Official Title:

The Use of a FDA Cleared, Drug-free, Breathing System for Anxiety and Panic Disorders in Children and Teens

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Study Protocol

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Research Problem and Importance of the Research

Panic disorder (PD) is an anxiety disorder with an estimated annual prevalence of 1-2% of the adult US population. PD patients are more likely to have completed suicides compared to patients with depression (Taylor 2006; Kumar 2008) and over 25% of them abuse alcohol (Ballenger 1994). Although a number of treatment opportunities exist, only 30-45% of pharmacotherapy patients remain well after discontinuing medication use (Ballinger 1994), with 54-83% of cognitive behavioral therapy (CBT) patients remaining panic-free at 6-month follow-up (Kumar 2008). Adults with PD also have frequent comorbidities such as generalized anxiety disorder (GAD) (74%), agoraphobia (56%) and major depression (MDD) (52%). In adolescents and children, PD is also particularly debilitating, with adolescents with PD demonstrating greater functional impairment than adolescents with either depression or anxiety (Massi 2000 17186364). For individuals under 18 years of age, 4-5% report at least one lifetime panic attack (Hayward 1992 1503139, Wittchen 1998 9819071), and 1-2% of adolescents meet full clinical criteria for PD (Whitaker 1990 2331210,Von Korff 1985 4061447, Wittchen 1998 9819071).

Abnormal basal respiratory function is among the possible predisposing factors for anxiety and panic disorders. Alterations in basal breathing rates and consequent physiological changes have been found in patients with PD (Gorman 1987; Martinez 2001; Nardi 2009; Hibbert 1984; Schwartz 1996; Meuret 2001). Anxiety episodes in PD patients are also often accompanied by severe respiratory distress, along with tachycardia and faintness (McNally 1995). Voluntary hyperventilation can also induce panic attacks in PD patients (Papp 1997; Rapee 1992), suggesting a respiratory trigger and mechanism for PD. When PD and social phobia (SoP) patients were asked to breathe rapidly, those patients with PD had a slower recovery (more subjective feelings of lack of breath, more abnormal skin conductance and more fear of suffocation) than the SoP group. They also had lower CO2 levels associated with increased sighing (Wilhelm 2001 11485118).

In adults, positive physiologic and psychological benefits are found in PD patients who undergo breathing biofeedback training, which is capable of reducing the number of panic attacks and improving other panic symptoms as measured by the Panic Disorder Severity Scale (PDSS) (Meuret 2008). Other clinical indicators also improve with breathing biofeedback in PD patients, including a global clinical rating (Clinician's Global Impression; CGI), and self-reported anxiety (Meuret 2008). The Capnometry-Assisted Respiratory Training (CART) protocol, provides breathing biofeedback training and its use has resulted in 62% absence of panic attacks in PD patients who underwent four weeks of breathing biofeedback, with a 68% panic-free rate at one-year follow-up (Meuret 2008). In a subsequent study, breathing biofeedback led to significant improvement in both levels of end-tidal CO2 (EtCO2) and respiratory rates, while cognitive skill training did not lead to significant improvement in either (Meuret 2010). Despite similar prevalence rates and impairment associated with PD in children and adolescents, breathing biofeedback has not had the benefit of an efficacy study in this age group. Due to its low side effect profile, and its

potential to allow afflicted youth to circumvent the need for time-consuming psychotherapy or psychotropic medication use to treat PD, a breathing biofeedback program to treat PD would be a highly beneficial option for youth.

The Freespira Breathing System (FBS; www.freespira.com) developed by Palo Alto Health Sciences, Inc, is a portable home device which incorporates the CART protocol, and has been employed in breathing biofeedback in adults with PD. Based on the CART studies, FBS has now received FDA clearance for the treatment of PD adults and is currently commercially available and more than 150 therapist have provided the service nationally. However, FBS has not yet been tested for efficacy in a pediatric populations. Due to its portability, FBS may pose an advantage for use in younger age groups, compared to multiple therapy sessions required for CBT or lower acceptability for long-term medication use for adolescent PD.

