THE OPENS TRIAL: OFFERING WOMEN PREP WITH EDUCATION, SHARED DECISION-MAKING, AND TRAUMA-INFORMED CARE (AIM 2)

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Statistical Analysis Plan

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Offering Women PrEP with Education, Shared Decision-making and Trauma-Informed Care

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LIST OF ABBREVIATIONS

Abbreviations	**Definitions**
AE	Adverse Events
DCS	Decisional Conflict Scale
DST	Decisional Support Tool
EMR	Electronic medical record
HIV	Human Immunodeficiency Virus
ITT	Intention-to-treat
MRN	Medical record number
PP	Per protocol
PrEP	Pre-exposure prophylaxis

1. Study overview

To address the significant barriers to PrEP implementation for those who were assigned female at birth and self-identify as a woman and address racial inequities in HIV prevention in the United States (US), a novel approach that accounts for multilevel influences is necessary. This study is the second part (Aim 2) of a multi-component project and involves a patient- and clinic-level intervention in a public health reproductive health clinic and an STI clinic in Duval County, Florida. The majority of patients attending these clinics are women of color. The area has one of the highest HIV incidence rates among women in the US. The investigators developed 1) a tablet-based decision support tool that helps users learn about HIV vulnerabilities and HIV prevention strategies to inform how they consider options for reducing their likelihood of acquiring HIV, and 2) clinic-wide trainings regarding shared decision making and trauma-informed care. In Aim 1 (previously completed, NCT04621760) participants were randomized to viewing an HIV decision support tool in a reproductive health clinic that had not received clinic-wide trainings. In the first phase of Aim 2, participants will receive care at reproductive health and STI clinics following the training; the DST will not be used. In the second phase of Aim 2, in addition to being seen at clinic-sites that received the trainings, participants will use the DST before their visits. Participants will be surveyed about experiences with HIV prevention counseling, intentions about the use of HIV prevention, and DST use. A subset of participants, individuals who self-identify as Black or Latina, will also complete a post-clinic visit interview. The investigators will assess whether participants initiated an HIV prevention method three months following their initial visits. The main outcomes will include a quantitative and qualitative assessment of PrEP or other HIV prevention use, decisional certainty, and satisfaction with information about HIV prevention options.

1.1 Study objective

To evaluate how clinic-wide trainings on shared decision making and trauma-informed care, on their own and paired with the decision support tool, affect patient counseling and decision making about PrEP.

1.2 Study Design and Randomization

The study uses a phase design and will recruit up to 366 participants from a family planning clinic and an STI clinic in Duval County, Florida (183 in Phase 1, 183 in Phase 2).

Phase 1: Participants in this arm will receive care in clinics where providers and staff have been trained in shared decision making and trauma-informed care. Participants will not view the decision support tool in this phase.

Phase 2: Participants in this arm will receive care in clinics where providers and staff have been trained in shared decision making and trauma-informed care, and will receive the HIV prevention DST intervention immediately before their provider visits.

Randomization procedures: Randomization to a qualitative interview and/or audio recording will be implemented using randomly permuted blocks of randomly selected size 2 and 4, stratified by clinic and race. All randomization will occur by research staff with the use of a REDCap randomization instrument.

1.3 Study Population

Inclusion Criteria:

- Identify as a woman
- Age 18 to 45 years old
- Not known to be living with HIV
- Not known to be taking PrEP
- English speaking
- Interested in participating in the study

Exclusion Criteria:

- Unable to consent
- Currently using PrEP
- Cisgender men
- Unwilling to be contacted in 3 months

1.4 Intervention

Clinic-wide Trainings: The clinic-wide training combines principles of shared decision-making and trauma informed care to inform providers and clinic staff of an equitable approach to offering HIV prevention information. These care delivery approaches have been used in health education and counseling in a range of contexts and are effective strategies for care provision. Participants in this arm will receive care from providers and staff who received the training.

