**Low-Cost, Virtual Reality System to Increase Access to Exposure Therapy for Anxiety and Obsessive Compulsive Disorders**

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**Study Protocol**

Children with childhood anxiety disorders (CADs) or obsessive compulsive disorder (OCD) and a parent will be recruited to test the VR system with a randomized controlled mixed methods study. Participants will be identified by through a Pediatric Anxiety Disorders Clinic using purposive sampling methods. All patients complete a standardized diagnostic assessment (including the MINI KIDS and Spence Child Anxiety Scales, Parent & Child report and begin treatment with psychoeducation on parent-coached exposure therapy for anxiety and OCD, create a treatment plan (i.e., fear hierarchy), and proceed to treatment sessions focused on completion of exposures. Participants will be recruited after their initial assessment and will begin the study in the early stages of treatment after completing psychoeducation and treatment planning.

Participants will be randomly assigned to home exposure practice with or without the VR system, i.e., intervention or control, respectively. All participants in the study will participate in an introductory session in which they complete two exposures related to content from their fear ladder, one with the VR system and an analogous imaginal exposure. Each family will receive instructions for how to use the exposure tracking form to record exposures during home practice. Participants will then be assigned one week of daily exposure homework for both the intervention and control conditions. Patients randomized to the intervention condition will take home the VR system for homework completion and participants assigned to control will be instructed to complete imaginal exposures. One week after the introductory session, all participants will return for a session in which they complete both types of exposure. They will also be assigned third generalization exposure, i.e., an exposure related to the baseline exposure that is higher on the fear ladder, to complete at their next anxiety clinic treatment session. Subjective Units of Distress (SUDS) ratings for each type of exposure will be recorded on paper with the exposure tracking form. During the follow up session, an independent interviewer will observe participants' engagement during exposures and will interview participants and their parents about their experience with both types of exposure.

<u>Study Population</u>
Potential participants will be ages 7 to 17 years old; have a diagnosis of CAD (i.e., generalized anxiety disorder, separation anxiety disorder, specific phobia, panic disorder with or without agoraphobia) or OCD; and have at least one fear fitting exposures covered by the VR system. Qualifying diagnoses will be based on standardized assessments in the Clinic (MiniKIDS). Potential participants will be excluded if they have a high likelihood of being lost to follow-up or contact; are unable to provide good data; have significant comorbidity that would interfere with participation (e.g., uncontrolled oppositional defiant disorder) or are at heightened risk of self-harm (e.g., presence of active suicidal ideation reported on clinical interview or endorsement on a self-report measures, such as the PHQ-9M). Research assistants (RA) will approach eligible patients and describe the study. The RA will then obtain written informed consent from the parents and written informed assent from the child. Every effort will be made to enroll subjects in proportion to the gender and racial/ethnic demographics of the treatment population.

<u>Study Protocol</u>
Following recruitment and consent and assent, participants will be randomly assigned to the intervention or control condition. Then, participants will complete a baseline study session with study staff at the Clinic. At this session, the staff member will follow a standardized protocol to instruct all participants and their parents on how to use the exposure tracking form to electronically record exposure practice. Because all study participants will have started treatment in the Clinic, including orientation to parent-coached exposure, participating families

will be familiar with parent-coached exposure procedures. Standard Clinic treatment includes parent-coached exposure in and between sessions. For the study baseline session, a Clinic psychologist/therapist will follow the standardized protocol to guide all participants through planning two exposures related to content from their personalized fear ladder, one with the VR system and an analogous imaginal exposure (order randomized). Parent-child dyads will complete these exposures in session with study staff present (in most cases, the research coordinator). During each exposure, the participant will record his or her anxiety using a 0 to 10 SUDS rating scale, the standard procedure during clinical care and between-session exposures. For the VR exposure, the staff member will ask the participant to follow instructions presented by the VR program. The conventional exposure will follow common clinical practice for imaginal exposures; specifically, the participant will write a story about their fears coming true and then read the story aloud. In each condition, the staff member will encourage the participant to repeat the exposure until anxiety ratings are reduced by 50%. Based on clinical experience and confirmed during earlier research, it is anticipated that participants' anxiety will be manageable throughout the exposure and will have habituated by the end of the exercise. Each of the study sessions will be approximately 90 minutes. In the unlikely event of difficulties during a study session, and in accordance with the safety monitoring plan, the lead psychologists will be available to evaluate the participant, address emotional distress, and arrange appropriate care. Throughout the course of the study (i.e., between study sessions), participants will have access to the lead psychologists as well as the supports of typical clinical care including the treating therapist, or a covering clinician through the Clinic Division of Child Psychiatry and Psychology will be available for research participants 24 hours a day, 7 days a week. The exposure activity and SUD ratings for each exposure will be recorded on paper with the exposure tracking form. Each participant will be asked to wear a sensor on their wrist during the in-office exposures. These sensors are similar to an activity tracker. The sensors will measure real-time physiological data (i.e. heart rate, acceleration, body temperature, etc). This information will allow the study team to note changes with the patient as they participate in the exposures. It will also provide valuable data that can be analyzed at the end of the study. These sensors do not collect any patient health information. The sensors will either Empatica E4 but in the event the study team cannot get the Empatica 4, they will use the Elite HRB CorSense.

Participants will then be assigned one week of daily exposure homework with or without VR, depending on condition, using a paper exposure tracking form to record each exposure and SUDS. Patients randomized to intervention will take home the VR system for homework completion, and participants assigned to control will not take the VR system home and will be instructed to complete imaginal exposures. Participants will be asked to record each exposure, even if it is not related to the fear addressed with the baseline exposures, in order to capture all exposures completed during the homework period.

