

# **STATISTICAL ANALYSIS PLAN**

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

# **STATISTICAL ANALYSIS PLAN**

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Revisions to the SAP were completed before data were locked.

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## STUDY SUMMARY (revised 1.24.23)

Title	Developing Efficient Intervention Technologies to Reduce Stigma-Related Stress, Mental Health Problems, and HIV Risk among Young Chinese MSM
Study Design	The design is a two-arm, parallel-assignment randomized controlled trial design to test the efficacy of an internet-based cognitive behavioral therapy (iCBT), Effective Skills to Empower Effective Men (ESTEEM), in comparison to self-monitoring control. The unit of randomization is the individual.
Study Duration	2.67 years
Trial Sites	Hunan province, China (Central South University)
Objective	The <u>primary objective</u> is to evaluate the preliminary efficacy of a Chinese-adapted version of iCBT ESTEEM on young men who have sex with men's (YMSM) HIV risk behavior compared to self-monitoring control. Secondary outcomes will include HIV social-cognitive risk factors, HIV/STI test results, mental health, universal psychosocial risk factors for mental and behavioral health problems, and minority stress. The <u>secondary objectives</u> of this study are to determine whether baseline minority stress exposure moderates treatment efficacy, such that participants with the most minority stress exposure benefit more from iCBT ESTEEM than from self-monitoring control.
Number of Subjects	120
Main Inclusion Criteria	<ul style="list-style-type: none"> <li>(1) 16-30 years old</li> <li>(2) Live in Hunan province, China</li> <li>(3) Current gender identity as male</li> <li>(4) Report past 12-month sex with men</li> <li>(5) Be confirmed HIV-negative upon at-home testing</li> <li>(6) Report past 3-month condomless/PrEP-less anal sex</li> <li>(7) 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</li> <li>(8) No past 3-month mental health services of more than 2 visits per month</li> <li>(9) Weekly access to internet on a laptop, desktop, or tablet device</li> <li>(10) Ability to read, write, and speak in Mandarin</li> <li>(11) Provision of informed consent</li> </ul>

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Intervention	<p>1) <u>ESTEEM iCBT</u>: This online CBT treatment consists of 10 weekly modules that participants will complete over the course of 4 months. 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 LGBTQ-specific content and feedback into homework reviews. This intervention was culturally adapted for Chinese YMSM and found to be acceptable and feasible.</p> <p>2) <u>Self-monitoring control</u>: 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. Participants will record these experiences once per week for 10 weeks.</p>
Duration of Intervention	10 weekly modules in up to 17 weeks (four months)
Primary Outcome	Number of past-30-day condomless anal sex (CAS) acts with primary or casual partners as measured by the Timeline Follow-Back at the 8-month follow-up assessment.
Primary Analysis	We will examine the efficacy of the intervention using a generalized linear mixed model to test whether receipt of ESTEEM iCBT vs the self-monitoring control affects changes in the number of past-30 day CAS with primary or casual partners from baseline to 8-month follow up.

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<p>Secondary Outcomes</p>	<p>Change from baseline to immediate post-intervention (4-month follow-up): Number of past-30-day CAS acts with primary or casual partners (TLFB), number of past-30-day CAS acts with casual partners (TLFB), safer sex self-efficacy (SSQ), decisional balance for condom use (DBCUS), past 4-month HIV/STI testing, depressive symptoms (PHQ-9), anxiety symptoms (GAD-7), alcohol use problems (AUDIT), drug use problems (DUDIT), suicidality (SIDAS), concealment motivation (LGBIS), acceptance concerns (LGBIS), internalized homonegativity (LGBIS), emotion dysregulation (DERS), social support (MSPSS), and rumination (RRS).</p> <p>Change from baseline to 8-month follow up: Number of past-30-day CAS acts with only casual partners (TLFB), safer sex self-efficacy (SSQ), decisional balance for condom use (DBCUS), past 4-month HIV/STI testing, depressive symptoms (PHQ-9), anxiety symptoms (GAD-7), alcohol use problems (AUDIT), drug use problems (DUDIT), suicidality (SIDAS), concealment motivation (LGBIS), acceptance concerns (LGBIS), internalized homonegativity (LGBIS), emotion dysregulation (DERS), social support (MSPSS), rumination (RRS), HIV testing results, and syphilis testing results.</p>
<p>Exploratory Outcomes</p>	<p>Change from baseline to immediate post-intervention (4-month follow-up): Depression severity and impairment (ODSIS), anxiety severity and impairment (OASIS), self-esteem (RSE).</p> <p>Change from baseline to 8-month follow-up: Depression severity and impairment (ODSIS), anxiety severity and impairment (OASIS), self-esteem (RSE).</p>