HIV Prevention Decision Support Tool (DST): The tool is founded on principles of decision-science and developed in a systematic manner including pilot testing. The tool will present HIV prevention information via a tablet in clinic. The decision support tool will address barriers to PrEP delivery, including 1) limited client knowledge about PrEP, 2) limited time to educate patients in busy clinics, 3) women's lack of knowledge of their own HIV vulnerability, and 4) hesitancy of women to initiate discussions about PrEP with providers due to judgmental attitudes and stigma. Also, the tool emphasizes the highly variable and individual nature of baseline risk of HIV acquisition.

1.5 Sample size calculation

Census data provided by the Department of Health suggests that 66 eligible patients are seen per month in the reproductive health clinic. Therefore, we planned an eight-month time period for each phase of Aim 2. We calculated that with a sample size of 183 participants per phase, we will have 80% power in 2-sided tests with a type-I error rate of 5% to detect increases in PrEP uptake of 4-6 percentage points between phases, and increases of 6-9 percentage points between Aim 1 Control Arm (Standard Counseling) and Aim 2 Phase 2 (Active Comparator: Clinic Trainings + DST), depending on the marginal uptake rate across phases, and accounting for loss of precision due to adjustment for linear secular trend as well as differences in patient characteristics across phases.

For binary outcomes such as satisfaction with counseling, we plan to use the data from participants who did not receive the intervention (Aim 1 Control) as the baseline data for comparisons across Aims 1 and 2. With our planned sample size of 183 for each of Aim 2's Phase 1 and Phase 2, we will have 80% power to detect increases of 14-18 percentage points between Aim 1 Control and Aim 2's Phase 1 (Experimental Arm: Clinic Training without the DST) and 13-16 percentage points between Aim 2 Phase 1 and Phase 2, and 20-30 percentage points between Aim 1 Control and Aim 2 Phase 2, again depending on the marginal outcome rate (assumed 50-75%), and accounting for loss of precision due to adjustment

for secular trend and patient characteristics. These estimates were obtained using simulations implemented in R.

1.6 Study Procedures

Both groups will complete surveys at three measurement timelines: baseline (t_0), immediately post-appointment (t_1), and at 3-months (t_2). Data collection will occur via electronic survey hosted on REDCap. Neither the participants nor the study team will be blinded.

Research assistants will approach eligible patients in the clinic waiting room prior to their appointments. They will assess eligible and complete consent procedures in a private location on-site. Participants will then complete a baseline questionnaire on a tablet. After completion of the initial questionnaire, participants in Phase 1 will proceed to their clinical visit and participants in Phase 2 will receive access to the DST via a tablet provided by the research assistant to review in advance of their clinical visit.

After the participant's visit with the provider, they will be asked to complete a post-visit survey about their clinic visit and counseling, risk perception, decision making, sexual history, and their experience with the decision support tool if they are in the experimental arm.

Three months post-visit, research staff will follow up with participants by phone, email, SMS or mail to administer a short survey and ask participants about their chosen HIV prevention method, and if they initiated PrEP.

Upon completion of the study, research staff will extract data from the medical record pertaining to participants' PrEP prescriptions, history of sexually transmitted infections, zip code, and insurance status.

2. Population of analysis

We will conduct an intention to treat (ITT) analysis as well as a per protocol (PP) analysis. ITT will serve as our primary analysis. For PP analyses, individuals in the intervention group will be considered members of the control group if they did not receive or did not interact with the DST at all.

2.1 VARIABLES

2.1.1 Background and demographic characteristics

Demography and baseline characteristics will be statistically summarized by treatment group.

Demographic variables include age, gender, race and ethnicity, income, parental income, educational attainment, housing status and language spoken at home.

Baseline behavioral variables include variables related to potential HIV exposure, including: sexual and drug use behaviors, past diagnoses of sexually-transmitted-infections, as well as reproductive behaviors including: pregnancy status and desire, contraceptive use.

2.1.2 Outcomes

2.1.2.1 Primary outcome variables

- **PrEP prescriptions:** The number of participants who received a PrEP prescription and date of prescription, obtained by chart extraction from the medical record.

