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Study protocol: a pilot randomized control trial of a dyadic mobile health intervention for Black sexual-minority male couples with HIV

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Abstract

Introduction: HIV care engagement is lower among Black sexual-minority men relative to other racial/ethnic groups of sexual minority men. Being in a primary relationship is generally associated with more successful HIV care engagement across various populations. However, among Black sexual-minority men, the association between primary-relationship status and HIV-related outcomes is inconsistent across the HIV care continuum. Given the ubiquity of mobile technology access and use among racial/ethnic minority communities, leveraging mobile technology for HIV care engagement appears a promising intervention strategy. This paper outlines the protocol of the LetSync study, a pilot randomized-controlled trial of an mHealth app intervention developed using the Framework of Dyadic HIV Care Engagement to improve care-engagement outcomes among Black sexual-minority male couples living with HIV.

Methods and Anaysis: Eighty Black sexual-minority men in couples (n= 160) will be enrolled to pilot test the *LetSync* app. At least one member of each dyad must be both HIV-positive and self-identify as Black/African American. Couples will be randomized to either a waitlist-control arm or an intervention that uses relationship-based approach to improve HIV care engagement. We will assess feasibility and acceptability of trial procedures and intervention protocols based on pre-defined metrics of feasibility and acceptability. Execution of the study will yield the opportunity to conduct analyses to test the measurement and analysis protocol on antiretroviral therapy (ART) adherence by comparing the intervention and waitlist-control arms on self-reported and biological (hair sample) measures of adherence.

Ethics and Dissemination: Study staff will obtain electronic consent from all participants. This study has been approved by the University of California (UCSF) Institutional Review Board. Study staff will work with the Community Advisory Board at the UCSF Center for AIDS

Prevention Studies Board to disseminate results to participants and the community via open discussions, presentations, journal publications, and/or social media.

Trial Registration

The study was registered on ClinicalTrials.gov (NCT04951544) on July 7, 2021.

Strengths and Limitations of This Study

- mHealth interventions have traditionally focused on a single users' experience and outcomes, which LetSync will challenge by harnessing couples resilience and ability to problem-solve together, both of which impact dyadic coordination and, in return, can improve HIV care engagement.
- Involving participants in the app development process can allow for higher chance of acceptability of future iterations.
- The remote nature of our study breaks down barriers to participation such as travel, time, and expenses.
- This intervention does not allow users to directly engage with the healthcare system.
- Due to this being a couples' study, it is possible that couples can break up during study participation which can impact feasibility results of the app.

Introduction

Black sexual-minority men (i.e., gay, bisexual, and other men who have sex with men [MSM]) account for 26% of 37,968 new HIV diagnoses in the US in 2018 and 37% of new diagnoses among all MSM.[1,2] Black MSM also show the least favorable HIV care engagement outcomes (i.e., testing, linkage to and retention in HIV care, viral suppression) relative to other racial/ethnic groups of MSM [3,4] Suboptimal adherence to antiretroviral therapy (ART) can lead

to transmission and detrimental clinical outcomes.[5,6] Based on current data, it is estimated that one in two Black MSM will be diagnosed with HIV during their lifetime.[7,8]

National estimates show that a third to a half of Black MSM with HIV are in a primary relationship,[9–11] which is associated with favorable outcomes in healthcare engagement via social support pathways.[12–15] Dyadic approaches are part of a multilevel intervention approach; yet, they remain poorly understood among Black MSM.[16] Emergent evidence show that Black MSM in couples help each other engage in HIV care and treatment but that many do so inconsistently.[17,18] Additional characteristics of the dyad may moderate the effect of a primary relationship on HIV care engagement.[14,15,19–21] For example, Black couples with HIV may engage in joint problem-solving, a collaborative problem-focused approach to coping with stress, and dyadic coordination, or the synchronization of activities and behaviors necessary in HIV care and treatment.[18,22]

With more than 75% of the US adult population owning smartphones,[23] mobile health (mHealth) has emerged as a promising tool in healthcare including HIV prevention, care, and management efforts.[24–26] Although mHealth has been shown to be feasible, acceptable, and effective among Black MSM,[26–35] no *dyadic* mHealth interventions exist for this population even as Black MSM face many unique barriers to care and treatment.[36] Compared to White MSM, Black MSM are 20% less likely to be linked to, engaged and retained in HIV care due to social and structural inequities such as racial discrimination,[37] access to ART,[38,39] food and housing insecurity,[40,41] and over-criminalization and policing of Black communities.[39] Low retention rates can also be explained by inequities in the healthcare system, such as experiencing stigma and shame from healthcare providers.[42] Black sexual-minority couples show great interest in using a couples-based app to facilitate joint problem-solving to coordinate care and treatment activities, and

provided ideas for the app features they want.[22,36] In contexts where same-sex relationships are highly stigmatized, Black sexual-minority couples may appreciate an app that focuses on their primary romantic relationships.

Guided by the Framework of Dyadic HIV Care Engagement (Fig. 1),[18,22] initial designs were created for a dyadic mHealth application (app) intervention called *LetSync*, for "let's synchronize," to target dyadic coordination and joint problem-solving skills to improve retention in care and ART adherence. *LetSync* aims to facilitate among couples the dyadic coordination and joint problem-solving necessary for optimal engagement in HIV care among Black MSM.

This protocol paper describes the pilot randomized control trial to assess the feasibility and acceptability of the study protocols and procedures, assess the feasibility and acceptability of using *LetSync*, and test measurement and analysis protocols on preliminary data of app use on ART adherence. Fully developing a couples-based mHealth intervention will require that we translate findings to inform *LetSync* designs and iteratively develop, refine, and pilot-test prototypes for a large-scale, future efficacy trial.

Fig.1

Framework of Dyadic HIV Care Engagement.

Methods and Analysis

SETTING AND PARTICIPANTS

LetSync is a single-site, pilot randomized control study with the primary goal of assessing feasibility and acceptability of the mobile app, *LetSync,* among 80 Black sexual-minority couples (n= 160) living in the US. The sample size was chosen to be adequate to gauge feasibility and

acceptability while remaining feasible for a pilot. Participants will be randomized to immediately begin the intervention or wait six months. A waitlist-control design (Fig. 2) will allow us to evaluate two versions of *LetSync*, a later version iteratively refined based on feedback about the previous version.[43] *LetSync* will be developed by a third-party app developer to be compatible with both iOS and Android.

Fig. 2

Timeline of LetSync Intervention.

Participation in the study will last 14 months, with assessments conducted at baseline, 6, 8, and 14 months. We will collect feasibility and acceptability data, as well as preliminary data on ART adherence as measured by antiretroviral (ARV) concentrations in hair. Participants will consent to the study and complete an initial baseline survey online. Study staff will communicate with participants through text, email, phone, and Zoom. The University of California, San Francisco (UCSF) Institutional Review Board (IRB) has reviewed and approved this study.

ELIGIBILITY

Black MSM who are at least 18 years old, living with HIV in the US, and in a primary relationship with another man for at least 2 months will be eligible to participate. A primary relationship will be defined as a commitment to someone over and above anyone else that has lasted at least three months and includes a sexual relationship.[44]

At least one member of the couple must be both African American/Black and living with HIV (Index) who is either not on ART or is <100% ART adherent as assessed via a 3-item adherence measure.[45] Their partners can be of any race or ethnicity, and any HIV status. Among couples

where both partners may be an Index, one will be chosen at random to be the Index and the other as the partner. Both partners must own or have access to a smartphone.

We will exclude individuals who (1) report fear of intimate partner violence resulting from participation as assessed at screening,[46,47] (2) are unwilling or unable to disclose HIV status to primary partner, or (3) are presenting evidence of severe cognitive impairment that would prevent comprehension of study procedures assessed during informed consent.