In this pilot intervention study, the efficacy of the FBS system in youth will be tested. In children adolescents, PD itself is less common than in adults, but when present, PD is commonly associated with and/or preceded by other anxiety conditions, including generalized anxiety disorder (GAD), social phobia (SoP) and separation anxiety (SAD). Thus, in children and adolescents, the breathing biofeedback intervention for panic, should include other anxiety disorders.

Research Hypothesis

FBS is an efficacious intervention for youth with anxiety as defined by having either 1) PD, 2) OCD or, 3) two of the following three anxiety disorders: GAD, SoP and SAD.

2. Objectives *(include all primary and secondary objectives)*

The primary objectives are:
A) To enroll 60 youth with anxiety disorders as defined above.
B) To examine the efficacy of FBS to reduce anxiety in youth through use of an anxiety measure (Screen for Child Anxiety and Related Disorders, SCARED).

The secondary objectives are:
a) To measure additional panic, OCD and anxiety ratings pre- and post-intervention
b) To measure respiratory rates and levels of EtCO2 pre- and post-intervention

3. Background *(briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)*

Overview of FBS

FBS, an FDA-cleared device for adults with PD, incorporates the CART protocol developed by Meuret et al which showed significant benefit in reducing panic attacks and symptoms of panic (Meuret 2008; Meuret 2009; Meuret 2010; Meuret 2010b). In Capnometry Assisted Biofeedback Training (CABT), the patient engages in feedback-driven and protocol-monitored adjustments to their own respiratory rate and volume. This protocol gradually normalizes end tidal CO2 (etCo2)

levels, given that normalized etCO2 is known to reduce the risk of hyperventilation-induced panic attacks. Enhancing mobility of the device, FBS uses a tablet-based application (FBS app) in place of the tape recorder used in the CART protocol, to provide verbal instruction during the training sessions. FBS has also been identified as being substantially equivalent to the technologies used in numerous existing FDA-cleared biofeedback breathing devices such as RESPeRATE (K020399), the LoFlo C5 CO2 sensor (K053174), and InterCure's Respi-Low (K000495) .

Previous studies

1. In the first study of the CART protocol (Meuret 2008), 37 patients with a principal diagnosis of panic disorder were randomly assigned to receive CART training (n=20, Breathing Retraining Therapy [BRT] group) or to be in a wait-list (control) group (n=17, WL group). Like FBS treatment, CART treatment included an initial session with the clinical psychologist in the clinic, followed by self-administered breathing training at home twice a day for 17 minutes per session for four weeks, and weekly one-hour sessions with the psychologist in the clinic during the four-week training period. When surveyed post-treatment, 40% of subjects who had undergone CART had experienced no panic attacks during the 4-week period. At the two-month follow-up 62% had not had a panic attack since the end of the training and 68% were panic attack free at one year. A 40% reduction in initial PDSS scores was achieved by 68% of the participants at post-treatment, 79% at two-month follow-up, and 93% at 12-month follow-up. Significant improvement was seen in in psychological measures between pre- and post-treatment in the BRT group, but not over the course of the waiting period in the waitlist (WL) group. Respiratory measures also improved in the BRT group, with pCO2 increasing and RR decreasing in the BRT group between pre and post treatment evaluations, but remaining unchanged in the WL group. After including the WL group, who underwent the full CART training after the waitlist delay, longitudinal mediation analyses demonstrated that pCO2, but not respiration rate, was a partial mediator of the changes in anxiety sensitivity (Meuret 2009). These results were supported by cross lag panel analyses which indicated that earlier pCO2 levels predicted later levels of anxiety sensitivity, but not vice versa, and changes in pCO2 levels led to changes in respiration rate. It is noted that the most robust outcome detected was at 8 weeks of intervention, and 4 weeks after trial end.