One week after the baseline session, all participants will return for a follow up session in which they complete both types of exposure (order randomized) and will receive an assignment to complete in their next Clinic therapy appointment a third generalization exposure, i.e., an exposure related to the baseline exposure that is higher on the fear ladder for the targeted fear, following procedures analogous to the baseline session. During the follow up session, staff from Clinic Health Care Policy & Research ("the interviewer") experienced in qualitative data analysis and not involved with the patients' medical care or development of the prototype system will observe, record, and code participants' engagement in the exposures and will interview participants about their experience with both types of exposure and then will ask for observations and opinions from the parent. A psychologist from the Clinic Health Care Policy & Research will work with the two lead child psychologists to identify questions and topics for a

semi-structured interview guide. The guide will be pilot-tested to ensure that questions and follow-up probes are easily comprehended and delivered in a sensitive manner. The semi-structured guide will follow guidelines for minimizing bias and increasing the reliability and validity of interview data[64,65]. All interviews will be audio-recorded.

During the participants' next therapy session, they will complete the assigned generalization exposure. SUDS ratings will be recorded for that exposure using the paper exposure tracking form, and participants will wear a sensor to obtain biometrics during the exposure.

Thus, study participation will include the two study sessions, completion and recording of exposures for one week between study sessions, and completion of a study-assigned exposure in a subsequent Clinic therapy session. Participation consent and assent will include agreement for clinically gathered assessments to be used for the study (i.e., initial structured interview, symptom rating scales completed at initial evaluation and clinic treatment follow up, number of treatment sessions attended, length of treatment). Study participants will continue with any treatment as usual during study participation.
Participant Recruitment & Participation Flow

| Initial Clinic visit | Baseline Study Visit | 1 week out-of-session exposure | Follow up Study Visit | Next Therapy Session | End of treatment assessments |
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| Complete diagnostic interview & questionnaires as part of usual clinic procedures; If the patient meets study criteria, the Clinic psychologist/therapist will invite the patient and parent to participate | Informed Consent/Assent.<br>2 Baseline exposures.<br>Participant will wear a sensor to obtain biometrics and SUDS ratings will be collected. | Participants will be instructed to practice daily either the VR exposure or imaginal exposure, depending on study condition, and to record exposures using the exposure tracking form | Repeat 2 baseline exposures.<br>Participant will wear a sensor to obtain biometrics and SUDS ratings will be collected.<br>Participants assigned generalization exposure to complete in next therapy session<br><br>Qualitative interview and observation.<br>Complete the Spence Child Anxiety Scales and the Child Sheehan Disability Scale.<br>Participant will wear a sensor to obtain biometrics. | Participant will complete the assigned generalization exposure during therapy session following the Follow up Study Visit<br><br>Participant will wear a sensor to obtain biometrics and SUDS ratings will be collected. | Participants complete questionnaires as part of usual clinic procedures.<br>Study staff records data related to treatment length and # treatment sessions.<br>Post-Treatment from Clinic |
| | Participants continue with any treatments as usual, including treatment through Clinic | | | | |

**Statistical Analysis Plan**

Analysis Plan

The primary outcomes of the study are: (1) difference in maximum SUDS ratings during time 1 exposures between VR and conventional, 2) difference in number of exposures completed to assigned item (as well as overall) between conditions; 3) difference in maximum SUDS rating in cross over exposure between conditions during time 2; and 4) difference in maximum SUDS rating in generalization exposure between conditions during time 2. We will also conduct exploratory analyses to see if decrease in anxiety symptoms, as measured by the Spence Child Anxiety Scales, Child and Parent reports, and improvement in functional impairment, as measured by the Child Sheehan Disability Scale, differ between groups.

Quantitative analysis: Descriptive and inferential statistics will be used, including means, standard deviations, medians, ranges, frequency distributions, t-tests, and Analyses of Variance (ANOVAs). Specifically: a) differences in maximum SUDS ratings during VR and traditional exposures during time 1 session will be examined using a paired-samples t-tests, b) change over time in the peak anxiety ratings for each modality (VR vs. imaginal) will be examined using Repeated Measures ANOVAs with VR status as the between subjects variable and change in anxiety rating (T1 to T2 difference in maximal SUDS for VR vs.T1 to T2 difference in maximal SUDS for imaginal) being the within subjects variable, c) differences between homework exposure conditions, on maximal anxiety in the generalization exposure at time 2 controlling for time 1 maximal SUDS averaged across exposure conditions will be examined using Analyses of Covariance (ANCOVA) with homework condition as the between subjects variable and number of completed exposures and average maximum anxiety across the two time 1 exposures as the covariates; and d) ANCOVA will be used to compare average number of homework exposures completed to target item (as well as overall exposures) during the study time frame between the conditions (i.e. VR vs. imaginal) controlling for patient characteristics (age, sex, diagnoses). Exploratory analyses will compare change in anxiety symptoms from time 1 to time 2 between conditions, controlling for patient characteristics, and examining number of completed exposures as a mediator of change.

Qualitative analysis: We will conduct semi-structured interviews during the second study session with both the child and parent. These interviews will collect data on the participant's experiences, opinions, perceived benefits and barriers, and engagement with the system. An inductive coding approach will be used to condense these data and to identify themes. The Division of Health Care Policy & Research employs approximately 386 allied health and 62 doctoral level staff including survey research, qualitative research, statistical support, and chart review personnel as well as a dedicated publication specialist on staff. HCPR has created a core of behavioral scientists with expertise in qualitative research. They psychologist from HCPR has experience in qualitative research in the evaluation of mental health interventions. Analysts with experience in qualitative data analysis will code interviews using methods of content analysis, i.e., systematic process of sorting and coding information based on themes. QSR's NVivo 2010 qualitative data software analysis program will be used to facilitate data coding and sorting.