UNIVERSITY of SOUTH FLORIDA
Research & Innovation

## PROTOCOL TITLE:

Doxy.me VR vs. Telemental Health-Based Exposure Therapy

## PRINCIPAL INVESTIGATOR:

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## VERSION NUMBER/DATE:

V6. April 16, 2024

## REVISION HISTORY

***This table should only be used during submission of a Modification application to the IRB.**

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 1 | 10.26.2023 | Added flyering on USF campus to recruitment methods | No |
| 2 | 11.21.2023 | Changed compensation structure to 50 at baseline, 50 at midtreatment, and 50 at final session. | Yes |
| 3 | 12.25.2024 | Added flyering off campus and posting advertisements in relevant online communities | No |
| 4 | 3.21.2024 | We are requesting a waiver of written documentation of consent because (1) our current Redcap version is not 21CFR Part 11 compliant for digital consent and signature and (2) subjects some times have difficulties using a cursor and typing their names into the consent form. The study clinician will continue consenting due to the Conflict of Interest management plan, which prevents the Dr. Bunnell and Janelle Barrera from conducting consenting activities. We revised the Protocol (Doxy.me VR), Consent (Doxy.me VR), and Informed Consent Checklist (Doxy.me VR) files and added the Consent Script (Doxy.me VR) file to reflect these changes. | Yes |
| 5 | 4.16.2024 | We are updating the history of epilepsy/seizures exclusion criterion from excluding potential participants with any history of seizures/epilepsy to excluding only those with history of photosensitive seizures or who believe they have seizures resulting from photosensitivity (Gray et al., 2023). Research | |

| | | | |
|---|---|---|---|
| | | suggests that only participants with photosensitive seizures are at heightened risk of seizures after VR headset use. | |

## Table of Contents

## 1.0 Study Summary

1.1

| | |
|---|---|
| **Study Title** | Doxy.me VR vs. Telemental Health-Based Exposure Therapy |
| **Study Design** | Feasibility randomized controlled efficacy trial |
| **Primary Objective/Purpose** | Assess the feasibility of conducting a randomized controlled efficacy trial comparing the delivery of exposure therapy via a telemedicine-based virtual reality clinic (Doxy.me VR) vs. standard telemental health (TMH) to adults with intense fear of dogs, snakes, and/or spiders. |
| **Secondary Objective(s)/Purposes** | Preliminarily examine the efficacy of using Doxy.me VR vs. TMH in reducing phobia severity. |
| **Research Intervention(s)** | Exposure Therapy |
| **ClinicalTrials.gov NCT #** | Registration on clinicaltrials.gov is pending |
| **Study Population** | Adults (≥18 years old) with intense fear of dogs, snakes, and/or spiders. |
| **Sample Size** | 30 |
| **Study Duration for individual subjects** | In total, participants will spend approximately 38 hours over 13 study visits (12 Therapy and 1 Baseline Assessment) engaging in study procedures over the course of three months. |
| **Study Specific Abbreviations/ Definitions** | telemedicine-based virtual reality clinic (Doxy.me VR); standard telemental health (TMH); Virtual Reality (VR); Cognitive Behavioral Therapy (CBT) |

## 2.0 Objectives

2.1 Primary Objective: Assess the feasibility of conducting a randomized controlled efficacy trial comparing the delivery of exposure therapy via a telemedicine-based virtual reality clinic (Doxy.me VR) vs. standard telemental health (TMH) to adults with intense fear of dogs, snakes, and/or spiders.

Secondary Objective: Preliminarily examine the efficacy of using Doxy.me VR vs. TMH in reducing phobia severity.

2.2 This is a feasibility trial and not powered for hypothesis testing.

## 3.0 Background

3.1 Telemedicine revolutionized mental health services (i.e., telemental health) by bringing accessible and personalized treatment at a distance.(Bunnell, Barrera, et al., 2020; Bunnell, Sprague, et al., 2020). Telemental health is equally to more effective than in-person care with higher patient satisfaction at reduced costs.(Adams et al., 2018; Flodgren et al., 2015; Hilty et al., 2013; Langarizadeh et al., 2017; Yuen et al., 2012) Further, telemedicine transcends socio-cultural (e.g., stigma) and geographic (e.g., transportation) barriers that have traditionally limited access and use of mental health services.(Baker et al., 2011; Rojas & Gagnon, 2008; Wootton et al., 2011) Telemedicine has become the standard of modern mental health care with 85% of all mental health services in the U.S. now delivered remotely, a trend that is fully expected to continue post-pandemic.(Doran & Lawson, 2021; Khan et al., 2020; Nguyen et al., 2020; Pierce et al., 2020) As telemedicine evolves, innovative solutions that enhance telemedicine utility and outcomes will be needed for providers to continue delivering state-of-the-art telemental health care.(Bunnell, Barrera, et al., 2020)

Virtual reality (VR) uses interactive and immersive simulation to facilitate mental health therapies.(Maples-Keller et al., 2017) Stressors that are physical (e.g., phobias, trauma, addiction) or psychological (e.g., body image, mood, identity) can be realistically recreated in VR for safe, repeatable, and effective therapy.(Jerdan et al., 2018; Maples-Keller et al., 2017; Srivastava et al., 2014) VR is engaging and improves treatment compliance and retention, making VR conducive to the vital practice of in- and between-session mental health exercises.(Bell et al., 2020) There is abundant support for VR mental health therapy in on-site settings.(Park et al., 2019; Pimentel et al., 2021) However, VR mental health therapy via telemedicine is limited to preliminary efficacy studies.(Dilgul et al., 2021; Goldenhersch et al., 2020; Tamplin et al., 2020) There is strong potential to combine the accessibility of telemedicine and clinical utility of VR as the next evolution of telemental health care.