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## 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.<sup>1</sup> The majority of newly diagnosed MSM are ages 16-30.<sup>2</sup> Structural and psychological forms of stigma toward young MSM (YMSM) fuel China's HIV epidemic.<sup>3-5</sup> Structurally, Chinese YMSM face a lack of equal rights and legal protections, including no same-sex marriage, same-sex education, or recourse against discrimination.<sup>6-8</sup> Not only are YMSM-focused evidence-based treatments lacking in China, but sexual orientation conversion therapy is promoted as a means to help YMSM who are often desperate to maintain heterosexual desires and create traditional families expected by Chinese culture.<sup>9-11</sup> As is true in other countries, this structural stigma gives rise to maladaptive coping processes among YMSM.<sup>12-14</sup> Known as minority stress, these processes include identity concealment, internalized homonegativity, and sensitivity to identity-based rejection,<sup>15-19</sup> and they drive the substantial mental health disparity borne by YMSM in China.<sup>20-24</sup> Both minority stress and poor mental health compromise HIV prevention and care behaviors through avoidant coping, low self-worth, impulsivity, and unassertiveness.<sup>25,26</sup>

Despite the promise of deploying evidence-based interventions to reduce the HIV epidemic among YMSM in China,<sup>27</sup> no interventions address this population'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.<sup>28-30</sup> 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.

## 2. AIMS

1. **Aim 1:** Evaluate the preliminary efficacy of a Chinese-adapted version of iCBT ESTEEM on young men who have sex with men's (YMSM) HIV risk behavior compared to self-monitoring control. Secondary outcomes will include HIV social-cognitive risk factors, HIV/STI test results, mental health, universal psychosocial risk factors for mental and behavioral health problems, and minority stress.
2. **Aim 2:** Determine whether baseline minority stress exposure moderates treatment efficacy, such that participants with the most minority stress exposure benefit more from iCBT ESTEEM than from self-monitoring control..

## 3. STUDY DESIGN

The design is a two-arm, parallel-assignment randomized controlled trial design to test the efficacy of iCBT ESTEEM compared to self-monitoring control. The unit of randomization is the individual. The primary outcome is number of past-30-day CAS with primary or casual partners at 8-mo follow-up, assessed via Timeline Follow-Back. A total of 120 YMSM participants were enrolled in the study ( $n = 60$  per condition).

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## 4. OUTCOMES

The primary and secondary outcome measures, each measured via self-report at baseline, immediate post-intervention (4-month follow-up), and 8-month follow-up (with the exception of HIV/STI testing results, which were measured via testing kits at baseline and 8-month follow-up), are summarized in Table 1.