PATIENT AND PUBLIC INVOLVEMENT

Prior to the design of LetSync, investigators conducted formative research with Black sexual-minority men in the San Francisco Bay Area. They found that Black sexual-minority couples have strong mHealth preferences, showing great interest in using a mobile app to facilitate joint problem-solving strategies to achieve optimal HIV care engagement.[36] We will also assemble a Community Advisory Board of Black sexual-minority couples to obtain feedback on *LetSync* prototypes and develop *LetSync* v1.0.

STUDY PROCEDURES

Recruitment

We will utilize a multi-pronged recruitment approach. Examples include attending virtual events hosted by community-based organizations serving Black/African American and/or sexual-minority communities impacted by HIV/AIDS, placing targeted online advertisements on social media (e.g., Facebook), and asking clinics that serve Black MSM with HIV to distribute flyers. We will also utilize UCSF Recruitment Letter Services and contact participants of other UCSF studies who gave consent to be contacted. Besides the San Francisco Bay Area, we will prioritize

recruiting from US cities with the highest prevalence of HIV among Black MSM (e.g., Atlanta, GA; Los Angeles, CA; Washington, D.C.; Houston, TX).

Screening

Study staff will provide a brief overview of the study to prospective participants, answer any questions, and complete an eligibility screening over the telephone. Targeted online advertisements will link to an online pre-screener that interested individuals can take to see if they qualify. Only those who are potentially eligible (based on screener responses) will be contacted by study staff. Ineligible responses will be recorded along with the reasons why (e.g., not living with HIV, not in relationship with a man).

Consent/Enrollment

If found to be eligible upon screening, individuals are sent an informed-consent form and baseline survey to complete electronically. Eligible individuals will be instructed to read the online consent form in full and ask any questions they may have.

INTERVENTION

Randomization

After obtaining informed consent from both members of the dyad, the Principal Investigator will randomize couples to the Intervention or Waitlist-Control groups using a randomization-plan generator. Study staff will then inform couples which group they have been randomly assigned to.

Intervention Content: *LetSync*

To enhance the couples' capacity for HIV care engagement, *LetSync* was designed with the core concepts of problem-solving therapy in mind. Problem-solving therapy consists of distinct steps to help identify problems one may have, possible solutions to follow, and the advantages and disadvantages to each.[48] Problem-solving therapy has shown to be effective in other mHealth interventions (e.g., iProblemSolve, a goal-setting app targeting individuals).[49]

The defining feature of *LetSync* is 'My Action Plan', which will guide the Index to arrive at a tailored action plan that addresses a component of HIV care engagement. The Index will identify current HIV care engagement and general health-related issues, choose strategies for addressing the issues (strategies already extant in the app plus new strategies the user can add), and evaluate those strategies in terms of likelihood of implementation. The Action Plan, which is composed of the strategies the user identified as most likely to be implemented, can then be shared with their partner through the app. The Action Plan will contain features to encourage the Index and their partner to engage in joint problem-solving and dyadic coordination. For example, partners will be prompted to make suggestions to Action Plans, download the Action Plans into their own mobile calendars, view goals and progress, coordinate activities around goals and appointments, and share encouragements.

Timeline

The study timeline will be split into four time points (T): T1 (baseline), T2 (6 months), T3 (8 months), and T4 (14 months) (Fig. 2).

At T1, participants in the intervention and waitlist-control arms will receive hair-sample collection kits in the mail with necessary supplies, an electronic link to an instructional video, and a pre-paid envelope for returning samples.[50,51] Participants in the intervention arm will

receive an electronic link to the baseline survey and will be scheduled their first study visit, which will occur via videoconference (e.g., Zoom). At the first study visit, study staff will give an overview of the study, answer any questions, and assist the participant in installing the app on their phone and provide necessary instructions for app use. The intervention group will use *LetSync* v1.0 for six months.

At all three subsequent time points (T2 – T4), participants in both arms will be sent a text or email informing them that the next study assessment is due, along with the link to complete the assessment. Simultaneously, we will mail all participants a hair-sample kit.

Between T1 and T2, we will collect data on acceptability and feasibility and use this to revise *LetSync* v1.0 and update it to *LetSync* v2.0.

At T3, participants in the waitlist-control arm will be scheduled a videoconference during which study staff will offer an overview of the study, answer any questions, and assist the participant in installing and using *LetSync* v2.0. Meanwhile, the participants in the intervention arm will continue to use *LetSync* v1.0.

At T4, we will conduct virtual exit interviews with participants from both arms over the phone or via videoconference. During exit interviews, we will ask for feedback about the randomization procedures to inform future RCT procedures. Interviews will be audio-recorded for transcription and data analyses.

Incentives

Participants will receive a $50 USD cash card, payment through a cash app, or reloadable debit card upon completing each survey, an additional $50 USD upon receipt of hair samples at T1,

T2, T3, and T4, and $30 USD for completing the exit interview at T4. Altogether, each member of the couple can receive up to $430.

OUTCOMES

Primary Outcome

The primary outcome is ART adherence. We will measure ART levels in hair samples across all four time points. Additionally, assessments at each timepoint will measure engagement in HIV care using a comprehensive behavioral composite of engagement in HIV care.[52]

Feasibility of App/Intervention

At T2 and T4, we will assess feasibility based on metrics in Table 1 and metadata (e.g., number of times the Action Plan was shared between partners, frequency of encouraging messages exchanged). We will code and tabulate these interactions to analyze dyadic HIV care engagement by, for example, the volume and sequence of activities planned. Participants can report glitches and other issues at any time through a reporting feature in the app or study website, or by contacting the study staff. All reports of issues will be tabulated.

Table 1. Metrics and thresholds to assess feasibility of the *LetSync* app

We will monitor rates of recruitment and effort (e.g., number of staff hours), number of screenings, proportion eligible and agreed to enroll, number of participants who withdraw after being randomized to condition and reason(s) for withdrawal, and the number of participants who complete each time point. We will record the number of rescheduled, cancelled and missed visits to inform estimation of future staffing needs. Using call/time logs, we will record the frequency and mode of contact with participants, when, and for how long. During remote visits, staff will

complete a checklist and take notes on study proceedings such as the procedures implemented, amount of time spent, and participants' reactions. These data will inform modifications to the intervention and protocols of a subsequent, full-scale efficacy trial.

We will compare HIV clinical outcomes and dyadic capacity measures between the two arms in exploratory analyses. We will evaluate feasibility and acceptability of *LetSync* v2.0 in the waitlist-control arm and evaluate persistent use of *LetSync* v1.0 over 14 months in the intervention arm.

Feasibility of Hair Sample Collection

Feasibility of hair collection will be evaluated by: 1) the number of samples per participant received by the study, 2) the time difference between when remote hair samples were due versus when samples were received by the study, and 3) rates of verifiable ARV results. Staff will monitor when hair collection kits were sent and received.

Acceptability

Acceptability-related outcomes that we will measure include app usability,[53] security and privacy of app use, study procedures and design, and remote hair collection. During the exit interview, we will ask participants about what was convenient/easy vs. inconvenient/difficult regarding remote study participation. The threshold for acceptability will be 80% of participants reporting being satisfied with the app content and delivery format. Table 2 contains examples of items used to capture each measure.

Throughout the intervention, we will contact participants in both arms monthly via text, call, and/or email. We will check in about their experiences of using the app, along with troubleshooting app-related issues and sending in hair samples.