With this goal, Doxy.me Inc. partnered with the University of South Florida to create Doxy.me VR is a standalone app currently available on Quest 2 headsets via invite only. The app is designed for a therapist to meet with a client in a private, comfortable VR clinic office. To join each other in VR, the therapist selects a room code and provides that code to their client, who joins by entering that code into the app. While joined in the same VR room, the therapist and client can interact by speaking with each other in

immersive VR. Therapists can also spawn a variety of small animals such as dogs, snakes, and spiders for use in treating specific phobias. Therapists can browse, select, maneuver, remove, and choose animations for the animals to exhibit once made visible to the client.

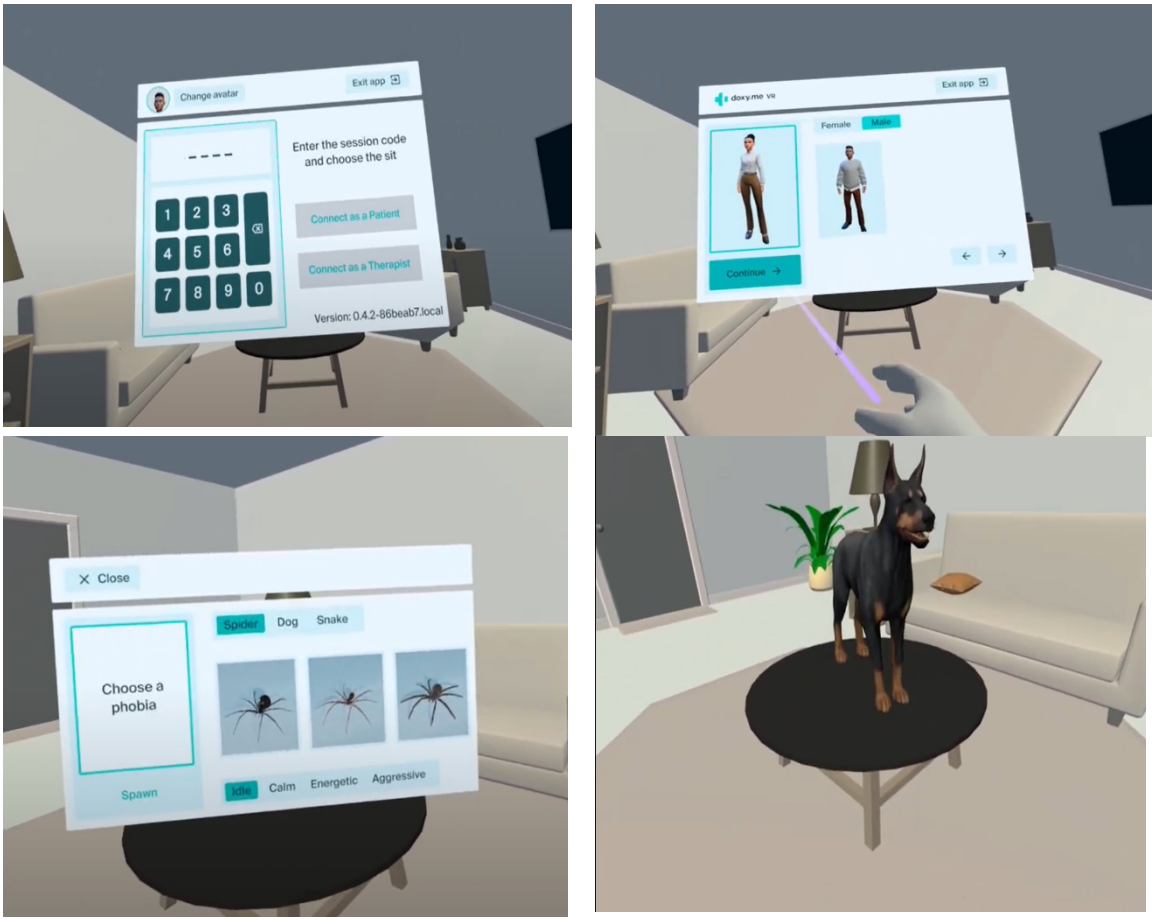



Figure 1. Screenshots of Doxy.me Virtual Reality clinic with stimuli

3.2 N/A

## 4.0 Study Intervention

4.1 This study aims to assess the feasibility of conducting a randomized controlled efficacy trial comparing the delivery of exposure therapy via a telemedicine-based virtual reality clinic (Doxy.me VR) *vs*. standard telemental health (TMH) to adults with intense fear of dogs, snakes, and/or spiders. Exposure therapy is a gold standard treatment for phobias and other anxiety-related mental health disorders (Taylor, 2003). Exposure therapy is acceptable, efficient, and produces durable effects (Vinograd & Craske, 2020). By exposing an individual to their fear-related stimuli (e.g., dog) in a controlled setting (e.g., therapist's office), the individual's fear response diminishes as their anxiety reduces over prolonged and repeated exposure (e.g., the individual is no longer fearful around dogs). The most common approach to this process includes gradual exposure which

begins with less intense stimuli and increases in intensity over time. One way to do gradual exposure is multimedia stimuli (e.g., photos, videos) and then gradually moving towards exposure to real life stimuli (i.e., in-vivo exposure). Another way is using VR stimuli in which patients are immersed in a virtual environment and interact with virtual stimuli (i.e., in virtuo exposure). VR-based exposure therapy is a safe, accessible, and engaging alternative to in-vivo exposure therapy that can be less stressful and more conducive to treatment success (Horigome et al., 2020; Meyerbröker & Emmelkamp, 2010; Parsons & Rizzo, 2008; Yoshinaga et al., 2020).