2. In a subsequent study, 41 patients with a diagnosis of PD were randomized to receive CART (n=21) or cognitive skill training (CT, n=20). Overall, pCO2 increased and respiratory rate significantly decreased in the CART group, but not the CT group. Psychological measures improved equally in both groups. End tidal pCO2 was found to be a powerful mediator of change in panic symptom severity in patients in the CART group, but not for patients in the CT group. These findings suggest that changes in pCO2 are directly responsible for some of the changes in panic symptom severity (Meuret 2010).

Feasibility Study at Hopkins

A pilot study was conducted at Hopkins (IRB00045070 "A Feasibility Study of the Freespira Breathing System in a Pediatric Sample") to test the feasibility and acceptability of FBS in youth. Given the high levels of comorbidity between PD and other anxiety disorders in youth including obsessive-compulsive disorder (OCD), social phobia, generalized anxiety disorder and separation anxiety disorder in youth, we chose to test the feasibility and acceptability in this broader patient

population. In this study 12 subjects who met inclusion criteria were consented for FBS. There was good acceptability and safety profiles for those using the FBS, with no adverse events reported. The main lesson gained from this protocol was that a proportion of participating youth (5/12) did not fully complete the protocol due to differences between life demands, motivation, insight and lack of perceived reward for using FBS. Moving forward, in the current protocol, the use of FBS in youth will thus add: 1) an initial interview to assess motivation and realistic expectations from parents and youth, using motivational interviewing techniques (Williams 2014 25242705), to assure greater compliance with FBS; 2) a reward system to motivate youth in real time based on findings from the initial interview; 3) a close monitoring approach and parental contact between live visits if sessions are missed to problem solve adherence. In support of these approaches, data from each SCARED - Child anxiety score at 4th and 8th weeks (Birmaher 1999)
session with the FBS is uploaded to a secure server for clinician review of compliance and progress.

4. Study Procedures

i. Study design, including the sequence and timing of study procedures

Recruitment

Participants will be recruited through community advertisements, targeting pediatric clinics which treat youth with anxiety, such as Dr. Grados' (child psychiatrist) and Dr. Specht's (child psychologist) clinics in the Division of Child & Adolescent Psychiatry at Johns Hopkins, , as well as Dr. Robert Findling's research participants from the Clinical Trials Unit (CTU) at Kennedy Krieger Institute (KKI). Dr. Findling, a study team member on this study, is currently running studies on ADHD, for which he is the Primary Investigator. His KKI study team has an IRB-approved database with contact information for individuals who did not meet criteria for those studies, but indicated that they are interested in participating in research. KKI research coordinators will refer those individuals as well as newly identified individuals who have indicated an interest in research, to the research coordinator for the research study described in this application.. For this purpose, flyers will be distributed in clinic for parents to contact the research team if interested. Only when parents contact the research team, a phone screen will be completed. Families who screen in will be scheduled for informed consent and interview. A second modality of recruitment will be from the Division of Child & Adolescent Psychiatry wait-list for therapy or pharmacology services. In the initial screen for services, clinic staff request information regarding interest in research from the callers by a single question ("Would you be interested in being contacted for research?"). The third modality of recruitment will be from several clinical databases: EPIC Hyperspace – Remote Browser, JHCP, and Kennedy Krieger Institute Electronic Health Records in order to find willing potential participants that fall within the inclusion criteria to participate in this study. Only those families which express interest in research will be contacted if they fall within the screening eligibility criteria(youth under 18 years with a chief complaint of anxiety). Flyers will also be made available to anxiety disorder support groups and meetings, as well as professional peer networks for website posting or regular distribution. In addition, the study team will be using IRB approved flyers as advertisements in newspapers. In addition, we will also list our study on ResearchMatch.org, an NIH-funded recruitment tool maintained by the Vanderbilt University Medical Center so that interested families can contact us about participating in the study.

