mChoice: Improving PrEP Uptake and Adherence among Minority MSM through Provider Training and Adherence Assistance in Two High Priority Settings

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Section B: Supporting Statement

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1. Respondent Universe and Sampling Methods

The Improving PrEP Uptake and Adherence among Minority MSM through Provider Training and Adherence Assistance in Two High Priority Settings(mChoice) project will train HIV pre-exposure prophylaxis (PrEP) providers, implement evidence-based PrEP support tools in clinical settings, and will increase our understanding of provider and patient factors that influence the choice of PrEP regimen by MSM in New York City (NYC), New York (NY) and Birmingham, Alabama (AL). The project will enroll and follow a longitudinal cohort of racially diverse young men who have sex with men (YMSM) using PrEP in order to better understand real-world patterns of PrEP use and the impact of the implementation of provider training and evidence-based PrEP support tools.

mChoice is focused on YMSM because of the disproportionately high rate of HIV diagnoses in this population. In the United States, men who have sex with men (MSM) have the highest annual rates of HIV incidence each year. Among MSM, the highest HIV incidence is among 13-24 and 25-34 year olds.[1] In particular, MSM who are African American or Black (hereafter referred to as Black) account for the vast majority of new infections – 25% (9,444) of the 37,968 HIV infection diagnoses and 38% of diagnoses among all MSM.[1] Rates of new infections among Hispanic or Latino YMSM are similarly striking.

Despite the efficacy and availability of PrEP, uptake and adherence to PrEP among YMSM remains low, limiting its impact on prevention of HIV infection. Adherence to PrEP is crucial for protection against HIV infection, yet youth struggle to use PrEP daily.[2-6] The mChoice project seeks to enhance and better understand HIV prevention efforts among YMSM.

Location Selection

mChoice sites include clinics located in NYC, NY and Birmingham, AL. These sites have substantial populations of Black and Hispanic/Latino YMSM and clinics with experience providing PrEP and serving these populations. The sites in the Northeast and South provide regional diversity in the project. mChoice will implement innovative provider PrEP training and evidence-based PrEP support tools in these clinical sites. mChoice participants at these sites will be provided with the CleverCap electronic medication monitor and mChoice mobile app to support their PrEP use. Consenting participants will also be enrolled in a longitudinal cohort that will provide data about longitudinal PrEP use patterns and choices among PrEP modalities. Clinic sites at each study location are:

- Columbia University Nurse Practitioner Primary Care Group (NYC, NY)
- Callen-Lorde Community Health Center (NYC, NY)
- University of Alabama at Birmingham (UAB) 1917 Clinic (Birmingham, AL)
- Birmingham AIDS Outreach (BAO) (Birmingham, AL)

Target population

The mChoice study will enroll 400 YMSM who reside in NYC, NY or Birmingham, AL. These 400 YMSM participants will receive the PrEP support tools including the mChoice mobile app. Thirty of the YMSM participants will enroll in in-depth interviews about their experiences with PrEP.

The study will also enroll 20 health care providers who work at study clinic locations to participate in PrEP provider training. PrEP training will include but are not limited to medical doctors, nurses, adherence counselors, pharmacists, and social workers. A provider can include any site employee who discusses PrEP with a patient.

- *Implementation and cohort study activities, 400 YMSM:*
  - Inclusion criteria:
    - Aged 18-39 years, inclusive
    - Male sex assigned at birth
    - Identify as male, non-binary or genderqueer
    - Understand and read English or Spanish
    - Using or initiating PrEP
    - Owns a smartphone
    - Has had sex with a man within the past 12 months
    - Lives in the NYC or Birmingham, AL area
  - Exclusion criteria:
    - Person has HIV infection
    - Not currently taking and not initiating PrEP
    - Unable to provide informed consent due to severe mental or physical illness or substance intoxication at the time of enrollment
    - Currently enrolled in any other PrEP-related research study
    - Planning to leave the NYC/Birmingham, AL area in the next 12 months.

