlled, rather, the reader of any resulting journal article will be alerted to the fact that these analyses were the result of *post-hoc* exploratory analyses, and that any statistically significant results may have resulted from a Type I error, and require replication.

1.10.2 Mediation

Mediation will be tested using structural equation modeling with Mplus 6.1. These models estimate the effect of the intervention on the potential mediator (path a, e.g., the effect of intervention on *information*) and the effect of the mediator on the outcome or next proximal intermediate outcome (path b, e.g., the effect of *information* on *motivation*). Longer mediation pathways can also be tested (e.g., a*b*c). There is significant mediation if the product of these two paths (a*b) is greater than zero. Statistical significance will be assessed using bias-corrected bootstrap confidence intervals on the product terms.[168] This test is by far the most powerful test of mediation[164] and can test multiple mediating pathways within a single structural model.

1.10.3 Ancillary Analyses

All intervention sessions will be audio-taped for quality assurance with the permission of the participant. Approximately 10% of the intervention sessions will be randomly selected and rated for fidelity to the three intervention conditions. A smaller subset, about 15% of the 10% will be rated by two raters. The double rated cases will be used to calculate a kappa statistic to assess the inter-rater reliability of the fidelity instrument. On the full sample of rated intervention sessions, a simple ANOVA will be used to compare the 3 conditions on the ratings of various behaviors performed during the intervention. Depending on the realized distribution of the ratings, a non-parametric test, the Kruskal-Wallis test, may be substituted for the ANOVA procedure. These means and the associated test-statistics will be reported in the primary outcome manuscript and the final report to describe intervention fidelity.

1.11 Factors for Stratification

Randomization will be stratified only by site. Site, baseline viral load, and baseline CD4 count will be used as covariates in the primary analysis.

1.12 Significance Testing

With various analyses (primary and secondary) proposed in this protocol, there is a multiplicity of analyses to be performed, which leads to an increased probability that at least one of the comparisons could be "significant" by chance. The primary analysis simultaneously tests three separate hypotheses, and the overall experiment-wise type I error is controlled to be no more than 0.05 via a simple closed testing procedure.

For the secondary analyses we will not consider significance level adjustment. However, we will be conservative in the interpretation of these analyses, taking into account the degree of significance, and consistency across analyses. In addition, to guard against spurious significance results, we limited and pre-specified the secondary analyses.

1.13 Missing Data and Dropouts

Missing data are a ubiquitous problem in substance use research, primarily due to dropping out and refusal. Missing data can lead to biased estimates and reduction of power, affecting the generalizability of the study. We will make every effort to minimize the amount of missing data and in the primary analyses we will include only participants with available data at 6 or 12 months, although study participants who have died will be considered a failure and not meeting virologic suppression. In all cases missingness patterns will be identified and analyses will be conducted to determine if there is differential non-death attrition by treatment arm, and if missingness is related to any of the covariates. In the case that covariates predict missingness, the data are called "Missing at Random," (MAR) (Little & Rubin, 1987). GEE analyses are only appropriate if data are "Missing Completely at Random," which means that no covariates predict the occurrence of missing data. Under the MAR assumption, the multiple imputations procedure can be used to fill in the data without artificially compressing the variance associated with the imputed data (Schafer, 1997). Therefore, if observed covariates predict the existence of missing data, multiple imputation will be used in a secondary analysis of the primary outcome to assess the effects of missingness on the reported results. If nonrandom missingness is of concern (Missing not at Random, MNAR), this problem will be addressed by applying pattern-mixture, propensity score or related models so that the effect of bias can be assessed in sensitivity analyses.

1.14 Poolability of Data

We intend to perform the primary treatment effect analysis by pooling data from all sites. It is possible that treatment effect will differ across sites and this will be investigated. We will fit a model with site by treatment interaction and if significant (at 0.05 level), we will present treatment effects by site. We will also explore treatment effect stability across subsets of sites in the case of a significant interaction. Although the study is not powered for detection of different treatment effects across sites, this analysis will provide insight into possible varied treatment effects across sites or reassure that data can reasonably be pooled over sites with respect to the treatment effect.

1.15 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for each arm of the study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25^{th} and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages. Since randomization is expected to produce balance at baseline among the three arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics should be more informal. In case differences among treatments arms are suspected, statistical testing will be performed. For comparisons of treatment groups with respect to continuous baseline variables we will use the two sample Wilcoxon test. Group comparisons with respect to discrete baseline variables will use the chi-square test or Fisher's Exact Test as appropriate.

1.16 Data Collected Out of Visit Window

It is possible that data on some of the study assessments were collected out of the established study visit window. The extent to which this occurred will be examined and if necessary, appropriate sensitivity analyses designed and conducted to determine if conclusions about the outcome are affected by the exclusion of these data from the analysis.

2.0 ANALYSIS OF SAFETY ENDPOINTS

2.1 Adverse Events

The only study intervention associated with risk for participants is the collection of blood samples. Adverse events and serious adverse events will be reported from the time of specimen collection through the remainder of that visit to capture events directly related to collection of blood samples. Adverse events (AEs) will be summarized using counts and frequencies for the severity and relatedness of each adverse event broken down by treatment arm. A detailed listing of adverse events will be provided. All adverse events will be coded using MedDRA®. Adverse event incidence rates will be summarized by system/organ/class (SOC) and preferred term (as determined by the coding) and by treatment arm. If a participant experiences multiple episodes of an event, then the event is only counted once. Information on any pregnancies will be reported.