2.1.2.2 Secondary variables

- **Number of Patients Reporting PrEP use:** Participants will be contacted at follow-up and asked if took PrEP in the past 3 months regardless of where it was obtained.
- **Patient-Perceived HIV risk:** Participants will be asked about how worried they are about getting HIV in the next 6 months.
- **Knowledge of PrEP:** Participants will be asked a series of questions about PrEP to assess PrEP knowledge.
- **Decisional Conflict:** Participants will be asked questions derived from the Decisional Conflict Scale to provide a measure of decision quality about their HIV prevention decision immediately following their visit.
- **Interpersonal Quality of HIV Prevention Care:** A scale for patient-centered HIV prevention counseling focusing on patient preferences and reflecting satisfaction and confidence in the counseling session, derived from the Interpersonal Quality of Family Planning Care Scale developed by the PI.
- **Interpersonal Quality of Health Services:** A scale for patient-centered health services focusing on patient preferences and reflecting satisfaction and confidence in services offered, derived from the Interpersonal Quality of Family Planning Care Scale developed by the PI.
- **Intention to Use Any HIV Prevention Method:** Participants will be asked if they plan to use any HIV prevention method after the initial visit.
- **Satisfaction with Information Received about HIV Prevention:** Participants will be asked about their satisfaction with HIV prevention counseling.
- **Confidence in decision to use an HIV prevention method:** A one-time, one-item measure of certainty of plan to use HIV prevention after the initial visit. Participants can select from 4 options: 1 ("completely unsure"), 2 ("mostly unsure"), 3 ("mostly sure, but not 100%"), or 4 ("100% sure").
- **Perceived Quality of Information Received about HIV Prevention:** Participants will be asked questions about the perceived quality of the HIV prevention information they received during their health care visit.
- **Perceived Quality of Health Information Received:** Participants will be asked questions about the perceived quality of health information they received during their health care visit.
- **Acceptability of HIV Prevention Methods:** Participants will be asked to rate their preference for a method (even if they never used it). Participants can select from condoms, PrEP, PEP, treatment as prevention, regular partner testing, or other method.
- **Acceptability of the Decision Support Tool:** Participants in the experimental arm are asked four questions about their experiences using the DST.
- **Perception of the Decision Support Tool:** Participants in the experimental arm will be asked about the degree to which they liked/disliked the tool. Response options vary: "I did not like it at all", "I somewhat disliked it", "I somewhat liked it", "I really liked it".
- **Willingness to Use the Decision Support Tool at Future Visits:** Participants in the experimental arm will be asked about whether they would use the tool again if they returned to the clinic. Response options are "yes", "no", "unsure".
- **Recommend the Decision Support Tool:** Participants in the experimental arm will be asked whether they would recommend the tool to a friend. Response options are "yes", "no", "unsure".
- **Satisfaction with the Decision Support Tool:** Participants in the experimental arm will be asked about the degree to which they were satisfied with the information in the tool. Response options vary from 1-5: "very unsatisfied" to "very satisfied".
- **HIV Prevention Method Use (any method – planned or new method):** A self-reported measure of HIV prevention method use, including those who reported discontinuing the initial HIV prevention

method(s) that were reported post-clinic visit. A response of “yes” to any of the following questions: since your [baseline] visit, have you used….for HIV prevention – abstinence, condoms, PEP, PrEP, regular HIV testing, treatment as prevention, regular sexually transmitted disease (STD) testing, other method. The outcome will be dichotomized to those who responded affirmatively vs other responses (“no”/”unsure”).

- **HIV Prevention Method Continuation:** A self-reported measure of HIV prevention method continuation.
- **HIV Prevention Method Use:** A self-reported measure of HIV prevention method use, including those who reported discontinuing the initial HIV prevention method(s) that were reported post-clinic visit.

2.1.3 Other metrics

- Percentage of missing answers in questionnaires
- Response times per questionnaire