- *PrEP experiences in-depth interviews, 30 YMSM:*
  - Recruited from participants in the cohort activities, so inclusion and exclusion criteria are the same as above.

- *Provider PrEP training, 20 health care providers:*
  - Inclusion criteria:
    - Confirmed to be providers at participating clinic sites
    - ≥18 years old
    - English speaking
    - Cognitively able to complete required activities
  - Exclusion criteria
    - Not a provider at one of the participating study sites
    - Less than 18 years old
    - Not fluent in written/spoken English
    - Cognitively unable to complete required activities

Exhibit 1.1: Summary of Recruitment Targets

Participant Type	Total
Young MSM • 18-39 years of age • Self-identify as cisgender male, non-binary, or genderqueer • Sex with a man in last 12 months • Using or starting PrEP • Speak and read English or Spanish	400
PrEP Providers • PrEP provider at participating clinic site • Speak and read English or Spanish	20

Total study enrollment	**420**

The onsite project coordinators will oversee and participate in recruitment efforts. mChoice will recruit participants using posted flyers in the NYC and Birmingham, AL areas and online advertisements. The mChoice study team has used a variety of recruitment venues for other similar studies and maintains strong working relationships with online advertising vendors and local community-based organizations. Although online venues are constantly evolving, in the past, major categories of recruitment have included social network sites (e.g., Facebook, Instagram, Twitter) and online sexual networking apps (e.g., Grindr, Scruff). Recruitment will also include community presentations about the study (for example, at community events like street fairs). Active in-clinic recruitment could include identifying potential participants out of the clinic's patient pool, particularly among YMSM patients who present for PrEP services and HIV and STI testing and who may meet the eligibility criteria. These methods have been used by prior studies conducted by this research collaboration to successfully recruit diverse samples of YMSM. Recruitment data will be reviewed weekly by the study team to assess for recruitment difficulties and assess progress toward enrollment of a diverse sample.

Rationale for proposed number of subjects

For the PrEP implementation and cohort portion of the study, 400 YMSM will be enrolled. The samples size is estimated for the evaluation of the effectiveness of CleverCap App on participants' clinical outcomes (PrEP adherence and persistence). The criterion for significance (alpha) has been set at 0.05 for two-sided tests with 80% power. Using the generalized linear mixed model (GLMM) our sample size calculations are based on these assumptions: 1) 20% attrition during post-intervention follow-ups; 2) an intraclass correlation coefficient (ICC) of 0.2 across sites; 3) a moderate to high positive correlation of participants' outcome at different time points. Therefore, it is reasonable to assume that correlation at different time points is in the range from 0.3 to 0.6; and 4) a wide range of outcome proportions at the baseline from 10% to 80%. This should include all possible baseline PrEP use proportions. A total of 400 participants is needed to detect a pre- and post-intervention change of OR of 1.7 or greater. The effect of OR≥1.7 is selected because a previous intervention study reported an effect of intervention on PrEP adherence of approximately OR=2.0, and OR=1.7 is within the small to medium effect size range.[13] The number of providers included in the provider training portion is a convenience sample of available providers that is expected to generate analyzable qualitative data.

2. Procedures for the Collection of Information

For the PrEP implementation and cohort portion of the study, participants will be followed for at least 12 months and up to 18 months, during which time PrEP uptake, adherence and persistence will be evaluated. These data include: continuous monitoring of CleverCap electronic medication monitor; self-report responses to CASI every 3 months; self-report of PrEP doses taken or missed; urine test for tenofovir levels for oral PrEP users; and medical record and prescription data which are collected from electronic health records (EHR). Participants who report using tenofovir-containing PrEP in the last week will take a urine sample to measure tenofovir levels during the baseline, 3-month, 6-month, 9-month and 12-month follow-ups. Participants will be provided a sterile collection container for urine samples during their follow-up visit, which will be conducted at the site clinic. The CASI will be completed online with study staff available for questions by phone or email. mChoice will also collect and evaluate mChoice app data, which reflect what participants are entering in the app. Data can be used to measure participant engagement based on how much the participant is using the app—overall, and by

the different components of the app. App data can also be used to measure sexual risk behaviors; tracking PrEP medication doses taken, missed, and days not tracked; and self-reported episodes of condom use based on what the participant enters in the app. To assess other aspects of PrEP care and outcomes, the mChoice team will extract participant EHR data every 6 months. To assess PrEP services at the clinic level the mChoice team will complete clinic assessment forms every 6 months.