Table 1. Primary (1'), Secondary (2'), and Exploratory (3') Outcome Measures		
Domain	Measure (1°, 2°, 3°)	Source
HIV-risk behavior	Condomless anal sex with primary or casual partners (1°; 2°)	Past 30-Day Timeline Follow-Back
	Condomless anal sex with casual partners only (2°)	Past 30-Day Timeline Follow-Back
	Safer sex self-efficacy (2°)	Safer Sex Questionnaire (SSQ)
	Decisional balance (2°)	Decisional Balance for Condom Use Scale (DBCUS)
	HIV/STI testing history (2°)	Past 4-month HIV/STI Testing Questionnaire
	HIV/STI testing results (2°)	Rapid testing kits for HIV and syphilis
Mental health and substance use	Depression symptoms (2°)	Patient Health Questionnaire-9 (PHQ-9)
	Depression severity and impairment (3°)	Overall Depression Severity & Impairment Scale (ODSIS)
	Anxiety symptoms (2°)	Generalized Anxiety Disorder-7 (GAD-7)
	Anxiety severity and impairment (3°)	Overall Anxiety Severity & Impairment Scale (OASIS)
	Alcohol and substance use (2°)	Alcohol Use Disorders Identification Test (AUDIT), Drug Use Disorders Identification Test (DUDIT)
	Suicidality (2°)	Suicidal Ideation Attributes Scale (SIDAS)
Minority Stress	Concealment motivation (2°)	Lesbian, Gay, and Bisexual Identity Scale (LGBIS) Concealment Motivation subscale
	Acceptance concerns (2°)	LGBIS Acceptance Concerns subscale
	Internalized Homonegativity (2°)	LGBIS Internalized Homonegativity subscale
	Self-esteem (3°)	Rosenberg Self-Esteem Scale (RSE)

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Universal Stress processes	Emotional Regulation (2°)	Difficulties in Emotion Regulation Scale-Short Form (DERS)
	Rumination (2°)	Ruminative Response Scale (RRS)
	Social Support (2°)	Multidimensional Scale of Perceived Social Support (MSPSS), LGBIS - LGB-Specific Family Support subscale

## 4.1 Primary Outcome

The primary outcome is past-30-day condomless anal sex with main or casual partners at 8-month follow-up assessed via Timeline Follow-Back.

## 4.2 Secondary Outcomes

### HIV/STI risk behaviors:

- *Condomless anal sex with primary or casual partners* – Timeline Follow-Back (4-mo)
- *Condomless anal sex with casual partners* – Timeline Follow-Back (4- and 8-mo)
- *Safer sex self-efficacy* – Safer Sex Questionnaire (4- and 8-mo)
- *Decisional balance for condom use* – Decisional Balance for Condom Use Scale (4- and 8-mo)
- *HIV/STI testing history* – Past 4-month HIV/STI Testing Questionnaire (4- and 8-mo)
- *HIV/STI test results* – Rapid testing kits for HIV and syphilis (8-mo follow-up only)

### Mental health outcomes:

- *Depressive symptoms* – Patient Health Questionnaire-9 (4- and 8-mo)
- *Anxiety symptoms* – Generalized Anxiety Disorder-7 (4- and 8-mo)
- *Suicidal ideation* – Suicidal Ideation Attributes Scale (4- and 8-mo)
- *Alcohol and substance use* – Alcohol Use Disorders Identification Test, Drug Use Disorders Identification Test (4- and 8-mo)

### Minority stress mechanism outcomes:

- *Concealment motivation* – Lesbian, Gay, and Bisexual Identity Scale (LGBIS) Concealment Motivation subscale (4- and 8-mo)
- *Acceptance concerns* – LGBIS Acceptance Concerns subscale (4- and 8-mo)
- *Internalized homonegativity* - LGBIS Internalized Homonegativity subscale (4- and 8-mo)

### Universal mechanism outcomes:

- *Emotion regulation* – Difficulties in Emotion Regulation Scale-Short Form (4- and 8-mo)



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- *Perceived social support* – Multidimensional Scale of Perceived Social Support, Chinese version of the LGBIS - LGB-Specific Family Support subscale (4- and 8-mo)
- *Rumination* – Ruminative Response Scale (4- and 8-mo)

## 4.3 Exploratory Outcomes

- *Depression severity and impairment* -- Overall Depression Severity and Impairment Scale (4- and 8-mo)
- *Anxiety severity and impairment* – Overall Anxiety Severity and Impairment Scale (4- and 8-mo)
- *Self-esteem* – Rosenberg Self-Esteem Scale (4- and 8-mo)

## 5. RANDOMIZATION

### 5.1 Method of Randomization

Randomization occurred on the participant level. Participants were randomly assigned to receive one of two conditions: iCBT ESTEEM or self-monitoring (N = 120). We used a 1:1 randomization scheme such that for every one participant randomized to iCBT ESTEEM, one participant was randomized to self-monitoring. Participant randomization was stratified based on mental health (i.e., eligible based on depressive symptoms, anxiety symptoms, or both based on the Brief Symptom Inventory-4). Stratified randomization occurred using a random number table generated by SPSS such that 60 participants were randomized to each condition.