2.2 Hypotheses

Aim 2 Hypotheses

1. The experimental arm (Aim 2 Phase 2) will result in significantly higher number of PrEP prescriptions compared to the active comparator (Aim 2 Phase 1).
2. The experimental arm will result in significantly higher number of individuals reporting PrEP initiation compared to the active comparator.
3. The experimental arm will report significantly higher PrEP knowledge compared to the active comparator.
4. The experimental arm will report significantly higher intention to initiate any HIV prevention method compared to the active comparator.
5. The experimental arm will report significantly higher satisfaction with information received about HIV prevention compared to the active comparator.
6. The experimental arm will report significantly higher acceptability of HIV prevention methods compared to the active comparator. T2 binary transformed
7. The experimental arm will report significantly higher satisfaction with other health information received compared to the active comparator.
8. The experimental arm will report significantly higher quality of HIV prevention care compared to the active comparator.
9. The experimental arm will report significantly higher quality of other health services compared to the active comparator.
10. The experimental arm will result in significantly higher level of patient-perceived HIV risk post-visit compared to the active comparator.
11. The experimental arm will report significantly higher confidence in decision to use an HIV prevention method compared to the active comparator.
12. The experimental arm will report significantly lower decisional conflict, as documented by the full scale and subscales, compared to the active comparator.
13. The experimental arm will report significantly higher proportions of ongoing PrEP use at 3 months post-visit compared to the active comparator.

14. A significantly higher proportion of the experimental arm will report use of any HIV prevention method at 3 months-post study initiation compared to the active comparator.
15. A significantly higher proportion of the experimental arm will report continuation of any HIV prevention method at 3 months-post study initiation compared to the active comparator.
16. The experimental arm will report high acceptability of the DST.
17. A high proportion of the experimental arm will report positive impression of the DST.
18. A high proportion of the experimental arm will report willingness to use the DST at a future visit.
19. A high proportion of the experimental arm will report willingness to recommend the DST to a friend.
20. The experimental arm will report high satisfaction with the DST.

Additional Planned Analyses Across Aims

In addition to analyses conducted independently for each Aim, we will compare outcomes between Aims 1 and 2 to evaluate the independent and combined effects of the clinic-wide trainings and the HIV prevention Decision Support tool (DST). These analyses leverage the complementary designs of the two study aims to address questions that cannot be evaluated within either trial alone.

Planned cross-aim comparisons include:

- **Clinic-wide trainings without the DST vs. control:** Compare participants receiving standard counseling following clinic-wide trainings (Aim 2, Phase 1) with participants receiving standard counseling prior to implementation of clinic-wide trainings (Aim 1 Control) to estimate the effect of the clinic-wide training intervention without use of the DST.
- **Clinic-wide trainings with the DST vs. control:** Compare participants receiving clinic-wide trainings plus the DST (Aim 2, Phase 2) with participants receiving standard counseling without clinic-wide trainings or the DST (Aim 1 Control) to estimate the combined effect of clinic-wide trainings and the DST.
- **Clinic-wide trainings with the DST vs. no training with the DST:** Compare participants receiving clinic-wide trainings plus the DST (Aim 2, Phase 2) with participants receiving the DST in clinics prior to clinic-wide trainings (Aim 1 intervention) to estimate any added benefit of the clinic-wide trainings to use of the DST.

These cross-aim analyses are hypothesis-driven. They will supplement the primary analyses conducted within each trial and will be interpreted in consideration of the non-concurrent study periods and any differences in participant characteristics or clinical context between the two study aims.

1. STATISTICAL METHODOLOGY

3.1 General methodology

All outcomes will be presented using descriptive statistics; normally distributed data by the mean and standard deviation (SD), skewed distributions by the median and interquartile range (IQR), and binary and categorical outcomes described by counts and proportions. Demography and baseline characteristics will be statistically summarized by treatment group. For continuous outcomes, we will use t-tests for independent samples that are normally distributed and Mann-Whitney U tests for those that are non-normally distributed, and for categorical outcome we will employ χ 2 or Fisher's exact-tests to examine baseline differences between experimental and active comparator groups in demographic data or measured variables. Categorical variables will be assessed and collapsed in cases of small cell

sizes for increased power. Scale items of questionnaires (e.g., Decisional Conflict Scale) will be recoded (where applicable) and a scale mean or sum score will be calculated and reported. Composite scale variables will be assessed for skewness through histograms and normal Q-Q plots. Where the normality assumption is not met, median and IQR will be reported. Mann-Whitney U tests will be used to detect differences between groups. Further, in instances where a strong skew is detected, with response concentrated to one pole, scales will be transformed into binary variables and analyzed as binary data. To estimate effect size, Cohen's D will be used for continuous, normally distributed outcomes, Cliff's Delta will be used for non-normal continuous outcomes, and odds ratios will be used for binary outcomes.

