**STUDY PROTOCOL**

**Social Behavioral Template**

# Developing Efficient Intervention Technologies to Reduce Stigma-Related Stress, Mental Health Problems, and HIV Risk among Young Chinese MSM

**Protocol Number**

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**Confidentiality Statement:**

# Synopsis

**Purpose**

The purpose of the proposed study is to assess the efficacy of a culturally adapted, 10-session SGM-affirmative, internet-based cognitive behavioral therapy (iCBT) among young men who have sex with men (YMSM) in Hunan province China. The therapy treatment called ESTEEM (Effective Skills to Empower Effective Men) is based on a minority stress-focused, CBT framework created in the US. In collaboration with colleagues at Central South University (CSU), we will assess in a 2-arm randomized controlled trial (RCT) whether a culturally adapted version of iCBT ESTEEM demonstrates significant reductions in human immunodeficiency virus (HIV) risk behavior and mental health symptoms (e.g., depression, anxiety) compared to self-monitoring of stress and mood (Aims 1 and 2). We will then conduct interviews with participants, counselors, and stakeholders to evaluate implementation barriers and facilitators (Aim 3).

**Objectives**

The primary objective is to evaluate the preliminary efficacy of a Chinese-adapted version of iCBT ESTEEM on YMSM's sexual health and HIV risk behavior. The secondary objectives of this study are to determine whether iCBT ESTEEM impacts HIV/sexually transmitted infections (STI) results and symptoms of depression and anxiety, as well as whether baseline minority stress exposure moderates treatment efficacy, such that participants with the most minority stress exposure benefit more from iCBT ESTEEM than those in the self-monitoring of stress and mood condition. An additional objective is to identify individual and institutional implementation barriers and facilitators of iCBT ESTEEM among Chinese YMSM.

**Study Population**

The study population for Aim 2 will consist of Chinese men (cisgender or transgender) between the ages of 16-30, fluent in Mandarin, living in Hunan province China, and identifying as gay, bisexual, and/or who report having sex with other men in the past 12 months, and specifically condomless anal sex (CAS)/pre-exposure prophylaxis-(PrEP) less anal sex with other men in the past 3 months. Participants will also be confirmed HIV-negative upon at home testing, report current symptoms of depression and/or anxiety, and report no use of mental health services in the past 3 months.

Participants will consist of YMSM in Hunan province China, as the study will be exclusively conducted in Hunan province with the study team's colleagues at CSU. We are restricting eligibility for this study to individuals with a current male gender identity because this group is a rapidly increasing risk group for HIV in China, with prevalence increasing from less than 1.0% in 2003 to 9.2% in 2016. The study will enroll participants ages 16-30 given that this age group contains the majority of newly diagnosed MSM in China and has experienced a severe lack of developmentally and culturally appropriate preventive intervention attention to date. The study will also include only MSM who are sexually active, ensuring that the intervention content is relevant to all participants. The upper age range was chosen given both the age group most affected by HIV in China is 16-30 and also based on our previous research showing that the identity-focused aspects of our intervention are most suited to those MSM who are closest in age to developmental identity-based stress (e.g., minority stressors such as concealment).

Aim 3 will include a proportion of Aim 2 participants whose window of study completion has ended. This aim will also incorporate community stakeholders, including government officials, medical providers, HIV-related NGO staff members, LGBTQ community center staff members, and community advocates.

**Number of Participants**

A total of 120 YMSM participants will be enrolled in this study ($n$ = 60 per condition). Assigning 60 participants to each condition (iCBT vs. self-monitoring) and accounting for 20% attrition, a liberal estimate based on our previous online RCTs (i.e., 93-100%), will provide ≥ 80% chance of detecting a difference ($p$ < .05) between the conditions of $d$ = .40, which is significantly lower than what we found when comparing in-person ESTEEM to waitlist ($d$ = .59 for CAS, $d$ = .55 for depression) and lower than even the smallest average meta-analytic effect ($d$ = .66) of iCBT compared to weak control conditions for depression. While we likely do not have power to detect changes in our biologic HIV/STI outcomes, including them 1) verifies study eligibility, 2) establishes self-testing protocols for our future adequately powered research, and 3) promotes public health. For Aim 3, a total of 55 participants, including (n = 20) Aim 2 participants, (n = 6) study therapists and supervisors, (n = 8) government administrators and leadership, (n=7) LGBTQ community organization staff, and (n = 7) and medical providers will be interviewed in order to identify themes in regard to barriers and facilitators of implementing iCBT ESTEEM among Chinese YMSM.

**Study Design**

Aim 2 of the proposed prospective study will follow a 2-arm RCT design where 120 Chinese YMSM participants will be randomly assigned to one of two conditions:

1) ESTEEM iCBT: This online CBT treatment consists of 10 weekly modules that participants will complete over the course of 10 weeks. Modules contain weekly psychoeducational text and vignettes about minority stress and mental health; brief videos illustrating the CBT skills; and homework exercises that therapists review and provide feedback on. Homework exercises include weekly tracking of stress and mood, practicing new skills (e.g., mindfulness, cognitive restructuring), and exercises related to considering the origins of stress and negative emotions that participants may be experiencing. Therapists provide feedback after each homework assignment, including reviewing each participant's treatment goals as part of the first session's homework. Therapists who support this condition will be instructed to incorporate SGM-specific content and feedback into homework reviews. In the US, modules were adapted directly from the in-person materials (e.g., therapist manual, participant handouts) used in our previously successful trials of this treatment. The treatment has also been recently culturally adapted for in-person treatment among Chinese YMSM and found to be acceptable and feasible.

2) Self-monitoring control: In this control condition, participants will be asked to indicate their past 7-day mood, stress experiences, and mental and behavioral health on an online survey. This type of self-monitoring has been shown to yield improvement in behavioral health outcomes. Self-reporting SGM stress experiences has also been shown to produce reductions in depression symptoms over time. Participants will record these experiences once per week for 10 weeks.

Prior to randomization, participants will complete an online screener, video screener on WeChat, at-home HIV/STI testing kit for HIV and syphilis, and consent call on WeChat (see Section 6.1 Study Procedures for more information about these steps of the study). For the at-home HIV/STI testing kit for HIV and syphilis, rapid test results will be ready to be read by participants in 20 minutes. HIV/STI test results will be discussed with participants by study counselors during the same day as testing via WeChat. A CSU research team member will contact participants on WeChat after 5 business days of sending the HIV/STI testing kit if the participant has not sent the CSU team a photo of their results. Specific procedures regarding risks for the at-home HIV/STI testing is outlined in Section 2.2.

To assess intervention efficacy, participants will be assessed at three time-points: baseline, immediately post-treatment (4-month follow-up), and 8-month follow-up. Participants will complete validated measures online of past-30-day HIV-risk behavior (e.g., condomless anal sex), mental health (e.g., depression, anxiety), and minority stressors (e.g., discrimination) at all three time points. At 8-month follow-up, participants will be mailed and asked to complete the same at-home HIV/STI testing kit for HIV and syphilis described above.

After completing the baseline assessment, participants randomized to ESTEEM iCBT will be assigned a study therapist and will be contacted by their therapist to schedule a 30-minute introductory call via WeChat (i.e., a Chinese multi-purpose messaging, social media, and payment app; comparable to US apps, such as Google Voice, which the Yale research team has utilized in other studies). During this conversation, therapists will explain the structure of the study and briefly discuss the participant's motivations and goals for participating in the study. Participants will then complete one session per week. If participants miss a session, as determined by daily therapist and RA review of session access and self-monitoring or homework completion, they will receive a reminder to complete the session. Participants will also be asked to schedule a check-in phone call with their study therapist two-weeks post-randomization to discuss their progress through the study sessions. Participants will have a window period of four months (approximately 17 weeks) to complete all 10 sessions.

Before we launch the full trial, we will ensure comprehension of the ESTEEM iCBT online module material with 10 separate YMSM, as well as gather their feedback on the usability of the iCBT online platform. Our two pilots for this proposal (i.e., cultural adaptation in China + iCBT usability testing in the US) have already led to the creation of the in-person delivery materials for Chinese ESTEEM (e.g., manual, participant handouts) and established the technical feasibility of our iCBT platform. As such, the Chinese-adapted materials (e.g., manual, handouts) are ready to be transformed into iCBT content (e.g., self-guided exercises, videos, counselor instructions). Given the previous efficacy testing of in-person Chinese ESTEEM and iCBT in our US study, this comprehension testing will occur over the course of 2 weeks with a focus on 10 YMSM reviewing the online treatment material, receiving counselor feedback, and providing feedback via answering brief questions after each module on its usability. For this comprehension testing, the only inclusion criteria for this comprehension test will be: 16-30 years old, live in Hunan province China, current gender identity as male, report past 12-month sex with men, weekly access to internet on a laptop, desktop, or tablet device, ability to read, write, and speak in Mandarin, and provision of informed consent (see Section 5.3 for inclusion criteria for the full study). These 10 YMSM for the comprehension testing will not complete the study measures, with the exception of the 30-day Timeline Follow-Back assessment at the end of the pilot in order to test the usability of this assessment on the Sojump platform. After review of the ESTEEM iCBT materials, participants will provide feedback to the CSU research team on their comprehension of the materials, as well as respond to questions from a qualitative interview conducted by the CSU research team about their experience.

Aim 3 of the study will identify barriers and facilitators for uptake and scale of Chinese ESTEEM iCBT within existing public and non-governmental organizations (NGO) settings. We will first review Aim 2 data for YMSM completion metrics (# sessions completed, points of drop-off) and moderators of intervention efficacy (as described below). Next, we will interview a subset of Aim 2 participants (*n*=20) as well as counselors and therapy supervisors (*n*=6) for their impressions of the acceptability of Chinese ESTEEM iCBT and needed improvements before implementation. We will also interview (n = 8) government

administrators and leadership, (n=7) LGBTQ community organization staff, and (n = 7) and medical providers who have expressed interest in online interventions for YMSM and who can ultimately implement this intervention, if efficacious.

**Study Duration**

The entire study, including data analysis, is expected to last until May 2023. Participation for the 10 YMSM in comprehension testing will begin by January 2021. Participation for the full study RCT will begin by October 2021. The final 8-month follow-up assessments are anticipated to end by November 2022. Participation for the qualitative interviews will begin by June 2022 (upon final survey completion of the first RCT participants). Data analysis is expected to occur beginning in December 2022 until May 2023.

**Outcome Variables**

Our primary outcome is YMSM's sexual health and HIV risk behavior, which will be assessed at three study time points (baseline, 4-month follow-up, 8-month follow-up) via the following measures:

- 30-Day Timeline Follow-Back
- Decisional Balance for Condom Use Scale
- Safer Sex Questionnaire
- Past 4-month HIV/STI Testing Questionnaire

Our secondary outcomes, which will also be measured at baseline, 4-month follow-up, and 8-month follow-up, (unless otherwise noted) include the following with their associated measures:

Mental health outcomes:

- *Depressive symptoms* – Patient Health Questionnaire-9, Overall Depression Severity & Impairment Scale
- *Anxiety symptoms* – Generalized Anxiety Disorder-7, Overall Anxiety Severity & Impairment Scale, Social Interaction Anxiety Scale
- *Suicidal ideation* – Suicidal Ideation Attributes Scale
- *Alcohol and substance use* – Alcohol Use Disorders Identification Test, Drug Use Disorders Identification Test

Minority stress mechanism outcomes:

- *Concealment motivation* – Lesbian, Gay, and Bisexual Identity Scale (LGBIS) Concealment Motivation subscale
- *Acceptance concerns* – LGBIS Acceptance Concerns subscale
- *Internalized homonegativity* - LGBIS Internalized Homonegativity subscale
- *Self-esteem* – Rosenberg Self-Esteem Scale

Universal mechanism outcomes:

- *Emotion regulation* – Difficulties in Emotion Regulation Scale-Short Form
- *Perceived social support* – Multidimensional Scale of Perceived Social Support, Chinese version of the LGBIS - LGB-Specific Family Support subscale
- *Rumination* – Ruminative Response Scale

Psychosocial variables:

- *Body image* – Multidimensional Body-Self Relations Questionnaire, Appearance Evaluation subscale, Body Appreciation Scale-2
- *Adverse childhood experiences (ACEs;* administered at baseline and 8-month follow-up*)* – Life History Interview of ACEs
- *COVID-19 experiences* – COVID-19 questionnaire

HIV/STI outcomes (only following video screener and at 8-month follow-up):

- At-home HIV/STI testing kit for HIV and syphilis

In addition to the assessments that will be administered at baseline, 4-month follow-up, and 8-month follow-up, three questionnaires will be administered weekly on the iCBT online platform for 10 weeks for the ESTEEM iCBT and self-monitoring conditions:

- Overall Depression Severity & Impairment Scale
- Overall Anxiety Severity & Impairment Scale
- Tracking Minority Stress Experiences Questionnaire

For the pilot study, the 10 YMSM will complete the following:

- Brief questionnaire (5 items) after completing each module
- Follow-up interview after completing all 10 modules
- 30-Day Timeline Follow-Back

For Aim 3, we will additionally review data for the following:

- Number of sessions completed by participants
- Points of study drop-off
- Acceptability and feasibility – participants' written responses to prompts within online modules will be coded for engagement and relevance to module content

**Locations/Facilities**

This study will be carried out in Hunan province China by our colleagues at CSU, who will serve as the site of study recruitment and all direct participant interaction. Yale University will serve as the primary scientific site of the study. Researchers at Yale will be responsible for ensuring the scientific, clinical, and technical robustness of the intervention, including its translation into the iCBT format and ongoing delivery. All participation will occur online and participants will be recruited in Hunan province, as specified below in Section 5.4 Recruitment Procedures.