### 5.2 Allocation Concealment

Concealment was not employed given that all measures involved self-report or objective HIV/STI test results.

## 6 SAMPLE SIZE

### 6.1 Preliminary Data

Sample size calculations were based on comparisons of in-person ESTEEM to waitlist for CAS<sup>29</sup> and meta-analytic effect sizes of iCBT compared to weak control conditions for depression.<sup>31-34</sup>

### 6.2 Sample Size Determination for the Primary Outcome

Assigning 60 YMSM to each condition (iCBT vs. self-monitoring) and accounting for 20% attrition, a liberal estimate based on our previous online RCT attrition of 0-17%, will provide  $\geq 80\%$  chance of detecting a difference ( $p < .05$ ) between the conditions of  $d = .40$ , which is lower than we found when comparing in-person ESTEEM to waitlist ( $d = .59$  for CAS).<sup>29</sup> While we likely do not have power to detect changes in our biologic HIV/STI outcomes, including them 1)

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verifies study eligibility, 2) establishes self-testing protocols for our future research, and 3) promotes public health.

## 6.3 Power for Secondary Outcomes

Comparisons of in-person ESTEEM to waitlist have produced effect sizes of  $d = .55$  for depression.<sup>29</sup> Average meta-analytic effects for depression ( $d = .66$ ) of iCBT compared to weak control conditions also suggest that randomizing 120 participants provides a  $\geq 80\%$  chance of detecting a significant difference ( $p < .05$ ) between the conditions.<sup>31-34</sup> Given the number of secondary outcomes and to guard against Type 1 error, we will focus our results interpretation primarily on effect sizes rather than statistical significance.

## 6.4 Power for Exploratory Outcomes

Power analyses were not conducted to inform exploratory outcomes.

## 7 INTERIM MONITORING

### 7.1 Overview

Interim monitoring focused on participant accrual, protocol adherence, loss to follow-up, data completeness and quality, safety, efficacy, and futility.

### 7.2 Safety

The principal investigators were responsible for monitoring the data and assuring protocol compliance. Unanticipated problems involving risks to subjects or others, including adverse events, were followed by a written report within five calendar days of the principal investigator becoming aware of the event to the institutional review board (IRB). Biannual DSMB meetings were held to review the research protocol and planning for data safety and monitoring and evaluate 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 outcomes. The principal investigators apprised the Data Safety Monitoring Board (DSMB) of all unanticipated problems and adverse events that occurred during the conduct of this research project. The DSMB was also informed of serious or unanticipated adverse events.

## 8 ANALYTIC PLAN

### 8.1 Overview

The analysis of the primary and secondary outcomes will be according to the principle of intent-to-treat, i.e., participants will be analyzed according to their original treatment assignment regardless of adherence to protocol. All analyses will include the participant as the unit of analysis. SAS 9.4, SPSS 26.0, MPlus 8.4, and the latest version of R (currently 4.0.2) software will be used for all analyses.

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## 8.2 Comparability of Treatment Groups

To determine randomization effectiveness, differences in baseline demographic characteristics will be assessed between iCBT and self-monitoring groups using appropriate graphical and statistical methods including summary statistics. The randomization is designed to produce balance on important covariates. If we find imbalance on key covariates, we will consider adjusting for those covariates.