The present study will use an exposure therapy protocol developed specifically for Virtual Reality (Stephane Bouchard et al., 2012; Côté & Bouchard, 2005; Michaliszyn et al., 2010; St-Jacques et al., 2010). Following the baseline assessment session (Study Visit 1), the treatment is comprised of 12, ≤ 60-minute therapy sessions: one psychoeducation and treatment planning session, 10 exposure sessions, and one relapse prevention session (Study Visits 2-13). During the first therapy session, patients learn about the principles of Cognitive Behavioral Therapy (CBT), what causes anxiety and specific phobias, procedures for exposure, and complete a fear hierarchy, which is a list of situations ranked from least to most anxiety provoking. These lists will include a text-based list of various virtual/multimedia situations (i.e., static, and active states of different types of feared animals) and 'in vivo'/live situations (e.g., petting a dog, touching a snake at a pet store). Therapy sessions 2-11 begin with a review of homework followed by a ~35-minute virtual exposure session. Patients report their anxiety level using a 1-100% scale on a 5-minute interval throughout the exposure and remain in the exposure until they report a 50% reduction in their anxiety rating following the introduction of the stimulus. Upon completion of the exposure, the study therapist (i.e., a Postdoctoral Fellow and Clinical Psychologist) and patient process thoughts and feelings related to the exposure, reframe appraisals of their feared stimuli through cognitive restructuring, and practice breathing retraining and relaxation methods. The Doxy.me VR group will conduct their in-session exposures in the VR clinic and the TMH group will conduct their in-session exposures using multimedia on the Doxy.me platform (e.g., screen sharing videos and photos). This intervention requires daily homework practicing virtual exposures conducted in session and eventually progressing to in vivo exposures. Once patients have progressed through all virtual situations in their hierarchy and have completed their first in vivo exposure for homework, weekly therapy sessions will be devoting to processing between-session in vivo exposures and will last approximately 45 minutes. See Treatment Manual in Local Site Documents for a more detailed outline of the intervention.

## 5.0 Procedures Involved

This study will use feasibility randomized controlled efficacy trial design. This single-site trial will include up to 60 adults with self-reported fear of dogs, snakes, and/or spiders who will be randomly assigned via the REDCap Randomization Module using a 1:1 allocation ratio to receive 12 sessions of exposure therapy over the course of 3 months via standard telemental health (TMH; n=15) vs. Doxy.me VR (n=15), a telemedicine-based virtual reality clinic. Participants randomized to the Doxy.me group will be provided with Quest 2 VR headsets with the Doxy.me VR application pre-loaded to the device. This VR clinic is a standalone app currently available on Quest 2 headsets via

invite only. The app is designed for a therapist to meet with a client in a private, comfortable VR clinic office. To join each other in VR, the therapist selects a room code and provides that code to their client, who joins by entering that code into the app. While in the same VR room, the therapist and client can interact by speaking with each other in immersive VR. Therapists can also spawn a variety of small animals such as dogs, snakes, and spiders for use in treating specific phobias. Therapists can browse, select, maneuver, remove, and choose animations for the animals to exhibit once made visible to the client.

Therapy sessions will be audio recorded and 20% will be observed by the PI to assess treatment fidelity. Primary clinical outcomes (i.e., phobia severity as measured by the SMSP) will be assessed at baseline and 3-months post-baseline. Intervention targets will include presence–assessed weekly via patient-report– and working alliance–assessed at mid- and post-treatment via study therapist- and patient-report. Benchmarks for feasibility will include enrolling up to 60 patients during months 1-9 of the trial (i.e., 3/month), 70% patient retention at 3-month follow-up, 70% of weekly self-report collected, and ≥80% treatment fidelity.

5.2 Please select the methods that will be employed in this study (select all that apply):

| | |
|---|---|
| ☒ Audio/Video Recording | ☐ Psychophysiological Recording |
| ☒ Behavioral Interventions | ☐ Record Review - Educational |
| ☐ Behavioral Observations and Experimentations | ☐ Record Review - Employee |
| ☐ Deception | ☐ Record Review- Medical |
| ☐ Focus Groups | ☐ Record Review - Other |
| ☒ Interviews | ☐ Specimen Collection or Analysis |
| ☐ Investigational Device – Non-Significant Risk (e.g. Mobile Applications) | ☒ Surveys and/or Questionnaires |
| ☐Psychometric Testing | ☐ Other Social-Behavioral Procedures |

**Recruitment**

Potential participants reached through Clinical Connection, Research Match, and Facebook ads (see Section 12.0 Recruitment Methods) will be provided with a link that will direct them to an Online Pre-Screening Questionnaire that will be administered via a REDCap survey (see Measures in Local Site Documents and Figure 2. Study Schema and Schedule of Events). Potential participants meeting preliminary eligibility criteria will be presented with an invitation to schedule an initial consent and baseline assessment visit via Microsoft Bookings and will receive a calendar invitation and text/email reminders 24 hours and 1 hour prior to the scheduled visit time. If potential participants do not meet eligibility criteria due to participating in ongoing mental health therapy from a non-study therapist or having had changes to psychotropic medication use within six weeks preceding enrollment in the trial, they will be presented with a message inviting them to revisit the pre-screening questionnaire at a later date if/when those conditions no longer apply.