# Abbreviations

| Abbreviation | Explanation |
|---|---|
| ACEs | Adverse Childhood Experiences |
| CAS | Condomless anal sex |
| CBT | Cognitive Behavioral Therapy |
| CSU | Central South University |
| EIA | Enzyme immunoassays |
| ESTEEM | Effective Skills to Empower Effective Men |
| GLMM | Generalized linear mixed model |
| HIV | Human immunodeficiency virus |
| iCBT | Internet-based, Cognitive Behavioral Therapy |
| LGBIS | Lesbian, Gay, and Bisexual Identity Scale |
| MSM | Men who have sex with men |
| NGO | Non-governmental |
| PI | Principal investigator |
| PrEP | Pre-exposure prophylaxis |
| RA | Research assistant |
| RCT | Randomized controlled trial |
| RMB | Renminbi (Chinese currency) |
| SGM | Sexual and gender minority |
| STI | Sexually transmitted infections |

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|---|---|
| **YMSM** | **Young men who have sex with men** |



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# Glossary of Terms

| Glossary | Explanation |
|---|---|
| **Cognitive-Behavioral Therapy (CBT)** | **A short term, structured, problem-solving form of evidence-based psychotherapy based on a framework focused on the relationship between thoughts, feelings, and behaviors.** |
| **Minority stress** | **The unique and chronic stress (or stigma) that sexual minority individuals experience because of the inferior social status that social structures, institutions, policies, and social interactions communicate about individuals who do not identify as heterosexual.** |



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# Protocol Revision History

| Version Date | Summary of Substantial Changes |
|---|---|
| 4/29/22 | Inclusion of Aim 3 qualitative interview procedures as well as participant in-session response coding, inclusion of COVID-19 questionnaire, revision of ACES survey instrument, addition of Ci Zhang to research team. |
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| | |

# 1 Background

## 1.1 Background

HIV prevalence among gay, bisexual, and other men who have sex with men (MSM) in China has increased from less than 1.0% in 2003 to 9.2% in 2016.[1]The majority of newly diagnosed MSM are ages 16-30.[2] China's epidemic is at a crossroads: widespread implementation of effective interventions now can stem this trend. Lack of action will see at least 1 in 6 Chinese MSM infected with HIV by 2025.[1]

Structural and psychological forms of stigma toward young MSM (YMSM) fuel China's HIV epidemic.[3-5] Structurally, Chinese YMSM face a lack of equal rights and legal protections, including no same-sex marriage, same-sex education, or recourse to discrimination.[6-9] Not only are YMSM-focused evidence-based treatments lacking in China, but sexual orientation conversion therapy is widely promoted as a means to help YMSM who are often desperate to maintain heterosexual desires and create traditional families expected by Chinese culture.[10-12] As is true in other countries, this structural stigma gives rise to maladaptive coping processes among YMSM.[13-16] Known as minority stress, these processes include identity concealment, internalized homonegativity, and sensitivity to identity-based rejection,[17-22] and they drive the substantial mental health disparity borne by YMSM in China.[23-31] Both minority stress and poor mental health compromise HIV prevention and care behaviors through avoidance coping, low self-worth, impulsivity, and unasseriveness.[32-34]

Chinese public and non-governmental (NGO) leaders are open to deploying evidence-based interventions to reduce the HIV epidemic,[35] yet no interventions address Chinese YMSM's minority stress and mental health to prevent HIV. Our team in the US has created such an intervention – ESTEEM (Effective Skills to Empower Effective Men), a minority-stress-focused cognitive-behavioral therapy (CBT) with strong preliminary efficacy across minority stress, mental health, and HIV risk behavior (R34MH096607).[36-38] Yet three features of ESTEEM currently hamper widespread implementation in China or elsewhere. Specifically, ESTEEM: 1) has only been tested in the US without cultural adaptation to high-stigma, non-US contexts, 2) currently requires in-person delivery of 10, 1-hour modules, and 3) has not been reviewed by multi-sector stakeholders to inform barriers and facilitators to its uptake within existing mental and sexual health services, both public and NGO.

## 1.2 Prior Experience (if applicable)

Our ESTEEM treatment for the proposed training has been previously developed and tested by the current research team. In the pilot testing of the treatment among a sample of gay and bisexual men[37], the treatment significantly reduced depressive, alcohol use problems, sexual compulsivity, and past-90-day condomless sex with casual partners, as well as improved condom use self-efficacy. The treatment yielded moderate and marginally significant improvements compared to a waitlist group in anxiety symptoms and past-90-day heavy drinking. Effects were generally maintained at follow-up.

Since the pilot, the research team has been in the process of testing the efficacy of the treatment among gay and bisexual men in an RCT against Community Mental Health Treatment and Voluntary Testing and Counselling for HIV (see IRB protocol: 1509016430).The research team has also adapted the SGM-affirmative CBT treatment for gender diverse, sexual minority women (see IRB protocol: 2000020997),[36] as well as for an online platform (see IRB protocol: 2000025803).

In terms of the cultural adaptation of the treatment, we have culturally adapted the in-person ESTEEM intervention (and measures) for Chinese YMSM over the past year across an 8-stage adaptation process with YMSM and stakeholders (*n* = 56), including a small open pilot with Chinese YMSM (*n* = 8). We also worked with our colleagues in Sweden at the Karolinska Institutet – world leaders in internet-based CBT (iCBT) – to create an iCBT version of ESTEEM. iCBT combines a self-guided interactive mobile web-platform with brief counselor feedback and online exercises and homework, requiring 80% less counselor time than in-person ESTEEM; caseloads can reach 200-300 per counselor. In a small US pilot (*n* = 10), iCBT ESTEEM was highly functional (see IRB protocol: 2000025803). Thus, we have incorporated these advances in the proposed study to develop Chinese ESTEEM iCBT – a highly efficient, private intervention that addresses minority stress and mental health as HIV prevention. Its mobile platform overcomes stigma-related barriers to broadly reach YMSM while still retaining in-person ESTEEM's robust ability to reduce YMSM's HIV risk.

# 2 Rationale/Significance

## 2.1 Rationale and Study Significance

The proposed study addresses several gaps in the literature on Chinese YMSM:

**Chinese YMSM are at high and increasing risk of HIV infection in the world's largest country**. Although for many years the HIV epidemic appeared to have stabilized in China, recent trends raise alarm. In 2018, China saw a 14% increase in new infections; the number of new cases per year is now estimated at 100,000.[1] While the early epidemic in China centered around injection drug use, sex work, and blood transfusions, MSM are now the highest-risk group in China, accounting for at least 28% of new infections,[1,40] likely an underestimate given normative lack of MSM disclosure.[41] HIV prevalence among Chinese MSM has increased from less than 1.0% in 2003 to 9.2% in 2016. At current trends, 1 in 6 MSM will be infected with HIV by 2025.[42] The majority of newly diagnosed MSM are young, under age 30 (YMSM).[2] A recent meta-analysis found that only 1/3 of Chinese YMSM consistently used condoms during anal intercourse, and their average number of past-6-mo sexual partners was approximately six. PrEP is not readily available in China.[43]

**Stigma drives the HIV epidemic among Chinese YMSM.**[3-5,23,24,44,45] Chinese YMSM are surrounded by stigma, which perpetuates maladaptive stress reactions and poor mental health.[3-5] Structural stigma toward YMSM in China includes a lack of legal protection against discrimination, lack of same-sex relationship recognition, and legal barriers to open self-expression.[3,9,46] Same-sex behavior was considered a psychiatric disorder in China until 2001.[3,46] This history yielded sexual orientation conversion therapy, now proliferating in China against a relatively unregulated mental health system, despite known harm.[10,11,47,48] Stigma toward YMSM is exacerbated by Chinese values of filial piety and China's collectivistic culture that emphasizes norm conformity; this drives family rejection and pressure to conceal.[12,24,49] Chinese YMSM's sex lives are thus often underground and out-of-reach of HIV-prevention services.[1,7,50] About half of Chinese MSM have never been tested for HIV and 62% have not been tested in the past 12 months, with fear of stigma as a primary barrier.[51]

**Minority stress underlies substantial mental health disparities affecting Chinese YMSM.** Our research shows that stigma gives rise to minority stress reactions including chronic, anxious expectations of rejection; internalized homonegativity; and identity concealment.[13,14,24,52,53] We estimate that 81% of YMSM in China conceal their sexual orientation from all or most others.[41] Structural stigma in Chinese cultural norms lead a significant proportion of Chinese MSM to have sex with women.[49,54,55] A meta-analysis showed that 26% of MSM had female sexual partners during the past 6 months and only

26% used condoms then.[56] An estimated 70% of MSM plan to eventually marry a woman.[3,56] These identity-related stressors help explain Chinese YMSM's 2-6-times greater odds of depression, anxiety, and alcohol abuse compared to heterosexual men.[12,24,27,43,57-61]

**Minority stress and mental health problems drive Chinese YMSM's HIV risk.** Minority stress and poor mental health are clear risks for Chinese YMSM's HIV transmission behaviors.[12,26-31,50,52,62] Specifically, enacted and internalize stigma predict concealment, [24] which in turn predicts lack of HIV-preventative knowledge and behaviors.[50,63] Minority stress is also associated with emotion dysregulation,[64-66] hopelessness,[67-69] impulsivity,[70] poor social support,[26,71-73] and low self esteem,[73] which are also associated with HIV-risk behaviors.[18,74,75] The mental health consequences of minority stress further predict HIV-risk behaviors: moderate depression is associated with MSM's condomless anal sex (CAS);[32,76-78] anxiety increases avoiding coping and poor condom use communication;[79-81] and substance use encourages impulsive sexual behaviors.[82-84]

**Evidence-based interventions to reduce minority stress reactions and poor mental health are increasingly recognized as highly promising solutions to YMSM's HIV risk**. Our ESTEEM intervention, developed for high-risk YMSM in the U.S. (R01MH109413), represents the only intervention tested for efficacy for reducing YMSM's HIV risk by addressing their minority stress and mental health.[36-38] ESTEEM utilizes a 10-session CBT framework to address the cognitive, affective, and behavioral minority stress mechanisms through which stigma depletes mental and sexual health.[18,36] Specifically, across an in-depth intervention development process involving consultation with 20 MSM and 21 expert YMSM providers (R34MH096607), we adapted the Unified Protocol (a transdiagnostic CBT manual)[85,86] to specifically target minority stress processes (rather than more general stress processes).[87] The resulting ESTEEM treatment teaches skills that specifically address minority stress mechanisms by: (1) normalizing the mental health consequences of minority stress, (2) reworking minority stress cognitions (e.g., low self-worth, internalized homonegativity), (3) decreasing avoidance-driven behaviors rooted in minority stress (e.g., compulsive sexuality, substance use), and (4) assertive responding to minority stress (e.g., authentic self-expression).[36] By addressing these mechanisms linking stigma to poor mental and sexual health, the treatment shows robust effect sizes across transdiagnostic outcomes: depression ($d$ = 0.55), alcohol abuse ($d$ = 1.03), and CAS ($d$ = 0.59). ESTEEM's transdiagnostic approach bypasses the need to train multi-sector providers to deliver multiple treatments (e.g., motivational interviewing, relapse prevention, behavioral activation), as ESTEEM encompasses the core elements of all these treatments. Increasingly, YMSM cite mental health concerns as their primary burden,[88,89] making mental health promotion an ideal opportunity for also intervening on HIV risk, given the synergistic relationship between mental health and HIV. Our work finds that Chinese YMSM, even those deeply closeted, are highly motivated to seek identity-affirming mental health services to cope with cultural pressures and developmental decisions, such as whether to marry a woman.[12]

**Internet-based CBT (iCBT) can overcome barriers to broad implementation of evidence-based HIV-prevention interventions.** iCBT, pioneered in Northern Europe to disseminate CBT broadly, involves participants engaging in several CBT tasks hosted on an online platform: reading self-guided psychoeducation, reviewing video demonstrations of more complex skills, completing CBT worksheets, and uploading between-session homework.[90-92] Counselors respond to participants' progress (e.g., motivational feedback on worksheets, suggesting homework tasks) within 1-2 days. Participants can also email counselors to clarify points of confusion. Because counselor and participant do not meet "live" at the same time, iCBT is asynchronous in that it allows participants to complete each module anytime anywhere and counselors to then spend an average of only 10 minutes reviewing each module within 1-2 days. Given its efficiency, iCBT counselor caseloads can

reach 200-300. Meta-analyses of iCBT find effects similar to those obtained in face-to-face CBT.[93,94] In a cultural context of normative concealment and conversion therapy, our highly secure identity-affirmative iCBT offers an urgently needed alternative for tailored, sensitive mental and sexual health support. Indeed, Chinese YMSM expressed strong preferences to receive online versus in-person supports.[95,96]

## 2.2 Risks

One risk of the proposed study is that participants will experience emotional discomfort as a result of completing the quantitative assessments or the intervention. Breach of participants' confidentiality presents another possible risk. The investigative team's strategies to protect against both risks are described below:

*Recruitment and Informed Consent*: The investigative team at CSU and research team at Yale have conducted a number of studies involving SGM young adults and adolescents, which have involved asking participants to complete potentially sensitive interviews and self-report measures. Thus, we have extensive protocols in place for all aspects of the study. All staff complete IRB (re)certification as required. All new staff and research volunteers will receive training in issues pertinent to research among SGM young adults and adolescents and will sign a confidentiality pledge prior to any contact with participants or data. No identifying information is collected prior to the moment at which a participant provides informed consent.