## 8.3 Analysis of Primary Outcome: HIV-Risk Behavior (Condomless Anal Sex)

Analysis	Primary analysis of primary outcome: Number of past-30-day condomless anal sex (CAS) acts with primary or casual partners as measured by the Timeline Follow-Back at the 8-month follow-up assessment.
Analysis population	All randomized participants
Endpoint	8-month follow-up
Unit of analysis	Participant
Method of analysis*	We will use repeated measures generalized linear mixed models with maximum likelihood estimation to test whether receipt of ESTEEM iCBT vs self-monitoring affects changes in the number of past-30-day CAS with primary or casual partners from baseline to 8-month follow up. We will use a contrast to test condition x time comparisons. We will test the best-fitting correlation structure, but based on our previous studies, expect it to be compound symmetrical. In the event of high skew or zero inflation, the appropriateness of modeling a negative binomial or Poisson distribution will be considered.
Handling of missing data	MAR assumption
Adjustment covariates	Adjustment for baseline covariates not balanced at randomization
Type I error	5% (2-sided)
Control of type I error	None

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Treatment effect estimate	Odds ratio with 95% confidence limits
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### 8.4 Analysis of Secondary Outcomes

A similar approach will be taken for our secondary outcomes (i.e., depression, anxiety, and minority stress variables) as described in Section 8.3.

#### 8.4.1 Analysis of Secondary Outcomes: HIV Risk Behavioral and Social-Cognitive Outcomes

Secondary HIV risk behavioral and social-cognitive outcomes at the immediate post-intervention timepoint (4-month follow-up) are: past-30-day condomless anal sex with main or casual partners, past-30-day condomless anal sex with casual partners only, safer sex self-efficacy (SSQ), decisional balance for condom use (DBCUS), and past 4-month HIV/STI testing. Secondary outcomes at 8-month follow-up include: 30-day condomless anal sex with main or casual partners, past 30-day condomless anal sex with casual partners only, safer sex self-efficacy (SSQ), decisional balance for condom use (DBCUS), past 4-month HIV/STI testing history, HIV testing results, and syphilis testing results.

Analysis	In these models, we will assess whether ESTEEM iCBT will yield greater reduction in HIV risk behavioral and social-cognitive secondary outcomes at the immediate post-intervention (4-month follow-up) timepoint and the 8-month follow-up. HIV secondary outcomes include: past 30-day condomless anal sex with main or casual partners (TLFB), past 30-day condomless anal sex with casual partners only (TLFB), decisional balance for condom use (DBCUS), past 4-month HIV/STI testing, HIV testing results, and syphilis testing results.
Analysis population	All participants
Endpoint	Immediate post-intervention and 8-month follow-up
Unit of analysis	Participant
Method of analysis	Depending on the outcome we will use repeated measures generalized linear mixed models (for continuous outcomes) and generalized linear mixed models with a logit link (for binary outcomes). We will use maximum likelihood estimation with contrasts to test condition x time comparisons at each relevant timepoint. We will test the best-fitting correlation structure, but based on our previous studies, expect it to be compound

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	symmetrical. In the event of high skew or zero inflation, the appropriateness of modeling a negative binomial or Poisson distribution will be considered.
Handling of missing data	MAR assumption
Adjustment covariates	Adjustment for baseline covariates not balanced at randomization
Type I error	5% (2-sided)
Control of type I error	To control for the false discovery rate, we will apply a Bonferroni correction for each set of moderators (e.g., mental health, minority stress). Primary interpretation will focus on effect sizes.
Treatment effect estimate	Odds ratio with 95% confidence limits

### 8.4.2 Analysis of Secondary Outcomes: Mental Health, Minority stress Mechanisms, Universal Mechanisms

Secondary mental health, minority stress, and universal mechanisms will be assessed at the immediate post-intervention (4-month follow-up) timepoint and the 8-month follow-up. Secondary mental health outcomes include depression symptoms (measured by PHQ-9), anxiety symptoms (measured by GAD-7), alcohol and substance use (measured by AUDIT, DUDIT), and suicidality (measured by SIDAS). Secondary minority stress outcomes include concealment motivation (LGBIS), acceptance concerns (LGBIS), and internalized homonegativity (LGBIS). Secondary universal mechanism outcomes include emotion dysregulation (DERS), social support (MSPSS, LGBIS), and rumination (RRS).

