Statistical Analysis Plan (SAP)

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Title	Using Social Media to Deliver HIV Self-Testing Kits and Link to Online PrEP Services (Social Media PrEP)
CRU/Department/Division/Center	University of California, Los Angeles National Institutes of Health Geisel School of Medicine at Dartmouth
Protocol Number	NIDA CTN Protocol 0083
Investigators:	
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Analysis Biostatistician(s)	
Biostatistics Supervisor	
Lead Biostatistician	
Subject Matter Expert	
Original Creation Date	
Version Date	05/26/2020 (Version 5.0)
Project Folder Location	
Project Goal(s)	Compare the relative effectiveness of social media sites, dating apps, and information search sites in promoting HIV self-testing among minority men who have sex with men (MSM) at an increased risk of HIV infection.
Submission Deadline(s)	
Effort Estimate (optional)	

Investigator Agreement	☐ All statistical analyses included in an abstract or manuscript should reflect the work of the biostatistician(s) listed on this SAP. No changes or additional analyses should be made to the results or findings without discussing with the project biostatistician(s). ☐ All biostatisticians on this SAP should be given sufficient time to review the full presentation, abstract, manuscript, or grant and be included as co-authors on any abstract or manuscript resulting from the analyses. ☐ If substantial additional analysis is necessary or the aims of the project change, a new SAP will need to be developed. ☐ Publications resulting from this SAP are supported in part by the Duke CTSA and must cite grant number UL1TR002553 and be submitted to PubMed Central. ☐I have reviewed the SAP and understand that any changes must be documented. *Acknowledged by:* Click or tap here to enter text. *Date:* Click or tap to enter a date.
Activity Log	We conducted a third wave of promotion and enrollment on Twitter, Yahoo, and Hornet. This wave was conducted between April 6, 2020, and May 6, 2020, during the first days of the public health emergency proclamation. Despite the promotional waves being active, no participants were enrolled, and no test kits were ordered during Wave 3, which made our statistical model inestimable. As enrollment during this period does not reflect "expected conditions" and scientific comparisons would not be accurate, we decided to exclude Wave 3 from all the analyses.
Acronyms	MSM Men who have sex with men PrEP Pre-Exposure Prophylaxis HIV Human Immunodeficiency Virus

1 Study Overview

Background/Introduction: The incidence of HIV infection remains high among minority men who have sex with men (MSM). Frequent testing for HIV infection can identify new infections early, and it is essential in ending the HIV epidemic.

Prevention studies and public health programs have been adopting HIV self-tests and combining them with new technologies, such as smartphone apps or smart devices, to reach populations with high incidence of HIV infection, such as Black and Latinx MSM. Despite multiple efforts, the uptake of HIV testing remains inadequate, especially among individuals at high risk for HIV infection. Thus, optimizing the promotion of HIV testing is important. Social media sites, dating apps, and information search sites have been used to reach individuals at high risk for HIV infection. However, it is not clear which platform is the most efficient in promoting home HIV self-testing, given that the users of various platforms may have different characteristics that impact their readiness for HIV testing. (From Study Manuscript)

1.1 Study Aims

This longitudinal observational cohort study aims to compare the relative effectiveness of social media sites, dating apps, and information search sites in promoting HIV self-testing among minority men who have sex with men (MSM) at an increased risk of HIV infection. Test kit order rates are used as a proxy to evaluate promotion effectiveness. In addition, we assess differences in characteristics between participants who ordered and did not order an HIV test kit. The primary outcome is the number of HIV self-test kits ordered per day through each type of internet-based platform (social media, dating, information site) during the period in which each wave was operational. As a secondary outcome, we explore the association of reported substance use, stage of change for HIV testing based on the transtheoretical model, attitudes toward HIV testing and treatment, HIV-related stigma, medical mistrust, and opinions about PrEP measures and self-test kit ordering. As an exploratory outcome, we record the advertisement metrics of each campaign to measure differences in the reach and cost.