**Consent and Baseline Assessment**

The consent and baseline assessment visit will be conducted via video-conferencing platform and will not be audio or video recorded. During this visit study staff will (1) confirm the potential participant's responses on the Online Pre-Screening Questionnaire, (2) provide detailed information about the study and explain the informed consent document, (3) assist participants in completing baseline questionnaires via REDCap survey, (4) administer the Specific Phobia and Risk Assessment modules of the Diagnostic Assessment Research Tool (DART; See Measures document for specific items), and (5) make a final determination on the participant's eligibility. Eligible participants will then be randomized using the REDCap Randomization Module and scheduled for their first treatment visit (see Measures in Local Site Documents and Figure 2. Study Schema and Schedule of Events).

**Treatment**

Participants will receive weekly ≤ 60-minute therapy sessions (see Section 4.0 Study Intervention). Therapy session visits will be scheduled using Microsoft Bookings and participants will receive a calendar invitation and email reminders 24 hours and 1 hour prior to the scheduled visit time (See Appointment invitations and reminders in Local Site Documents). All therapy sessions will be conducted via videoconferencing, with the Doxy.me VR group transitioning to the Doxy.me VR clinic for the exposure exercise portion of the session. Participants in this group will be mailed a Meta Quest 2 VR headset with the Doxy.me VR app pre-loaded on the device. This headset will be owned by the University of South Florida and will be required to be returned when participants complete the study. Postage will be covered by the study. All therapy sessions will include the assignment of homework, including reading an informational handout after therapy session 1 and exposure therapy assignments after therapy sessions 2-11. Daily exposure-based homework assignments will require participants to practice the same exposure exercises they completed during that week's therapy session for a minimum of 30 minutes, with the specific situation being assigned to participants by the study therapist (i.e., Postdoctoral Fellow). Participants will receive text/email reminders with links to REDCap surveys that will provide instructions for the homework assignment, including situation to be used in the exposure exercise, and ask participants to report the results of the homework exercise including anxiety levels during the exposure exercise (see Treatment Data Collection Forms in Local Site Documents). At the end of each therapy session the study therapist (i.e., Postdoctoral Fellow) will send participants a link via the videoconference platforms messaging feature to a REDCap survey with the weekly assessment, which participants will be asked to complete before the end of the therapy session (see Measures in Local Site Documents and Figure 2. Study Schema and Schedule of Events). Therapy sessions will be audio recorded and 20% of recordings will be observed by the PI to rate fidelity to the protocol. All therapy session notes will be completed and stored in REDCap and signed by both the therapist (i.e., Postdoctoral Fellow) and supervisor (PI).

**Assessment Strategy and Measures**

All trial assessments are listed in Table 1 and were chosen considering several factors including (1) sound psychometric properties, (2) ease of administration, (3) past use in similar clinical trials, and (4) brevity. All questionnaires will be completed via REDCap

survey with study staff present via videoconference to answer any questions (see Measures in Local Site Documents and Figure 2. Study Schema and Schedule of Events).