Screening

Potential participants, including those who answer the flyer or are contacted from the clinic waitlist after expressing interest in research, are contacted by phone by the study recruiter, who will determine possible eligibility related to inclusion and exclusion criteria (*see Screening Phone Script)*. The Screen for Child Anxiety Related Emotional Disorders Revised (SCARED-R; Muris 1998) will be used to screen for eligibility in youth with anxiety. In keeping with guidelines for the use of the SCARED, a score of $\geq$ 25, indicating the presence of an anxiety disorder, will be required for inclusion. A clinical screen interview will also include questions regarding prior diagnoses, symptoms present in the last month (with emphasis on three most currently-pressing symptoms), and whether symptoms are causing distress (s*ee Anxiety Disorder Screen)*

Positive Screen. A positive screen is determined by: a) 25 or greater on the SCARED

Informed Consent and Preparatory visit

If a patient screens positive, he/she and the parent are scheduled for a face-to-face informed consent with the PI or the consent designee. At least 20 minutes will be dedicated to informed consent for participation in the randomized study with parent and oral assent from the child. Care will be taken to probe understanding of the informed consent by the parent and youth using the ask-tell-ask technique. If the participant is deaf or hearing-impaired, a family member or a sign language interpreter may be asked to communicate to the child to confirm understanding of the study and to assist.

In this preparatory visit, after consent is obtained, the initial random allocation of the patient will be determined and if the patient is selected for the initial Freespira treatment group, the family will be introduced to the FBS and the protocol reviewed. To be covered in this session are:

A) Use of FBS. Explanation of the 28 days use, twice per day for 17 minutes each session; conditions for use of the loaned device (Equipment Loaner Form reviewed); facilitation of data upload after use.

B) Psychoeducation and Motivational Interviewing. Basic psychoeducation concepts on anxiety will be provided and questions from parents and child answered. Motivational interviewing techniques will be used to encourage parent and child to adhere to the FBS use.

C) Consideration of a Reward System for Completion. For 9-12 year old children a token system may be customized for the child and parent. Behavioral reinforcers for completion will be discussed with parents and planned. For adolescents, discussion of reasons for participation and completing the protocol will be assessed and motivation will be reinforced. At session end, scheduling for the second visit (Week 1) will take place.

D) Explanation of the Randomization Procedure (detailed in Consent). The control waitlist is an active control group with weekly telephone or online check-ins and weekly surveys for symptom severity.

First Study Visit (Week 1)

Active Intervention Group. In Week 1, the initial visit, a two and one-half hours session will be conducted. In this visit the family will receive a detailed explanation of the FBS. In this session the project coordinator will describe the major tenets of breathing control and anxiety. Subjects will be instructed in the use of the CO_2 sensor, Freespira App on the Nexus 7 tablet and panic diary. At this time a clinical interview for anxiety disorders and OCD is administered by the PI (Grados), as well as eight paper-and-pencil questionnaires administered to rate anxiety, panic and OCD symptoms. The clinical global impression scale (CGI) at baseline (consent visit) will be completed as a blinded best-estimate CGI at study conclusion by 2 independent clinician raters through a review of the clinical data. CGIs will be completed in this way for the baseline consent visit and for the outcome visit at week8.

The relationship between level of CO2 and depth of breath will be explained to patients at this time, and weekly breathing rate changes will be demonstrated.

A full 17-minute breathing biofeedback session will occur at this time, consistent with protocol recommendations for use in adults. After instruction, families will then take the tablet and CO2 sensor equipment home. Full instructions are provided for using the breathing device loaned to the participants, with parents assisting youth in breathing exercises for 17 minutes, twice a day, for four weeks. Youth are also given a daily panic attack diary to track frequency, symptoms, and severity of any panic attacks they experience over the four weeks of breathing biofeedback. The panic diary will also evaluate the ease with which the subject completed the breathing session (i.e. whether it was hard to follow the tone, match the target respiratory rate, etc.) The panic diary will be completed after the second biofeedback session each day (1 panic diary per day for the 4 weeks that active intervention participants are using the device). We will ask about any changes to the child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since they last study visit.