1.2 Study Hypotheses

The study evaluates the relative effectiveness of using social media sites (i.e., Facebook, Instagram, Twitter), informational sites (i.e., Google, Bing, Yahoo), and dating apps (i.e., Grindr/alternative, Hornet, Jack'd) to promote self-testing of HIV infection among MSM who are at increased risk of HIV exposure and/or infection.

The null hypothesis for the primary outcome is that all platforms in the same wave have the same rate of kits ordered, while the alternative hypothesis is that there is a difference between at least one pairwise contrast between platforms.

The null hypothesis for the secondary analysis is that there is no difference between the answer to various questions for those who ordered a HIV self-test kit and those who didn't, while the alternative hypothesis is that there is a difference between these groups.

2 Study Population

Advertisements targeted young (18-30 years old) and minority (Black or Latinx) MSM at risk of HIV exposure.

2.1 Inclusion Criteria

- MSM aged 18-30 years who identified as Latinx or Black/African American people (including multiracial and multiethnic individuals of these groups)
- Reported having condomless anal sex in the past 90 days or having more than 1 male sex partner in the past 90 days
- Have a Facebook account (for identity validation to reduce duplicate attempts at enrollment)
- Be willing to provide contact information (phone number, email) to the study team

2.2 Exclusion Criteria

- HIV-positive
- Tested for HIV infection in the past 90 days
- Taking PrEP currently or at any time during the past 6 months before enrollment

2.3 Data Acquisition

Fill in all relevant information:

Study design	Longitudinal observational cohort study
Data source/how the data were collected	Participants from social media sites, dating applications and informational sites who order

	HIV home self-test kits through advertisements developed by the study team
Contact information for team member responsible for data collection/acquisition	
Date or version (if downloaded, provide date)	
Data transfer method and date	
Where dataset is stored	

Notes:

Description:

Culturally appropriate advertisements were placed on popular sites of three different platforms: social media sites (Facebook, Instagram), dating apps (Grindr, Jack'D), and information search sites (Google, Bing). Advertisements targeted young (18-30 years old) and minority (Black or Latinx) MSM at risk of HIV exposure. Recruitment occurred in 2 waves, with each wave running advertisements on 1 platform of each type over the same period. Participants completed a baseline survey assessing sexual or injection use behavior, substance use including alcohol, psychological readiness to test, attitudes toward HIV testing and treatment, and HIV-related stigma. Participants received an electronic code to order a free home-based HIV self-test kit. Follow-up assessments were conducted to assess HIV self-test kit use and uptake of pre-exposure prophylaxis (PrEP) at 14 and 60 days post enrollment.

3 Outcomes, Exposures, and Additional Variables of Interest

3.1 Primary Outcome(s)

Outcome	Description	Variables and Source	Specifications
The number of HIV home self-test kits ordered per day	This can be calculated by dividing the sum of ora_redeemed for each platform by the length of the recruitment wave	ora_redeemed	Char, Yes; No; Over 60 days

3.2 Secondary Outcome(s)

Outcome	Description	Variables and Source	Specifications
The number of participants who used the study-provided HIV home self-test kit by 60- day follow-up.		Q2_1_fu1	Num, 1=Yes;2=No

The number of participants who tested positive for HIV using the study-provided home test kit by 60-day follow-up.		Q3_2_fu1	1=Positive for HIV; 2=Negative for HIV; 3=still waiting for results
The number of participants who reported a high-risk substance abuse profile at baseline who ordered an HIV home self-test kit			
Relation between "People in my life would leave if I had HIV" and ordering a HIV self-test kit at baseline		Q15_5	Num, 1=Agree; 2=Disagree
Relation between "I think that new HIV/AIDS treatments can eradicate the virus from your body" and ordering a HIV self-test kit at baseline		Q94_13	Num
Relation between "I could not be friends with someone who has HIV/AIDS." and ordering a HIV self-test kit at baseline		Q14_3	Num 1=Strongly agree; 2=Agree; 3=Somewhat agree; 4=Neither agree nor disagree; 5=Somewhat disagree; 6=Disagree; 7=Strongly disagree