For the in-depth interview cohort portion of the study, depth interviews will be conducted according to the interview guide, and transcriptions will be qualitatively analyzed for thematic elements. Qualitative data will be analyzed alongside quantitative data from Aim 1 to provide additional insights into real-world PrEP use and the perceived efficacy of the mChoice app and associated PrEP support materials.

For the provider PrEP training portion of the study, the mChoice team will provide participating providers with access to the online training modules as well as pre and post-training surveys. Providers will also have access to a module about cultural competency and humility. The provider trainings include implementation of PrEP support tools, national PrEP guidelines, and best practices in sexual health.

3. Methods to Maximize Response Rates and Deal with Non-responses

It is expected that attrition in this study will be minimal. The mChoice study team has a record of success in participant engagement and retention. The mChoice mobile app and CleverCap medication monitor facilitates participant engagement and retention. Study staff will utilize retention strategies such as contacting hard to reach participants multiple times on different days and at different times of the day, utilizing participants' preferred methods of communication, reminding participants of appointments ahead of time, and keeping locator information up to date.

The mChoice team will monitor recruitment and retention rates, site compliance with study procedures, and provide technical assistance for queries and concerns. Data quality will be examined weekly (e.g., missing data, assessment of distributional assumptions, identification of outliers) allowing for issues to be identified in a timely fashion and corrective action taken if indicated. Consistent attention to data quality and completeness during data collection will facilitate study staff efforts to retain participants and ensure complete reporting from participating sites.

Participant retention will also be facilitated through tokens of appreciation, provided as follows:

For the PrEP implementation and cohort portion of the study,

- Surveys and app download:
    - $40 for baseline survey and app download
    - $45 for 3-month follow-up survey
    - $55 for 6-month follow-up survey
    - $60 for 9-month follow-up survey
    - $70 for 12-month follow-up survey
    - $80 for 18-month follow-up survey

For the in-depth interview portion of the study,

- $35 for completing the interview

For the provider PrEP training portion of the study,

- $50 for completing training modules
- $100 for completing interviews with research staff

Data comparability between sites and states will be examined. Data will be aggregated for general analysis purposes; however, if significant differences emerge, separate analyses comparing outcomes between sites or states detailing differences will be conducted. Missing scale data will not be estimated.

Prior to performing any outcome analyses, the study team will evaluate the amount, reasons, and patterns of missing data. Missing data unrelated to both observed and unobserved outcome variables of interest will be considered missing completely at random, and complete case analysis will still generate unbiased estimates. The mChoice team will conduct sensitivity analyses to compare estimates of treatment effects with and without multiple imputation to assess the effect of missing data on statistical inference. The mChoice team proposes a GLMM to analyze data, the main advantages being unbiased estimates when there are missing outcomes during the follow-up period if the probability of missing is not related to the outcome value. For the missing values at the baseline or partial baseline collected data, the study team will use a multiple imputation approach. Models will also be run on the raw, non-imputed data with full information maximum likelihood estimation. Inferences for the trial arm, wave, and interaction between trial arm and wave do not differ between the analyses of the raw and multiply imputed data. Rates of reduction will be calculated from population-averaged rates, which control for all other covariates in the multivariable model. Models will be calculated by using the GLIMMIX and MIANALYZE procedures in SAS, version 9.4, and model fit will be evaluated by diagnostic statistics and residual plots.

4. Tests of Procedures or Methods to be Undertaken

The mChoice study staff have considerable experience collecting sensitive data, administering technology-based interventions, and successfully managing data and processes for multi-site projects. Methods and tools used in this study are based on relevant prior studies.[9-12] All study staff will complete training including an overview of the study; study procedures and human subjects issues (informed consent process, confidentiality); a demonstration of all technology components; methods for establishing comfort with the sensitive issues that may arise in the course of the focus groups or assessments; Human Subjects Protection; Good Clinical Practice; informed consent; quality management; confidentiality; and reporting of adverse events.