The primary mode of communication between the CSU team and participants will be via WeChat, (i.e., a Chinese multi-purpose messaging, social media, and payment app; comparable to US apps, such as Google voice, which the Yale research team has utilized in other studies). Dr. Li and her research team at CSU have successfully used WeChat to correspond with their participants in several other studies.

At the end of the WeChat video screen (described in further detail in Sections 4 and 6), a research assistant (RA) at CSU will send eligible participants a copy of the consent form via WeChat and review the consent document with them. The RA will ensure that the participant understands the risks associated with the disclosure of information that could indicate imminent threat to self or others. Verification of comprehension of informed consent will be accomplished by asking participants to recall central points in the consent process during a separately scheduled consent call over WeChat; points of confusion will also be clarified. Once participants have fully understood the consent, they will be asked to provide verbal consent. The RA will be instructed to contact the CSU PI (Dr. Xianhong Li) or CSU project coordinator (Si Pan) if they are unsure about any participant's capacity to consent.

For participant who are minors (i.e., 16-17-years-old), a waiver of parental consent has been requested, as described in Section 5.5.

*Protections Against Emotional Discomfort*: It is possible that participants may experience emotional discomfort in responding to assessments or session material. While every possible step will be taken to minimize such risk, consent documentation will make it clear that if participants have any concerns about any aspect of the study they may refuse to continue with the study at any time, without penalty. In addition, participants will be reminded during the course of their assessments that they can refuse to answer any questions and may discontinue participation at any time. Research staff and counselors at CSU will be thoroughly trained in appropriate responses to participant distress through trainings by a licensed clinical psychologist. This training will address the appropriate handling of imminent threats and provision of referrals to counseling services in less imminent clinical situations. Protocols have been developed by the research teams at CSU and Yale for mitigating such risks as employed in our other online and in-person treatment studies with YMSM.

HIV/STI testing might invoke some emotional discomfort. The CSU project coordinator, trained by PI, Dr. Li, and staff from Zuo An Cai Hong, all of whom have previous experience conducting at-home HIV/STI testing with YMSM, will seek HIV/STI testing consent from all participants during the video screen consent process, prior to study commencement. HIV/STI counseling and testing will be led by study counselors, in consultation with Zuo An Cai Hong, which contributes an 11-year experience in HIV/STI testing and care and demonstrates high YMSM-sensitive testing expertise. Prior to study commencement, we will convene the counselors and review all protocols and reporting procedures (both to the Chinese epidemiological tracking system overseen and our study data system).

Confidentiality of results will be stressed during consent and contact with counselors, and on the at home HIV/STI kit instructions. A positive test is insufficient for diagnosis and participants will be directed to the nearby Zuo An Cai Hong clinic for treatment and follow up, unless the participant prefers to access care at health clinic of his choice. Counselors will urge participants to access testing at these sites beyond study-related testing. We will make every effort to ensure that participants with positive results are referred and have access to care with a Zuo An Cai Hong clinic for confirmatory testing and follow-up care. Zuo An Cai Hong will also report positive HIV/STI test results to the national reporting system for HIV and STIs.

Appropriate risk-reduction counseling will be provided to all participants at time of testing, as well as through the ESTEEM iCBT content they will receive. Enclosed within testing kits, all participants will receive lubricant and condoms. The rapid test results for both HIV and syphilis will be ready to be read by participants in 20 minutes. HIV/STI test results will be discussed with participants by study counselors during the same day as testing via WeChat. Like conventional HIV enzyme immunoassays (EIAs), rapid HIV/STI tests are screening (i.e., not diagnostic) tests that require diagnostic confirmation by Western Blots if reactive (positive). Participants who test preliminarily positive (or have inconclusive tests) will be immediately linked to Zuo An Cai Hong who would refer them to CDC for confirmatory testing, care, and treatment. Study counselors will offer to make an appointment for participants at a local Zuo An Cai Hong, which has 7 offices across Hunan province. Participants testing HIV positive will not be randomized into the study, as HIV negative status is one of the inclusion criteria, so they will receive immediate counseling by our counselors, followed by medical attention referred by Zuo An Cai Hong to which they will be promptly linked. Further, we will employ the same procedures as above to address potential distress upon realization of an HIV-positive status after the rapid test. See Section 6 of the protocol for further information in regard to procedures around the at home HIV/STI testing for the study.

*Protections against breach of confidentiality*: The likelihood that any additional breaches of confidentiality would occur is minimal, as steps will be taken to guard against this risk. All counselors and research staff will undergo rigorous training in maintaining participants' privacy and confidentiality and will be in possession of valid Collaborative Institutional Training Initiative (CITI) certificates or comparable trainings. Further, immediately upon providing consent, all participants will be assigned a unique study code number, which will only be kept on an electronic database that will be password-protected and located on a designated study computer at CSU that will not be connected to the Internet (i.e., offline). This information will not be stored with any other data and no other identifying information will appear on any form. All contact with participants will be made by counselors and research staff under explicit guidelines to preserve confidentiality when corresponding with participants. All materials with identifying information will be kept in one password-protected electronic file. Participants will provide alternative contact information (e.g., WeChat account

information) for compensation and study retention purposes. This information will be treated in the same confidential manner as all participant information, as described here.

Our iCBT platform employs numerous physical access controls (e.g., steel walls, keycard access system), systems access controls (e.g., login via two-factor authentication, encrypted passwords, required regular password changes), personal data access controls (e.g., privilege systems ensuring that study staff only can view information and edit settings that pertain to their role), data separation controls (e.g., study-specific database), data transfer access controls, intrusion and malware protection, audit logs, safety backups, and data erasure protocols. These protections ensure that participants' data will remain secure throughout the duration of the study and beyond. Additionally, no identifiable information will be stored on the iCBT platform at any point during the study.

Study data will be stored on either the secure Sojump survey platform, Karolinksa Institutet's secure server, Yale's HIPAA-compliant Secure Box, and/or an offline computer in Dr. Li's lab at CSU. Session homework assignment data will be received at the Karolinska Institutet's server, which hosts the iCBT online platform for both study conditions (i.e., Chinese ESTEEM iCBT and self-monitoring). These session homework assignment data will also be downloaded to Yale's Secure Box drive upon retrieval from the Karolinska Institutet server, which will not include identifiable participant information; it will also remain on the Karolinska Institutet server after transfer to Yale. Participant session notes will be stored on Yale's Secure Box. One password-protected linking database containing participant names and ID codes will be kept on an offline computer in Dr. Li's lab at CSU and will only be accessible by CSU study staff via a separate password.

Participant tracking and scheduling data will be recorded on a study database stored on an offline computer in Dr. Li's lab at CSU. All study measures will be administered online via the secure Sojump survey platform. Dr. Li and her team at CSU have used Sojump for several past studies. For data safety, Dr. Li has a signed confidentiality contract with Sojump. Per the Sojump confidentiality contract, requisite technical measures will be implemented to ensure the security of our data stored on the Sojump server. Sojump is hosted in Allyun BGP room, data is stored in RAID (disk array), protected by enterprise-level firewall, and combined with daily backup to ensure the data security. Sojump supports multiple public level settings and password protection for questionnaires and results. Their staff is tightly regulated and restricted in their access to our data to ensure that our critical data will not be leaked." As part of this contract for this study, only one account login and password are provided to ensure confidentiality. Furthermore, each login requires a phone-based dual text authentication. All data from Sojump will be downloaded onto an offline computer. For weekly self-monitoring assessments and iCBT ESTEEM homework assignments conducted on the iCBT online platform, only participant IDs will be used; no participants' names or other identifying information will be used or stored on the iCBT online platform. For qualitative interviews, participant names will not be recorded and any identifying information will be removed from recordings prior to transcription. Interviews will be recorded on a secure offline device and transferred to an offline computer kept in Dr. Li's lab at CSU along with transcriptions.

Reporting requirements might be invoked in the case of participants reporting suicidality, homicidality, severe distress, or violence. Our lab's clinical protocol at Yale has successfully guided reporting of instances of suicidality, homicidality, severe emotional distress, violence, and child abuse/maltreatment in our other online-based RCTs (see IRB #2000025803). At CSU, a similar protocol has been adapted, and will be followed for participants reporting suicidality, homicidality, severe distress, violence, or child abuse/maltreatment. The protocol specifies that, in the event that a participant is at imminent risk of harming themselves or another person, as determined by a study staff member with mental health training, study

staff will contact local police (110) or paramedics (120). Only the minimal necessary identifying information will be provided to these personnel. In less imminent instances of distress, we will refer distressed participants to local mental or behavioral health services available in their area. All therapy homework will be reviewed every 24-48 hours by a clinical staff member trained in suicide assessment. Research and clinical staff members will receive an alert if the participant answers the online questionnaires in a manner that signals distress; such participants will be called by a clinical staff member to assess risk. Participants will be notified of the reporting requirements under these circumstances during the consent process. See the attached Clinical Protocol on IRES for detailed information regarding this clinical protocol.

### 2.3 Anticipated Benefits

Mental health problems and associated behavioral health risks (e.g., substance abuse, suicidality, sexual risk) among YMSM is a clear public health concern in need of easy-to-disseminate solutions. All participants in the present study will be exposed to information about mental and sexual health in relation to social stress. We anticipate that participants will acquire knowledge and skills and will receive support needed to improve their capacity for managing mental and sexual health risk.

Benefits to society in general are anticipated through the dissemination of intervention findings and community trainings in the ESTEEM treatment approach. Results will better inform local and international public health agencies about potentially effective outreach and prevention strategies that can be delivered to YMSM who experience stress-sensitive mental health disorders, such as depression and anxiety, and related behavioral risks, such as HIV-risk behavior. In sum, the potential benefits outweigh the potential risks to subjects.

# 3 Study Purpose and Objectives

### 3.1 Purpose

The purpose of the proposed study is to assess the efficacy of a culturally adapted, 10-session SGM-affirmative, internet-based cognitive behavioral therapy (iCBT) YMSM in Hunan province China. The affirmative treatment called ESTEEM (Effective Skills to Empower Effective Men) is based on a minority stress-focused, CBT framework. In collaboration with colleagues at CSU, we will assess in a 2-arm RCT whether a culturally adapted version of iCBT ESTEEM demonstrates significant reductions in HIV risk behavior and mental health symptoms (e.g., depression, anxiety) compared to self-monitoring of stress and mood. (Aims 1 and 2). We will then conduct interviews with participants, counselors, and stakeholders to evaluate implementation barriers and facilitators (Aim 3).

### 3.2 Hypothesis

It is hypothesized that Chinese ESTEEM iCBT will yield significantly greater reductions in HIV-risk behavior, specifically CAS, and mental health problems (e.g., depression and anxiety) compared to weekly self-monitoring of stigma-related minority stress experiences, mental health, and HIV-risk behavior among Chinese YMSM.

### 3.3 Objectives

The primary objective is to evaluate the preliminary efficacy of a Chinese-adapted version of iCBT ESTEEM on YMSM's sexual health and HIV risk behavior.

The secondary objectives of this study are to determine whether iCBT ESTEEM impacts HIV/STI results and symptoms of depression and anxiety, as well as whether baseline minority stress exposure moderates treatment efficacy, such that participants with the most minority stress exposure benefit more from iCBT ESTEEM than those in the self-monitoring

of stress and mood condition. An additional objective is to identify individual and institutional implementation barriers and facilitators of iCBT ESTEEM among Chinese YMSM.