3.3 Additional Variables of Interest

Variable	**Description**	**Variables and Source**	**Specifications**
Age in years			Continuous
Ethnicity			Categorical
Race			Categorical

History of PrEP uptake			Categorical
Condom use			Categorical
If tested for HIV			Binary Yes/No
Main reasons cited by the participants for not getting tested			Categorical
Advertisement metrics of each campaign	An exploratory outcome to measure differences in the reach and cost		

4 Statistical Analysis Plan

4.1 Demographic and Clinical Characteristics ("Table 1")

Participant's baseline demographics and characteristics will be presented using summary statistics. Descriptive summaries of the distribution of continuous variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies/counts and percentages.

Variables will include age in years, ethnicity, race, history of PrEP uptake, condom use, condomless receptive anal sex in the past 90 days, ever tested for HIV during lifetime, months since last HIV test and main reasons cited by the 63 participants for not getting tested.

4.2 Analyses Plan

In this longitudinal observational cohort study, advertisements promoting free HIV self-testing were placed on three platform types: social media (Facebook, Instagram), dating apps (Grindr, Hornet), and information search sites (Google, Bing)
The advertisements were organized in 2 "waves," with each wave consisting of 1 social media website, 1 dating app, and 1 information search site. The Wave 1 (Facebook, Grindr, Google) recruitment stopped early, as Grindr unexpectedly stopped running all self-service platform advertisements (including the study advertisement) due to a change in corporate ownership. We continued with Wave 2 (Instagram, Jack'D, Bing) as planned and a relaunched Wave 1 (Facebook, Grindr, Google) once Grindr access was restored. Before launching each wave, we allocated the same amount of funds for each of the 3 sites and optimized them to run for at least 30 calendar days by dividing the available funds in the prespecified promotional period. However, due to slow enrollment during the COVID-19 pandemic, we extended thesecond phase of Wave 1 up to 63 days. The advertisement usedon social media and dating apps was an image that included a person and text ("Get a FREE HIV test"), whereas promotional keywords related to HIV testing and PrEP were selected forinformation search sites (as images are not allowed). The same image and keywords were used in all waves. The advertisements were launched in the District of Columbia (DC) and 8 states (Florida, Georgia, Louisiana, Maryland, Mississippi, Nevada, South Carolina, and Texas), which were selected based on theirhigh incidence of HIV infection. Upon clicking on the study advertisement, website users landed on the study information page,

where they received general information about the study, underwent eligibility screening, and reviewed study procedures.

The primary outcome is the number of HIV home self-test kits ordered per day (i.e., number of study participants ordering an HIV home self-test kit per day) by promotional platform (social media, informational, dating sites). Without loss of generalizability, the primary outcome can also be defined as the number of HIV home self-test kits ordered per a given period since this is simply a transformation. For example, one could calculate the number of kits ordered per 30 days, per 100 days, etc. The number and timing of HIV self-testing kit orders will be recorded and analyzed to evaluate the effectiveness of the sites in promoting HIV self-testing. We assume that it will be rare for participants to order multiple copies of kits. If this occurs, we will analyze only the first occurrence. The analysis model will be a Poisson regression model that will use time as an offset. Secondary and exploratory analyses will be conducted using univariate tests and descriptive statistics such as counts, percentages, and 95% confidence intervals.

The primary analysis model will be a Poisson regression model using time as an offset (Hardin & Hilbe, 2018), in which:

$$log(o_{ij}) = log\,(t_i)\ + \alpha + \beta_i + \gamma_j + \beta\gamma_{ij}$$

where

o_{ij} is the number of kits ordered by the site in Wave i (i.e. time period i), platform type j.
t_i is the time that the Wave platforms were recruiting.
β_i is the main effect of wave.
γ_j is the main effect of platform type.
$\beta\gamma_{ij}$ is the interaction term.