Table 2. Items and measures to assess acceptability of the *LetSync* app

DATA COLLECTION AND ANALYSIS

Quantitative Data Collection and Analysis

Assessments at baseline, 6 months, 8 months, and 14 months will be administered online and will measure HIV care engagement using a comprehensive behavioral composite of engagement in HIV care;[52] engagement and retention in care using the Index of Engagement in HIV Care (e.g., "How well do you follow through on your HIV care when things in your life get tough?");[54] and self-reported ART adherence (e.g., "In the last 30 days, on how many days did you miss at least one dose of any of your medication? ")[55] and viral suppression (e.g., "Was your last viral load detectable or undetectable?"). Guided by our conceptual framework (Fig. 1),[22] we will measure dyadic capacity using the Dyadic Coping Inventory,[56] Couple Health Support, Partner Support for HIV Treatment;[57] and relationship factors using the Power Imbalance in Couples Scale (PICS),[58] and the Couple Sexual Satisfaction Scale (CSSS) (Conroy AA, Development and Validation of the Couple Sexual Satisfaction Scale for HIV and Sexual Health Research, Under Review). We will also assess individual-level factors as indicated by our conceptual framework, including the HIV Stigma Scale.[59]

Frequency tables will be generated for all clinical outcomes. One-way frequency tables will be generated for the number of rescheduled, cancelled, and missed visits. Relative frequencies will be calculated for the number of participants enrolled in the study, those who were eligible in general, and lost to follow-up. We will also tabulate and summarize acceptability outcomes in one-way frequency tables.

We will fit linear mixed models (LMM) to continuous outcomes (e.g., ARV levels in hair) and fit generalized linear mixed models (GLMM) to discrete (e.g., viral suppression) and non-normally distributed continuous outcomes (e.g., self-reported ART adherence) to model outcome data. These analyses will include couple sero-status (sero-concordant HIV-positive vs. sero-discordant) as a covariate as required by the stratified randomized design.[60,61] Following guidelines in the literature[62,63] and from NIH,[64] hypothesis testing will de-emphasized. Instead, we will perform these analyses to ensure that all measures and procedures are well established to perform a subsequent efficacy trial.

Qualitative Data Collection and Analysis

At T4, staff will conduct remote exit interviews with all participants. Exit interviews will explore participants' experiences with the study protocol and procedures. Interviews will be audio-recorded and professionally transcribed.

We will read all individual transcripts and develop a codebook based on the interview guides, our theoretical framework, and emergent themes. To establish intercoder agreement, a primary coder will apply codes based to a subset of transcripts to test and revise the codebook. A secondary analyst will apply the revised set of codes on a random subset of transcripts. Discrepancies in coding will be discussed by the team until an agreement is reached.

Power Analyses

We estimated minimum detectable effect sizes (MDEs) for the assessments of feasibility and acceptability proposed to address the pilot RCT. We anticipate 80 couples (40 seroconcordant-positive and 40 serodiscordant per condition) at the beginning of the study and 64 couples at T4 following 20% estimated attrition. The effective sample size (ESS) will depend on the unit of

analysis (couple vs. individual), which participants are included in the analysis, and when the outcome is measured. For instance, the enrollment proportion to assess feasibility is a couple-level variable measured at the outset of the study. Assuming α=.05, power=.80, and 70% enrollment for 114 couples contacted to yield 80 couples (70% of 114), the width of the confidence interval for single enrollment proportions is 19% (standardized distance to the limit: .20). In contrast, acceptability scores will be measured at the individual level at the study endpoint among participants in each condition.

We also performed power analyses for proposed outcome analyses in order to supply additional information. For individual-level outcomes, the ESS will depend on the degree of within couple correlation of responses, ρ, within couples. We set ρ based on prior dyadic research in which the average within-couple correlation of virologic control measurements was ρ=.23. Accordingly, we lowered the ESS inputted for the power analyses to be ESS=N/DEFF, where N is the endpoint sample size and DEFF is the design effect or variance inflation attributable to using correlated data. DEFF is computed as 1+(M-1)*ρ, where M is the number of participants per dyad (i.e., 2). Therefore, DEFF=1+(2-1)*.23=1.23, so ESS=80x.80=64/1.23=52. Under these assumptions, distance from the observed mean to the confidence limit is estimated to be .28. For longitudinal analyses to evaluate ART adherence, outcomes will be measured at the individual level at every time point among HIV+ participants in both arms. An 80% retention rate means 20x.80=16 seroconcordant-positive couples yielding 32 HIV+ participants where ESS=32/1.23=26 plus 20x.80=16 serodiscordant couples yielding 16 HIV+ participants for a total endpoint study sample of 42 per arm. Assuming α=.05, power=.80, and 4 time points with *r*=.30 correlation between repeated measures (in Dr. Johnson's study, the average within-subject *r*'s for ART adherence and viral suppression were .24 and .28, respectively), the minimum

detectable standardized mean differences for continuous outcomes is .421. For binary outcomes, using the same inputs as above plus small, medium, and large base rates of 10%, 30%, and 50%, respectively, raw proportion differences range from 16.1% to 20.5% (standardized difference=.422-.429). H1-H3 will be directly tested by contrasts derived from the longitudinal analytic models. For H1 and H3, we estimated the MDEs of those contrasts by reassessing the power of the longitudinal analyses with only 2 time points. The resulting effect sizes ranged from .493 to .503, which are medium standardized effects. For H2, MDEs for a non-zero longitudinal change in a group mean or proportion range from .407 to .470, which are small to medium standardized effects. As noted previously, hypothesis testing will be de-emphasized in this pilot feasibility and acceptability study.

DISCUSSION

This paper describes the protocol for a randomized waitlist-controlled pilot of a dyadic app intervention, *LetSync,* focused on Black sexual-minority couples living with HIV. Barriers to HIV care for Black MSM are multilevel, often at the social (e.g., HIV stigma) and structural (e.g., transportation) levels, while extant interventions target barriers at the individual level. *LetSync* addresses this gap by targeting, at the dyadic level, Black MSM couple dynamics, emphasizing the roles of dyadic coordination and joint problem-solving in improving HIV care engagement.

Although Black MSM-centered mHealth interventions exist in general,[32,65] there is a paucity of couples-based mHealth studies for this population despite the demonstrated power of dyadic coordination in care, and couples facing many unique barriers to care and treatment.

A search in the literature yielded only one couples-based mHealth study for Black MSM. In 2010, an existing evidence-based intervention originally developed for heterosexual couples was adapted for Black MSM to reduce sexually transmitted infections (STIs; including HIV and other STIs) and drug use outcomes. This adaptation was recently piloted with 34 MSM dyads with promising results.[66,67] Of the seven couple-based HIV studies that have been conducted since the start of the HIV epidemic, only three have included MSM in general, and none included Black MSM .[66]

Our study addresses the lack of couples-based interventions for Black MSM in several innovative ways. It seeks to harness couples' resilience and ability to synchronize problem-solving approaches, both of which are likely to impact dyadic coordination and joint problem-solving - thus improving HIV care engagement.[14] It is also informed by our theoretical framework, the Framework of Dyadic HIV Care Engagement, which is formulated by preliminary and existing research. Rather than focus on single users' experiences and outcomes, as is the case for most traditional mHealth designs (including HIV prevention),[34,68] the design of *LetSync* targets the dyad where each user's outcomes are dependent on the joint, collaborative, synchronized behaviors of both users. The dyadic level is often missing in multilevel HIV prevention efforts, but retention in care and ART adherence often occur in the dyadic context for Black sexual-minority couples.[14] Lastly, our study is the first of its kind to include the use of remote hair collection to measure ART adherence among Black sexual-minority couples. Hair concentrations of ARVs are stronger predictors of virologic suppression than self-reported adherence or plasma ARV levels in large cohort studies of patients with HIV.[69] Self-collection of hair samples at home reduces travel time and expenses, and assessing our primary outcome via remote collection of hair is congruent with the mobile nature of the intervention.