The role of the parent in this study will be to fill out the required questionnaires, bring their children to study visits and to monitor their child's compliance in using the Freespira Breathing System.

Active Control Waitlist. An online or telephone check-in will be made to the active-control family during Week 1 of the study. We will ask about any changes to the child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since the last study visit.

Sessions Weeks 2 and 3 – Online/Phone Check-in

Active Intervention Group. At Weeks 2 and 3 of the intervention, an online/phone contact will be made with participants through SKYPE to ascertain that no major issues have arisen in the use of the FBS. The team will be available for questions and problem solve any issues with adherence to the use of FBS. We will ask about any changes to the child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since they last study visit.

Active Control Waitlist. An online/telephone check-in will be made to the active-control . The participant will be asked about any panic attacks. All follow-ups for control participants will be conducted in this manner. Severity will be assessed and randomization stopped if clinically appropriate, in case symptoms reach a severity of clinical impairment unacceptable to the family and

through the judgment of the PI, a board-certified child and adolescent psychiatrist. We will ask about any changes to the child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since they last study visit.

Second Study Visit (Week 4)

Active Intervention Group. Participants will come to the office at week4 for the follow-up visit to complete measures and the 4-minute breathing session. In select cases, this visit will be done in the home setting when determined necessary by the PI. The interview portion can also be done by phone within a window of one week. In this session families will review the results of the breathing sessions with the research team, and go over any questions or concerns they may have and complete paper-and-pencil questionnaires. Clients may do a breathing session at each meeting in the office. The panic diaries will be reviewed during these sessions. Any particularly anxious days and corresponding low levels of CO2 on this day as measured by FBS will be discussed. We will ask about any changes to the child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since they last study visit.

Active Control Waitlist. An online/telephone check-in will be made to the active-controls and will complete same questionnares as active intervention group in week4. In case symptoms reach a severity of clinical impairment unacceptable to the family and through the judgment of the PI, a board-certified child and adolescent psychiatrist. The interview portion can also be done by phone within a window of one week.We will ask about any changes to the child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since they last study visit.

Third Study Visit (Week 8)

Both Active Control Waitlist and Active Intervention Groups. At two months from the initial session, families will either have in-home visit or come back in to research study office to receive a final assessment that includes the clinical interview and paper-and-pencil questionnaires The interview portion can also be done by phone within a window of one week. Adolescents will complete a four-minute recorded breathing session with the CO_2 sensor to record the final breathing rate and et CO_2 (post-treatment). We will ask about any changes to the child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since they last study visit. If the parent is unable to complete his/her paper-and-pencil questionnaires within the office visit window, but another caretaker is able to bring the child to the office visit, the child can complete his/her questionnaires and the breathing session within the window and the parent can complete the rest of the questionnaires remotely by phone/SKYPE.

The whole session will last about 45 minutes.

Active Control Waitlist Only. Following the Week 8 visit, families in the active control group will have the option to be treated with the FBS per the above protocol for visits 1-4 in weeks 1-8. We will ask about any changes to your child's medication since the last study visit. We will also ask how many therapy sessions the child has attended since they last study visit.

First Follow-up (6-month Online/Phone Check-In)
At six months following treatment, an online/telephone contact will be made with participants to ascertain status and to administer SCARED,PDSS-A surveys, K-SADS (anxiety disorders),CY-BOCS (OCD symptoms). The interview portion can also be done within a window of one week. If a participant was unable to be reached at 6 month follow-up, they may be re-contacted again to see if they would be available for the 12-month phone call follow-up.