Under this model, the rate for any site ij is given by:

$$rate_{ij} = exp(\alpha + \beta_i + \gamma_j + \beta\gamma_{ij})$$

Culturally appropriate advertisements (designed specifically for the study population and advertisement method) for promoting HIV testing and PrEP uptake will be created by the study team. These advertisements will be placed on social media sites (Facebook, Instagram, Twitter), informational sites (Google, Bing, Yahoo) and dating apps (Grindr/alternative, Hornet, Jack'd) in the form of blast advertisements ("ads"). The advertisements will display on specific days and times (e.g., high traffic utilization) in the geographical locations selected for participation in the study.

Participants will be followed up at two intervals after the baseline assessment. The first will occur 14 days post-baseline, where participants will be asked about their test use and may be asked if they visited a PrEP provider and/or if they started PrEP and about PrEP opinions and facilitators and barriers. If they tested positive for HIV on the home self-test kit, they will be asked whether they have visited an HIV treatment provider. Participants will be asked to upload a picture of their test result for validation on the secure Qualtrics server during the 14-day follow-up assessment. Photographs will be interpreted by the study team and the result will be entered into the study database; photographs will then be deleted.

At the 60-day follow-up, all participants will be asked to respond to study evaluation questions. Additionally, participants may respond to a subset of the questions that is the same as the 14-day follow-up, based on their responses on the first follow-up survey. Those who reported that they received a negative HIV self-test result and started PrEP at the 14-day follow-up will not be asked to answer these questions at the 60-day follow-up. Participants who either did not take the HIV test or did not start PrEP by the 14-day follow-up may be asked about PrEP facilitators and barriers, their

self-test use, if they visited a PrEP provider, whether they started PrEP, and if applicable, whether they have visited an HIV treatment provider, depending on their responses during the 14-day follow-up. Participants will be asked to upload a picture of their test result (unless provided at the 14-day follow-up) for validation on the secure Qualtrics server during the 60-day follow-up assessment. Photographs will be interpreted by the study team and the result will be entered into the study database; photographs will then be deleted.

Participants who report a preliminary positive, invalid, or indeterminate result on the HIV home self-test kit will be referred to local brick-and-mortar clinics for additional services and asked to continue participating in follow-up assessments. Regardless of their result, all participants will be offered information on HIV and STD prevention, and locations of clinics and PrEP providers near them. Data will be collected both indirectly from each website's metrics and directly from the online questionnaires that the participants will complete.

Each participant will be part of the study for approximately two months. Participation in the study will begin with study enrollment (including eligibility screening, review of the study information sheet) and the completion of the baseline assessment (which in rare instances may occur over a period of days; if so, the date of completion shall be considered the baseline date). Follow-up assessments will be scheduled via email for 14- and 60-days post-baseline.

Overall, enrollment for participants is anticipated to take approximately 9 months, with final data collection spanning up to two additional months; data lock is anticipated for approximately 12 months post-baseline. This is not an intervention study, participants will not be randomized.

The only study activity associated with risk is the participant learning he is HIV positive. Only adverse events directly related to learning of HIV status will be captured and reported to the UCLA IRB. This is a minimal risk study and we do not anticipate any serious adverse events that could lead to the pause or early termination of the study. No interim looks at primary or secondary outcomes are planned for this study.

During the first phase of the project, the study team will develop culturally appropriate advertisement materials promoting HIV testing. The study aims to recruit participants from three distinct web-based platforms: social media sites (Facebook, Instagram, Twitter), dating apps (Grindr/alternative, Hornet, Jack'd) and informational sites (Google, Bing, Yahoo). These platforms will allow us to purchase advertisements and target the message to specific groups with particular characteristics (e.g., age, gender, location, etc.). Recruitment will occur in 3 waves: (1). Google, Facebook and Grindr/alternative, (2). Bing, Instagram and Jack'd, (3). Yahoo, Twitter and Hornet. Each wave will be open for 1 month to enroll at least 133 participants. The enrollment will stop if the wave hits the target sample size (N=133 kits ordered), otherwise might be extended beyond 1 month to achieve the target sample size.