# 4 Study Design

Aim 2 of the proposed prospective study will follow a 2-arm RCT design where 120 Chinese YMSM participants will be randomly assigned to one of two conditions:

1) ESTEEM iCBT: This online CBT treatment consists of 10 weekly modules that participants will complete over the course of 10 weeks. Modules contain weekly psychoeducational text and vignettes about minority stress and mental health; brief videos illustrating the CBT skills; and homework exercises that therapists review and provide feedback on. Homework exercises include weekly tracking of stressful situations and mood, practicing new skills (e.g., mindfulness, cognitive restructuring), and exercises related to considering the origins of stress and negative emotions that participants may be experiencing. Therapists provide feedback after each homework assignment, including reviewing each participant's treatment goals as part of the first session's homework. Therapists who support this condition will be instructed to incorporate SGM-specific content and feedback into homework reviews. Therapists will be mental health counselors in Dr. Li's lab at CSU who possess an advanced degree in a mental health field with significant prior experience treating Chinese YMSM with sexual and mental health concerns. In the US, modules were adapted directly from the in-person materials (e.g., therapist manual, participant handouts) used in our previously successful trials of this treatment. The treatment has also been recently, culturally adapted for in-person treatment among Chinese YMSM and found to be acceptable and feasible.

2) Self-monitoring control: In this control condition, participants will be asked to indicate their past 7-day mood, stress experiences, and mental and behavioral health on an online survey. This type of self-monitoring has been shown to yield improvement in behavioral health outcomes. Self-reporting SGM stress experiences has also been shown to produce reductions in depression symptoms over time. Participants will record these experiences once per week for 10 weeks.

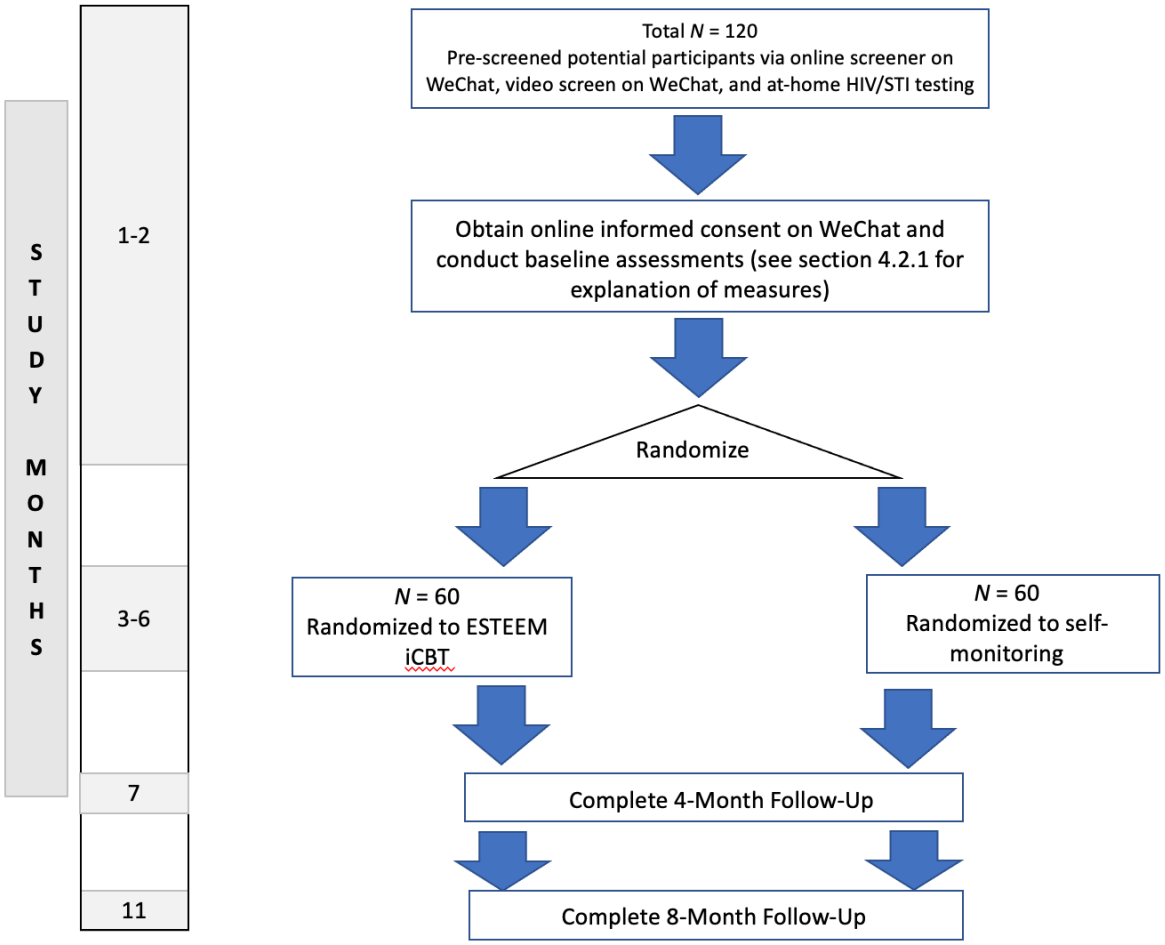
Prior to randomization, participants will complete an online screener, video screener on WeChat, at-home HIV/STI testing kit for HIV and syphilis, and consent call on WeChat (see Section 6.1 Study Procedures for more information about these steps of the study). For the at-home HIV/STI testing kit for HIV and syphilis, rapid test results will be ready to be read by participants in 20 minutes. HIV/STI test results will be discussed with participants by study counselors during the same day as testing via WeChat. A CSU research team member will contact participants on WeChat after 5 business days of sending the HIV/STI testing kit if the participant has not sent the CSU team a photo of their results. Specific procedures regarding risks for the at-home HIV/STI testing is outlined in Section 2.2.

To assess intervention efficacy, participants will be assessed at three time-points: baseline, immediately post-treatment (4-month follow-up), and 8-month follow-up. Participants will complete validated measures online of past-30-day HIV-risk behavior (e.g., condomless anal sex), mental health (e.g., depression, anxiety), and minority stressors (e.g., discrimination) at all three times points. At 8-month follow-up, participants will be mailed and asked to complete the same at-home HIV/STI testing kit for HIB and syphilis described above.

After completing the baseline assessment, participants randomized to ESTEEM iCBT will be assigned a study therapist and will be contacted by their therapist to schedule a 30-minute

introductory call via WeChat. During this conversation, therapists will explain the structure of the study and briefly discuss the participant's motivations and goals for participating in the study. Participants will then complete one session per week. If participants miss a session, as determined by daily therapist and RA review of session access and self-monitoring or homework completion, they will receive a reminder to complete the session. Participants will also be asked to schedule a check-in phone call with their study therapist two-weeks post-randomization to discuss their progress through the study sessions. Participants will have a window period of four months (approximately 17 weeks) to complete all 10 sessions.
Before we randomize participants into the full trial, we will test the ESTEEM iCBT treatment with 10 YMSM to ensure their comprehension of the online module material, as well gather their feedback on the usability of the iCBT online platform. Our two pilots for this proposal (i.e., cultural adaptation in China + iCBT usability testing in the US) have already led to the creation of the in-person delivery materials for Chinese ESTEEM (e.g., manual, participant handouts) and established the technical feasibility of our iCBT platform. As such, the Chinese-adapted materials (e.g., manual, handouts) are ready to be transformed into iCBT content (e.g., self-guided exercises, videos, counselor instructions). Given the previous efficacy testing of in-person Chinese ESTEEM and iCBT in our US study, pilot testing will occur over the course of 2 weeks with a focus on 10 YMSM reviewing the online treatment material, receiving feedback from the counselor, and providing feedback via answering brief questions after each module on its usability. For this pilot, the only inclusion criteria will be 16-30 years old, live in Hunan province China, current gender identity as male, report past 12-month sex with men, weekly access to internet on a laptop, desktop, or tablet device, ability to read, write, and speak in Mandarin, and provision of informed consent (see Section 5.3 for inclusion criteria for the full study). These 10 YMSM for the pilot will not complete the study measures, with the exception of the 30-day Timeline Follow-Back assessment at the end of the pilot in order to test the usability of this assessment on Sojump. After review of the ESTEEM iCBT materials, participants will provide feedback to the CSU research team on their comprehension of the materials, as well as respond to questions from a qualitative interview conducted by the CSU research team about their experience.

**Flow Diagram for the 2-Arm RCT China ESTEEM iCBT Design**




Aim 3 of the study will identify barriers and facilitators for uptake and scale of Chinese ESTEEM iCBT within existing public and non-governmental organizations (NGO) settings. We will first review Aim 2 data for YMSM completion metrics (# sessions completed, points of drop-off) and moderators of intervention efficacy (as described below). Next, we will interview a subset of Aim 2 participants (*n*=20) as well as counselors and therapy supervisors (*n*=6) for their impressions of the acceptability of Chinese ESTEEM iCBT and needed improvements before implementation. We will also interview (n = 8) government administrators and leadership, (n=7) LGBTQ community organization staff, and (n = 7) and medical providers who have expressed interest in online interventions for YMSM and who can ultimately implement this intervention, if efficacious.

## 4.1 Study Duration

The entire study, including data analysis, is expected to last until May 2023. Participation for the 10 YMSM in pilot testing will begin by January 2021. Participation for the full study RCT will begin by October 2021. The final 8-month follow-up assessments are anticipated to end by November 2022. Participation for the qualitative interviews will begin by June 2022 (upon final survey completion of the first RCT participants). Data analysis is expected to occur beginning in December 2022 until May 2023.

## 4.2 Outcome Variables/Endpoints

Our primary outcome is YMSM's sexual health and HIV risk behavior, which will be assessed at three study time points (baseline, 4-month follow-up, 8-month follow-up) via the following measures:

- 30-Day Timeline Follow-Back

- Decisional Balance for Condom Use Scale
- Safer Sex Questionnaire
- Past 4-month HIV/STI Testing Questionnaire

Our secondary outcomes, which will also be measured at baseline, 4-month follow-up, 8-month follow-up, (unless otherwise noted) include the following with their associated measures:

Mental health outcomes:

- *Depressive symptoms* – Patient Health Questionnaire-9, Overall Depression Severity & Impairment Scale
- *Anxiety symptoms* – Generalized Anxiety Disorder-7, Overall Anxiety Severity & Impairment Scale; Social Interaction Anxiety Scale
- *Suicidal ideation* – Suicidal Ideation Attributes Scale
- *Alcohol and substance use* – Alcohol Use Disorders Identification Test, Drug Use Disorders Identification Test

Minority stress mechanism outcomes:

- *Concealment motivation* – Lesbian, Gay, and Bisexual Identity Scale (LGBIS) Concealment Motivation subscale
- *Acceptance concerns* – LGBIS Acceptance Concerns subscale
- *Internalized homonegativity* - LGBIS Internalized Homonegativity subscale
- *Self-esteem* – Rosenberg Self-Esteem Scale

Universal mechanism outcomes:

- *Emotion regulation* – Difficulties in Emotion Regulation Scale-Short Form
- *Perceived social support* – Multidimensional Scale of Perceived Social Support, Chinese version of the LGBIS - LGB-Specific Family Support subscale
- *Rumination* – Ruminative Response Scale

Psychosocial variables:

- *Body image* – Multidimensional Body-Self Relations Questionnaire, Appearance Evaluation subscale, Body Appreciation Scale-2
- *Adverse childhood experiences (ACEs;* administered at baseline and 8-month follow-up) – Life History Interview of ACEs
- *COVID-19 experiences* (administered at 8-month follow-up) – COVID-19 questionnaire

HIV/STI outcomes (only following video screener and at 8-month follow-up):

- At-home HIV/STI testing kit for HIV and syphilis

In addition to the assessments that will be administered at baseline, 4-month follow-up, and 8-month follow-up, three questionnaires will be administered weekly on the iCBT online platform for 10 weeks for the ESTEEM iCBT and self-monitoring conditions:

- Overall Depression Severity & Impairment Scale
- Overall Anxiety Severity & Impairment Scale
- Tracking Minority Stress Experiences Questionnaire

For the pilot study, the 10 YMSM will complete the following:

- Brief questionnaire (5 items) after completing each module
- Follow-up interview after completing all 10 modules
- 30-Day Timeline Follow-Back

For Aim 3, we will additionally review data for the following:

- Number of sessions completed by participants
- Points of study drop-off
- Acceptability and feasibility – participants' written responses to prompts within online modules will be coded for engagement and relevance to module content

See Sections 4.2.1 and 4.2.2. for further explanations of each measure.

### 4.2.1 Primary Outcome Variables/Endpoints

The following is the primary outcome variable and associated measures that will be administered at baseline, 4-month follow-up, and 8-month follow-up:

- YMSM's sexual health and HIV risk behavior
    - 30-Day Timeline Follow-Back – assesses retrospective estimates of sexual behavior. Participants are first asked to enter questions related to any current main partners or casual partners in the past 30 days. Participants are then asked to indicate days in the past 30 days that they engaged in sexual behavior. For the present study, the CSU will use a Chinese-translated version of the measure.
    - Decisional Balance for Condom Use Scale – 18-items based on a 5-point Likert scale assessing to what extent participants consider the importance of each statement related to having anal sex with or without condoms. The Chinese version of the measure will be used for the present study.
    - Safer Sex Questionnaire – 13-items based on a 5-point Likert scale assessing one's confidence in avoiding having anal sex without a condom in various contexts. A translated version of the measure in Chinese will be developed for the present study.
    - Past 4-month HIV/STI Testing Questionnaire – 7 multiple choice questions previously developed by Yale PI, Dr. Pachankis, of the present study for another RCT asking participants about their HIV/STI testing history. A translated version of the measure in Chinese will be developed for the present study.