There are several challenges to this study. Suboptimal app engagement poses a challenge in mHealth data collection. To optimize app engagement, we will program pop-up reminders to appear on a weekly basis if the app has not been opened. We will assess the feasibility and acceptability of this feature during exit interviews. To minimize participant attrition, which is intrinsic to longitudinal designs, we will collect at least three methods of personal contact such as social media handles and additional phone numbers. We will also maintain regular contact with participants by sending reminders about virtual check-ins and sending in hair samples, and asking about any app-related issues. Lastly, addressing break-ups is necessary as our study involves couples. If break-up occurs between screening and randomization, the couple will become ineligible and referrals for support will be offered to both participants. If break-up occurs after randomization, participants may still take part in the remaining data collection time points as scheduled, and the breakup will be noted in the retention and tracking study databases.

This paper documents the protocol for the LetSync study, which was designed to help couples work together to improve HIV-related outcomes. While the number of HIV-centered mHealth interventions have proliferated in recent years, very few exist that focus on Black MSM in couples. mHealth for dyadic HIV care engagement holds promise in being cost-efficient and transcending common barriers to intervention and care, which our study aims to demonstrate. Findings from the proposed research are needed for a subsequent large-scale, randomized, controlled trial to test the efficacy of *LetSync* in improving HIV care and treatment outcomes among Black MSM. These findings may inform future studies and protocols for other chronic conditions where the dyad is an important unit of intervention.

Abbreviations

ART: antiretroviral therapy

ARV: antiretroviral

HIV: human immunodeficiency virus

IPV: intimate partner violence

Declarations

Ethics approval and consent to participate

Ethics approval was granted by the University of California, San Francisco Institutional Review Board (IRB # 15-18042).

Consent for publication

Not applicable.

Availability of Data and Materials

Not applicable as this manuscript does not contain data.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

JYT designed the study, obtained funding, provided leadership in the execution of the study, and contributed to revising the manuscript. TBN, LMP, PS, EA, and SMK contributed to study

conception; TBN and LMP also contributed to trial design. The paper was drafted by HCK, and all authors, including DJB and RWW, read and approved the final manuscript.

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Table 1. Metrics and thresholds to assess feasibility of the *LetSync* app.

Main Feasibility Outcomes	Metrics Threshold
Enrollment in both arms	≥ 70% of eligible individuals enrolled
Retention in both arms at T2	≥ 75% retained
Retention in both arms at T4	≥ 80% retained
Number of app launches, log-ins	Mean of once/week
Number of minutes of app use	Mean of 10 minutes/week
Use of the *Our Action Plan* feature	≥ 1 Action Plan generated/month
Number of Action Plans created	Mean of 1/month
Communication between partners	Mean of 1 message/month

Use of joint task feature	Mean of 1 joint task completed/month
Access of other *LetSync* features	Mean of twice/month
App opens following pop-up reminders	Mean of 50% of all pop-ups
Number of app glitches	Mean of ≤ 1 user-reported glitch/week
Amount of time for RA to field app questions	Mean of ≤ 1 hour/week/participant

Table 2. Items and measures to assess acceptability of the *LetSync* app

Measure	Item
App Usability	"I am satisfied with the app." "I would want to use the app even if I was not receiving study incentives."
Security and Privacy	"How secure did you feel about your data when using the app?"
Study Procedures and Design	"How helpful was the User's Guide video you watched?" "How satisfied were you with your communication with the staff?"
Remote Hair Collection	"How easy or difficult was it to use the hair kits?" "How easy or difficult was it to mail your hair in?" "How helpful was the demonstration video?"
Remote Study Participation	"How satisfied were you with participating in a remote research project?"

Fig. 1

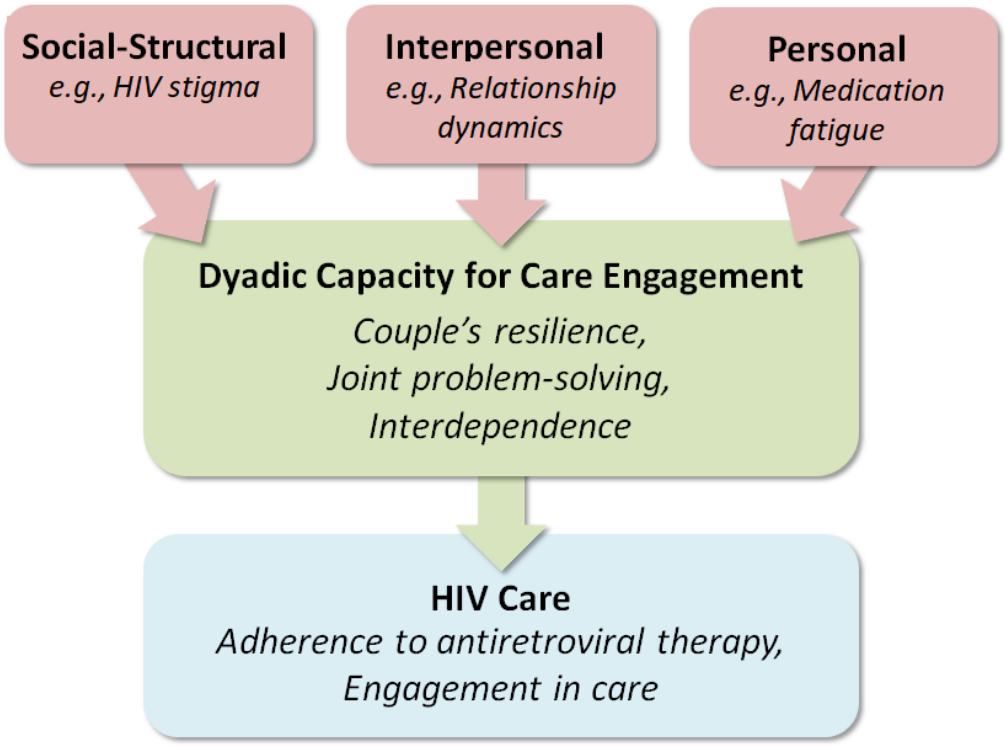
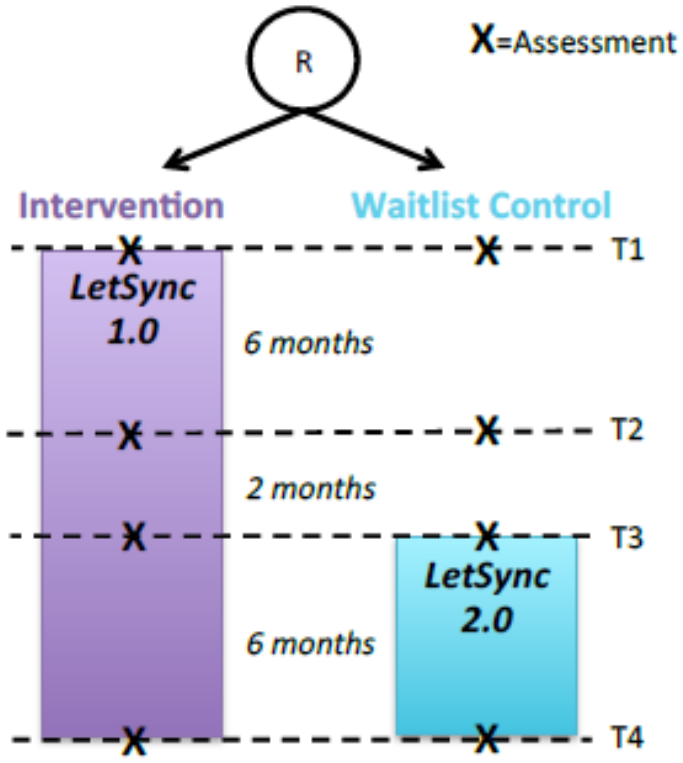


Fig. 2



Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n/a
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a

Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a

Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Study protocol: a pilot randomized waitlist-controlled trial of a dyadic mobile health intervention for Black sexual-minority male couples with HIV in the U.S.

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Public health
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, PUBLIC HEALTH, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

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Study protocol: a pilot randomized waitlist-controlled trial of a dyadic mobile health intervention for Black sexual-minority male couples with HIV in the U.S.