Study implementation including development of tools to support PrEP use and provider trainings are being developed as part of formative work with engagement from YMSM and PrEP providers. This engagement will ensure that study implementation addresses the needs and preferences of YMSM and PrEP providers.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

Exhibit 5.1 below lists the project team members who were consulted on the aspects of research design and those who will be collecting and analyzing the data. Please note: The CDC staff are primarily responsible for providing technical assistance in the design and implementation of the research; assisting in the development of the research protocol and data collection instruments for CDC Project

Determination and local IRB reviews; working with investigators to facilitate appropriate research activities; and analyzing data and presenting findings at meetings and in publications. CDC staff will neither interact with nor collect data from study participants. Data will be collected by members of grantee project staff listed. No individual identifiers will be linkable to collected data shared with or accessible by CDC staff, and no individually identifiable private information will be shared with or accessible by CDC staff.

6. Analysis Plan

For the implementation and cohort activities, the mChoice team will use GLMM, also called individual growth models and multilevel models, with appropriate link function will be used to compare the pre- and post-intervention difference for each outcome. The GLMM allows different trajectories for each participant, and this method is appropriate to compare outcome changes after the implementation of the intervention, with the control of baseline values. In this study, the GLMM is used for repeated measured data at months 0, 3, 6, 9, and 12 and clustering of participants within each of the four study sites. The mChoice team will conduct all analyses for the full sample and by study locations (NYC and Birmingham), separately. In the GLMM, the main independent variable is time. Let $yijt$ be the outcome for person jj from site ii at time tt (coded as a categorical variable). The mean value of $y$ijt, $EE(yijt) = \mu ijt$, will be modeled as $h(\mu ijt) = \beta 0ij + \beta 1ijt + \beta 2COV$, where $h(*)$ is appropriate link function: if the outcome is a binary (proportion) measure, $h(*)$ is the logit function; if the outcome is a count measure, $h(*)$ is the log function; if the outcome is a continuous measure, $h(*)$ is the identity function. COV is a vector of time-dependent covariates. $\beta 0ij$ and $\beta 1ij$ are random intercept and random slope, respectively: $\beta 0ij = \varphi\varphi 00 + \upsilon 0ij + \upsilon\upsilon 0iiii$ and $\beta 1ij = \varphi\varphi 10 + \upsilon 1ij + \upsilon\upsilon 1iiii$, where $\upsilon 0ij$ and $\upsilon 1ij$ are individual level random effects and $\upsilon\upsilon 0ii$ and $\upsilon\upsilon 1ii$ are site level random effects. In this model, time tt is served as an indicator of intervention status too. The pre- and post- intervention difference will be evaluated by examining $\beta 1ij$. The study team will compare mean score change from baseline to each of post-intervention time points. Because PrEP adherence may decline gradually over time, adherence rate may be lower at later follow-up times. To deal with this problem, the study team will (1) examine changes from baseline to immediately after intervention (i.e., from baseline to 3 months); and/or (2) to conduct a non-inferiority test for the pre- and post-intervention change: if it is demonstrated that PrEP adherence rates do not decline over time, then the intervention is effective.

Similar GLMMs will be used for analyzing secondary outcomes. The study team will conduct a multi-group comparison in pre- and post-intervention difference (i.e., the difference- indifference analysis) using a GLMM, by adding variable Group and interaction term of Group with time t in the GLMM described above. Because the PrEP regimen cannot be randomized, the study team will use the propensity score method to reduce the between-group bias. The study team will use the inverse probability of treatment weighting based on the propensity score to create synthetic groups of participants of different PrEP regimens so that these groups will be similar in their baseline characteristics. Logistic regressions will be used to estimate probability for each participant to be in each group, according to participants' baseline characteristics.

