Pre-Analysis Plan for Study "Interventions to Improve HIV Antiretroviral Therapy Adherence in Beira, Mozambique"

September 10, 2018

This document outlines the pre-analysis plan for the project "Interventions to improve HIV antiretroviral therapy adherence in Beira, Mozambique." The primary objective of the study is to test whether financial incentives and phone-call reminders improve medication adherence of patients on antiretroviral therapy (ART). Participants were randomly assigned at the individual level to one of four experimental groups:

1. Treatment Group 1 – receive **financial incentives** for refilling ART medications on time for six months

2. Treatment Group 2 – receive phone-call **reminders** before their ART medication refill date for six months

3. Treatment Group 3 – receive phone-call **reminders** before their ART medication refill date and **financial incentives** for on-time refills for six months

4. Control Group – no intervention.

Outcomes of Interest and Hypotheses

We list the outcome variables that we will analyze below. We have a single *primary outcome of interest*. Because we examine three treatments, we will apply a multiple hypothesis correction within the set of three treatment effect coefficients for this outcome variable.

We have *secondary outcomes of interest* as well. These include versions of the primary outcome of interest, specified differently, as well as highly related outcome measures. We will apply multiple hypothesis correction procedures to account for multiple outcome measures and multiple treatment groups. The secondary outcomes, as a group, will be considered separately from the primary outcome when the multiple hypothesis correction is applied.

Our multiple hypothesis correction procedure will be that of List, Shaikh, and Xu (2016), which incorporates information about the joint dependence structure of the test statistics, leading to gains in statistical power compared to more traditional approaches (such as Bonferroni (1935) and Holm (1979)). This approach is particularly attractive when working with outcome measures that are highly correlated.

Primary Outcome of Interest and Hypotheses

Medication possession ratio (MPR) at least 95%, 6-month window

This is a binary variable equal to 1 if MPR is greater than or equal to 95%, and 0 otherwise. MPR is the proportion of days that a participant is in possession of at least one ART dose. MPR is computed from pharmacy dispensing records. The measurement window is the 6-month follow up period. The measurement window will be truncated to the date that patients transfer clinics, opt out of future study participation, or die.

Hypotheses:

1. Hypothesis 1: Participants who receive the financial incentive intervention will have higher adherence to ART than those who receive no intervention.
2. Hypothesis 2: Participants who receive the phone-call reminder intervention will have higher adherence to ART than those who receive no intervention.
3. Hypothesis 3: Participants who receive both the financial incentive and the phone-call reminder interventions will have higher adherence to ART than those who receive only one intervention.

Secondary Outcomes of Interest

We will examine secondary outcomes that represent alternative ways to define medication adherence, to confirm that our results are robust to these alternate definitions. Hypotheses for these outcomes are analogous to those outlined above for the primary outcome.

We will examine the following alternate binary MPR variables as secondary outcomes. Definitions are analogous to the definition of the primary outcome of interest, but with modified adherence thresholds and/or measurement windows:

- Medication possession ratio (MPR) at least 95%, 3-month window
- Medication possession ratio (MPR) at least 80%, 6-month window
- Medication possession ratio (MPR) at least 80%, 3-month window

We will also examine the medication possession ratio (MPR) as a continuous variable, over two different measurement windows. This variable's definition, analogous to the definition of the primary outcome variable, is the proportion of days that a participant is in possession of at least one ART dose. It takes on values between 0 and 1 (inclusive). MPR is computed from pharmacy dispensing records. The measurement window will be truncated to the date that patients transfer clinics, opt out of future study participation, or die.

- Medication possession ratio (MPR), continuous variable, 6-month window
- Medication possession ratio (MPR), continuous variable, 3-month window

We also examine the following two additional variables that are relevant for ART adherence:

- Appointment attendance rate (AAR): AAR is the proportion of scheduled visits completed during the observation period. A visit is considered "completed" if the patient visits the clinic on the scheduled appointment date, or up to 7 days before that date. AAR is computed from clinic records. Measurement window truncated to last visit date for patients who transfer clinics, opt out of future study participation, or die.
- Lost to follow-up (LTFU): LTFU is a binary variable equal to 1 if a patient missed the last appointment and 90 or more days have elapsed since the patient's last scheduled appointment date, with no clinic record of contact since that date; and 0 otherwise. Patients who transfer clinics or opt out of future study participation are excluded from the LTFU denominator, but those who die are retained in the LTFU denominator.