5 Limitations

The study is conducted in 9 areas with high HIV incidence; thus, the conclusions may not be generalizable to the whole country. Low enrollment and participation in waves affect our capacity to make broader comparisons between platforms and potentially between sites. In addition, we select the most popular apps and sites as enrollment sites, grouping them into "platforms" with similar characteristics. Our goal is to investigate differences between the platforms. Thus, our findings are specific to the sites included in the campaigns.

6 Addendum for Additional Analyses

Follow-up assessments will occur 14 days after completion of the baseline assessment, and again at 60 days post-baseline. Participants will be reminded via email or text message to participate in the follow-up assessment. Participants will have to participate within 7 days after the receipt of their first reminder. During those days, participants will receive daily automated emails or texts to participate in the follow-up assessments. Both the 14-day and 60-day assessments will be performed online. During the first follow-up time point (14 days after the baseline assessment), participants will be asked to fill out an online questionnaire that will request information on HIV home self-test kit use, their test kit result and PrEP uptake. The assessments required at the 14-day follow-up are detailed in the Table of Assessments (Section 11.1). Participants will be requested to submit a photograph of their test kit result, which will be sent to a secure server. If this is not feasible or if they do not wish to share a picture, they will be allowed to simply report their result. Participants who report a preliminary positive HIV result will receive information via email on local testing clinics and they will be encouraged to visit the clinics for confirmatory testing. A study team member will follow-up with them within 72 hours to discuss confirmatory testing. Participants with a negative result who report that they did not start PrEP will be asked the reasons for not starting PrEP (considering they reviewed the initial packet of PrEP information), their opinions on PrEP as a preventive measure, and their willingness to start PrEP. Finally, participants will be offered different options to acquire PrEP via email: a list of local brick-and-mortar clinics that provide PrEP or a voucher for PlushCare.com that can be redeemed for the initial PrEP appointment and laboratory testing. Participants who report an invalid or indeterminate HIV result will receive information via email on local testing clinics and they will be encouraged to visit the clinics for confirmatory testing. A study team member will follow-up with them within 72 hours to discuss confirmatory testing.

For the second follow-up time point (60-days post-baseline), participants will be asked to fill out a questionnaire that will vary depending on their responses to the 14-day follow-up. This questionnaire may include questions that request information on HIV self-test kit use, their test kit result, and PrEP uptake, if this information was not previously reported. The assessments at the 60-day follow-up are detailed in the Table of Assessments (Section 11.1). Participants who previously reported that they had not used the test kit will be inquired about using the kit, their result, and asked to submit a picture. As with the first follow-up visit, participants with a preliminary positive or invalid/indeterminate result will be encouraged to visit local clinics for testing. A study team member will follow-up with them within 72 hours to discuss confirmatory testing. Participants with a negative result who report that they didn't start PrEP will be asked the reasons for not starting PrEP (considering they reviewed the initial packet of PrEP information), their opinions on PrEP as a preventive measure, and their willingness to start PrEP. Finally, participants will be offered different options to acquire PrEP: a list of local brick-and-mortar clinics that provide PrEP or a voucher for PlushCare.com.

Within 72 hours from their participation after each follow-up assessment, a research assistant will email a $25 electronic gift card to the participant, using the contact information that was provided at Baseline.

Data will be managed by the site staff at UCLA. A web-based distributed data entry model will be implemented. This electronic data capture system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld. We will use UCLA Health Qualtrics Survey Software to collect participant data. This is a HIPAA and FERPA- compliant secure online survey platform. The study team will enter reportable AEs and SAEs into a database (e.g., an online database and/ or a protected spreadsheet) at UCLA. Additional information may need to be gathered to evaluate SAEs, and this information will also be captured in the database. Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

There will be no missing data or dropouts for the primary outcome since only participants who meet eligibility criteria and order HIV home self-testing kits will be included in the analysis. The primary

outcome is the number of participants ordering an HIV self-test kit through the three promotional platforms. This information is automatically tracked in the system and should not be any missing data. For secondary outcomes, missing data can arise if a participant orders the HIV self-testing kit at baseline but misses the 14-day or 60-day follow-up visit. Every effort will be done to minimize missing data and dropouts. At baseline, participants who haven't completed all the questions of the questionnaires and did not provide their information to order a test kit will receive up to three automated reminder emails. During the follow-up visits, each participant will receive up to five automated reminder emails that will encourage to provide their test result and complete the follow-up assessment.