#### 8.4.2.1 Mental Health, Minority stress Mechanisms, Universal Mechanisms

Analysis	In these models, we will assess whether Chinese ESTEEM iCBT will yield greater reduction in secondary outcomes (i.e., depression, anxiety, minority stress, and universal mechanisms) at the immediate post-intervention (4-month follow-up) timepoint and the 8-month follow-up. Mental health outcomes include depression symptoms (PHQ-9); Anxiety symptoms (GAD-7,); alcohol and substance use (AUDIT, DUDIT); and suicidality (SIDAS). Secondary minority stress outcomes include concealment motivation (LGBIS), acceptance concerns (LGBIS), internalized homonegativity (LGBIS). Secondary universal mechanism outcomes include emotion dysregulation (DERS), social support (MSPSS, LGBIS), and rumination (RRS).
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Analysis population	All participants
Endpoint	Immediate post-intervention (4-month follow-up) and 8-month follow-up
Unit of analysis	Participant
Method of analysis	Depending on the outcome we will use repeated measures generalized linear mixed models (for continuous outcomes) and generalized linear mixed models with a logit link (for binary outcomes). We will use maximum likelihood estimation with contrasts to test condition x time comparisons at each relevant timepoint. We will test the best-fitting correlation structure, but based on our previous studies, expect it to be compound symmetrical. In the event of high skew or zero inflation, the appropriateness of modeling a negative binomial or Poisson distribution will be considered.
Handling of missing data	MAR assumption
Adjustment covariates	Adjustment for baseline covariates not balanced at randomization
Type I error	5% (2-sided)
Control of type I error	To control for the false discovery rate, we will apply a Bonferroni correction for each set of moderators (e.g., mental health, minority stress). Primary interpretation will focus on effect sizes.
Treatment effect estimate	Odds ratio with 95% confidence limits

### 8.4.3 Moderation Analyses of Treatment Efficacy

Moderation analyses of treatment efficacy will examine

#### 8.4.3.1 Moderation Analyses of Treatment Efficacy

Analysis	In these models, we will examine baseline depression (PHQ-9), anxiety (GAD-7), and minority stressors including concealment motivation (LGBIS), acceptance concerns (LGBIS), and internalized homonegativity (LGBIS) as potential moderators of
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	ESTEEM iCBT efficacy, hypothesizing that YMSM with higher baseline depression, anxiety, and minority stress benefit most.
Analysis population	All participants
Endpoint	Immediate post-intervention (4-month follow-up) and 8-month follow-up
Unit of analysis	Participant
Method of analysis	<p>For all moderators (i.e., depression, anxiety, concealment motivation, acceptance concerns, and internalized homonegativity), a linear mixed model analysis will be performed. Moderation analysis models will include terms for condition, time, moderator, Condition X Time, Condition X Moderator, Time X Moderator, and Condition X Time X Moderator. To probe significant three-way interactions, we will perform simple slopes analyses and differences in slopes will be compared using z-score transformations.<sup>35</sup></p> <p>We will test the best-fitting correlation structure, but based on our previous studies, expect it to be compound symmetrical. In the event of high skew or zero inflation, the appropriateness of modeling a negative binomial or Poisson distribution will be considered.</p>
Handling of missing data	MAR assumption
Adjustment covariates	Adjustment for baseline covariates not balanced at randomization
Type I error	5% (2-sided)
Control of type I error	To control for the false discovery rate, we will apply a Bonferroni correction for each set of moderators (e.g., mental health, minority stress). Primary interpretation will focus on effect sizes.
Treatment effect estimate	Odds ratio with 95% confidence limits

### 8.5. Qualitative Analyses

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Qualitative analyses will be conducted to contextualize the quantitative results. Qualitative data will be derived from interviews with participants and therapists. We will also assess 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 MPI 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.

### **8.6. Exploratory Analyses**

Using the same quantitative approach detailed in section 8.4.2.1, we will assess whether ESTEEM iCBT will yield greater reduction in the following exploratory outcomes: depression severity and impairment (as measured by the Overall Depression Severity and Impairment Scale), anxiety severity and impairment (as measured by the Overall Anxiety Severity and Impairment Scale) and self-esteem (as measured by the Rosenberg Self-Esteem Scale) at both immediate post-intervention (4-month follow-up) and 8-month follow-up timepoints.



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