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Abstract

Introduction: HIV care engagement is lower among Black sexual-minority men relative to other racial/ethnic groups of sexual minority men. Being in a primary relationship is generally associated with more successful HIV care engagement across various populations. However, among Black sexual-minority men, the association between primary-relationship status and HIV-related outcomes is inconsistent across the HIV care continuum. Given the ubiquity of mobile technology access and use among racial/ethnic minority communities, leveraging mobile technology for HIV care engagement appears a promising intervention strategy. This paper outlines the protocol of the LetSync study, a pilot randomized-controlled trial of an mHealth app intervention developed using the Framework of Dyadic HIV Care Engagement to improve care-engagement outcomes among Black sexual-minority male couples living with HIV.

Methods and Anaysis: Eighty Black sexual-minority men in couples (n= 160) will be enrolled to pilot test the *LetSync* app. At least one member of each dyad must be both HIV-positive and self-identify as Black/African American. Couples will be randomized to either a waitlist-control arm or an intervention that uses relationship-based approach to improve HIV care engagement. We will assess feasibility and acceptability of trial procedures and intervention protocols based on pre-defined metrics of feasibility and acceptability. Execution of the study will yield the opportunity to conduct analyses to test the measurement and analysis protocol on antiretroviral therapy (ART) adherence by comparing the intervention and waitlist-control arms on self-reported and biological (hair sample) measures of adherence.

Ethics and Dissemination: Study staff will obtain electronic consent from all participants. This study has been approved by the University of California (UCSF) Institutional Review Board. Study staff will work with the Community Advisory Board at the UCSF Center for AIDS

Prevention Studies Board to disseminate results to participants and the community via open discussions, presentations, journal publications, and/or social media.

Trial Registration

The study was registered on ClinicalTrials.gov (NCT04951544) on July 7, 2021.

Strengths and Limitations of This Study

- mHealth interventions have traditionally focused on a single users' experience and outcomes, which LetSync will challenge by harnessing couple's resilience and ability to problem-solve together, both of which impact dyadic coordination and, in return, can improve HIV care engagement.
- Involving participants in the app development process can allow for higher chance of acceptability of future iterations.
- The remote nature of our study breaks down barriers to participation such as travel, time, and expenses.
- This intervention does not allow users to directly engage with the healthcare system.
- Due to this being a couples' study, it is possible that couples can break up during study participation which can impact feasibility results of the app.

Introduction

Black sexual-minority men (i.e., gay, bisexual, and other men who have sex with men [MSM]) account for 26% of 37,968 new HIV diagnoses in the US in 2018 and 37% of new diagnoses among all MSM.[1,2] Black MSM also show the least favorable HIV care engagement outcomes (i.e., testing, linkage to and retention in HIV care, viral suppression) relative to other racial/ethnic groups of MSM [3,4] Suboptimal adherence to antiretroviral therapy (ART) can lead

to transmission and detrimental clinical outcomes.[5,6] Based on current data, it is estimated that one in two Black MSM will be diagnosed with HIV during their lifetime.[7,8]

National estimates show that a third to a half of Black MSM with HIV are in a primary relationship,[9–11] which is associated with favorable outcomes in healthcare engagement via social support pathways.[12–15] Dyadic approaches are part of a multilevel intervention approach; yet, they remain poorly understood among Black MSM.[16] Emergent evidence show that Black MSM in couples help each other engage in HIV care and treatment but that many do so inconsistently.[17,18] Additional characteristics of the dyad may moderate the effect of a primary relationship on HIV care engagement.[14,15,19–21] For example, Black couples with HIV may engage in joint problem-solving, a collaborative problem-focused approach to coping with stress, and dyadic coordination, or the synchronization of activities and behaviors necessary in HIV care and treatment.[18,22]

With more than 75% of the US adult population owning smartphones,[23] mobile health (mHealth) has emerged as a promising tool in healthcare including HIV prevention, care, and management efforts.[24–26] Although mHealth has been shown to be feasible, acceptable, and effective among Black MSM,[26–35] no *dyadic* mHealth interventions exist for this population even as Black MSM face many unique barriers to care and treatment.[36] Compared to White MSM, Black MSM are 20% less likely to be linked to, engaged and retained in HIV care due to social and structural inequities such as racial discrimination,[37] access to ART,[38,39] food and housing insecurity,[40,41] and over-criminalization and policing of Black communities.[39] Low retention rates can also be explained by inequities in the healthcare system, such as experiencing stigma and shame from healthcare providers.[42] Black sexual-minority couples show great interest in using a couples-based app to facilitate joint problem-solving to coordinate care and treatment activities, and

provided ideas for the app features they want.[22,36] In contexts where same-sex relationships are highly stigmatized, Black sexual-minority couples may appreciate an app that focuses on their primary romantic relationships.

Guided by the Framework of Dyadic HIV Care Engagement (Fig. 1),[18,22] initial designs were created for a dyadic mHealth application (app) intervention called *LetSync*, for "let's synchronize," to target dyadic coordination and joint problem-solving skills to improve retention in care and ART adherence. *LetSync* aims to facilitate among couples the dyadic coordination and joint problem-solving necessary for optimal engagement in HIV care among Black MSM.

This protocol paper describes the pilot randomized waitlist-controlled trial to assess the feasibility and acceptability of the study protocols and procedures, assess the feasibility and acceptability of using *LetSync*, and test measurement and analysis protocols on preliminary data of app use on ART adherence. Fully developing a couples-based mHealth intervention will require that we translate findings to inform *LetSync* designs and iteratively develop, refine, and pilot-test prototypes for a large-scale, future efficacy trial.

Fig.1

Framework of Dyadic HIV Care Engagement.

Methods and Analysis

SETTING AND PARTICIPANTS

LetSync is a single-site, pilot randomized waitlist-controlled trial with the primary goal of assessing feasibility and acceptability of the mobile app, *LetSync,* among 80 Black sexual-minority couples (n= 160) living in the US. The sample size was chosen to be adequate to gauge

feasibility and acceptability while remaining feasible for a pilot. Participants will be randomized to immediately begin the intervention or wait six months. A waitlist-control design (Fig. 2) will allow us to evaluate two versions of *LetSync*, a later version iteratively refined based on feedback about the previous version.[43] *LetSync* will be developed by a third-party app developer to be compatible with both iOS and Android.

Fig. 2

Timeline of LetSync Intervention.

Participation in the study will last 14 months, with assessments conducted at baseline, 6, 8, and 14 months. We will collect feasibility and acceptability data, as well as preliminary data on ART adherence as measured by antiretroviral (ARV) concentrations in hair. Participants will consent to the study and complete an initial baseline survey online. Study staff will communicate with participants through text, email, phone, and Zoom. The University of California, San Francisco (UCSF) Institutional Review Board (IRB) has reviewed and approved this study.

ELIGIBILITY

Black MSM who are at least 18 years old, living with HIV in the US, and in a primary relationship with another man for at least 2 months will be eligible to participate. A primary relationship will be defined as a commitment to someone over and above anyone else that has lasted at least three months and includes a sexual relationship.[44]

At least one member of the couple must be African American/Black and living with HIV (Index) who is either not on ART or is <100% ART adherent as assessed via a 3-item adherence measure.[45] Their primary partner can be of any race or ethnicity, and any HIV status. Among

couples where both partners meet eligibility as an Index, one will be chosen at random to be the Index. Both members of the couple must own or have access to a smartphone.

We will exclude individuals who (1) report fear of intimate partner violence resulting from participation as assessed at screening,[46,47] (2) are unwilling or unable to disclose HIV status to primary partner, or (3) are presenting evidence of severe cognitive impairment that would prevent comprehension of study procedures assessed during informed consent.