### 4.2.2 Secondary and Exploratory Outcome Variables/Endpoints (if applicable)

The following are the secondary outcome variables and associated measures that will be administered at baseline, 4-month follow-up, and 8-month follow-up (unless otherwise noted):

- Mental health outcomes
    - Patient-Health Questionnaire-9 – 10-items from a psychometrically validated measure of depression based on a 4-point Likert scale. The Chinese version of the measure will be used for the present study.
    - Overall Depression Severity & Impairment Scale – 5-items from a measure that has previously been used by the Yale research team to assess changes in depressive symptoms among gay and bisexual men in the US. A translated version of the measure in Chinese will be developed for the present study.
    - Generalized Anxiety Disorder-7 – 8-items from a psychometrically validated measure of depression based on a 4-point Likert scale. The Chinese version of the measure will be used for the present study.
    - Overall Anxiety Severity & Impairment Scale - 5-items from a measure that has previously been used by the Yale research team to assess changes in anxiety symptoms among gay and bisexual men in the US. A translated version of the measure in Chinese will be developed for the present study.

- Social Interaction Anxiety Scale - 20-items that specifically assess symptoms of anxiety in social situation based on a 5-point Likert scale. The Chinese version of the measure will be used for the present study.
- Suicidal Ideation Attributes Scale – 5-items that assess thoughts related to suicide in the past month based on Likert scales from 0 to 10. The Chinese version of the measure will be used for the present study.
- Alcohol Use Disorders Identification Test – 10-items based on eight 4-point Likert scales and two 3-point Likert scales assessing alcohol use behavior. The Chinese version of the measure will be used for the present study.
- Drug Use Disorders Identification Test – 11-items based on nine 4-point Likert scales and two 3-point Likert scales assessing substance use behavior other than alcohol. The Chinese version of the measure will be used for the present study.

- Minority stress mechanism outcomes
  - LGBIS Concealment Motivation subscale – a 3-item subscale from the LGBIS assessing sexual orientation concealment based on a 6-point Likert scale. The Chinese version of the measure's subscale will be used for the present study.
  - LGBIS Acceptance Concerns subscale – a 3-item subscale from the LGBIS assessing rejection sensitivity based on a 6-point Likert scale. The Chinese version of the measure's subscale will be used for the present study.
  - LGBIS Internalized Homonegativity subscale – a 3-item subscale from the LGBIS assessing internalized homonegativity based on a 6-point Likert scale. The Chinese version of the measure's subscale will be used for the present study.
  - Rosenberg Self-Esteem Scale – 10-items based on a 4-point Likert scale assessing general aspects of self-esteem. The Chinese version of the measure will be used for the present study.

- Universal mechanism outcomes
  - Difficulties in Emotion Regulation Scale-Short Form – 18-items that comprise a total score and six subscales related to emotion (dys)regulation with each item based on a 5-point Likert scale. The Chinese version of the measure will be used for the present study.
  - Multidimensional Scale of Perceived Social Support – 12-items assessing perceived social support from a significant other, family, and friends based on a 7-point Likert scale. A translated version of the measure in Chinese will be developed for the present study.
  - Chinese version of the LGBIS - LGB-Specific Family Support subscale – a 3-item subscale from the LGBIS assessing social support specifically related to family support based on a 6-point Likert scale. The Chinese version of the measure's subscale will be used for the present study.
  - Ruminative Response Scale – 5-items asking individuals to rate on a 4-point Likert-scale how they generally think when feeling down, sad, or depressed. The Chinese version of the measure will be used for the present study.

- Psychosocial variables
  - Multidimensional Body-Self Relations Questionnaire, Appearance Evaluation subscale – 7-items focused on feelings of body (dis)satisfaction with one's physical appearance. All items are based on a 5-point Likert scale. The Chinese version of the measure's subscale will be used for the present study.
  - Body Appreciation Scale-2 – 10-items assessing the level of acceptance people have for their bodies regardless of size or shape, respect and attendance to bodily needs, and protecting the body from internalization of

society's pressure and standards of beauty. All items are based on a 5-point Likert scale. The Chinese version of the measure's subscale will be used for the present study.
    - Life History Interview of ACEs – 10-items assessing whether participants have experienced different types ACES throughout their lives. The Chinese version of the measure will be used for the present study.
    - COVID-19 Questionnaire – 21 questions adapted from prior research by PI Pachankis for the current study. The questionnaire consists of 9 multiple-choice questions assessing participants' experiences related to the COVID-19 pandemic, including diagnosis with COVID-19 and district lockdowns, and 6 items based on a 10-point Likert scale assessing perceived impact of the pandemic on health and behaviors, with 6 follow-up questions to discern the direction of impact. A translated version of all measures will be used for the present study.

- HIV/STI outcomes (only at pre-baseline [between video screener and consent video call] and 8-month follow-up):
    - At-home HIV/STI testing kit for HIV and syphilis – see Section 6.1 Study Procedures for more information about the at-home HIV/STI testing kit

The following are the weekly assessments that will be administered for 10 weeks on the iCBT online platform to both the ESTEEM iCBT and self-monitoring conditions:

- Weekly surveys
    - Overall Depression Severity & Impairment Scale – see description above.
    - Overall Anxiety Severity & Impairment Scale - see description above.
    - Tracking Minority Stress Experiences Questionnaire – 14-items (13 on a Likert scale and 1 open-ended response item) assessing different type of sexual minority related stressors in the past week. A translated version of the measure in Chinese will be developed for the present study.

For the pilot study, the 10 YMSM will complete the following:

- Brief questionnaire – 5-items assessing participants' feedback on the usability of each session module
- Follow-up interview after completing all 10 modules – an approximately 1-hour interview via WeChat with an RA at CSU asking questions about participants' feedback on the ESTEEM iCBT treatment in terms of comprehension and usability, as well as about the 30-day Timeline Follow-Back assessment
- 30-Day Timeline Follow-Back – see above for a description of this measure

For Aim 3, we will additionally review data for the following:

- Number of sessions completed by participants
- Points of study drop-off
- Acceptability and feasibility – participants' written responses to prompts within online modules will be coded for engagement and relevance to module content

# 5 Study Participants

## 5.1 Study Population

The study population for Aim 2 will consist of participants who are between the ages of 16-30 living in Hunan province China and identify their gender identity as male as well as endorse having sex with men in the past 12 months.

We are restricting eligibility for this study to individuals with a current male gender identity because this group is a rapidly increasing risk group for HIV in China, with prevalence increasing from less than 1.0% in 2003 to 9.2% in 2016. As in our previous intervention studies with this population, transgender men who have sex with men will be included.

The study will enroll participants ages 16-30 given that this age group contains the majority of newly diagnosed MSM in China and has experienced a severe lack of developmentally and culturally appropriate preventive intervention attention to date. The upper age range was chosen given both the age group most affected by HIV in China is 16-30 and also our previous research showing that the identity-focused aspects of our intervention are most suited to those MSM who are closest in age to developmental identity-based stress (e.g., minority stressors such as concealment).

Hunan province, the site of this study, contains 41 ethnic groups, all of which would be considered “Asian” according to the NIH-recognized racial/ethnic minority categories. Approximately 90% of residents of Hunan are Han, whereas the other 10% are Tujia, Miao, Dong, Yao, Bai, Hui, Zhuang, Uyghurs, and so forth. We therefore anticipate that our sample will be 100% “Asian” with the majority of participants being Han and the remainder following the general breakdown of ethnic minority groups in Hunan.

The study will also include only MSM who are sexually active, ensuring that the intervention content is relevant to all participants.

Aim 3 will include a proportion of Aim 2 participants whose window of study completion has ended. This aim will also incorporate community stakeholders, including government officials, medical providers, HIV-related NGO staff members, LGBTQ community center staff members, and community advocates.

## 5.2 Number of Participants

A total of 120 YMSM participants will be enrolled in Aim 2 of study ($n$ = 60 per condition). Assigning 60 participants to each condition (iCBT vs. self-monitoring) and accounting for 20% attrition, a liberal estimate based on our previous online RCTs (i.e., 93-100%), will provide ≥ 80% chance of detecting a difference ($p < .05$) between the conditions of $d = .40$, which is significantly lower than what we found when comparing in-person ESTEEM to waitlist ($d = .59$ for CAS, $d = .55$ for depression) and lower than even the smallest average meta-analytic effect ($d = .66$) of iCBT compared to weak control conditions for depression. For Aim 3, a total of 55 participants, including (n = 20) Aim 2 participants, (n = 6) study therapists and supervisors, (n = 8) government administrators and leadership, (n=7) LGBTQ community organization staff, and (n = 7) and medical providers will be interviewed in order to identify themes in regard to barriers and facilitators of implementing iCBT ESTEEM among Chinese YMSM.

## 5.3 Eligibility Criteria

In order to be eligible for inclusion in Aim 2 of the study, an individual must meet all of the following criteria:

- 16-30 years old
- Live in Hunan province China
- Current gender identity as male
- Report past 12-month sex with men
- Be confirmed HIV-negative upon at-home testing
- Report past 3-month condomless/PrEP-less anal sex

- Past-week symptoms of depression or anxiety using the Brief Symptom Inventory-4 cutoff of 2.5 on either the depression subscale, anxiety subscale, or both
- No past 3-month mental health services of more than 2 visits per month
- Weekly access to internet on a laptop, desktop, or tablet device
- Ability to read, write, and speak in Mandarin
- Provision of informed consent

Any individual who meets any of the following criteria will be excluded from participation in this study:

- Current active suicidality or homicidality (defined as active intent or concrete plan, as opposed to passive ideation)
- Evidence of active and untreated mania or psychosis that could interfere with the participant's ability to volitionally consent to research or interfere with their ability to safely and reliably complete research

## 5.4 Recruitment Procedures

*Recruitment strategy:* For both the full RCT and pilot study, we will recruit YMSM via advertisements on YMSM's social networking platforms (e.g., QQ, WeChat, Blued) and the lobbies of Zuo An Cai Hong (Cai Hong = "rainbow"), an SGM-friendly community-based organization with 7 offices in 7 cities of Hunan province that provides ~11,000 HIV tests/year and free counseling to YMSM and has a strong collaboration with the Chinese CDC Hunan office.

We will create online and paper (e.g., posters, flyers; see attached recruitment flyers on IRES) advertisements for this study to post widely on the above virtual and physical sites. Based on prior experience, we have allocated substantial recruitment funds to cover the cost of recruitment materials and outreach (e.g., in the unforeseen circumstance that QQ begins charging researchers to post recruitment ads).

The CSU team has a graduate student under Dr. Li's supervision who will serve in the role as a full-time recruiter. This individual, along with Dr. Li, has deep social connections with the YMSM community and is familiar with existing and emerging virtual and physical sites where YMSM socialize. They also possess knowledge of means to reach YMSM who might not be out (e.g., via virtual and physical cruising grounds), who therefore might be particularly suitable for our minority-stress-focused intervention.

*Comprehension test:* Before we randomize participants into the full trial, we will conduct a comprehension test the ESTEEM iCBT treatment with 10 YMSM to ensure their comprehension of the module material, as well as glean their feedback on the usability of the iCBT online platform. Our two pilots for this proposal (i.e., cultural adaptation in China + iCBT usability testing in the US) have already led to the creation of the in-person delivery materials for Chinese ESTEEM (e.g., manual, participant handouts) and established the technical feasibility of our iCBT platform. As such, the Chinese-adapted materials (e.g., manual, handouts) are ready to be transformed into iCBT content (e.g., self-guided exercises, videos, counselor instructions). Given the previous efficacy testing of in-person Chinese ESTEEM and iCBT in our US study, comprehension testing will occur over the course of 2 weeks with a focus on 10 YMSM reviewing the online treatment material, receiving counselor feedback, and providing feedback on the materials via answering brief questions after each module on its usability. For this comprehension test, the only inclusion criteria will be:

- 16-30 years old
- Live in Hunan province China
- Current gender identity as male

- Report past 12-month sex with men
- Weekly access to internet on a laptop, desktop, or tablet device
- Ability to read, write, and speak in Mandarin
- Provision of informed consent

These 10 YMSM for the comprehension test will not complete the study measures, with the exception of the 30-day Timeline Follow-Back assessment at the end of the pilot in order to test the usability of this assessment on the Sojump platform. After review of the ESTEEM iCBT materials, participants will provide feedback to the CSU research team on their comprehension of the materials, as well as respond to questions from a qualitative interview conducted by the CSU research team about their experience.

