Statistical Analysis Plan

September 15, 2015

Optimizing PrEP Uptake & Adherence Among Male Sex Workers (MSW)
Using a 2-stage Randomization Design
(NCT03086057)

Specific Aim 2: Pilot RCT. Initially, the distribution of all variables will be assessed, as will the autocorrelations across time between all study variables and the primary outcomes. Dependent variables will be examined to determine which distributional models are most appropriate for subsequent statistical procedures. We will examine the equivalence of the random assignment of groups with regards to key baseline characteristics, including socio-demographics and sexual risk-related variables. In the unlikely event that randomization does not work to balance these characteristics at baseline, we will assess whether baseline differences may account for differences in outcomes. Attrition effects will be evaluated by testing whether systematic differences exist between those participants who complete the research versus those who drop out. In this way, we can determine the nature of the potential bias introduced by attrition from the study.

Primary Analysis. The primary analysis for Stage 1 will compare PrEP initiation at 1-month post Stage 1 randomization between the study arms. For stage 2, the primary analysis will compare adherence (defined by percent of drug in blood) at the 3 and 6 month visits between the study arms. Changes in self-reported adherence, sexual behavior adjustment and substance use will also be examined. Moreover, group differences in number of PrEP clinic appointments kept will be compared. All analyses will use two-tailed tests of significance, with significance at alpha = 0.05. We will use generalized linear models (GLM) with properly-chosen link functions to analyze longitudinal data for each analysis. The GLMs will be estimated using generalized estimating equations with robust standard error estimates (GEE)[67,68], which provides an extension of regression analysis to the case of correlated or repeated observations and allows for inclusion of both categorical and count dependent variables and for appropriate modeling of covariance structures when observations are correlated across time. We will follow an intent-to-treat model, analyzing participants in the study arm to which they were assigned, regardless of fidelity to assigned group.

Mediation analysis. If the intervention does achieve adherence in significantly greater magnitude than the comparison condition, we will preliminarily explore the extent to which this relationship works through several possible mediators, as detailed above. A multiple mediator analysis, which examines the effects of the potential mediators simultaneously in the same statistical model and is consistent with Baron and Kenny as updated by Kraemer[69,70], will be used to quantify the magnitude of the mediation.

Moderator analysis. To preliminarily explore effect modification, we will add interaction terms one-by-one for the intervention condition and the potential moderators. Significant or large interaction terms suggest that the effects of the intervention differ for different subgroups, as defined by the moderators.

For the mediation and moderator analyses, given the aim of the study is to pilot the intervention to assess participant acceptability and determine feasibility of all study procedures, we will assess whether the intervention impacts the hypothesized mediators and moderators in the expected direction per our conceptual model, not rely on statistical significance.

Power and Sample Size Considerations. As a pilot study, the primary emphasis is on feasibility of the two arms and hence power is limited; and to find statistical significance, the effect sizes would need to be large. However, the number of repeated measures does increase power for the longitudinal analyses. For stage 1, proportion of participants in each condition who initiate PrEP, with a two-tailed p-value of 0.05, and 53 participants per arm, we would need at least a 30 percentage point difference across the two conditions (e.g., if 20% of the comparison arm and 50% of the intervention arm initiated PrEP) to achieve 80% power. For stage 2, percent adherence since the last visit will be assessed yielding 3 repeated blood-drug levels across baseline, 3, and 6. With a two-tailed p-value of 0.05, group sample sizes of 22 participants per arm, assuming a correlation of 0.80 between repeated adherence measures and with up to 10% attrition there will greater than 80% power to detect in excess of a medium effect size difference (approximately 10% in the slope) between the intervention and comparison groups. For categorical outcomes (e.g. percent of patients in each condition achieving at least 90% adherence via blood drug levels), with a two-tailed p-value of 0.05, the three repeated measures, and 22 patients per arm, we would need at least a 25 percentage point difference across the two conditions (e.g., if 50% of the comparison arm and 75% of the intervention arm had at least 90% adherence) to achieve 80% power.

Missing Data. We will assess for patterns of missing data, which are expected to be low as the study utilizes A-CASI. We will explore strategies for imputing missing data based on patterns of missingness and apply appropriate techniques, applying sensitivity analysis to determine the optimal method of handling the missingness[71-73].