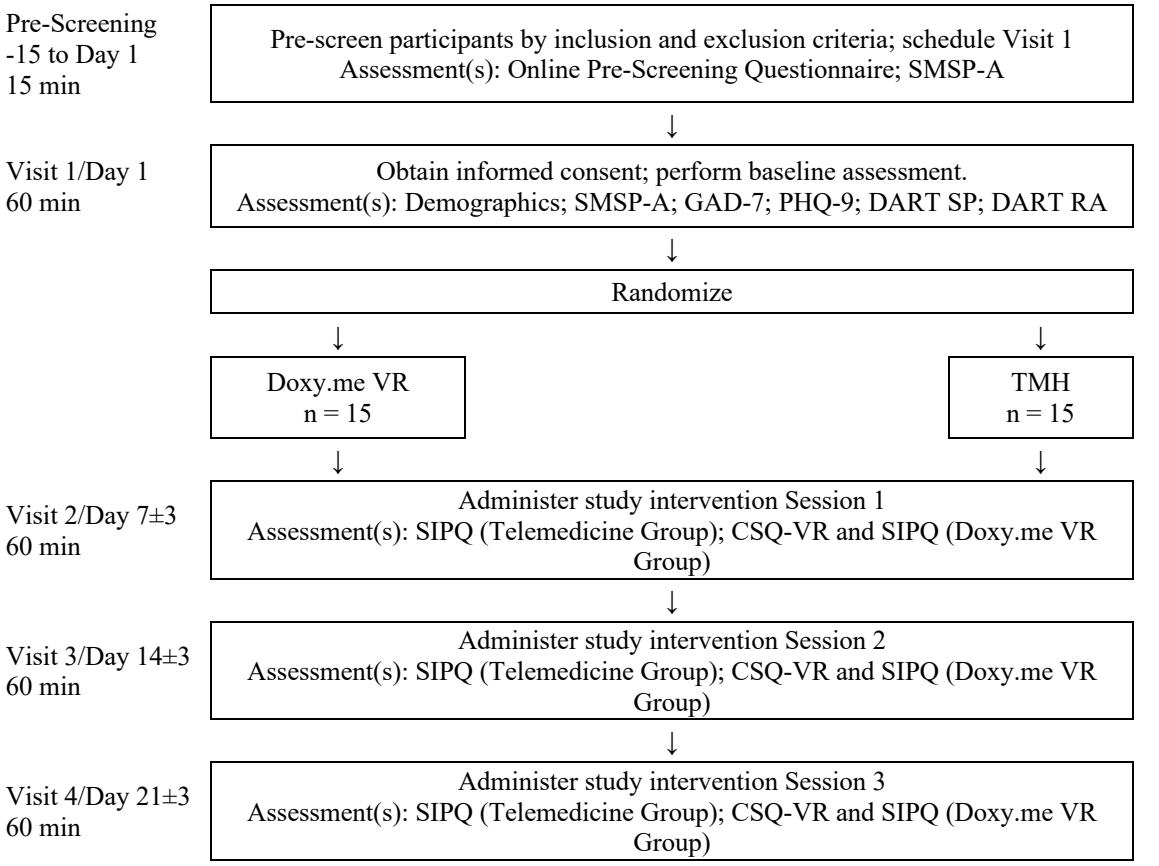
**Table 1. Study Assessments**

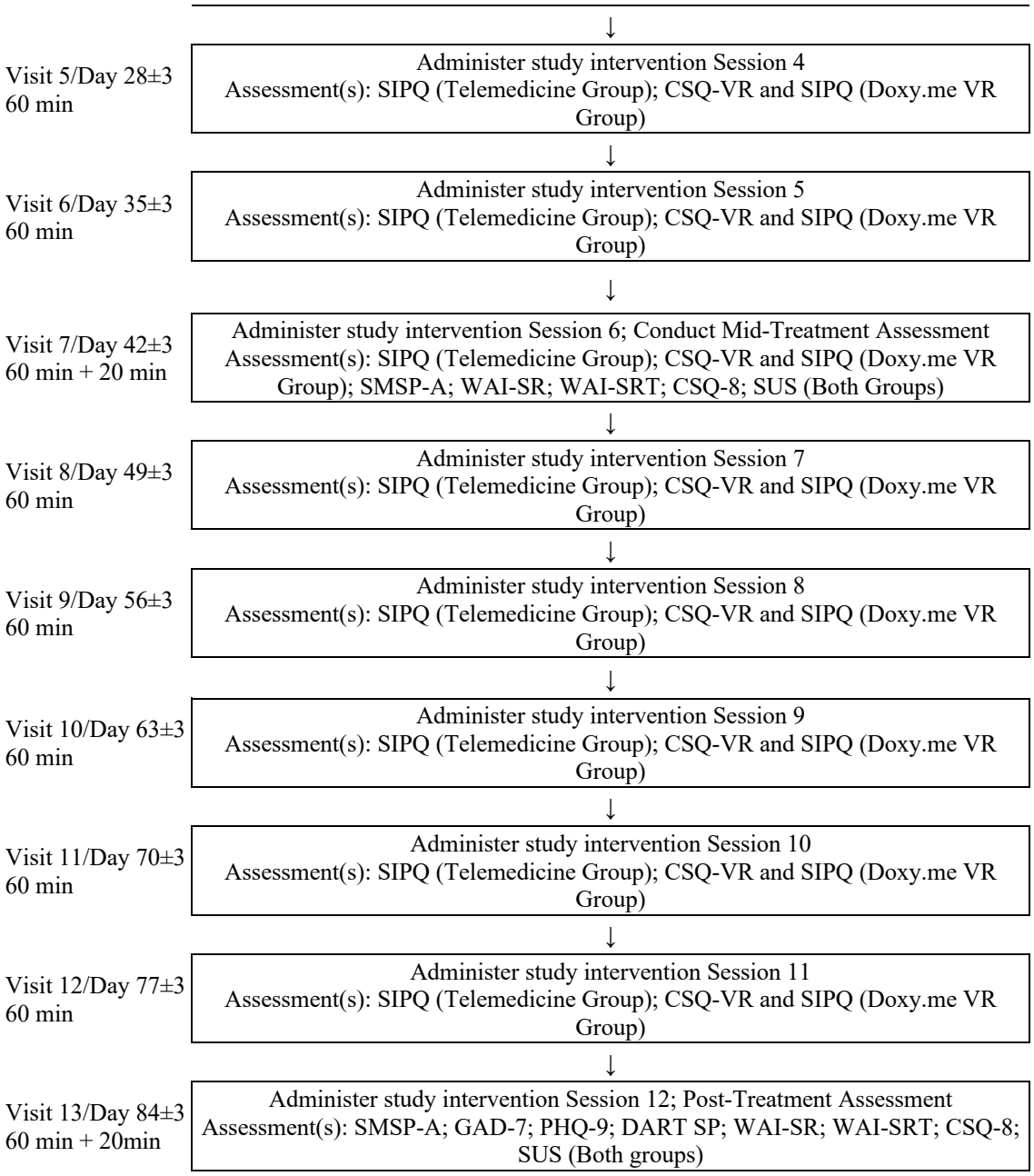
| Domain | Informant | Measure |
|---|---|---|
| Demographics | Patient | Patient Demographics Questionnaire |
| Anxiety Severity | Patient | General Anxiety Disorder-7 (GAD-7)(Johnson et al., 2019; Spitzer et al., 2006) |
| Depression Severity | Patient | Patient Health Questionnaire-9 (PHQ-9)(Kroenke et al., 2011, 2009) |
| Therapeutic Alliance | Patient<br>Provider | Working Alliance Inventory- Short Revised (WAI-SR)(Hatcher & Gillaspy, 2006) Working Alliance Inventory – Short Revised Therapist (WAI-SRT; (Hatcher & Gillaspy, 2006) |
| Treatment Satisfaction | Patient | Client Satisfaction Questionnaire (CSQ-8)(Larsen et al., 1979) |
| Specific Phobia Severity | Patient | Severity Measure for Specific Phobia-Adult (SMSP-A; (Craske et al., 2013); |
| Specific Phobia Diagnosis | | Diagnostic Assessment Research Tool (DART;(Schneider et al., 2022) |
| Presence | Patient | Single Item Presence Questionnaire (SIPQ; (S. Bouchard et al., 2005) |
| Cybersickness | Patient | Cybersickness in Virtual Reality Questionnaire (CSQ-VR; (Kourtesis et al., 2023) |
| Usability | Patient | System Usability Scale (Peres et al., 2013) |

## Treatment Fidelity

All treatment sessions will be recorded and 20% will be rated by the Supervisor (PI) using a Treatment Fidelity Checklist based on the treatment manual (see Treatment Data Collection Forms in Local Site Documents).

