STATISTICAL ANALYSIS PLAN

Crowdsourcing to Reduce HIV Stigma Among Adolescents and Young Adults in Kazakhstan

National Clinical Trial (NCT) Identified Number: NCT05107401

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1. INTRODUCTION

The JasSpark study used a community-based participatory approach that engaged local adolescents and young adults (AYA) in Kazakhstan to develop a crowdsourced digital HIV stigma reduction and self-testing intervention to reduce HIV stigma and increase HIV testing among AYA in Kazakhstan. We then pilot tested this crowdsourced HIV stigma reduction and self-testing intervention in a preliminary efficacy trial to assess feasibility and acceptability and obtain preliminary estimates of its effects on decreasing HIV stigma (primary outcome) and increasing HIV testing (secondary outcome) among AYA who received the intervention compared to individuals who did not.

This document outlines the statistical analysis plan that will be followed to assess outcomes.

Primary Outcome: To evaluate the change in HIV stigma score (follow-up stigma score minus baseline stigma score) from baseline to the three-month follow-up between the intervention and control arms.

Secondary Outcome 1: To compare HIV self-testing uptake by the three-month follow-up period between AYA in the intervention and control arms.

2. HYPOTHESES

The **primary** null (H_0) and alternative (H_A) statistical hypotheses are:

H_{P0}: HIV stigma throughout the three-month follow-up period will not differ between the intervention and control arms.

H_{PA}: HIV stigma at three-months follow-up will significantly decrease in the intervention arm compared to the control arm.

The **first secondary** null (H_0) and alternative (H_A) statistical hypotheses are:

H_{S10}: HIV self-testing uptake by three-months follow-up will not differ between the intervention and control arms.

H_{S1A}: HIV self-testing uptake by the three-month follow-up will be higher in the intervention arm compared to the control arm.

The **second secondary** null (H_0) and alternative (H_A) statistical hypotheses are:

H_{S20}: Changes in HIV stigma from baseline to the three-month follow-up period will not be moderated by sex at birth.

H_{S2A}: Changes in HIV stigma from baseline to the three-month follow-up period will be moderated by sex at birth.

3. METHODS

This section contains information about the study design and statistical analysis that will be performed to assess the hypotheses.

3.1. Study Design

We conducted a randomized controlled trial among 216 AYA in Almaty, Kazakhstan. Participants were randomized 1:1 to the intervention or control arm. Participants randomized to the intervention arm viewed AYA-crowdsourced digital materials (video, audio, images, text) over a five-week period. Participants randomized to the control arm viewed existing multi-media materials obtained from Kazakhstani health organizations over the same period. Intervention and control materials were administered online through weekly emails via Qualtrics for five weeks (after baseline survey (week 0) to the one-month follow-up (week 4)), with content scheduled to be delivered at the same time on a weekly basis (2-3 items shown per week). Viewing length of weekly content was approximately 5-10 minutes. We varied weekly content by type (video, image, text) and aimed to match control content by type and length to the intervention content. Participants in both arms were assessed at three time points: baseline "pre-intervention", immediately post-intervention (one-month follow-up), and three-month follow-up.

3.2. Trial Randomization

A research assistant (RA) assigned participants 1:1 to the intervention or control arm using a computer-generated randomization sequence and scheduled the participants to receive surveys and their assigned intervention or control content. AYA were blinded to their arm assignment and did not know whether they were receiving intervention or control materials.

3.3. Data Sources

3.2.1. Participant Surveys.

Participants completed online surveys via Qualtrics at three timepoints -- baseline "pre-intervention", immediately post-intervention (one-month follow-up), and three-month follow-up. Among the many topics assessed, surveys included sociodemographic items, the HIV stigma scale,[1] and a link to an online form to order an HIV self-test kit.

3.2.2. HIV Self-Testing Uptake.

AYA who clicked on the survey link could fill out an online form to order an HIV self-test kit. The kit could be mailed to their home address or another location of their choosing, or ordered for pick-up at a local non-governmental organization. Participants sent pictures of their self-test results via WhatsApp to an RA. Participants who screened positive for HIV would be referred to a youth clinic and the Almaty City AIDS Center for confirmatory testing. However, none of our participants screened positive for HIV.

3.4. Statistical Interim Analysis and Stopping Guidance

There are no interim analyses or interim stopping rules that must be considered for this statistical analysis plan (SAP).

3.5. Sample Size

Power analyses were conducted with G*Power (v3.1.0) based on the primary outcome of HIV stigma reduction using a Wilcoxon-Mann-Whitney test approach and α=.05. With 108 participants per arm, we would have 80% power to detect a small-to-medium effect size (d=0.39).

4. STATISTICAL PRINCIPLES AND ANALYSIS

4.1 Confidence Intervals and P-values

All statistical computations will be performed by the PI (Dr. Davis), who is an epidemiologist, in consultation with quantitative data scientists. For descriptive summaries of study data, the following will be presented:

- Nominal/categorical measures will be summarized using frequencies and percentages;
- Interval or ratio scale measures will be summarized using means and standard deviations;
- Ordinal measures will be summarized depending on the number of levels. An ordinal measure with five levels or less will be summarized as a nominal measure. An ordinal measure with more than five levels will be summarized as an interval or ratio scale measure.