2.2 Serious Adverse Events

Serious Adverse Events (SAEs) will be summarized by treatment arm using counts and frequencies for the relatedness and type of each SAE. A detailed listing of serious adverse events will be provided.

3.0 DATA AND STATISTICS CENTER 2 (DSC 2) RESPONSIBILITIES

The CTN's DSC 2 will conduct analyses for the Final Study Report as outlined in Section 4.0 below, along with the analysis for the primary outcome paper, including those related to the primary outcome measure and other important secondary analyses, as discussed by and decided upon by the Lead Node, DSC 2 and Center for Clinical Trials Network (CCTN).

4.0 PROPOSED CONTENT OF TABLES AND GRAPHS FOR FINAL STUDY REPORT

Category	Table Number	Title
Enrollment, Participant Disposition and Follow-up	1	Distribution of Treatment Assignments by CTP and Stratum
	Figure 1	Expected vs Actual Randomizations across all CTPs
	2	Summary of Pre-Screens, Screenings and Randomizations by CTP
	3	Summary of Participants Not Meeting Eligibility Criteria by CTP
	4	Summary of Participants Screen Failed Despite Meeting Eligibility Criteria by CTP
	5	Summary of Participant Disposition by CTP
	6	Summary of Participant Disposition by Treatment Arm
	7	Primary Reasons for Early Study Termination by CTP
	8	Primary Reasons for Early Study Termination by Treatment Arm
	9	Attendance at 6 Month Visit by CTP
	10	Attendance at 6 Month Visit by Treatment Arm
	11	Attendance at 12 Month Visit by CTP
	12	Attendance at 12 Month Visit by Treatment Arm
	13	Summary of Reasons for Missed Visits
Participant Characteristics at Baseline	14	Summary of Baseline Demographics by CTP
	15	Summary of Baseline Demographics by Treatment Arm
	16	Summary of Baseline Characteristics by CTP
	17	Summary of Baseline Characteristics by Treatment Arm
Treatment Exposure	18	Treatment Exposure by CTP
	19	Treatment Exposure by Treatment Arm
	20	Completion of Navigator Sessions Among Participants Randomized to One of the Two Patient Navigator Arms by CTP
	21	Completion of Navigator Sessions Among Participants Randomized to One of the Two Patient Navigator Arms by Treatment Arm
Primary Efficacy Outcome Summaries	22	Summary of Primary Outcome Availability by Treatment Arm
	23	Summary of Primary Outcome by Treatment Arm
	23A	Summary of Primary Outcome by Treatment Arm in Jackson Memorial Hospital Participants
	23B	Summary of Primary Outcome by Treatment Arm in Grady Memorial Hospital Participants

Category	Table Number	Title
Primary Efficacy Outcome Summaries (cont.)	23C	Summary of Primary Outcome by Treatment Arm in Boston Medical Center Participants
	23D	Summary of Primary Outcome by Treatment Arm in Hahnemann University Hospital Participants
	23E	Summary of Primary Outcome by Treatment Arm in Rush University/Stroger Cook County Participants
	23F	Summary of Primary Outcome by Treatment Arm in Parkland Health and Human Services Participants
	23G	Summary of Primary Outcome by Treatment Arm in University of Pittsburgh Medical Center Participants
	23H	Summary of Primary Outcome by Treatment Arm in Harbor-UCLA Participants
	23I	Summary of Primary Outcome by Treatment Arm in University Hospital at University of Pittsburgh Participants
	23J	Summary of Primary Outcome by Treatment Arm in St. Luke's Participants
	24	Summary of Primary Outcome by Gender and Treatment Arm
	25	Summary of Primary Outcome by Race and Treatment Arm
	26	Summary of Primary Outcome by Ethnicity and Treatment Arm
Safety Outcome Summaries	27	Summary of Adverse Events by Treatment Arm
	28	Summary of Serious Adverse Events by Treatment Arm
	29	Summary of MedDRA Coded Adverse Events by Treatment Arm
	30	Summary of MedDRA Coded Serious Adverse Events by Treatment Arm
	31	Summary of Emergency Room Visits by Treatment Arm
	32	Summary of Inpatient Hospitalizations by Treatment Arm
	33	Summary of Suicidality based on Concise Health Risk Tracking – Self Report Assessment
	34	Summary of Suicidality based on Brief Symptom Inventory
Protocol Violations	35	Summary of Protocol Violations in Randomized Participants by CTP
	36	Summary of Protocol Violations in Randomized Participants by Treatment Arm
	37	Summary of Protocol Violations in Screen Failures by CTP
Appendices	1	Listing of Adverse Events by Treatment Arm
	2	Listing of Serious Adverse Events by Treatment Arm
	3	Death Narratives
	4	Listing of Protocol Violations in Randomized Participants, by Violation Category
	5	Listing of Protocol Violations in Screen Failures, by Violation Category