**Figure 2. Study Schema and Schedule of Events**






5.3 There are no procedures or interventions that are going to be conducted as part of this research project that would have been conducted even if the research was not occurring. We are conducting the procedures solely for research purposes.

5.4 There are no additional foreseeable risks to the above procedures in need of further mitigation beyond those ordinarily incurred in working with this population. Standard operational procedures of the USF Department of Psychiatry and Behavioral Neurosciences specify responsibilities for handling dangers to self and others, safety planning, and mandatory reporting responsibilities.

5.5 N/A
5.6 N/A
5.7 N/A

## 6.0 Data and Specimen Storage for Future Research

6.1 N/A
6.2 N/A
6.3 N/A

## 7.0 Sharing of Results with Subjects

7.1 An individual participant's assessment results from questionnaires and interviews will be shared with that individual participant verbally at the end of each visit during which the assessment occurred (i.e., baseline, mid-treatment, post-treatment).

## 8.0 Study Timelines

8.1 The study timeline with estimated visits and their accompanying durations can be viewed in Figure 2. Study Schema and Schedule of Events. Participants will participate in a ≤60-minute initial consent and baseline assessment visit (Visit 1). They will then participate in 12 ≤60-minute therapy sessions (Visits 2-13) and up to 6, ~30-minute homework assignments per week over 12 weeks. Participants will also participate in 20-minute mid- and post-treatment assessments, which will occur during Visits 7 and 13, respectively. In total, participants will spend approximately 38 hours over 13 study visits (i.e., Baseline + 12 Therapy Sessions) engaging in study procedures over the course of three months.

## 9.0 Inclusion and Exclusion Criteria

9.1 In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Is an adult ≥ 18 years old
2. Has a self-reported fear of dogs, snakes, and/or spiders
3. Indicates *Subthreshold* or *Present* Specific Phobia symptoms as determined by the study therapist via administration of the Diagnostic Assessment Research Tool (DART) Specific Phobia Module
4. Has access to the internet AND a computer OR smartphone with video conferencing capabilities
5. Will reside in the state of Florida for the duration of the study

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

1. Is participating in ongoing mental health therapy from a non-study therapist
2. Has had changes to psychotropic medication use within six weeks preceding enrollment in the trial
3. Reports active suicidal and/or homicidal intent or plan as determined by the study therapist via administration of the Diagnostic Assessment Research Tool (DART) Risk Assessment Module

4. Reports active auditory, visual, and/or tactile hallucinations via the Diagnostic Assessment Research Tool (DART) Psychosis Module screening question
5. Reports having a diagnosis of photosensitive epilepsy by a medical doctor or a history of experiencing seizures that they believe were caused by photosensitivity

9.3 An individual who meets any of the following criteria will become ineligible to continue on the study after enrollment:

1. Begins participating in ongoing mental health therapy from a non-study therapist
2. Has changes to psychotropic medication use
3. Does not indicate *Subthreshold* or *Present* Specific Phobia symptoms as determined by the study therapist via administration of the Diagnostic Assessment Research Tool (DART) Specific Phobia Module
4. Reports active suicidal and/or homicidal intent or plan as determined by the study therapist via administration of the Diagnostic Assessment Research Tool (DART) Risk Assessment Module
5. Moves out of the State of Florida during the study period

9.4 N/A

## 10.0 Vulnerable Populations

10.1 N/A

## 11.0 Local Number of Subjects

11.1 We aim to complete treatment with and obtain post-treatment assessment data from a total of 30 participants (15 in TMH and 15 in VR group). We will enroll up to 60 participants in the trial as needed to account for screen fails, withdrawals, and drops.

## 12.0 Recruitment Methods

12.1 Potential participants will be identified through Clinical Connection, Research Match, Facebook ads, and distributing flyers on University of South Florida campus.

**Clinical Connection** is a national clinical trial participant recruiter. Clinical Connection matches potential study participants with clinical trials in a 50-mile radius of their location. Study sites post listings for clinical trials and potential participants are notified that a new clinical trial has been posted if they are signed up for alerts. Study sites can also send direct emails to potential participants every 30 days. Interested potential participants review the clinical trial description and fill out a contact form. The study site receives an email with the potential participant's contact information and reaches out to them directly. Clinical Connection also posts paid advertisements for clinical trials on popular search engines. The study team will contact Clinical Connection referrals within one business day of submission to provide study information, assess eligibility, obtain

informed consent from patients, and assist participant in completing baseline assessments. IRB approval is required prior to launching the study on Clinical Connection. There are four documents in Local Site Documents related to Clinical Connection: Clinical Connection Advertisement Example, Clinical Connection Research Site Profile Example, Clinical Connection Research Site Profile Text, and Clinical Connection Advertisement Text. These documents provide examples of posted studies and the text we intend to use on the advertisements for this study.

**ResearchMatch** connects volunteers with researchers. Volunteers and researchers register for the site, and researchers can contact deidentified volunteers with information about their study. Volunteers registered for the site will be contacted through direct message on ResearchMatch. If a ResearchMatch volunteer expresses interest, the study team will contact them within one business day to provide study information, assess eligibility, obtain informed consent from patients, and assist participant in completing baseline assessments. At present, there are 80 English-speaking adults with a phobia diagnosis registered on Research Match.

**Facebook advertisements** will target relevant Facebook users. Potential participants will complete a contact form. As with the previous recruitment methods, potential participants will be contacted by the study team within one business day.

