Pilot RCT of Patient Centered eHealth Intervention for Nonadherent HIV+ Substance Users. NCT Unique protocol ID 18938. Document Date Oct 31, 2022

Pos4Health Statistical Analysis Plan

1. **Is stratification/randomization involved?**Yes, Randomization

► IF YES, describe the stratification/ randomization scheme.
Randomization will be achieved using a random number generator. Equal numbers of participants will be assigned to the two arms. The participants will be blinded to the randomization. Because the consent form describes the two arms, it is possible that participants will deduce which treatment arm they are in. The statistician will generate randomization for the participants. The project coordinator will remain blind to the randomization until it is time to randomize participants (after study consent and TLFB). At that point, the coordinator will learn which treatment that participant will receive and will provide participants with the instructions relevant to their assigned conditions. Co-investigators will have access to the randomization.

► IF YES, who will generate the randomization scheme?
__X__ UVa Statistician. Holly Lord, PhD

2. What are the statistical considerations for the protocol?
Study Design: 2 group (experimental and control) pilot RCT with assessments at pre-treatment and post-treatment, with a focus on assessing feasibility and acceptability, along with preliminary efficacy.

1. Endpoints and precision estimates for feasibility: Feasibility will be judged by the rates of study acceptance and completion of the trial. Study Acceptance will be determined by consents obtained divided by patients approached for the study. *We will judge this trial feasible if the acceptance rate among eligible patients is equal to or greater than 56%.* This cut-off was chosen so that if we meet this criterion, we can be 95% certain that the population proportion of acceptance is at least 50%. We will interview a subset of participants who completed the intervention. Completion rate will be n completed follow-up interviews divided by n baseline interviews. *We will judge a larger scale trial feasible if our completion rate at the 3M follow-up is 80%.* This decision rule was chosen so that if it is met, we can be 95% certain that the proportion of patients for whom this is feasible is at least 75%.
2. Endpoints for Acceptability: We will judge acceptability by participant ratings, and by actual program usage data. Participants will rate the Intervention at follow-up. The range of items on this scale is from 1 to 7. An item mean of 3.5 would be mid-range. Basic descriptive information will be gathered from the tracking system about whether participants logged in, how many times, and for how long. Time spent in each Core will be tracked and summarized. We will judge *eHealth Positive* acceptable if if the average score on the evaluation was $\geq$ 5.6, which is 80% of the highest score (range 1-7), and if 75% of participants completed at least half of the Cores and provide 4 of 7daily diaries of adherence on at least 4 weeks.

3. Endpoints for preliminary efficacy components: PRIMARY: HIV viral suppression rates for the experimental vs. control group SECONDARY: adherence (6M average pharmacy refill rate), retention in care (6M missed visit proportion), and substance using days per 30 day period. Because this is a pilot study, we are not estimating power and precision, but rather, gathering information on effect size to assist in estimating power for a subsequent definitive trial.

Pilot Study, no early stopping, no interim analyses, no stratification.

3. Provide a justification for the sample size used in this protocol.

Because this is a pilot study, we are not estimating power and precision, but rather, gathering information on effect size to assist in estimating power for a subsequent definitive trial. Rather, in our experience with pilot trials of behavioral interventions, and of Internet interventions, an n of 25 per group is usually sufficient for detecting a signal and for estimating effect size. As detailed above, we may consent 100 participants to get 71 fully enrolled and an n of 50 (25 per group) with all data available for analysis.

4. What is your plan for primary variable analysis?

Primary research questions and analytic approach:

1. **Is the intervention trial feasible?** The main reason to conduct this project is to develop a feasible intervention to prepare for a randomized trial. Feasibility standards are based on a synthesis of criteria for behavioral research trials.[131] Feasibility will be judged by the rates of study acceptance and completion of the trial. Study Acceptance will be determined by consents obtained divided by patients approached for the study. *We will judge this trial feasible if the acceptance rate among eligible patients is equal to or greater than 56%.* This cut-off was chosen so that if we meet this criterion, we can be 95% certain that the population proportion of acceptance is at least 50%. We will also evaluate factors that influence some eligible candidates to refuse participation (Study Refusal). We will query eligible refusers about the recruitment process, the informed consent process, the study description, how they learned about the study, and other factors, to learn how these might be improved. Some who enroll will not complete the study (Dropout). We will ask dropouts about the time commitment, difficulties understanding the study, problems with the web program or their device, privacy concerns, or other reasons they discontinued participation. We will interview a subset of participants who completed the intervention to permit comparisons of refusers vs. enrollers and completers vs. dropouts. Completion rate will be n completed follow-up interviews divided by n baseline interviews. *We will judge a larger scale trial feasible if our completion rate at the 3M follow-up is 80%.* This decision rule was chosen so that if it is met, we can be 95% certain that the proportion of patients for whom this is feasible is at least 75%.

2. **Is the intervention acceptable?** We will judge acceptability by participant ratings, and by actual program usage data. Participants will rate the Intervention at follow-up. The range of items on this scale is from 1 to 7. An item mean of 3.5 would be mid-range.

Basic descriptive information will be gathered from the tracking system about whether participants logged in, how many times, and for how long. Time spent in each Core will be tracked and summarized. We will judge *eHealth Positive* acceptable if if the average score on the evaluation was ≥ 5.6, which is 80% of the highest score (range 1-7), and if 75% of participants completed at least half of the Cores and provide 4 of 7daily diaries of adherence on at least 4 weeks.

3. **Does eHealth Positive show promise, showing impact on knowledge and usage of coping strategies? Preliminary efficacy.** To assess the promise of Pos4Health, we will test it in a pilot RCT among 50 nonadherent PLWH recruited from throughout the South, Virginia, and the United States--particularly areas with rural and nonurban occupants. The study will compare Pos4Health to a static Patient Education website for its impact on the primary outcome of viral suppression rate. Additionally, to inform a subsequent RCT, we will record the impact on secondary outcome variables of adherence (6M average pharmacy refill rate), retention in care (6M missed visit proportion), and on substance using days per 30 day period. The pilot test will also provide data on varied types of substance users, allowing some basic comparisons between non-injection and injection drug users, or between drinkers and drug users. While this pilot study will not be powered for direct statistical comparisons, we will examine the data for each primary and secondary outcome by these groups. If the data indicate potential differences, we will examine these in simple regression analyses. Data will be collected in person and through the web program, and electronically from the electronic medical records of clinics and pharmacies. We will characterize the data using standard methods (means, medians, standard deviations, confidence intervals). Prior to analyses, psychometric analyses will be conducted to assess reliability of the measures and to adjust for abnormal distributions. We will also characterize patterns of missing data. Paired t- tests will compare change over time from baseline to post-treatment follow-up. We anticipate the use of nonparametric tests to allow for non-normality. Linear regression models will be used to adjust for effects of relevant covariates on participant responses over time. We will assess the magnitude of associations among the outcome variables using Pearson's correlation coefficients.

5. What is your plan for secondary variable analysis?
Secondary research question and analytic approach:

How do adherence and engagement in care measures perform as future primary outcomes? Obviously, the ultimate goal for the intervention is to improve adherence and engagement in care, although we will not answer this definitively in this pilot trial. At this stage, we will examine the data quality of adherence and engagement in care indicators (Pharmacy Refill Rate, Missed Visit Proportion) to determine which ones are suitable as outcome measures in a future RCT. *The purpose is to calculate effect sizes for the planned randomized trial*.

6. Have you been working with a statistician in designing this protocol? YES

IF YES, what is their name? Holly Lord, PhD

7. **Will data from multiple sites be combined during analysis?** NO