7 Appendix

Study manuscript: https://pmc.ncbi.nlm.nih.gov/articles/PMC9591705/pdf/formative_v6i9e35648.pdf
NIDA page: https://datashare.nida.nih.gov/data/nida-ctn-0083

A full data dictionary can be found in CTN0083-Data-Dictionary.xlsx in the NIDA page.
An original study protocol can be found in CTN0083-Protocol-Social-Media-PrEP.pdf in the NIDA page.

8 References

Statistical Analysis Plan Checklist

Below you will find a checklist of recommended items to include in a statistical analysis plan. Some of these are specific to clinical trials (based on this JAMA paper) and some are other are specific to observational studies (based on STROBE/RECORD guidelines), so every item will not be necessary for every project. The biostatistician should start with the SAP template above and add in necessary information from the checklist. Item numbers that are starred (*) are not explicitly included in the SAP template and should be added by the author if relevant to the project. This checklist was developed using the CONSORT 2010 Checklist.

Section/Topic	Item #	Description	Included (Yes/No/NA)
Administrative Information			
Study Information	1a	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle	Yes
	1b	Trial registration number, protocol version number, and/or IRB number.	Yes
	1c	CRU/Department/Division/Center/other collaborative unit that the study falls under	Yes
Roles and responsibility	2a	Listing of principal investigators, clinical leads, and co-authors (if known)	Yes
	2b	Name and affiliation of SAP author(s)	Yes
	2c	Names, affiliations, and roles of other SAP contributors (e.g. senior statistician)	Yes
SAP Information	3	SAP version number, with date of current version and original creation date	Yes
Project Information	4a	Project folder location	No
	4b	Project goals (e.g. manuscript, abstract, presentation, etc.)	Yes
	4c	Project deadlines (of listed goals)	No
	4d	Effort estimate	No
Investigator Agreement			
Investigator Agreement	5	Confirmation that BERD Method Core's collaborative process has been reviewed, that all statistical analyses included in an abstract or manuscript should reflect the SAP, no changes should be made to the SAP without discussing with the SAP author, all biostatisticians on the SAP are co-authors on the manuscript, and that publications resulting from the SAP must cite grant number UL1TR002553 and be submitted to PubMed Central	NA
Signatures	6	Signatures of SAP author, senior statistician, and principal investigator(s)	NA
Activity Log			
SAP revisions	7a	SAP revision history with dates	NA
	7b	Justification for each SAP revision	NA
	7c*	Timing of SAP revision in relation to any interim analyses or submissions	NA

Study Overview

[1]Turner L, Shamseer L, Altman DG, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev*. 2012;11:MR000030. Published 2012 Nov 14. doi:10.1002/14651858.MR000030.pub2