**Distributing Flyers on USF Campus** will involve placing flyers at USF Counseling Center, USF Student Health Center, and areas throughout campus where students congregate. As with the previous recruitment methods, potential participants will be contacted by the study team within one business day.

**Distributing Flyers Off-Campus** will involve placing flyers in community centers and businesses where people congregate. Examples include but are not limited to public libraries, coffee shops, recreation centers. As with the previous recruitment methods, potential participants will be contacted by the study team within one business day.

**Distributing Flyers in Online Communities** will involve posting advertisements in online mental health forums and groups including but not limited to Reddit. As with the previous recruitment methods, potential participants will be contacted by the study team within one business day.

12.2

| | |
|---|---|
| ☐ Email | ☐ Record Review |
| ☒ Flyer | ☐ SONA |
| ☐ Letter | ☒ ResearchMatch (must upload HRP-500 template) |
| ☐ News Advertisement | ☒ Other: Clinical Connection |
| ☒ Online/Social Media Advertisement | |

12.3 N/A

## 13.0 Withdrawal of Subjects

13.1 Anticipated circumstances under which participants will be withdrawn from the research without their consent include the event that they:

1. Begin participating in ongoing mental health therapy from a non-study therapist
2. Have changes to psychotropic medication use
3. Begin to report active suicidal and/or homicidal intent or plan
4. Begin to report active auditory, visual, and/or tactile hallucinations
5. Begin to report the occurrence of photosensitive epilepsy or seizures
6. Moves out of the State of Florida during the study period

13.2 If subjects completely withdraw from the research, study staff will attempt to provide them with a referral to a therapist in their area. If subjects partially withdraw from the research, study staff will attempt to administer mid- and post-treatment assessments. Subjects will be given the option to completely withdraw from the study including withdrawing previously collected data.

## 14.0 Risks to Subjects

14.1 Physical, psychological, social, cultural, financial, and legal risks, and risks to privacy and/or confidentiality associated with this research are minimal because the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily lives of the general population or during the performance of routine physical or psychological examinations or tests.

These minimal risks include:

1. Possible breach of participant privacy and/or confidentiality
2. Possible breach of the security of participant online data
3. Possible participant discomfort due to completing psychological questionnaires and assessments
4. Possible participant discomfort due to having therapy sessions recorded
5. Participant discomfort during exposure therapy exercises. This discomfort is temporary but necessary for treatment gains to occur.
6. Possible participant discomfort or cybersickness as a result of using the VR system, the duration of which is typically 5-10 minutes, and which will be assessed following each VR-based exposure using the CSQ-VR.
7. Possible disclosure of suicidality or homicidality requiring mandatory reporting if participants are at imminent risk of endangering themselves or others. Standard operational procedures of the USF Department of Psychiatry and Behavioral Neurosciences specify responsibilities for handling dangers to self and others, safety planning, and mandatory reporting responsibilities.

14.2 N/A
14.3 N/A

## 15.0 Potential Benefits to Subjects or Others

15.1 Potential direct benefits to participants include reductions in anxiety associated with feared stimuli.

15.2 The general public and scientific community will benefit from the knowledge produced in this research. This includes preliminary knowledge about the comparative efficacy of a telemedicine-based VR clinic vs. Standard TMH in the treatment of specific phobias.

## 16.0 Data Management and Confidentiality

16.1 We will assess feasibility of the proposed trial methodology using the following benchmarks: 30 participants will be enrolled in months 1-9 of trial, 70% of participants will be retained at three-month follow-up, 70% of weekly self-report assessments will be completed, and we will reach 80% or greater treatment fidelity.

The small sample size prevents any conclusions about efficacy; however, Analysis of Covariance will be used to conduct a preliminary assessment of between-group differences in clinical outcomes while co-varying for pre-treatment scores. We also will conduct a preliminary examination of associations between study targets including therapeutic alliance and presence.

16.2 D.
We will use the following security measures to protect data sources:

1. Data collected during the trial will be securely stored in a HIPAA compliant USF REDCap database, including informed consent documents, questionnaire data, and session notes.
2. Consent forms and de-identified data will be downloaded and stored in a secure HIPAA compliant Box folder.
3. All research data exported from REDCap will include ID numbers only.
4. Audio recordings will be stored in a secure HIPAA compliant USF Box folder.
5. Only IRB-approved and trained study personnel will have access to the REDCap project and box folder.
6. Computers, programs, and box folders containing data will be password-protected to prohibit unauthorized access.
7. The codes that link the name of the participant and the study ID will be kept confidential in REDCap along with other identifiers including first name, last name, full date of birth, address, email address, and cell phone number.
8. We have obtained a Certificate of Confidentiality from the National Institutes of Health so that we cannot be forced to disclose information that may identify participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

16.3 We will use the following quality assurance measures for subject recruitment, enrollment, enrollment targets, and for the validity and integrity of the data:

1. study staff will complete and maintain up-to-date CITI and GCP training

2. study staff will be trained and supervised weekly by the PI
3. Standard Operating Procedures (SOPs) and study checklists will be used to train study staff and ensure fidelity to the study protocol
4. informed consent will be obtained and documented by study staff to provide an audit trail
9. any contact with study participants or potential study participants will be documented to provide an audit trail
10. participant screening, recruitment, enrollment and enrollment targets, and data collection will be tracked to provide weekly updates to the PI
11. assessment data will be entered directly by participants into REDCap
12. automated validity checks will be in place for any data collection
13. data checks for ranges, cross-validity, and completion will be completed proximal to data collection
14. collection of any study data will be documented by study staff to provide an audit trail
15. the USF Conflict of Interest (COI) Office will maintain and monitor study progress according to ongoing conflict of interest management plans to ensure compliance with all requirements

16.4 Identifiable information in this study will include patient names, dates of birth, phone numbers, email addresses, and physical addresses. Analyzed data will not include participant's identifiable information and will only be shared with the public in aggregate form. Human subjects research records, including the original signed and dated consent documents, will be stored for at least 5 years after study completion. Signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations will be stored for at least 5 years after study completion. After this time data will be deleted from REDCap. Patient assessment results and session notes will be shared with their healthcare provider upon submission of a signed release of information form, as stated in the informed consent document.