The study team will also examine factors that are associated with the likelihood that participants change their regimens during the 12 months of the study. Since the study team will know the date of change of PrEP regimen (from the EHR data), the study team will apply a Cox proportion hazard ratio model with time-varying covariates (e.g., sexual activity, insurance, side effect) to examine time to change regimen.

For a Markov process with kk transient states ss = (1, 2, 3, 4) for the three regimens plus one for not use PrEP, and one absorbing state ss = 5 for drop out of the study. Let $p$ti,jii = Pr (st+1 = jj|$ssii$t = ii) be transition probability from state ii at time tt to state jj at time tt + 1. We will estimate the instantaneous transition rates between different two states, from log-linear models with time dependent variables (sexual activity, insurance, side effects, etc.) as predictors. The log-linear model is used to deal with different days between two interviews for different participants. In addition, we will be collecting qualitative data so we can triangulate the qualitative and quantitative data and to better understand the participants' decisions for choosing a regimen.

For the in-depth interview activities, the team will adhere to qualitative research processes to ensure the credibility, confirmability, dependability, and transferability of the qualitative data from these analyses. To support the credibility of the data, we will conduct peer debriefing and triangulate findings across multiple data sources (surveys, in- depth interviews). In addition, the team will use "member checks," i.e., sharing of initial data interpretations with participants to ensure accurate interpretations. Triangulation of findings, along with reflexivity, will enhance the confirmability of the interpretations. The investigators will carefully record an audit trail and keep extensive field notes to facilitate transferability of study findings into other contexts.

All in-depth interviews will be transcribed verbatim and then coded. Directly identifying information will be removed during the transcription process. Thematic analysis will be used for the development of a coding scheme, which is an integral component of the data analysis process. It enables the systematic examination and interpretation of the data related to the primary analytic foci. The coding scheme is conceptualized as a multilevel structure. At the highest level are the primary analytic foci coded as headings. Specific aspects or dimensions of the headings are assigned core codes. Specific aspects or dimensions of the core codes are assigned sub-codes. The study team will use NVivo™ (QSR International, Victoria, Australia), a software program for qualitative analysis, to facilitate the analysis.

The following seven steps will be used to develop the coding scheme:

Step 1: Identify the principal issues discussed by participants.
Step 2: Construct definitions of the primary analytic themes.
Step 3: Develop and apply core codes and sub-codes to the initial set of interviews.
Step 4: Develop a provisional coding scheme.
Step 5: Test and refine the provisional coding scheme.
Step 6: Reconcile coding differences and construct an updated and final coding scheme.
Step 7: Apply the coding scheme to the full data set and assess inter-coder reliability.

After all transcripts have been coded, the study team will extract and examine the content of text segments linked to core codes and sub-codes relevant to understanding barriers and facilitators to the use of PrEP and the CleverCap App. Based on the coded data, the study team will propose ways in which certain themes are analytically related. A careful examination of the coded text will reveal the associations among these themes and may lead to more refined data searches. Once the study team establishes patterns of relationships among themes and issues, the study team will identify participants' accounts that support or refute these patterns. Identifying and accounting for cases that deviate from an interpretative pattern will allow testing and confirmation of the pattern's validity and robustness.

For the provider training data, mean scale scores for the pre- and post-administration of the PrEP knowledge items will be evaluated for significance of difference using the non-parametric Wilcoxon

signed-rank test for hypothesis testing of repeated measurements on a single sample. Categorical data for assessing differences in proportion of participants in -agreement with individual items before and after participating in the knowledge module will be analyzed using McNemar's test of marginal homogeneity as this tests the significance of difference in categorical responses in repeated measurements on a sample. The study team will use a non-parametric test as these tests make fewer assumptions about the distribution of responses among participants, as the study team cannot rely on the data being normally distributed.

Quantitative data will be analyzed with SAS, a computer-assisted quantitative data analysis software. Qualitative data will be analyzed with NVivo™ and Dedoose.

Exhibit 5.1: Statistical Consultants

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Mary Tanner	Project Officer	CDC	mtanner@cdc.gov
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