The balance or imbalance of baseline characteristics will be studied and reported, particularly for analyses comparing the two study arms.

Reported p-values will be based on two-sided tests at an α=0.05 unless otherwise specified. When p-value correction is appropriate, Benjamini-Hochberg[2] False Discovery Rate adjustments will be used to address multiplicity and preserve Type I error rate.

Unless required otherwise by a journal, the following rules are standard:

- Test statistics will be reported to two decimal places.
- P-values will be reported to two significant figures. If less than 0.001, p-values will be reported as '<0.001'.
- No preliminary rounding will be performed; rounding will only occur after analysis. To round, consider digit to right of last significant digit: if < 5 round down, if ≥ 5 round up.

4.2. Dependent Variables

The dependent variables in this analysis are:

1. Self-Reported HIV Stigma – Assessed by a 17-item HIV stigma scale that was originally developed for community members not living with HIV in South Africa and Zambia.[1] The scale was reviewed by our Community Collaborative Research Board (CCRB), and we conducted cognitive interviews with 10 Russian-speaking AYA and nine Kazakh-speaking AYA. AYA and our CCRB provided feedback on the cultural and age-appropriateness of the items, and gave recommendations on item modification. Item response options were on a five-point Likert scale (1 – strongly disagree to 5 – strongly agree). The total score across the 17 items was calculated, with a maximum total score of 85. Scale reliability was high in our sample (α=.871).

2. HIV Self-Testing Uptake – Number of AYA in each arm who ordered an HIV self-test kit in the follow-up period after the pre-intervention assessment.

4.3. Independent Variables

The key independent variables in this analysis are:

Study Arm – Randomized to the Intervention arm or the Control arm.

Timing of Assessment – baseline (pre-intervention), immediately post-intervention (one-month follow-up), three-month follow-up.

4.4. Covariates

As appropriate in the analyses, multivariable modeling of changes in HIV stigma will include adjustment for the following participant-level characteristics:

a. Age
b. Sex
c. Sexual orientation
d. Baseline levels of HIV stigma
e. Submission of crowdsourcing entry to the JasSpark study contest
f. Prior HIV testing (baseline and prior to the study)

4.5. Statistical Analysis Methods

Descriptive statistics of key independent variables and covariates will be summarized within each arm using frequencies or means (standard deviations) as appropriate. Overall participation rates will be reported in each arm based on the proportion of baseline participants who completed the three-month follow-up assessment.

To test **hypothesis 1 (H1)**, we will conduct multilevel linear mixed models to assess for differences in changes in the overall HIV stigma score between study arms. As a secondary analysis, we will also assess changes in each of the stigma subscale scores (perceived stigma in the community, fear and judgement, perceived stigma in healthcare settings, and HIV testing stigma). To account for multiple comparisons arising from analyses of subscales, the false discovery rate (FDR) was controlled using Benjamini-Hochberg procedures in a tiered approach.[2]

To test **hypothesis 2 (H2)**, we will use a generalized linear model using a binomial distribution to examine whether the intervention was associated with increased HIV self-testing uptake in the follow-up period. The model was adjusted for history of HIV testing (pre-intervention testing and testing prior to the study), whether the participant had submitted content to the JasSpark contest, and if the participant had a main intimate partner (e.g., girlfriend/boyfriend, spouse).

To test **hypothesis 3 (H3)**, we examined potential moderation effects of sex at birth on stigma changes. Fixed effects corresponding to the two-way interactions involving sex, time, and/or arm, as well as the three-way interaction of sex, time, and arm, were added to the models from

H1. To account for multiple comparisons arising from analyses of moderating effects, the false discovery rate (FDR) was controlled using Benjamini-Hochberg procedures in a tiered approach.[2]

The model testing H3 is summarized as Equation H3:

HIV stigma score = Intercept + B_1(Arm) + B_2(Categorical variable corresponding to timepoint of stigma assessment; two degrees of freedom) + **B_3 (Arm * Timepoint of stigma assessment**; two degrees of freedom**)** + B_4(Baseline stigma level) + B_5(Respondent Sexual orientation) + B_6(Respondent Age) + B_7 (Respondent Sex) + B_8 (Respondent Submitted entry to JasSpark contest) + B_9 (Respondent HIV testing prior to study) + B_{10} (Respondent HIV testing baseline) + Error
+ Random effects for the clustering within participant across timepoints and by dyad.

If the statistical test for the interaction between arm and timepoint is significant at the α=0.05 level, then we conclude that study arm significantly impacts the change in HIV stigma. Within arm, adjusted estimates of changes in adherence will be presented along with 95% confidence intervals.

4.6. Missing Data

The analysis sample is restricted to participants with data for the outcomes and with key demographic information. Missing data for outcomes or demographics will not be imputed.

5. REFERENCES

1. Stangl AL, Lilleston P, Mathema H, et al. Development of parallel measures to assess HIV stigma and discrimination among people living with HIV, community members and health workers in the HPTN 071 (PopART) trial in Zambia and South Africa. J Intern AIDS Soc 2019;22(12):e25421.

2. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B: Statistical Methodology 1995;57(1):289–300.