Background and introduction	8	Synopsis of scientific background and rationale for the study	Yes
Aims and Hypotheses	9a	List of all scientific aims/objectives of the study, with specifications of primary, secondary, etc.	Yes
	9b	List of all statistical hypotheses (corresponding to the scientific aims), with specifications of primary, secondary, etc.	Yes
Variables of Interest	10a	List of all outcome/endpoint variables, with a description of their coding/units, timing, and source, corresponding to the statistical hypotheses. If any variables are defined using ICD or CPT codes, list them out.	Yes
	10b	List of all exposure variables, with a description of their coding/units, timing, and source, corresponding to the statistical hypotheses. If any variables are defined using ICD or CPT codes, list them out.	Yes
	10c	List of any additional variables of interest (e.g. covariates, potential confounders, effect modifiers, etc.) in the analysis	Yes
	10d*	Location of data dictionary (or provided as an appendix)	Yes
	10e*	Report category boundaries if continuous variables are collapsed into categories, and describe any other relevant data transformations	Yes
Causal Graph	11*	May be helpful to include a DAG or other graph/diagram that describes the way the variables of interest are presumed to relate to each other	No
Study Methods			
Study Plan and Design	12a	Description of the study design (e.g. parallel group randomized trial, case-control study, cohort study, etc.)	Yes
	12b*	Study setting, location, and relevant dates (e.g. periods of enrolment, exposure, follow-up, and collection)	Yes
	12c*	Description of intervention or exposure groups, with allocation ratios, and details of any matching criteria	Yes
	12d*	Details on randomization (e.g. stratification factors) and blinding procedures	Yes
	12e	List of eligibility and/or inclusion/exclusion criteria	Yes
	12f*	Description of screening/enrolment/recruitment processes	Yes
	12g*	Description of patient flow (e.g. CONSORT diagram)	No
	12h*	Description of analysis population (e.g. intention to treat, per protocol, etc.)	Yes
	12i*	Definitions of adherence/compliance, protocol deviations, loss-to-follow-up, adverse events, etc.	Yes
	12j*	Time points at which outcomes are measured	Yes
	12k*	Timing of final analyses (are all outcomes analysed collectively, or will short-term outcomes be analysed separately from long-term outcomes, etc.)	Yes
Sample Size	13a*	Sample size calculation or justification (either provided in full or summarized, with link to original source)	Yes

	13b*	Description of pre-planned subgroup analyses, power for these analyses, and planned multiple comparison adjustment procedures	No
Interim Analyses	14a*	Description of what interim analyses will be conducted at which time points, and what methods used to adjust significance levels due to the interim analysis	No
	14b*	Details of any guidelines (e.g. safety, futility) for stopping the study early	Yes
	14c*	Details of any changes to trial design due to interim analyses (e.g. enrolling more patients)	NA
Data	15a	Description of data collection/acquisition process, with contact information for team member responsible	No
	15b	Description of data flow/transfer from primary data collection through to creation of final analysis dataset	No
	15c	Data transfer method and date	Yes
	15d	Folder location where datasets are stored	No
	15e*	Description of any additional data management, quality control, or processing undertaken	Yes
	15f*	If any data are extracted from a database, a description of the database and the query used for the extraction, and whether/how it was merged with any data from outside that database. If the study involved linkage of databases, consider use of a flow diagram to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Yes
	15f*	Description of any other data sources incorporated in the analysis	NA
Missing Data	16a*	Description of sources and magnitudes of missing data	Yes
	16b*	Description of how missing data patterns will be presented/summarized (may be helpful to have a table shell or draft CONSORT-style diagram)	Yes
	16c*	Description of contingency plans for handling missing data in analysis	Yes
Simulations	17a*	If conducting a simulation, a description of the purpose of the simulation and its design (e.g. fully factorial, partially factorial, grid search, etc.)	NA
	17b*	Define the fixed and variable factors or parameters in the simulation, the estimands/targets of the simulation, and the performance measures to be estimated (with justifications of their relevance to the estimands/targets)	NA
	17c*	Description of the tabular and graphical presentations of simulation results and their interpretation	NA
Statistical Analysis Plan			
Statistical Significance	18a*	Hypothesis testing framework (e.g. superiority, equivalence, non-inferiority), or description of alternative analytic framework (e.g. evaluation of a posterior in a Bayesian analysis, etc.)	No
	18b*	Level of significance for primary hypotheses, including a description and rationale for any multiple comparisons adjustment or Type I error control procedures	No