16.5 If you will review/access and/or collect/obtain Protected Health Information (PHI) during recruitment or the main study, select all that apply:

| | |
|---|---|
| ☐ Obtaining Signed Authorization | ☐ Waiver of HIPAA Authorization for Recruitment/Screening Purposes Only |
| ☐ Obtaining Online or Verbal Authorization (Alteration of HIPAA Authorization) | ☐ Waiver of HIPAA Authorization for Entire Study |
| ☐ Data Use Agreement | ☐ Business Associate Agreement |

No Protected Health Information will be obtained during recruitment or the main study. As stated above, all identifiable information will be provided by the participant within the context of the study. No medical or insurance records will be accessed.

16.6 Members of this research team are dedicated to the timely dissemination of study products and results. This includes the data used to inform Doxy.me VR features and

exercises and resulting publications from analyses. We will prepare both brief and comprehensive reports for NIH, which will be circulated for review and comment to our colleagues in the field and the NIH. We will provide relevant information to senior leaders, supervisors, and providers at community health clinics and academic clinics located locally, regionally, and nationally. Results will be shared via professional, peer-review, and lay publications, as well as presentations and forums, websites, newsletters, among others.

## 17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

17.1 Some questions asked during assessments and exposure exercises may cause participants distress, but this distress is expected to be similar to what participants would experience with routine care for specific fears/Phobias. The study therapist (i.e., Postdoctoral Fellow) will ensure that any questions causing distress are discussed with participants and will provide them with techniques to reduce distress. A temporary increase in the severity of anxiety is expected at the beginning of exposure therapy, along with a gradual decline in severity over the course of treatment. If participants are distressed and unable to participate in the study following baseline assessments, or at the end of the study participants feel that they are in need of further treatment, the study therapist (i.e., Postdoctoral Fellow) will provide a referral to therapist(s) in the participants local area. This will be provided verbally to participants and the study therapist (i.e., Postdoctoral Fellow) will follow up in one week via telephone to inquire as to the state of the referral and provide further assistance as necessary.

17.2 N/A

## 18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 The research will be conducted via telephone, online, video conferencing, and virtual reality by IRB approved study staff located in a closed private clinic office in the University of South Florida Department of Psychiatry and Behavioral Neurosciences.

18.2 Study participants will provide informed consent. We will not access any previously existing records.

## 19.0 Compensation for Research-Related Injury

19.1 N/A

## 20.0 Subject Costs and Compensation

20.1 Patients who participate in this study will have internet and smartphone access, so we anticipate that they will have data and text message plans that will allow them to participate without any additional costs. However, there is the small risk that some participants may exceed their monthly data or text message limits during this study resulting in additional costs, for which they will be responsible. This risk will be discussed during the informed consent process.

20.2 If you will provide compensation to subjects, select all that apply:

| | |
|---|---|
| ☐ No Compensation | ☐ Tokens (pens, food items, etc.) |
| ☒ Financial Compensation (cash, gift cards) | ☐ Other |
| ☐ Course Credit (i.e. extra credit, SONA points) | |

Participants will receive a $50 eGift card for completing the baseline assessment, $50 eGift card for completing the 6th therapy session, and a $50 e-gift card for completing the 3-month follow-up assessment. There will be no partial compensation for partially completing either assessment.

## 21.0 Consent Process

21.1

| | |
|---|---|
| ☐ Obtaining Signed Consent (Subject or Legally Authorized Representative) | ☐ Obtaining Consent Online (Waiver of Written Documentation of Consent ) |
| ☐ Obtaining Signed Parental Permission | ☒ Obtaining Verbal Consent (Waiver of Written Documentation of Consent) |
| ☐ Obtaining Signed Assent for Children or Adults Unable to Consent | ☐ Waiving Consent and/or Parental Permission (Waiver of Consent Process) |
| ☐ Obtaining Verbal Assent for Children or Adults Unable to Consent | ☐ Waiving Assent/Assent is Not Appropriate |
| ☐ Obtaining eConsent Signatures (Subject or Legally Authorized Representative) | ☐ Obtaining eConsent Parental Permission |
| ☐ Obtaining eConsent Assent for Children | |

21.2 N/A

21.3 Study staff will obtain verbal consent from participants during the ≤60-minute videoconference-based consent and baseline assessment visit. We are requesting a waiver of written documentation of consent because any subjects face challenges with using a cursor and some encounter difficulties when typing their names. Participants will be sent a copy of the consent form, which will be screenshared for participants while it is being explained by the study therapist. The study therapist will ensure that participants understand all aspects of the study and consent form, and adequate time will be provided for questions relating to treatment, use of VR, audio recording sessions, and assessments. We will use an Informed Consent Checklist to document this process (see Informed Consent Checklist in Local Site Documents). The study therapist will obtain informed consent as the Conflict of Interest management plan prevents the PI and the coordinator (Barrera) from conducting consenting activities.

21.4 N/A

21.5 N/A
21.6 N/A

## 22.0 Setting

22.1 The research will be conducted via telephone, online, video conferencing, and virtual reality from the University of South Florida Department of Psychiatry and Behavioral Neurosciences.

## 23.0 References

23.1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