PATIENT AND PUBLIC INVOLVEMENT

Prior to the design of *LetSync*, investigators conducted formative research with Black sexual-minority men in the San Francisco Bay Area. Black sexual-minority couples showed strong mHealth preferences and interest in using a mobile app to facilitate joint problem-solving to achieve optimal HIV care engagement.[36] We will also assemble a Community Advisory Board of Black sexual-minority couples to obtain feedback on *LetSync* prototypes and develop *LetSync* v1.0.

STUDY PROCEDURES

Recruitment

We will use a multi-pronged recruitment approach that includes in-person and virtual engagement. In addition to the San Francisco Bay Area, we will prioritize recruiting from US cities with the highest prevalence of HIV among Black MSM (e.g., Atlanta, GA; Los Angeles, CA; Washington, D.C.; Houston, TX). We will attend virtual events hosted by community-based organizations serving Black/African American and/or sexual-minority communities impacted by HIV/AIDS, placing targeted online advertisements on social media (e.g., Facebook), and asking clinics that serve Black MSM with HIV to distribute flyers. We will also recruit from within

UCSF clinics via the UCSF Recruitment Letter Services. We will also contact participants of other UCSF studies who gave consent to be contacted.

Screening

Study staff will provide a brief overview of the study to prospective participants, answer any questions, and complete an eligibility screening over the telephone. Targeted online advertisements will link to an online pre-screener that interested individuals can take to see if they qualify. Only those who are potentially eligible (based on screener responses) will be contacted by study staff. Ineligible responses will be recorded along with the reasons why (e.g., not living with HIV, not in relationship with a man).

Consent/Enrollment

If found to be eligible upon screening, individuals will be sent an informed-consent form online. Eligible individuals will be instructed to read the consent form in full and ask any questions they may have prior to giving consent. Study staff will be available to respond to any questions or concerns and to ensure comprehension.

INTERVENTION

Randomization

After obtaining informed consent from both members of the dyad, we will randomize couples to the Intervention or Waitlist-Control groups using a randomization-plan generator.

Intervention Content: *LetSync*

To enhance the couples' capacity for HIV care engagement, *LetSync* was designed based on problem-solving therapy. Problem-solving therapy consists of distinct steps to help identify

problems one may have, possible solutions to follow, and the advantages and disadvantages to each.[48] Problem-solving therapy has shown to be effective in other mHealth interventions (e.g., iProblemSolve, a goal-setting app targeting individuals).[49]

The defining feature of *LetSync* is 'My Action Plan', which will guide the Index to arrive at a tailored action plan that addresses a component of HIV care engagement. The Index will identify current HIV care engagement and general health-related issues, choose strategies for addressing the issues (strategies already extant in the app plus new strategies the user can add), and evaluate those strategies in terms of likelihood of implementation. The Action Plan, which is composed of the strategies the user identified as most likely to be implemented, can then be shared with their partner through the app. The Action Plan will contain features to encourage the Index and their partner to engage in joint problem-solving and dyadic coordination. For example, partners will be prompted to make suggestions to Action Plans, download the Action Plans into their own mobile calendars, view goals and progress, coordinate activities around goals and appointments, and share encouragements.

Timeline

The study timeline will be split into four time points (T): T1 (baseline), T2 (6 months), T3 (8 months), and T4 (14 months) (Fig. 2).

At T1, participants in the intervention and waitlist-control arms will receive hair-sample collection kits in the mail with necessary supplies, an electronic link to an instructional video, and a pre-paid envelope for returning samples.[50,51] Participants in the intervention arm will receive an electronic link to the baseline survey and will be scheduled their first study visit, which will occur via videoconference (e.g., Zoom). At the first study visit, study staff will give

an overview of the study, answer any questions, and assist the participant in installing the app on their phone and provide necessary instructions for app use. The intervention group will use *LetSync* v1.0 for six months.

At all three subsequent time points (T2 – T4), participants in both arms will receive a text or email informing them that the next study assessment is due, along with the link to complete the assessment. Simultaneously, we will mail all participants a hair-sample kit.

Between T1 and T2, we will collect data on acceptability and feasibility and use this to revise *LetSync* v1.0 and update it to *LetSync* v2.0.

At T3, participants in the waitlist-control arm will attend a videoconference during which study staff will offer an overview of the study, answer any questions, and assist the participant in installing and using *LetSync* v2.0. Meanwhile, the participants in the intervention arm will continue to use *LetSync* v1.0.

At T4, we will conduct virtual exit interviews with participants from both arms over the phone or via videoconference. During exit interviews, we will ask for feedback about the randomization procedures to inform future RCT procedures. Interviews will be audio-recorded for transcription and data analyses.

Incentives

Participants will receive a $50 USD cash card, payment through a cash app, or reloadable debit card upon completing each survey, an additional $50 USD upon receipt of hair samples at T1, T2, T3, and T4, and $30 USD for completing the exit interview at T4. Altogether, each member of the couple can receive up to $430.

OUTCOMES

Primary Outcome

The primary outcome is ART adherence. We will measure ART levels in hair samples across all four time points. Additionally, assessments at each timepoint will measure engagement in HIV care using a comprehensive behavioral composite of engagement in HIV care.[52]

Feasibility of App/Intervention

At T2 and T4, we will assess feasibility based on metrics in Table 1 and metadata (e.g., number of times the Action Plan was shared between partners, frequency of encouraging messages exchanged). We will code and tabulate these interactions to analyze dyadic HIV care engagement by, for example, the volume and sequence of activities planned. Participants can report glitches and other issues at any time through a reporting feature in the app or study website, or by contacting the study staff. All reports of issues will be tabulated.

Table 1. Metrics and thresholds to assess feasibility of the *LetSync* app

We will monitor rates of recruitment and effort (e.g., number of staff hours), number of screenings, proportion eligible and agreed to enroll, number of participants who withdraw after being randomized to condition and reason(s) for withdrawal, and the number of participants who complete each time point. We will record the number of rescheduled, cancelled and missed visits to inform estimation of future staffing needs. Using call/time logs, we will record the frequency and mode of contact with participants, when, and for how long. During remote visits, staff will complete a checklist and take notes on study proceedings such as the procedures implemented, amount of time spent, and participants' reactions. These data will inform modifications to the intervention and protocols of a subsequent, full-scale efficacy trial.

We will compare HIV clinical outcomes and dyadic capacity measures between the two arms in exploratory analyses. We will evaluate feasibility and acceptability of *LetSync* v2.0 in the waitlist-control arm and evaluate persistent use of *LetSync* v1.0 over 14 months in the intervention arm.

Feasibility of Hair Sample Collection

Feasibility of hair collection will be evaluated by: 1) the number of samples per participant received by the study, 2) the time difference between when remote hair samples were due versus when samples were received by the study, and 3) rates of verifiable ARV results. Staff will document when hair collection kits were sent and received.

Acceptability

Acceptability will be evaluated via a measure of app usability,[53] and self-reported satisfaction with security and privacy of app use, study procedures and design, and remote hair collection. During the exit interview, we will ask participants about what was convenient/easy vs. inconvenient/difficult regarding remote study participation. The threshold for acceptability will be 80% of participants reporting being satisfied with the app content and delivery format. Table 2 contains examples of items used to capture each measure.

Throughout the intervention, we will contact participants in both arms monthly via text, call, and/or email. We will check in about their experiences of using the app, along with troubleshooting app-related issues and sending in hair samples.