Second Follow-up (12-month Check-In)
At twelve months from the final session, families will either have a phone call visit or come to Hopkins to receive a final assessment that includes the clinical interview and paper-and-pencil questionnaires. The whole session will last about 30 minutes. SCARED,PDSS-A, K-SADS (anxiety disorders),CY-BOCS (OCD symptoms) surveys will be administered. The interview portion can also be done by phone within a window of one week.

Families in the *Active Control Waitlist* group will receive 6-month and 12-month follow-ups as specified above at these time points following completion of their Freespira treatment, if they choose the option of enrolling in the intervention protocol after the waitlist period.

Table 1. Timeline and Burden for Freespira Breathing System Study

Activity	**Informed Consent & Prep Visit**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**6 mo follow up**	**12 mo follow up**	**Time**
Location	Office/In-Home	Office/In-Home	Home	Home	Office/In-Home	Office/In-Home	Home	Office/In-Home	
Visit Window	None	None	None	None	0 to 21 days	0 to 21 days	0 to 21 days	0 to 21 days	
Informed Consent	**X**								20 mins
SCARED parent (anxiety)	**X**				**X**	**X**	**X**	**X**	10 mins
SCARED child (anxiety)	**X**				**X**	**X**	**X**	**X**	10 mins
K-SADS (anxiety disorders)	**X**				**X**	**X**	**X**	**X**	20 mins
PDSS-A (panic symptoms)	**X**				**X**	**X**	**X**	**X**	10 mins
CY-BOCS (OCD symptoms)	**X**				**X**	**X**	**X**	**X**	15 mins
CDI2 (depression symptoms)	**X**				**X**	**X**			5 mins

CSDS (disability measure)	**X**				**X**	**X**	3 min
CASI (anxiety sensitivity)	**X**				**X**	**X**	5 min
JTCI (temperament)	**X**						12 mins
Review of educational material involving breathing	**X**						15 mins
Review of FBS Use in Home	**X**						15 mins
Review patient questions or concerns	**X**	**X**	**X**	**X**	**X**	**X**	
Set-up and demonstration of FBS		**X**					
Practice of breathing techniques with patients in demo mode		**X**					10 mins
Concomitant Medications Review		**X**	**X**	**X**	**X**	**X**	5 mins
Therapy Sessions Attended		**X**	**X**	**X**	**X**	**X**	5 mins
Discuss expectations for future sessions		**X**					10 mins
Full 17-minute breathing training session		**X**					20 mins
4-minute breathing session for RR, EtCO2					**X**	**X**	4 mins
Review Panic Attack Diary			**X**	**X**	**X**		5 mins
Side-Effect Drugs/ Substances/ Devices Questionnaire					**X**		5 mins
Satisfaction Questionnaire					**X**		

ii. Study duration and number of study visits required of research participants.

The study will proceed for 18 months, with participants entering on a rolling basis. The participants will require a consent/preparatory visit, four visits during use of FBS and a final follow-up visit. Follow-up visits will occur at 8, 26 and 52 weeks post-treatment.

iii. Blinding, including justification for blinding or not blinding the trial, if applicable.

The study will be un-blinded to the research team. A randomization procedure will occur at the informed consent/preparatory visit via a random number generator (STATA 12.1). If the random number is even the child will be a case, if odd the child will an active control.

iv. Justification of why participants will not receive routine care or will have current therapy stopped.

If on psychotropic medication(s), subjects must be on a stable dose for a minimum of one month prior to study enrollment. During the study routine care as usual will continue by their physician. The active control waitlist will be 8 weeks for use of FBS, which is within the time frame that is common for patients in the clinic.

v. Justification for inclusion of a placebo or non-treatment group.

A sham treatment group for the FBS will not be used. The non-treatment group will be a waitlist control, which will be offered the FBS at the end of 8 weeks.

vi. Definition of treatment failure or participant removal criteria.