*Evidence for successful attainment of recruitment goals*: While recruiting 120 participants within a 10-month timespan is ambitious, we have easily exceeded this recruitment goal in equally high-stigma regions of much smaller population size. For instance, in our trial of a brief online intervention for sexual minorities in rural Appalachia, an area also with high stigma, we recruited 108 participants in 8 months, despite the six Appalachian counties of our geographic recruitment zone having 0.5M inhabitants (IRB #1512016952). By contrast, Hunan province, characterized by equally high stigma toward YMSM, has a population of nearly 70M (140 times more inhabitants than live in our Appalachia recruitment zone). Dr. Li has used the strategies proposed in this study (e.g., passive and active recruitment, leveraging her deep connections with YMSM-friendly community organizations) to previously enroll 80 MSM across 9 months into a multi-session motivational interviewing intervention. Finally, Dr. Pachankis has shown through his research with YMSM in Romania that he can meet this recruitment goal. In his current NIMH RCT in Romania, the research team has enrolled 60 YMSM over the first 6 months. This matches the rate at which he has recruited YMSM into his US-based RCTs, which have achieved sample sizes of 250 YMSM in approximately 25 months.

*Retention:* We have refined our retention strategies across several previous studies with YMSM in China, low-and-middle income countries, and in high-stigma regions of the US. First, to retain participants across the study, we will use all communication permitted by participants, including a study WeChat account, and frequent reminders. Second, to ensure high engagement with the iCBT sessions, we have built-in lessons-learned from our US-based usability test. For instance, we now include an introductory phone call between the counselor and participant. Also, one of our videos – shown at the start of the intervention – includes a brief “how-to” demonstration that shows participants how to navigate the iCBT platform itself. Third, we include reasonable financial incentives in Chinese currency (i.e., Renminbi; RMB) to compensate participants for their time spent on study-related tasks, amounting to 50RMB per iCBT session (for those in the iCBT ESTEEM condition), 30RMB for each weekly self-monitoring survey (for those in the self-monitoring condition), and 150RMB per assessment (baseline, 4-month follow-up, 8-month follow-up).

We have used these retention strategies previously to attain very high retention in our online RCTs. Dr. Pachankis attained 100% retention with 77 YMSM in his first online RCT. Dr. Pachankis also retained 88% of participants at follow-up in an online HIV-prevention RCT in Romania. Using near-identical strategies as will be used here, Dr. Li retained 83% of YMSM in her in-person motivational interviewing-based HIV-prevention RCT in Hunan. We estimate that we will retain at least 80% of participants, a quite liberal goal given that we have exceeded this goal in our previous studies with YMSM in high-stigma contexts. Nonetheless, our study is powered with even 20% attrition, to detect effects smaller than those found for identical outcomes (e.g., condomless anal sex, depression) in our previous RCTs with YMSM.

*Qualitative Interviews*: For the interviews conducted with LGBTQ organization staff, government administrators and leadership, and medical providers, the PI at CSU and her research team will contact the governmental and NGO professionals in their network about participating in these interviews. All participants will be compensated 200 RMB ($31.48) for their participation in interviews.

## 5.5 Consent/Assent Procedures/HIPAA Authorization

*Comprehension test.* A waiver of documentation of consent is planned for the all portions of this comprehension test study (see attachments on IRES for the online screener). For the comprehension test, potential participants will take the online screener for the study via the secure CSU Sojump survey software. As previously noted, the only inclusion criteria for the comprehension test will be: 16-30 years old, live in Hunan province China, current gender identity as male, report past 12-month sex with men, weekly access to internet on a laptop, desktop, or tablet device, ability to read, write, and speak in Mandarin, and provision of informed consent (see Section 5.3 for inclusion criteria for the full study). An RA at CSU will schedule a WeChat call with 10 YMSM participants who express interest in participating in the comprehension test. Prior to the WeChat call, the CSU RA will send a copy of the consent form via WeChat to the participant and ask them to review the form before the WeChat call. During the WeChat call, the CSU RA will read through the consent form and answer any questions from the participants. Participants will be informed on the consent form that they will receive 200RMB for reviewing the 10 iCBT session modules and 50RMB for participating in a follow-up interview. Any ineligible participants will be informed at the end of the online screener of their ineligibility for the study.

*RCT.* For the full RCT study (Aim 2), consent will be obtained at three time points. A waiver of documentation of consent is planned for all portions of this study:

First, participants will complete an initial online screener via the secure CSU Sojump survey software (see attachments on IRES for the online screener).

Second, if participants are eligible for the study based on the online screen, a CSU RA will schedule a video screen via WeChat for further assessment. At the beginning of this video call, participants will provide verbal consent before continuing with the video screen (see the Measure Packet uploaded on IRES for the script that will be followed for the video screener). Ineligible participants will be informed at the end of the video screener of their ineligibility for the study. If participants are eligible following the video screener, an at home HIV/STI testing kit will be sent to the participant via mail within 2 days of the video screener.

Third, a CSU RA will send participants who screen negative based on the at-home HIV testing a copy of the consent form via WeChat. A WeChat call will then be scheduled with each participant to review the consent form and assess whether participants understand the information in the consent form. As such, a waiver of signed documentation of consent is planned for the full RCT study (see attachments on IRES for the full RCT consent form).

Participants will be informed on the consent form that they will receive 50RMB per iCBT session (for those in the iCBT ESTEEM condition), 30RMB for each weekly self-monitoring survey (for those in the self-monitoring condition), and 150RMB per assessment (baseline, 4-month follow-up, 8-month follow-up).

Participants will be provided with the PI's contact information at CSU and directed to call or email the PI if they have any questions or concerns. The PI at CSU, Dr. Li, will be responsible for ensuring that online consent has been obtained.

*Waiver of Parental Consent for Participants Ages 16-17.* Involving Chinese adolescent YMSM in research to develop interventions for reducing depression, anxiety, and suicidality is essential for addressing the substantial mental health disparities affecting this population. Sexual orientation disparities in depression, anxiety, and suicidality are well-documented among Chinese adolescent YMSM (Huang et al., 2018; Zhang, Wong, Ip, Fan, & Yip, 2017); however, no evidence-based intervention has been developed to address the unique stressors faced by Chinese adolescent YMSM to reduce their disproportionate burden of mental health problems. To develop an intervention tailored to the needs of this population, our research involvement.

As such, the present study proposes to waive parental consent for adolescents ages 16-17 in the Hunan province of China for this study. Several reasons are presented in support of waiving parental consent. First, waiving parental consent would not adversely affect the rights and welfare of the participants and, in fact, obtaining parental consent would be impractical for many participants and potentially increase risk given the stigma toward sexual minorities in China. Parental rejection of one's sexual orientation is a robust risk factors for resultant depression, anxiety, and suicidality (Puckett et al., 2015; Ryan et al., 2010). Requiring parental consent and, thus, concurrent disclosure of sexual minority identity, increases the risk of such rejection. In some cases, parental consent can also hinder sexual minority participants' willingness to participate in research (e.g., Fisher, Fried, Puri, Macapagal, & Mustanski, 2018; Flores, McKinney, Arscott, & Barroso, 2018; Macapagal, Coventry, Arbeit, Fisher, & Mustanski, 2017; Taylor, 2018). For these reasons, parental consent for this study is not a reasonable ethical requirement to protect sexual minority adolescents in those states that do not require parental consent for adolescents ages 16-17 to receive mental health treatment.

Second, based on previous research (Melton, 1983; Susman, Dorn, & Fletcher, 1992; Weithorm, 1994), adolescents are fully capable of not only providing informed consent in situations in which parental consent poses significant risks, but are also as capable as adults of the decision-making capacity to provide informed consent.

Third, throughout the multiple points of consent, research staff at CSU will provide substitutes for parental consent to protect all study participants, including those ages 16-17. These protections include those listed in our current IRB-approved protocol for this study, including: (1) reviewing all participant survey responses and therapy-related exercises for indications of suicidality and severe distress by a member of the CSU's clinical team; (2) responding quickly to such distress by encouraging access to a 24/7 crisis hotline (see clinical protocol for more details); and, (3) contacting participants who indicate distress by our own clinical staff within one business day. The Clinical Protocol, successfully employed in our other studies of this treatment and its components when delivered both in-person and online, continues to guide the protection of study participants.

Lastly, as described in Section 7.3 and throughout this protocol, the present study poses minimal risk. As previously described, Chinese adolescent YMSM present at greater risk for depression, anxiety, and suicidality compared to their heterosexual peers (Huang et al., 2018; Zhang et al., 2017). The research procedures of the present study are not expected to increase this risk, but instead are intended to decrease it, as demonstrated in our pilot studies of this treatment and its components delivered both in person and online to young adults ages 18 to 35 (e.g., Pachankis, Hatzenbuehler et al., 2015; Pachankis, Williams et al., 2019). Indeed, participation in our previous similar intervention studies, including an in-person pilot study of the same intervention in China, reduced participants' average risk of depression and suicidality from baseline levels. The research procedures of the present study involve completing sexual and mental health questionnaires, reading written materials about mental health and stress, and engaging in asynchronous (i.e., not live) communication

with a study counselor about mental health and stress. These procedures do not pose greater risk than those encountered in daily life (e.g., taking a health education class) or other activities not requiring parental consent for sexual minority adolescents (e.g., attending a community LGBTQ meeting).

*Qualitative Interviews*: For the qualitative interviews (Aim 3), all RCT participants will already have completed eligibility screening and associated consent procedures. Thus, participants will provide additional consent for the interview at the time of the interview. The interviewer and participant will together review a consent form together that details interview risks/benefits and precautions against risk. Once participants have demonstrated that they fully understood the consent, they will be asked to provide verbal consent as well as sign an interview consent form using the Sojump survey platform (see attached in IRES). We foresee minimal risk for the potential of emotional distress as a result of the interview. If participants do not feel comfortable/experience distress answering specific questions, they will be informed that they may refrain from answering any question. Nonetheless, in the event of disclosure of emotional distress, the same procedures will be followed as in Aim 2. Interviews with community stakeholders are unlikely to pose risks given these individuals' professional involvement with LGBTQ-related stressors and therapies on a regular basis.

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# 6 Study Methods/Procedures

## 6.1 Study Procedures

We propose to test the efficacy of an online CBT intervention (ESTEEM iCBT) among 120 Chinese YMSM. The proposed prospective study will follow a 2-arm RCT design where participants will be randomized into either the ESTEEM iCBT treatment group or self-monitoring control group (both conditions described in further detail in Section 4, Study Design).

For the comprehension test, 10 YMSM will be recruited to review the ESTEEM iCBT treatment materials in order to assess their comprehension of the online treatment materials, as well as glean feedback in regard to usability of the iCBT online platform. In contrast to the full RCT, the only inclusion criteria for this comprehension test will be:

- 16-30 years old
- Live in Hunan province China
- Current gender identity as male
- Report past 12-month sex with men
- Weekly access to internet on a laptop, desktop, or tablet device
- Ability to read, write, and speak in Mandarin
- Provision of informed consent

Additionally, these participants will not complete baseline surveys as will be conducted for the full RCT. Also, since the purpose of the pilot is to ensure comprehension of the treatment material, participants will be asked to complete the 10 modules of the treatment over the course of 2 weeks. These 10 YMSM participants will be asked to share their feedback about their experience with the online CBT intervention via a WeChat call with a CSU research team member at the end of their participation.

For the full RCT study, 120 YMSM will be recruited via strategies and based on eligibility criteria described in Sections 5.4 and 5.3, respectively. Participants will first complete an online screener on the secure Sojump survey platform. If eligible, participants will be directed

to a separate Sojump survey where they will be asked to provide their contact information in order to be contacted for participation in the study. For participants who provide contact information, RAs at CSU will contact participants via their preferred contact method and ask to schedule a video screener on WeChat. Upon completion and deemed eligible from the video screener, participants will be mailed an at home HIV/STI testing kit. The estimated time of arrival based on the mailing system in Hunan province is 1-2 days. The RA at CSU will be able to check the mailing status of the testing kit. A CSU research team member will contact participants on WeChat after 5 business days of sending the HIV/STI testing kit if the participant has not sent the CSU team their results.

The kit will consist of a self-HIV testing kit using Alere Determine HIV 1/2 rapid assay (Alere Medical Co., Japan), a type of finger-prick-based HIV testing kit, approved by China's State Food and Drug Administration and the US Food and Drug Administration (sensitivity: 100.00%; specificity: 99.68%) on all participants. The same counseling and testing clinical protocol will be followed for syphilis testing, which will utilize the Treponema pallidum antibodies rapid test (emulsion process) (Abon biomedicine co., Hangzhou), a type of blood-based testing kit to detect syphilis (sensitivity: 99.01%, specificity: 99.35%). Participants will self-administer these sample collections following instructions that will be provided via QR code that will be enclosed in their kits.

Appropriate risk-reduction counseling will be provided to all participants on the same day of testing. Enclosed within testing kits, all participants will receive lubricant and condoms. The rapid test results for both HIV and syphilis will be ready to be read by participants in 20 minutes. HIV/STI test results will be discussed with participants by study counselors. Like conventional HIV enzyme immunoassays (EIAs), rapid HIV/STI tests are screening (i.e., not diagnostic) tests that require diagnostic confirmation by Western Blots if reactive (positive). Participants who test preliminarily positive (or have inconclusive tests) will be immediately linked to Zuo An Cai Hong for confirmatory testing, care, and treatment. Counselors will offer to make an appointment for participants at a local Zuo An Cai Hong, which has 7 offices across Hunan province. Participants testing HIV positive will not be randomized into the study, as HIV negative status is one of the inclusion criteria, so they will receive immediate HIV/STI counseling by one of our counselors, followed by medical attention by Zuo An Cai Hong to which they will be promptly linked. Participants who test negative will be given the option of continuing to move forward with the research study.