Table 2. Items and measures to assess acceptability of the *LetSync* app

DATA COLLECTION AND ANALYSIS

Quantitative Data Collection and Analysis

Assessments at baseline, 6 months, 8 months, and 14 months will be administered online and will measure HIV care engagement using a comprehensive behavioral composite of engagement in HIV care;[52] engagement and retention in care using the Index of Engagement in HIV Care (e.g., "How well do you follow through on your HIV care when things in your life get tough?");[54] and self-reported ART adherence (e.g., "In the last 30 days, on how many days did you miss at least one dose of any of your medication? ")[55] and viral suppression (e.g., "Was your last viral load detectable or undetectable?"). Guided by our conceptual framework (Fig. 1),[22] we will measure dyadic capacity using the Dyadic Coping Inventory,[56] Couple Health Support, Partner Support for HIV Treatment;[57] and relationship factors using the Power Imbalance in Couples Scale (PICS),[58] and the Couple Sexual Satisfaction Scale (CSSS) (Conroy AA, Development and Validation of the Couple Sexual Satisfaction Scale for HIV and Sexual Health Research, Under Review). We will also assess individual-level factors as indicated by our conceptual framework, including the HIV Stigma Scale.[59]

Frequency tables will be generated for all clinical outcomes. One-way frequency tables will be generated for the number of rescheduled, cancelled, and missed visits. Relative frequencies will be calculated for the number of participants enrolled in the study, those who were eligible in general, and lost to follow-up. We will also tabulate and summarize acceptability outcomes in one-way frequency tables.

We will fit linear mixed models (LMM) to continuous outcomes (e.g., ARV levels in hair) and fit generalized linear mixed models (GLMM) to discrete (e.g., viral suppression) and non-normally distributed continuous outcomes (e.g., self-reported ART adherence) to model outcome data. These analyses will include couple sero-status (sero-concordant HIV-positive vs. sero-

discordant) as a covariate as required by the stratified randomized design.[60,61] Following guidelines in the literature[62,63] and from NIH,[64] hypothesis testing will de-emphasized. Instead, we will perform these analyses to ensure that all measures and procedures are well established to perform a subsequent efficacy trial.

Qualitative Data Collection and Analysis

At T4, staff will conduct remote exit interviews with all participants. Exit interviews will explore participants' experiences with the study protocol and procedures. Interviews will be audio-recorded and professionally transcribed.

We will read all individual transcripts and develop a codebook based on the interview guides, our theoretical framework, and emergent themes. To establish intercoder agreement, a primary coder will apply codes based to a subset of transcripts to test and revise the codebook. A secondary analyst will apply the revised set of codes on a random subset of transcripts. Discrepancies in coding will be discussed by the team until an agreement is reached.

Power Analyses

We estimated minimum detectable effect sizes (MDEs) for the assessments of feasibility and acceptability proposed to address the pilot RCT. We anticipate 80 couples (40 seroconcordant-positive and 40 serodiscordant per condition) at the beginning of the study and 64 couples at T4 following 20% estimated attrition. The effective sample size (ESS) will depend on the unit of analysis (couple vs. individual), which participants are included in the analysis, and when the outcome is measured. For instance, the enrollment proportion to assess feasibility is a couple-level variable measured at the outset of the study. Assuming α=.05, power=.80, and 70% enrollment for 114 couples contacted to yield 80 couples (70% of 114), the width of the

confidence interval for single enrollment proportions is 19% (standardized distance to the limit: .20). In contrast, acceptability scores will be measured at the individual level at the study endpoint among participants in each condition.

We also performed power analyses for proposed outcome analyses in order to supply additional information. For individual-level outcomes, the ESS will depend on the degree of within couple correlation of responses, ρ, within couples. We set ρ based on prior dyadic research in which the average within-couple correlation of virologic control measurements was ρ=.23. Accordingly, we lowered the ESS inputted for the power analyses to be ESS=N/DEFF, where N is the endpoint sample size and DEFF is the design effect or variance inflation attributable to using correlated data. DEFF is computed as 1+(M-1)*ρ, where M is the number of participants per dyad (i.e., 2). Therefore, DEFF=1+(2-1)*.23=1.23, so ESS=80x.80=64/1.23=52. Under these assumptions, distance from the observed mean to the confidence limit is estimated to be .28. For longitudinal analyses to evaluate ART adherence, outcomes will be measured at the individual level at every time point among HIV+ participants in both arms. An 80% retention rate means 20x.80=16 seroconcordant-positive couples yielding 32 HIV+ participants where ESS=32/1.23=26 plus 20x.80=16 serodiscordant couples yielding 16 HIV+ participants for a total endpoint study sample of 42 per arm. Assuming α=.05, power=.80, and 4 time points with *r*=.30 correlation between repeated measures (in Dr. Johnson's study, the average within-subject *r*'s for ART adherence and viral suppression were .24 and .28, respectively), the minimum detectable standardized mean differences for continuous outcomes is .421. For binary outcomes, using the same inputs as above plus small, medium, and large base rates of 10%, 30%, and 50%, respectively, raw proportion differences range from 16.1% to 20.5% (standardized difference=.422-.429). H1-H3 will be directly tested by contrasts derived from the longitudinal

analytic models. For H1 and H3, we estimated the MDEs of those contrasts by reassessing the power of the longitudinal analyses with only 2 time points. The resulting effect sizes ranged from .493 to .503, which are medium standardized effects. For H2, MDEs for a non-zero longitudinal change in a group mean or proportion range from .407 to .470, which are small to medium standardized effects. As noted previously, hypothesis testing will be de-emphasized in this pilot feasibility and acceptability study.

DISCUSSION

This paper describes the protocol for a randomized waitlist-controlled pilot of a dyadic app intervention, *LetSync,* focused on Black sexual-minority couples living with HIV. Barriers to HIV care for Black MSM are multilevel, often at the social (e.g., HIV stigma) and structural (e.g., transportation) levels, while extant interventions target barriers at the individual level. *LetSync* addresses this gap by targeting, at the dyadic level, Black MSM couple dynamics, emphasizing the roles of dyadic coordination and joint problem-solving in improving HIV care engagement.

Although Black MSM-centered mHealth interventions exist in general,[32,65] there is a paucity of couples-based mHealth studies for this population despite the demonstrated power of dyadic coordination in care, and couples facing many unique barriers to care and treatment.

A search in the literature yielded only one couples-based mHealth study for Black MSM. In 2010, an existing evidence-based intervention originally developed for heterosexual couples was adapted for Black MSM to reduce sexually transmitted infections (STIs; including HIV and other STIs) and drug use outcomes. This adaptation was recently piloted with 34 MSM dyads with promising results.[66,67] Of the seven couple-based HIV studies that have been conducted since the

start of the HIV epidemic, only three have included MSM in general, and none included Black MSM .[66]

Our study addresses the lack of couples-based interventions for Black MSM in several innovative ways. It seeks to harness couples' resilience and ability to synchronize problem-solving approaches, both of which are likely to impact dyadic coordination and joint problem-solving - thus improving HIV care engagement.[14] It is also informed by our theoretical framework, the Framework of Dyadic HIV Care Engagement, which is formulated by preliminary and existing research. Rather than focus on single users' experiences and outcomes, as is the case for most traditional mHealth designs (including HIV prevention),[34,68] the design of *LetSync* targets the dyad where each user's outcomes are dependent on the joint, collaborative, synchronized behaviors of both users. The dyadic level is often missing in multilevel HIV prevention efforts, but retention in care and ART adherence often occur in the dyadic context for Black sexual-minority couples.[14] Lastly, our study is the first of its kind to include the use of remote hair collection to measure ART adherence. Hair concentrations of ARVs are stronger predictors of virologic suppression than self-reported adherence or plasma ARV levels in large cohort studies of patients with HIV.[69] Self-collection of hair samples at home reduces travel time and expenses, and assessing our primary outcome via remote collection of hair is congruent with the mobile nature of the intervention.

There are several challenges to this study. Suboptimal app engagement poses a challenge in mHealth data collection. To optimize app engagement, we will program pop-up reminders to appear on a weekly basis if the app has not been opened. We will assess the feasibility and acceptability of this feature during exit interviews. To minimize participant attrition, which is intrinsic to longitudinal designs, we will collect at least three methods of personal contact such as

social media handles and additional phone numbers. We will also maintain regular contact with participants by sending reminders about virtual check-ins and sending in hair samples and asking about any app-related issues. Lastly, addressing break-ups is necessary as our study involves couples. If break-up occurs between screening and randomization, the couple will become ineligible and referrals for support will be offered to both participants. If break-up occurs after randomization, participants may still take part in the remaining data collection time points as scheduled, and the breakup will be noted in the retention and tracking study databases.