Participants are removed only if they fail to complete the required breathing exercises for over 50% of the allotted time, as efficacy would not be able to be assessed. If during the study, participants are found to be depressed or exhibit suicidal ideation while completing surveys, they will be referred to the P.I. Dr. Marco Grados, a board-certified child and adolescent psychiatrist, who will evaluate them and make the appropriate treatment referral. Treatment failure will be assessed at the 4-week post-treatment interval (8 weeks from study initiation).). If participant is unable to complete Week 4, Week 8, and 12 Month visits within visit windows (Table 1) they will be contacted by study PI, and if the issue is not able to be resolved they will receive a research study withdrawal letter in the mail explaining why they are being withdrawn from the research study.

vii. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants who have completed the FBS may choose to pursue further treatment of anxiety, with referrals facilitated by the study team. Dr. Grados, the PI for the study, is also clinical director of the Division of Child & Adolescent Psychiatry, and will be available to answer referral questions. Subjects will also not be denied future treatment by JHH because the study has been terminated or consent was withdrawn.

5. Inclusion Criteria

1) Must have a SCARED > 25; meet DSM-V criteria for OCD, PD; or, meet criteria for <u>two</u> of the following three disorders: GAD, SoP or SAD

2) Participants must be 9-17 years of age
3) If on psychotropic medication(s), participant must be on a stable dose at least one month prior to study enrollment

Exclusion Criteria

1) Anxiety has occurred exclusively during a major depressive episode, other psychiatric diagnoses, dementia, intellectual disability, or brain disease
2) 3) Currently enrolled in another device or drug study or less than 30 days has elapsed since participation in such a study
4) Currently undergoing breathing biofeedback elsewhere
5) Demonstrate evidence of severe suicidality or psychosis
6) There is an active condition of asthma

6. Drugs/ Substances/ Devices

i. The rationale for choosing the drug and dose or for choosing the device to be used.

FBS is an evidence-based, FDA-cleared device currently in use in adults with documented success in treating symptoms of panic (Meuret 2008, Meuret 2010). A pilot study has been completed in children and adolescent at Hopkins in 2015. Although identified as substantially equivalent to several alternative FDA-cleared devices, the current device merits investigation into its efficacy in a pediatric sample. The feasibility study conducted encountered no side effects or adverse events to its use in children. The main drawback encountered was encouragement to complete the sessions. There is a plan to further ensure adherence in the current protocol, which draws on evidence-based adherence protocols in pediatric populations.

ii. *Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.*

N/A

iv. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

i. Primary outcome variable.

The primary outcome is the SCARED Parent anxiety score (Muris 1998) at the 8-week assessment. This is in keeping with prior experience with FBS in adults.

ii. Secondary outcome variables.

I. Clinician's Global Impression (CGI; Guy, 1976)
II. SCARED Parent anxiety score at 4th week (Muris 1998)
III. SCARED Child anxiety score at 4th and 8th week (Birhamer,1999)
IV. End-tidal CO2 at 4 weeks
V. Respiratory rate at 4 weeks

VI. Decrease in frequency and severity of panic attacks as documented in panic diary (only for participants with panic attacks)
VII. Panic Disorder Severity Scale for Adolescents [PDSS-A]
VIII. Child Yale Brown Obsessive-Compulsive Scale (CY-BOCS; Goodman 1991)

iii. Phenotype variables

I. Children's Depression Inventory 2nd Edition (CDI2; Kovacs 2010)
II. Child Sheehan Disability Scale (CSDS; Whiteside, 2009)
III. Child Anxiety Sensitivity Index (CASI; Silverman 1991)
IV. Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman 1989)
V. Junior Temperament and Character Inventory (JTCI; Luby 1999)
VI. Medications history in Visit#1 , Week 1-4, Week 8.
VII. Psychotheraphy history in Visit#1 , Week 1-4, Week 8.

iv. Statistical plan including sample size justification and interim data analysis.