Participants who continue to express interest in the study will be sent a copy of the consent form via WeChat. Participants will be asked to read the consent form on their own. CSU RAs will schedule a consent call with participants via WeChat to read over the consent form with them, as well as check their understanding of the consent form via asking questions about the content of the study and ability for participants to withdraw from the study at any time. After participants provide verbal consent, we will assign them a username and password for the Karolinksa Institutet's secure iCBT online platform that houses the ESTEEM iCBT treatment and self-monitoring weekly assessment for both conditions. Participants will be required to login to the Karolinksa Institutet's secure iCBT platform before they are sent the baseline assessments. Upon signing into the iCBT online platform, a CSU RA will send a hyperlink to the participant via WeChat to complete the baseline surveys on Sojump. After completion of the baseline completion, a CSU RA will schedule a final WeChat call with each participant for their randomization into either the ESTEEM iCBT or self-monitoring condition.

For participants assigned to ESTEEM iCBT, they will be assigned a study therapist and will be contacted by their therapist to schedule a 30-minute introductory call via WeChat. During this conversation, therapists will explain the structure of the study and briefly discuss the participant's motivations and goals for participating in the study. All participants will then complete one session (i.e., ESTEEM iCBT or self-monitoring) per week. If participants miss

a session, as determined by daily therapist and RA review of session access and self-monitoring or homework completion, they will receive a reminder via a WeChat message to complete the session. Participants will also be asked to schedule a check-in WeChat call with their study therapist two-weeks post-randomization to discuss their progress through the study sessions. Participants will have a window period of four months (i.e., 17 weeks) to complete all 10 sessions.

Lastly, all participants will be sent messages on WeChat to complete 4-month and 8-month follow-up assessments. For all assessment time points, automatically generated alerts from Sojump will be sent to CSU study staff in response to any participants who indicate suicidality in response to suicidality assessments, at which point a clinical staff member part of the CSU team will implement the clinical protocol. For the 8-month follow-up, a second at-home HIV/STI testing kit will be mailed to participants. The same procedure as described above will be followed in regard to participants administering this test and reporting results to CSU study counselors for follow-up.

See Table 1 in Section 11.1 for a Visit Schedule Table with study procedures listing all points of data collection.

For Aim 3 qualitative interviews, a proportion of participants will be contacted following completion of their 8-month follow-up window to schedule the interview using their preferred method of contact. During the interview, the interviewer will ask about participants' experience with the study, its online format, and its perceived efficacy (see IRES for attached interview guide). Community stakeholders will be contacted over email by the PI at CSU, Dr. Li, to participate in focus group discussions with other participants of similar professions/roles. Community stakeholder participants will be shown a brief presentation on the format and content of the treatment intervention, as well as preliminary findings. These participants will then be asked about barriers and facilitators to implementation (see IRES for attached interview guide).

### 6.1.1 Data Collection

Data collection will begin with the online screener. Additional data will be collected during the video screener, baseline assessments, ESTEEM iCBT treatment and weekly self-monitoring surveys, 4-month follow-up assessments, and 8-month follow-up assessments.

All data collection will occur online both via the secure Sojump survey platform and Karolinksa Institutet's secure server that houses the iCBT platform. In-session text responses and session homework assignment data will be received at Karolinska Institutet's server, which hosts the online platform for both study conditions (i.e., Chinese ESTEEM iCBT and self-monitoring). No identifiable data will be collected on the iCBT online platform.

For data safety in regard to Sojump, Dr. Li has a signed confidentiality contract with Sojump. As part of this contract, only one account login and password is provided to ensure confidentiality. Furthermore, each login requires a phone-based dual text authentication. All the data from Sojump will be downloaded onto an offline computer. Both online assessments and the iCBT platform use will not ask for participants' name or other identifying information, only participant ID number. The one exception will be a separate Sojump survey to which eligible participants will be directed after completing the online survey. This information will be collected in order to contact participants. This contact information will be stored in a contact database (previously discussed in Section 2.2) that will only be accessible by Dr. Li and the CSU team on their offline computer in Dr. Li's lab. This contact database will be password-protected to further ensure participant

confidentiality. Aside from the password-protected contact database that will link participants' names with their study IDs that will be kept on the offline CSU computer in Dr. Li's lab, only participant IDs will be used in all other parts of the study.

For Aim 3, interviews will be conducted using Voov, a secure video conferencing software, and digital recording will be disabled for all participants. Interviews will be recorded following participant consent with an offline, independent voice recording device in a private environment by research staff. Recordings will then be uploaded to an offline computer; recordings will be destroyed from offline recording devices immediately after uploading. Qualitative interview recordings and Aim 3 participant tracking data will be kept in encrypted folders on two separate offline computers in Dr. Li's lab, to which only Dr. Li and the CSU team will have access. Interview recordings will be transcribed by a member of the research team blind to participant identifying information, and transcriptions will be kept alongside recordings on an offline computer.

## 6.2 Method of Assignment/Randomization (if applicable)

Participants who are confirmed eligible via the study screeners and who test negative for HIV based on the at home HIV/STI testing kit will then be randomized to ESTEEM iCBT or the weekly self-monitoring condition. Participant randomization will be stratified based on mental health (i.e., eligible based on depressive symptoms, anxiety symptoms, or both on the Brief Symptoms Inventory-4). Randomization will occur via use of a random number table generated by SPSS, which has been used reliably by Dr. Li and her team successfully when implementing stratified randomization for previous studies.

## 6.3 Adverse Events Definition and Reporting

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans. An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project (e.g., through regular study meetings, via email as they are reviewed by the principal investigator.) The protocol's Data and Safety Monitoring Board will be informed of serious or unanticipated adverse events within 5 days of the event becoming known to the principal investigator.

## 6.4 Reaction Management

Participants will be reminded that they can stop participation at any time, skip any question, or take a break if experiencing mild distress during the assessments. In the unlikely event that a participant experiences considerable distress, the CSU research team will make a referral (if needed) for clinical assessment and/or counseling. Participants will be given the names and office phone numbers of the PI at CSU. In the event that a participant discloses intent to harm oneself or others, the PI at CSU will report disclosures of intent to harm to the

appropriate authorities immediately. Identified clinically trained staff members at CSU will be on call for emergency consultation. In the unlikely event that such an incident should occur, we will notify the Yale IRB within 5 days and appropriate measures will be taken, including necessary reporting to the IRB.

### 6.5 Withdrawal Procedures

Of the participants who are eligible and consent to the research study, participants will be able to withdraw from the study at any point. The online consent forms will clearly state the voluntary nature of the study and possibility of withdrawal at any point. Additionally, participants will have the option of having their data destroyed.

### 6.6 Locations/Facilities

This study will be carried out in Hunan province China by our colleagues at CSU, who will serve as the site of study recruitment and all direct participant interaction. Yale University will serve as the primary scientific site of the study. Researchers at Yale will be responsible for ensuring the scientific, clinical, and technical robustness of the intervention, including its translation into the iCBT format and ongoing delivery. All participation will occur online and participants will be recruited in Hunan province, as specified below in Section 5.4 Recruitment Procedures.

# 7 Statistical Design

### 7.1 Sample Size Considerations

A total of 120 YMSM participants will be enrolled in this study ($n$ = 60 per condition). Assigning 60 participants to each condition (iCBT vs. self-monitoring) and accounting for 20% attrition, a liberal estimate based on our previous online RCTs (i.e., 93-100%), will provide ≥ 80% chance of detecting a difference ($p < .05$) between the conditions of $d = .40$, which is significantly lower than what we found when comparing in-person ESTEEM to waitlist ($d = .59$ for CAS, $d = .55$ for depression) and lower than even the smallest average meta-analytic effect ($d = .66$) of iCBT compared to weak control conditions for depression. While we likely do not have power to detect changes in our biologic HIV/STI outcomes, including them 1) verifies study eligibility, 2) establishes self-testing protocols for our future adequately powered research, and 3) promotes public health.

### 7.2 Planned Analyses

Our primary hypothesis is that Chinese ESTEEM iCBT will yield significantly greater reductions in CAS and HIV risk behavior than weekly self-monitoring. Repeated measures intent-to-treat generalized linear mixed models (GLMM) with negative binomial distributions and maximum likelihood estimation will be fit to CAS at 4- and 8-month follow-up adjusted for baseline CAS with intervention arm as a covariate. We will test the best-fitting correlation structure, but based on our previous studies, expect it to be compound symmetrical. We will conduct exploratory analyses to determine within- and across-condition effects of each arm over time, including appropriate parameters for any trends evident over time. These models may be adjusted for any potential covariates (e.g., urban vs. rural residence; level of outness or education) that are associated with our outcomes if the intervention arms are not balanced on these variables.

#### 7.2.1 Secondary Objective Analyses (if applicable)

A similar approach will be taken for our secondary outcomes (i.e., depression, anxiety, and minority stress variables) as described in Section 7.2. We will also examine baseline depression, anxiety, and minority stress as potential moderators of ESTEEM iCBT efficacy, hypothesizing that YMSM with higher baseline minority stress benefit most. To do so, we will

run the GLMMs described previously including two-way moderator x arm interactions with post hoc probing of significant interactions via simple slopes. Based on similar moderator analyses with in-person ESTEEM, our expected sample size will provide ≥ .80 power to detect medium effects ($f^2$=0.15, $p < 0.05$).

In addition, we will assess preliminary acceptability and feasibility of the ESTEEM iCBT intervention through textual analysis of participants' written responses on the iCBT online platform. Select responses from each module of the treatment will be coded to assess participant engagement and relevance of writing content to the treatment; consensus meetings will be held with Co-PI Li and Co-I Sun to resolve disagreement in response codes. Linking IDs will be used to mask coders to participant IDs, and scores for response codes will be linked to participant IDs for analysis by research staff not involved in coding. Engagement in treatment and relevant of writing content will be examined as moderators of treatment efficacy by the approaches outlined above.

### 7.2.2 Analysis of Subject Characteristics (if applicable)

We will collect demographic data including age, ethnicity, sex assigned at birth, gender identity, sexual orientation, education level, marital/relationship status, family income, and migrant status. A complete list of all demographic variables is presented in the attached measures packet on IRES. All subject characteristics will be reported descriptively utilizing means and standard deviations for continuous variables and proportions for categorical variables.

### 7.2.3 Interim Analysis (if applicable)

The DSMB will review all risk-related data (e.g., HIV risk behavior, suicidality, and depression) by condition during each annual meeting. The DSMB will decide whether to review this information while masked to condition assignment.

## 7.3 Data Relevance

In this study, our primary objective is to evaluate the preliminary efficacy of a Chinese-adapted version of iCBT ESTEEM on YMSM's sexual health and HIV risk behavior. The data that we will collect in this study is highly relevant to our primary objective. Our primary outcome measures will be an online version of a Timeline Follow-Back, which has been by both the research team at Yale and CSU conducted among MSM participants, as well as self-report questionnaires assessing sexual risk behavior. In alignment with our secondary objective to assess symptoms of depression and anxiety, as well as assessing whether baseline minority stress exposure moderates treatment efficacy, we will assess mental health symptoms and minority stress-related variables via several quantitative survey items. Of note, the majority of these survey items have previously been validated among Chinese samples. Finally, we will assess acceptability and feasibility of the intervention using qualitative coding of participants' written responses to inform the adaptability of the iCBT ESTEEM intervention beyond the study and analyze these variables as moderators of treatment efficacy. All data collected as part of this study is highly relevant to our research questions.

## 7.4 Data Coding

Data will be scored based on each measure's pre-specified ratings scale (see Measures packet on IRES). Outcomes utilized in statistical analyses will be continuous sum or mean scores, as applicable. Participant responses will be coded based on ratings of engagement and relevance of written responses to treatment content.

## 7.5 Data Analysis Tools

Data will be managed and analyzed utilizing SPSS Statistics and SAS.

### 7.6 Data Monitoring

The PIs at Yale and CSU are responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews quarterly. During the review process, the PIs will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

Additionally, a four-member monitoring committee will be convened to determine safe and effective study conduct and recommend conclusion of the study if significant risks develop or if the trial is unlikely to be concluded successfully. See Section 8.7 for more details regarding the Data and Safety Monitoring Board.

### 7.7 Handling of Missing Data

We will use an intent-to-treat analysis including all eligible cases. Maximum likelihood estimation will be employed, which is robust to missing data at followup.

# 8 Data/Specimen Handling and Record Keeping

### 8.1 Subject Data Confidentiality

Participant confidentiality and privacy is strictly held in confidence by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research activities will be conducted in as private a setting as possible. Representatives of the IRB may inspect all documents and records required to be maintained by the investigator for the participants in this study.