3.2 Subject disposition

The number and proportion of screened, randomized, treated and analyzed subjects will be provided. Where necessary, the CONSORT flow chart will be presented to describe the subject disposition in the statistical analysis report.

3.3 Primary and secondary data analyses

In primary and secondary data analyses, all stated hypotheses will be tested. In all analyses, an error probability of α = .05 will be set a priori for descriptive statistics calculations. In addition to statistical significance, effect sizes will be reported. Publication of results will follow CONSORT guidelines for transparent reporting of randomized trials.

3.3.1 Primary analysis (H1)

PrEP prescriptions within 3 months of primary study visit will be extracted from participants' electronic medical records (EMRs). Data will be matched to survey data using participant medical record numbers (MRNs). Summary statistics will be presented by treatment group. Differences in PrEP prescriptions between groups will be examined by $\chi 2$ or Fisher's exact-tests as appropriate, and effect size will be calculated using odds ratio.

3.3.2 Secondary data analyses

The analysis plan for H2-H9 is as follows:

Summary statistics will be presented by treatment group. Differences between study groups at t_2 will be assessed through $\chi 2$ or Fisher's exact tests as appropriate. Variables for H5-H7 will be transformed into binary variables using topbox approach, given predicted skew toward the pole of agreeability. Scales used for H8-H9 will be summed and transformed into binary topbox scores following the methodology of the Person-Centered Contraceptive Counseling measure on which they are based. Odds ratios will be calculated as a measure of effect size as appropriate.

The analysis plan for H10 is as follows:

Full scale and subscales will be scored as instructed in the Decisional Conflict Scale manual. Summary statistics will be presented by treatment group for the full scale and by subscale. To assess differences in scale score distribution between groups, we will perform t-tests or Mann-Whitney U tests as appropriate. In case of high positive skew (as is commonly found in the literature), we will create binary variables demarcating no conflict versus any conflict and perform $\chi 2$ tests. Effect size will be estimated using linear, quantile, or logistic regression as appropriate.

The analysis plan for H11-H12 is as follows:

Summary statistics will be presented by treatment group. Differences between study groups at t_2 will be assessed through t-tests or Mann-Whitney U tests as appropriate. In case of high positive skew (as is commonly found in measures of satisfaction and confidence), we will create binary variables demarcating no conflict versus any conflict and perform $\chi 2$ tests. Effect size will be estimated using linear, quantile, or logistic regression as appropriate.

The analysis plan for H13-H15 is as follows:

Summary statistics will be presented by treatment group. Differences between study groups at t_3 will be assessed through $\chi 2$ or Fisher's exact tests as appropriate. Odds ratios will be calculated as a measure of effect size as appropriate.

The analysis plan for H16-H20 is as follows:

Summary statistics will be presented for the intervention group.

3.3.3 Planned cross-aim analysis

For analyses across the two aims (e.g. inclusive of the four total arms), a 2x2 factorial methodology will be applied to explore the main effects of each intervention component and the combined effect. Each model will test main effects for DST versus no DST (1/0) and training versus no training (1/0). An interaction term will be included in the model to estimate combined effect. This model will be assessed for fit, inclusion estimated precision. Other models that treat the arms as nominal, independent groups and as pairwise comparisons (e.g. DST v. no DST) may be employed to address additional questions or as methodologically appropriate. We will use logistic, poisson, ordinary least square, or quantile regression as appropriate by outcome.

3.4 Safety analysis

3.4.1 Analysis of adverse events (AEs)

The number and percentage of subjects who had at least one serious adverse event, classification of serious adverse event, adverse events of special interest and classification of adverse events of special interest from the study will be provided.

4. DATA PROCESSING CONVENTIONS

4.1 Definition of baseline

In this study, baseline values are defined as those data collected before intervention (screening visit).

4.2 Missing data

We will report proportions of missing values for all collected variables where needed. Baseline characteristics missing data will be imputed by multiple imputation with chained equations (MICE) procedures as appropriate.

4.3 Statistical analysis software

All statistical analysis and summary statistics will be carried out using Stata version 16.1 or higher.