This paper documents the protocol for the LetSync study, which was designed to help couples work together to improve HIV-related outcomes. While the number of HIV-centered mHealth interventions have proliferated in recent years, very few exist that focus on Black MSM in couples. mHealth for dyadic HIV care engagement holds promise in being cost-efficient and transcending common barriers to intervention and care, which our study aims to demonstrate. Findings from the proposed research are needed for a subsequent large-scale, randomized, controlled trial to test the efficacy of *LetSync* in improving HIV care and treatment outcomes among Black MSM. These findings may inform future studies and protocols for other chronic conditions where the dyad is an important unit of intervention.

Ethics and Dissemination

Informed consent will be obtained electronically (e.g., via Qualtrics). Participants will be informed that their participation in the study is voluntary and that they may decline to participate for any reason without any negative consequences. Referrals for emotional support and mental health will be available.

Results of the pilot randomized-controlled trial will be disseminated through peer-reviewed publications, conferences, and presentations and reports to participants and stakeholders. We will also hold Town Halls with the UCSF Center for AIDS Prevention Studies (CAPS) and symposia with community-based organizations that serve people living with HIV.

Abbreviations

ART: antiretroviral therapy

ARV: antiretroviral

HIV: human immunodeficiency virus

IPV: intimate partner violence

Declarations

Ethics approval and consent to participate

Ethics approval was granted by the University of California, San Francisco Institutional Review Board (IRB # 15-18042).

Consent for publication

Not applicable.

Availability of Data and Materials

Not applicable as this manuscript does not contain data.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

JYT designed the study, obtained funding, provided leadership in the execution of the study, and contributed to revising the manuscript. TBN, LMP, PS, EA, and SMK contributed to study conception; TBN and LMP also contributed to trial design. The paper was drafted by HCK, and all authors, including DJB and RWW, read and approved the final manuscript.

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Table 1. Metrics and thresholds to assess feasibility of the *LetSync* app.

Main Feasibility Outcomes	Metrics Threshold
Enrollment in both arms	≥ 70% of eligible individuals enrolled
Retention in both arms at T2	≥ 75% retained
Retention in both arms at T4	≥ 80% retained
Number of app launches, log-ins	Mean of once/week
Number of minutes of app use	Mean of 10 minutes/week
Use of the *Our Action Plan* feature	≥ 1 Action Plan generated/month
Number of Action Plans created	Mean of 1/month
Communication between partners	Mean of 1 message/month
Use of joint task feature	Mean of 1 joint task completed/month
Access of other *LetSync* features	Mean of twice/month
App opens following pop-up reminders	Mean of 50% of all pop-ups
Number of app glitches	Mean of ≤ 1 user-reported glitch/week
Amount of time for RA to field app questions	Mean of ≤ 1 hour/week/participant

Table 2. Items and measures to assess acceptability of the *LetSync* app

Measure	Item
App Usability	"I am satisfied with the app." "I would want to use the app even if I was not receiving study incentives."
Security and Privacy	"How secure did you feel about your data when using the app?"
Study Procedures and Design	"How helpful was the User's Guide video you watched?" "How satisfied were you with your communication with the staff?"
Remote Hair Collection	"How easy or difficult was it to use the hair kits?" "How easy or difficult was it to mail your hair in?" "How helpful was the demonstration video?"
Remote Study Participation	"How satisfied were you with participating in a remote research project?"

Fig. 1

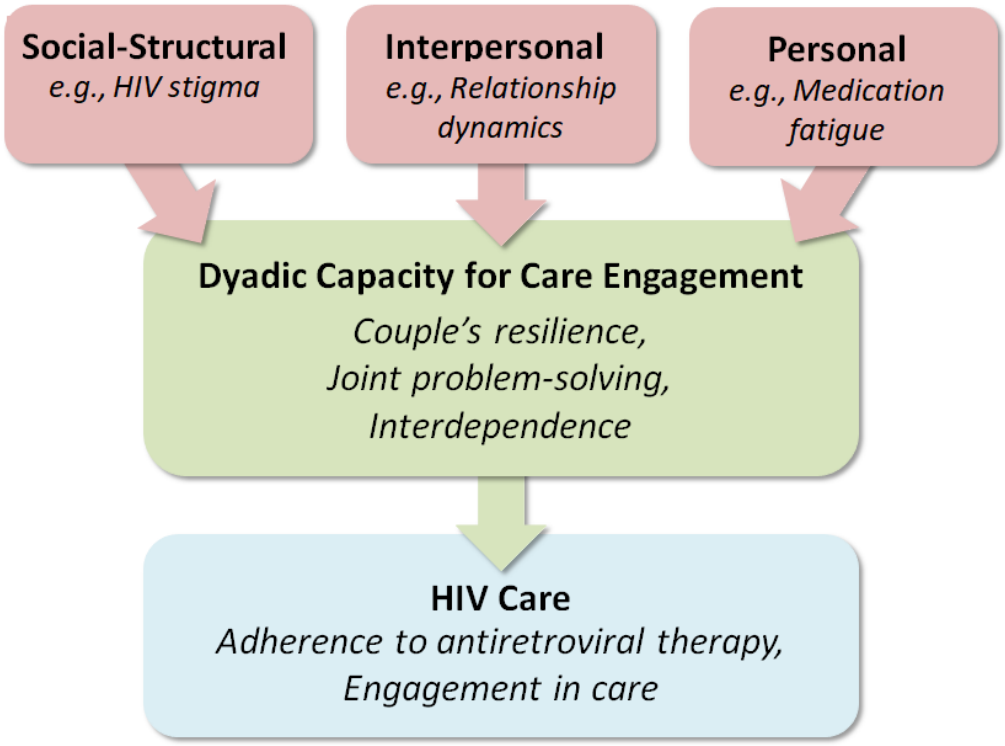
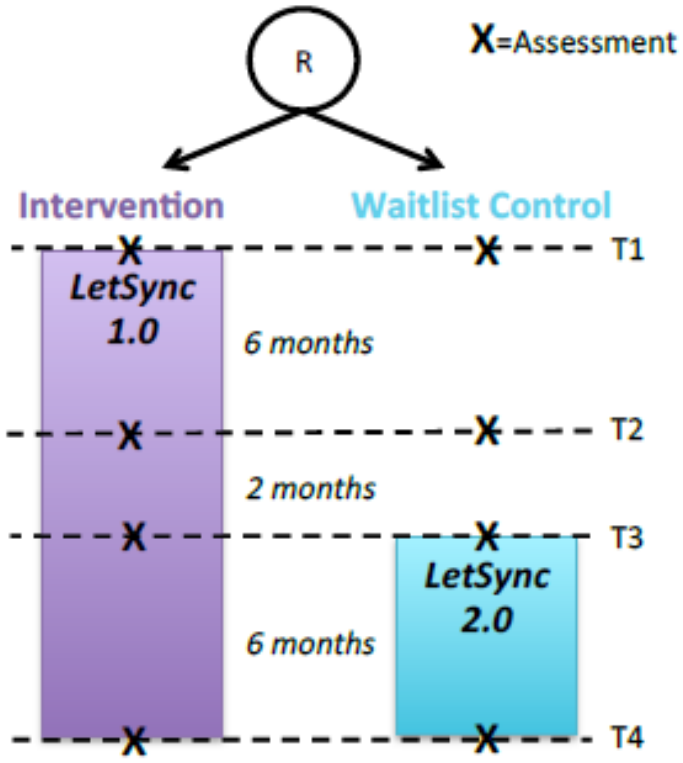


Fig. 2



Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n/a
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a

Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a

Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a