To maximize privacy and ensure confidentiality, participant names, which will only be recorded during the initial online screener, will be kept separate from all other data. All data will be collected via the secure Sojump survey server and on Karolinksa Institutet's secure server, which hosts the online platform for both study conditions. Data will also remain on the Karolinska Institutet server after transfer to Yale for storage on Yale's Secure Box. Participants will be assigned a unique code number prior to completion of a video screener, as well as a separate unique code after randomization to one of the two study conditions. The use of the unique code will permit linkage of the data being collected across all time points in the study. A master link file will connect participants' names and WeChat accounts to their study code number. The link file will be password-protected and only accessible to the CSU PI and study team members on an offline computer. Upon collection of the study data, de-identified data will be stored on password-protected folders on Yale Secure Box that requires dual-factor authentication to access. De-identified survey data will be downloaded and organized in SPSS files or SAS files and stored on password-protected computers by the Yale and CSU study team. Taken together, these measures are anticipated to be highly effective in protecting the privacy and confidentiality of participants and have proven successful in other studies that the PIs and their research teams have implemented.

The study participants' contact information will be held securely during the study. At the end of the study, all records will continue to be kept in a secure location for three years. After three years, all records for the study will be destroyed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on a secure Yale Secure Box folder only accessible by the Yale and CSU research study team members. As previously noted, this will not include the participants' identifying information. Rather, individual participants and their research data will be identified by a unique study code number. The study data entry and study management systems used will be secured and password-protected. At the end of the study, all study databases will be de-identified and archived on a secure Yale Box folder.

## 8.2 Data Quality Assurance

All assessment measures for the online screener, baseline surveys, 4-month follow-up, and 8-month follow-up will be administered via the secure Sojump survey platform using contact list functions to accurately and consistently administer surveys to participants. Additionally, attention check questions will be placed throughout the survey at each time point in order to better ensure participant attention when answer the survey questions. CSU RAs and study therapists will be trained in using the iCBT platform by a consultant from Karolinksa Institutet, as well as Yale's postdoctoral associate and senior RA on the research team who have previous experience working with the iCBT platform.

## 8.3 Data or Specimen Storage/Security

Participant names, which will only be recorded on a separate survey for those who are eligible based on the online screener, will be kept separate from all other data collection surveys. All data will be collected via the secure Sojump survey platform. Participants will be assigned a unique study code number upon providing consent to participant in the study. The use of the unique code will permit linkage of the data being collected across study time points. As previously noted, a master link file will connect participants' names and WeChat accounts to their study code number. The link file will be password protected and only accessible to the CSU PI and study team members on an offline computer. Upon collection of the study data, de-identified data will be stored on password protected folders on Yale Secure Box that requires dual-factor authentication to access. De-identified survey data will be downloaded and organized in SPSS files or SAS files and stored on password-protected computers by the Yale and CSU study team.

Study participant research data from CSU will be transmitted to and stored on a Yale Secure Box folder only accessible by the research study team members. This will not include the participant's identifying information. Rather, individual participants and their research data will be identified by a unique study code number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on a secure Yale Box folder.

## 8.4 Study Records

Study records will consist of responses from self-report surveys. The PIs at CSU and Yale will be responsible for maintaining the study documentation, which will be maintained on an offline computer at CSU PI's lab, as well as a Yale Secure Box folder.

## 8.5 Access to Source

Source data will consist of surveys and other study measures that will all be administered online via the secure Sojump survey platform, as well as the iCBT platform through Karolinksa Institutet's secure server. All source data will be electronic (i.e., no surveys with handwritten responses). Research data will only be accessible on an offline computer at CSU PI's lab and a Yale Secure Box folder. Unidentifiable data, including homework assignments from ESTEEM iCBT participants and weekly self-monitoring surveys from all participants, will also be stored on the Karolinksa Institutet's secure server.

## 8.6 Retention of Records

At the end of the study, all records will continue to be kept in a Yale Secure Box folder and an offline computer at CSU PI's lab. After three years, all identifiable records for the study will be destroyed.

## 8.7 Data and Safety Monitoring Plan

The PIs at Yale and CSU are responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews quarterly. During the review process, the PIs will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

Additionally, a four-member monitoring committee will be convened to determine safe and effective study conduct and recommend conclusion of the study if significant risks develop or if the trial is unlikely to be concluded successfully.

DSMB members will have expertise in YMSM mental and sexual health, RCTs of HIV-prevention interventions, and biostatistics. Notably, Yale and CSU have had a training grant for the past 9 years from Fogarty (R25 TW007700) specifically to enhance the ability of Chinese researchers to uphold ethical research standards. Thus, we are highly optimistic that we will find highly qualified DSMB members in both the US and China. The DSMB will hold biannual meetings (or more as needed), which will be facilitated by the two PIs via Zoom.

The DSMB shall be responsible for the following:

- Reviewing the research protocol and planning for data and safety monitoring.
- Monitoring that will take place on a regular basis (at least biannually or more as needed).
- Evaluating the progress of the trial, including periodic assessments of data quality and timeliness, participant session attendance and assessment completion, participant risk versus benefit, and other factors that may affect study outcome. Monitoring may also consider factors external to the study when interpreting the data, such as scientific developments that may have an impact on the safety of the participants or ethical issues related to the study.
- Inquiring for further information as necessary to accomplish their goals.
- Maintaining confidentiality during all phases of the trial including the monitoring, preparation of interim results, review, and response to monitoring recommendations.
- Generating a report that will be provided to the PI, the IRBs, and the NIH project officer.

The DSMB will conduct an open session prior to the initiation of the study. The DSMB will have been provided with all material associated with the trial and have had sufficient opportunity to review the documents. At the open session, all members will discuss any potential concerns for the safe and effective conduct of the impending study.

PIs Pachankis and Li shall be responsible for the following:

- Preparation and establishment of a plan for the data and safety monitoring.
- Evaluation of any members of the DSMB for a conflict of interest or financial stake in the outcome of the trial.
- Delegation of the ongoing monitoring of the trial to the DSMB.
- Ensuring that monitoring is timely and effective and that the DSMB is composed of individuals with appropriate expertise to accomplish their assigned tasks.

- Overseeing the monitoring activities.
- Responding to and addressing recommendations that result from monitoring activities.
- Provision of adverse event reports and other safety data to the DSMB, as well as any changes in the trial or annual reports to the IRBs and NIH.
- Contributing to the report that the DSMB generates, which will be distributed to the IRBs and NIH.
- Submitting the DSMB report to the IRBs.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the PI becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project (e.g., through regular study meetings, via email as they are reviewed by the principal investigator.) The protocol's DSMB will be informed of serious or unanticipated adverse events within 5 days of the event becoming known to the principal investigator.

# 9 Study Considerations

## 9.1 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. An IRB protocol will also be submitted at CSU. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required. Study closure will be submitted to the IRB after all research activities have been completed. Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale policies.

## 9.2 Research Personnel Training

This study involves collaboration across four sites – Yale University (US; PI: Pachankis), Central South University (China; PI: Li), Karolinska Institutet (Sweden; Consultant: Ljóttson), and Brown University (USA; Co-Investigator: Sun).

(1) Yale University will serve as the primary scientific site of the study. Researchers at Yale will be responsible for ensuring the scientific, clinical, and technical robustness of the intervention, including its translation into the iCBT format and ongoing delivery. Yale researchers will ensure supervision of all study counselors and will also oversee all data analysis, both quantitative and qualitative. In addition to the Dr. Pachankis as PI, Yale study team members will consist of Zachary Soulliard (postdoctoral associate), who will oversee preparation of the IRB protocol, ongoing reports to Yale's IRB, scheduling DSMB meetings, and scheduling full research team meetings. Kriti Behari (senior RA) and Ben Eisenstadt (senior RA) will support Dr. Soulliard in the abovementioned tasks. Dr. Ashley Hagaman (Assistant Professor of Public Health) will assist with qualitative data analysis.

(2) Central South University will serve as the site of study recruitment and all direct-to-participant interaction. Researchers and staff at CSU will ensure that all recruitment goals

are met, that data are collected with rigor, and that participant interactions occur ethically. As one of the study PIs, Dr. Xianhong Li will supervise the entire flow of the study, as well as provide oversight of the data storage and eventual manuscript writing. She will also work closely with study therapists to ensure delivery of the counseling intervention on the iCBT platform. Along with Dr. Li, Si Pan will serve as the project coordinator of the study, and thus, will coordinate preparation of the CSU IRB concurrently with Dr. Soulliard's oversight of the Yale IRB. Si Pan will also provide oversight to the CSU RA. Mengyao Yi will serve as the lead RA at CSU. Study therapists at CSU will include Xiangyu Li and Yang Xiong, who are both SGM-affirmative counselors with advanced training in working with Chinese YMSM. Mrs. Yang Xiong, MSN, RN, will also be the primary contact (in addition to Drs. Ying He and Xianhong Li) in regard to the clinical protocol. Ci Zhang, MSN, RN, is a graduate student working with Dr. Li who will interview counselors and supervisors as part of the qualitative interview process. Lastly, Dr. Ying He is a psychiatrist who will assist and provide support with the at home HIV/STI testing completed by participants. She will also be responsible for monitoring any clinical issues and make timely referrals as needed.

(3) Dr. Ljóttson at the Karolinska Institutet will provide technical support for this study, including hosting the iCBT platform and providing training and trouble-shooting assistance regarding the iCBT platform across the study period. Karolinska Institutet also provides highly secure data collection servers where iCBT data will be stored, since the iCBT platform itself is also located there.

(4) Brown University will provide supervision of study counselors. Dr. Sun will provide Chinese-language supervision and cross-cultural translation of intervention concepts and materials between the China and US teams.

## 9.3 Study Monitoring

The study will be monitored internally by the CSU study team members on a weekly basis and in joint meetings with the Yale-CSU team on a biweekly basis.

## 9.4 Unanticipated Problems and Protocol Deviations

A protocol deviation is any noncompliance with the protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the principal investigator to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents and the reviewing IRB per their policies.

Unanticipated problems (UP) involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the study team becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by via email.

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB within 5 days of the investigator becoming aware of the event.

## 9.5 Study Discontinuation

The research team will discuss discontinuation of the study in the event that participants in either condition experience unanticipated adverse events (e.g., increased active suicidality) over the course of study completion. The DSMB and IRB will be involved in such a discussion.

## 9.6 Study Completion

Data collection for the study will end by November 30, 2022. Data analysis is expected to occur from December 2022 to May 2023. The study is anticipated to be completed by June 1, 2023.

## 9.7 Conflict of Interest Management Plan

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

## 9.8 Funding Source

The study is funded by the 1R21TW011762-01 grant awarded to the MPIs (Drs. Li and Pachankis) of this study.

## 9.9 Publication Plan

Upon the completion of data analysis by May 2023, the research team anticipates submitting an initial manuscript for publication by August 31, 2023 that describes the primary efficacy of the study. It will be the MPIs' responsibility for publishing the study results.

# 10 Appendices

| Appendix # | Title | Sections | Topic |
|---|---|---|---|
| **1** | **References** | **1 & 2** | **Background & Rationale/Significance** |

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# 11 List of Tables

## 11.1 Table 1 – Visit Schedule Table of Full Study Conditions and Measures

| | *Online consent for initial online screener* | *Video Screener on WeChat + At home HIV/STI Testing* | *Consent Call on WeChat* | *Randomization Call on WeChat* | *Visit 1: Baseline surveys (Day 1 ± 7)* | *Visit 2: Study Intervention (ESTEEM iCBT or Self-Monitoring) (Day 7 to 70-119)* | *Visit 3: 4-month follow-up surveys (Day 119 ± 126)* | *Visit 4: 8-month follow-up surveys (Day 126 ± 133)* |
|---|---|---|---|---|---|---|---|---|
| ***Informed Consent*** | X | X | X | | | | | |
| ***Randomization*** | | | | X | | | | |
| ***Demographics Assessment*** | | | | | X | | | |
| ***Primary Measures*** | | | | | | | | |
| *30-Day TimeLine Follow Back* | | | | | X | | X | X |
| *Decisional Balance for Condom Use Scale* | | | | | X | | X | X |
| *Safer Sex Questionnaire* | | | | | X | | X | X |
| *Past 4-month HIV/STI Testing Questionnaire* | | | | | X | | X | X |
| ***Secondary Measures**** | | | | | | | | |
| *Mental Health Measures* | | | | | X | | X | X |
| *Minority Stress Variables & Collective Self-Esteem Measures* | | | | | X | | X | X |
| *Potential Mechanism Variables* | | | | | X | | X | X |
| *Psychosocial Variable Measures* | | | | | X | | X | X |
| *HIV/STI outcomes* | | X | | | | | | X |
| ***ESTEEM iCBT Treatment*** | | | | | | X (ESTEEM iCBT group ONLY) | | |
| ***Weekly self-monitoring of mood and minority stress*** | | | | | | X | | |
| ***Adverse Event Reporting*** | | X | | | X | X | X | X |

* = See Section 4.2.2. for a full list of secondary measures