As described above, the primary endpoint of this study will be a quantitative improvement in anxiety as measured using the SCARED scale.

Primary Effectiveness Hypothesis, Outcome Measure and Statistical Method

Hypothesis:
From baseline to the 2-month post-treatment, at least 65% of study participants in the Freespira (test) group will experience a clinically meaningful change in their total SCARED score (41-item) version vs. 20% in the active waitlist control group.

Outcome Measure:
Success is defined as a reduction in SCARED score of 25%.

A clinically meaningful change in the SCARED score is a decrease in approximately 16 points (1 SD in anxiety published norms) in the total score of the full scale (range 0-82) (Birmaher 1999), although for individual patients, a 25% decrease is considered significant clinically.

Statistical Method:
The proportion of subjects in each group showing an improvement in each measure from baseline will be compared using Chi-square or Fisher's Exact tests. Change in mean SCARED scores for each group will be analyzed by t-test. Analysis will be based on an intention to treat (ITT) and per protocol (PP) basis. Only those subjects who have a measurement for both baseline and at 8 weeks will be entered into the primary analysis.

Supportive analyses will be conducted for all subjects entering the trial using a multiple imputation method appropriate for outcome rates which exhibit trends over time.

Sample size derivation:
The design includes a study of independent cases and controls with 1 control per case. Prior data indicate that the probability of success among controls is 0.2. If the true probability of success among test subjects is 0.65, we will need to study 23 case patients and 23 control patients to be able to reject the null hypothesis that the success rates for case and controls are equal with probability

(power) 0.897. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. Allowing for a dropout rate of 20%, a total of 60 patients will be recruited and studied (Pocock 1983; Dupont 1990).

v. Early stopping rules.
The study may be discontinued in the event of the discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled or a decision on the part of the investigator. The IRB will be notified in writing in the event of study termination.

8. Risks

i. Medical risks, listing all procedures, their major and minor risks and expected frequency.

There are no serious risks from the proposed intervention. This has been evidence from prior studies with FBS and with the feasibility study conducted at Hopkins. There is a potential risk of psychological distress from discussing anxiety. Risks specific to the FBS protocol were obtained from users of FBS from adult clinics and the feasibility study. Possible side effects noted are headaches, light-headedness or dizziness, which may occur in the first several breathing biofeedback sessions. These side effects typically diminish during later sessions.

ii. Steps taken to minimize the risks.

We try to approach each participant according to his or her initial knowledge and attitude and to carefully answer all questions with that in mind. Confidentially is carefully protected.

iii. Plan for reporting unanticipated problems or study deviations.

We will encourage participants to contact the PI whenever there is an unanticipated problem related to the FBS protocol or other study. The PI is responsible for reporting adverse events to the IRB.

iv. Legal risks such as the risks that would be associated with breach of confidentiality.

The risk of breach of confidentiality is present but will be minimized by use of locked paper files and password-secured computer hard drives that only research team members can access.

v. Financial risks to the participants.

In the event that participants misplace the device or terminate their participation without returning the device they will be liable for $500, which represents a portion of the cost of the device. The cost is listed in the informed consent and loaner form and represents only a fraction of the actual device cost.

9. Benefits

i. Description of the probable benefits for the participant and for society.

Participants will receive at study start (Week 1) or at the 2-month time frame (for waitlist controls) the FBS intervention which has proven effective in approximately 60% of adults with anxiety, with a low side effect profile. Society will benefit from the possible future implementation of a low-cost, acceptable treatment for youth with anxiety.

10. Payment and Remuneration

i. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be given a $30 Amazon gift card during the Consent visit, Week 4 visit, and Week 8 visit. . The study team will also provide parking vouchers.

11. Costs

i. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to participants, unless the device lost/misplaced device. In this case, families will be responsible for $500 payment. This payment will not be requested in the event of a device damaged in the course of normal use and handling. The credit card information will be destroyed when the FBS is returned.

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