Control variables

Regression specifications for analysis of treatment effects we will also include control variables to absorb residual variation and reduce standard errors of estimates. The control variables will be:

- Indicator: respondent is female
- Indicator: respondent is married
- Age (in years)
- Completed education (in years)
- One way travel time to clinic (in minutes)
- Knowledge about risk of missing ART doses (fraction of 4 questions answered correctly; takes on values of 0, .25, .5, .75, 1)[1]
- Indicator: respondent is food insecure (ever skipped or reduced meal size in the last 12 months)
- Indicator variables for day of week of enrollment (one indicator for each of the following days of week: Monday, Tuesday, Wednesday, Thursday; Friday omitted)
- Indicator variable for enumerator (project staff member) administering enrollment and baseline survey (one indicator variable for each enumerator)

Because respondents are allowed to skip questions on the baseline survey, there may be missing values for some of these control variables. If any missing value exists for some variable "X", we will create an indicator variable for variable X to flag missing status (1 if missing, 0 otherwise), replace the missing value of the variable X with zero, and include the variable X missing indicator variable in the set of control variables.

Data Adjustments to Be Conducted While Blind to Treatment Assignment

Observations will be excluded from the sample for analysis under the following circumstances.

1. MPR cannot be calculated
2. Three (3) or more control variables are missing values.

Balance Tests

We will test for balance of baseline characteristics across treatment groups. For each baseline variable, we will show p-values of F-tests of the joint hypothesis that means across all treatment conditions (Control and Groups 1, 2, and 3) are equal. We will also show the p-value of the single F-test of the joint hypothesis of equality of means across all treatment conditions, across all variables listed below.

- Indicator: respondent is female
- Indicator: respondent is married
- Age (in years)
- Completed education (in years)
- One way travel time to clinic (in minutes)
- Knowledge about risk of missing ART doses (fraction of 4 questions answered correctly; takes on values of 0, .25, .5, .75, 1)
- Indicator: respondent is food insecure (ever skipped or reduced meal size in the last 12 months)

[1] The component questions are all true or false responses to the following statements presented in the baseline survey (correct answers in parentheses): 1) Failure to adhere to ART doses does not increase the risk of transmitting (false), 2) Failure to adhere to ART can cause drug resistance and lead to treatment failure (true), 3) Failure to adhere to ART can increase the risk of AIDS (true), 4) Even if I stop medication, my immune system will function normally (false).

Regression Specifications and Hypothesis Tests

The primary regression specification is:

$$Y_i = \alpha + \beta_1 G_i^1 + \beta_2 G_i^2 + \beta_3 G_i^3 + \boldsymbol{X}_i + \epsilon_i.$$

The regression is run at the individual level. Y_i is the outcome of interest for individual i. G_i^1, G_i^2, and G_i^3 are treatment group indicators, that are equal to 1 if individual i is in the Treatment Group 1, 2, or 3, respectively, and 0 otherwise. $\boldsymbol{X}_i$ is the vector of control variables described previously.

We will use a t-test $\beta_1 = 0$ to assess Hypothesis 1, t-test $\beta_2 = 0$ to assess Hypothesis 2, and t-test $\beta_3 = \beta_1$ and $\beta_3 = \beta_2$ to assess Hypothesis 3.

Subgroup Analysis

The regression for the primary outcome (MPR > 95%, 6-month window) will also be run in subgroups to assess heterogeneity of treatment effects. We will run regressions separately for subgroups defined below. For each of the treatment effects (β_1, β_2, and β_3), we will run a pair of regressions in corresponding subgroups, and test whether the coefficient is equal across the subgroups (e.g., between males and females).

- Male vs. Female
- Above or equal to median education vs. Below median education
- Food insecure vs. Not food insecure[2]
- Above or equal to median distance to the clinic vs. Below median distance to the clinic
- Above or equal to median knowledge about the risk of missing doses vs. Below median knowledge about the risk of missing doses

To correct for multiple hypothesis testing in this subgroup analysis, we will also use the method of List, Shaikh, and Xu (2016), accounting simultaneously for multiple subgroups and multiple treatments.

References

Bonferroni, C. E., *Il calcolo delle assicurazioni su gruppi di teste.* Tipografia del Senato, 1935.

Holm, S., "A Simple Sequentially Rejective Multiple Test Procedure," *Scandinavian Journal of Statistics*, 1979, pp. 65-70.

List, John, Azeem Shaikh, and Yang Xu, "Multiple Hypothesis Testing in Experimental Economics," NBER Working Paper 21875, January 2016.

[2] Food insecure is defined, as in the control variable, as having skipped or reduced the size of meals in the household in the last 12 months.