	18c*	Description of any decision-making rules based on confidence intervals, credible intervals, prediction intervals, Bayes' factors, or other alternative inferential methods	Yes
	18d*	Description of how the results of any hypothesis tests (or alternative inferential methods) will be interpreted with respect to both the statistical hypotheses and scientific aims/objectives of the study	No
Descriptive Statistics	19a*	List of characteristics (e.g. demographic, clinical) to be summarized descriptively (e.g. "Table 1")	Yes
	19b*	Description of how these characteristics will be summarized descriptively (e.g. means/medians vs. N (%), tabular displays, graphical displays, etc.)	Yes
	19c*	Summarize follow-up time (e.g. average and total amount) and number of events	Yes
Analysis Methods	20a	For each aim/hypothesis (see items 9a/9b), a description of what analysis method will be used and how the results from this method will be reported and interpreted	Yes
	20b*	Description of any transformations, standardizations, covariate or confounder adjustments, weighting, or stratification methods to be used and why.	NA
	20c*	For each analytic method proposed, a description of the assumptions of that method and what processes will be used to evaluate whether or not those assumptions hold	No
	20d*	Details of contingency plans/alternative methods to be used if the assumptions are found not to hold	No
	20e*	In the case of non-standard test statistics, formulas provided for the test statistic with a description of the mathematical null hypothesis, how significance is determined, and how the test statistic is interpreted	NA
	20f*	In the case of regression models, formulas provided for the full model with a description of which parameters are to be used, how they will be interpreted, how confidence intervals will be constructed, etc.	Yes
	20g*	In the case of survey, hierarchical/nested, or clustered data, a description of what methods will be used to adjust for the data structure and why (e.g. if using a GEE, describing which correlation structure and why it was chosen, etc.)	No
	20h*	For non-continuous outcomes, clearly explain the effect used (e.g. risk difference, risk ratio, odds ratio, etc.), whether it is relative or absolute, and justify why that was chosen as the effect measure of interest	No
	20i*	Documentation of any non-standard methods used (e.g. using alternative degree of freedom calculation methods, using a non-canonical link function, etc.)	NA
	20j*	Description of any limitations, sources of bias, internal/external validity, and other relevant discussions concerning the interpretation and generalizability of the design or methods used	Yes
Additional Analysis Methods	21a*	Description of any pre-planned sensitivity analyses and how they will be interpreted	No
	21b*	Description of pre-planned subgroup analyses, power for these analyses, and planned multiple comparison adjustment procedures	No
	21c*	Description of any additional post-hoc calculations or analyses (e.g. evaluating interaction/modification effects, calculating mediation or local average treatment effects, evaluation of AUROC curves, etc.)	No
	21d*	If conducting any bootstrap analyses, a description of the sampling algorithm and number of iterations used	No

	21e*	If conducting any cross-validation procedures, a description of how the cross-validation is conducted (e.g. leave-one-out, train/validation/test, etc.)	No
Exploratory Analyses	22a*	Description and justification for any pre-planned exploratory analyses and what methods will be used to conduct them	Yes
	22b*	Framework for conducting any unplanned exploratory analyses and how they will be integrated into the planned analysis	No
Software	23*	List of statistical software (along with version numbers) to be used for each phase of the analysis; in the case of R or Stata, additionally list any requisite installed packages and their version numbers	No
Other	24*	Description of any additional planned analyses of the data (e.g. a safety analysis looking at adverse event rates for a Data Safety Monitoring Board, etc.)	Yes
Tables and Figures			
Table Shells	25*	Example tables related to any of the conducted analyses; if possible including any available preliminary data	No
Example Figures	26*	Example figures related to any of the conducted analyses; if possible including any available preliminary data.	No
References			
References	27a	References for any non-standard statistical methods used	NA
	27b	References (and locations) for any relevant protocols, standard operating procedures, or other documents cited in the SAP	Yes
Additional Information			
Appendices	28*	If necessary, appendices may be included (e.g. a full data dictionary, a copy of a Case Report Form, etc.)	Yes
Addendums	29*	Any additional analyses conducted that were not included in the SAP should be documented in an addendum, describing the purpose of the additional analysis, when it was conducted, and by whom	