Protocol Outline

Protocol Title: Self-Administered Hypnotherapy for Functional Dyspepsia
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Principal Investigator: Sarah Kinsinger, PhD
Research Team: Sarah Kinsinger, PhD, Mukund Venu, MD, Olafur Palsson, PsyD
(University of North Carolina, Chapel Hill)

I. Abstract

Functional dyspepsia (FD) is a very common health problem, affecting up to 20% of the world's population, characterized by upper gastrointestinal (GI) tract symptoms, including epigastric pain, postprandial fullness, and early satiety[1]. These symptoms occur in the absence of any structural abnormalities[2]. FD has significant economic impact due to financial cost related to health care utilization as well as indirect cost associated with missing work and impaired work performance. Patients with FD also report significant reductions in quality of life and increased rates of psychological distress[3]. There are few effective treatment options for FD. Medications typically include trials of proton pump inhibitors, prokinetic agents, or tricyclic antidepressants[4]. However, there is limited efficacy for these pharmacological treatments and current treatment approaches are considered unsatisfactory[4,5].

Psychological treatments have demonstrated good efficacy for functional GI disorders such as irritable bowel syndrome (IBS). For example, gut-directed hypnotherapy has been studied extensively as a treatment for IBS with over 24 published trials, 10 of which are randomized controlled trials[6]. These studies consistently demonstrate significant improvements in central IBS symptoms (abdominal pain, bowel habits) following a course of hypnotherapy[6]. FD and IBS are thought to have overlapping pathophysiology, including altered gut motility, visceral hypersensitivity, and abnormal central processing of visceral signals. Many of these underlying mechanisms in FD can potentially be targeted by hypnotherapy via brain-gut pathways. For example, hypnosis has been shown to decrease gastric emptying time in patients with dyspepsia.[7]

To date there has only been one published trial of gut-directed hypnotherapy for functional dyspepsia, but with promising results[8]. Calvert and colleagues found that 73% of patients in the hypnotherapy group had significant improvement in dyspeptic symptoms at long-term follow-up, compared to 34% of patients receiving supportive therapy plus a placebo pill and 43% of patients receiving medical treatment. Additionally, patients in the hypnotherapy group had dramatic reductions in medication use and physician consultations at follow up.

The goal of the current study is to develop and conduct a pilot test of effectiveness of a self-administered gut-directed hypnotherapy intervention for treatment of FD, with the aim of assessing its potential as an inexpensive, easy-to-use and efficacious treatment for the disorder.

II. Background and Significance/Preliminary Studies

Background and Significance

Both patients and providers are frustrated by the limited treatment options for FD. This is a chronic condition and many patients continue to seek medical care for poorly managed symptoms, including multiple physician office visits and investigative procedures. More effective treatment options are needed to reduce this health care burden. Behavioral treatments (e.g., gut-directed hypnotherapy) are highly effective for other functional gastrointestinal disorders and have shown promise for FD.[6] However, additional research is needed to establish behavioral treatment as an efficacious and realistic approach for this condition.

There have been a few trials of very diverse forms of psychotherapy in FD with varying degree of reported success[8-18]; however, no treatment has had adequate testing and all of them involve a course of many visits to a highly specialized mental health professional which is expensive and not available in most places. To date, one of the most successful and best designed trials of this kind has been Calvert et al.'s randomized controlled study of hypnotherapy for FD[8]. This trial found significant improvements in FD symptoms and significant reductions in health-care utilization following a course of hypnotherapy with superior results compared to the two control groups and there was full maintenance of the treatment effect beyond one year follow-up. These therapeutic effects demonstrate impressive potential for hypnosis as a therapy option in FD. However, it is notable that the intervention tested by Calvert et al. consisted of a 12-session course of treatment with a specialized GI hypnotherapist, which means that generalizability of this approach is very limited due to significant cost barriers and limited availability of therapy expertise. However, other work in GI hypnosis, including two studies of co-investigator Palsson, has demonstrated that hypnosis treatment that is self-administered by patients via audio recordings without any therapist involvement can be highly efficacious in improving GI symptoms[19,20]. That form of delivery could make hypnotherapy a much more widely available treatment option if proven effective, as it could be delivered in a very inexpensive and easily disseminated form. Our present study therefore aims to replicate the findings by Calvert et al. demonstrating that hypnosis treatment (HYP) can lead to clinically significant improvements in dyspeptic symptoms, while testing it in an audio-recorded easy-to-use self-administered format.

Patients are increasingly skeptical of long-term medication use for conditions such as FD due to concerns about risks and side-effects of medications like proton pump inhibitors. A large number of patients with FGIDs are already using complementary and alternative medicine approaches[21] and we suspect that patients will be receptive to a non-pharmacological treatment program that they can participate in from home.

The results of the current study have the potential to significantly impact the clinical management of patients with FD. Although there is strong scientific support for the role of interventions targeting brain-gut pathways and psychological factors in symptom severity for patients with FD, psychological treatments are not commonly recommended for this population. Our study would provide further support for hypnotherapy as a behavioral treatment for this condition and our proposed administration of the treatment (self-administered via audio recordings) would increase the generalizability and accessibility of this treatment.

A common criticism of psychological treatments for GI disorders is poor dissemination and access to treatment, in part due to the cost of treatment, which generally requires between 6 and 12 sessions with a therapist. For example, gut-directed hypnotherapy and cognitive behavioral therapy are well established evidence-based treatments for IBS; however, these treatments are unavailable to many individuals. Barriers to accessing these treatments include a limited number of well-trained psychologists to offer these specialized treatments and the significant cost and time commitment required of patients. Our study aims to address these barriers by offering a self-administered treatment. Patients would administer the hypnotherapy treatment in their home by using convenient, web-based audio recordings. This methodology has been used previously in hypnotherapy trials for IBS and pediatric abdominal pain with good results[22,23]. If the self-administered home hypnosis treatment tested in this trial proves efficacious, this will reduce treatment cost and enable us to make it available nationwide to the many patients who live too far from a specialized center to be able to attend multiple therapist sessions typically required. This innovative delivery method will also have the potential to improve the care of large numbers of patients by establishing a highly generalizable and inexpensive non-pharmacological treatment for this population.
Additionally, our study is innovative in that we will test delivery of the treatment with a custom-designed easy-to-use secure online platform that can be used on practically any device and is designed to help motivate patients and direct them through the treatment course (an important consideration in self-administered treatment) by providing adherence feedback and presenting them automatically with the right content at the appropriate time points in the treatment course.

Preliminary Studies

A published pilot study of hypnotherapy for IBS delivered entirely through audio recordings by co-investigator Palsson and his colleagues serves as a model for the hypnosis treatment in this FD trial[19]. That study found that IBS patients who completed a seven-session self-administered audio home hypnosis treatment course were twice as likely (53% vs 26%) to have a reduction in their gastrointestinal symptoms by half or more at 6 months compared to matched control patients of the same age and sex and equal symptom severity who only received standard medical care. We will script the audio-recorded hypnosis protocol in the present trial to be similar in structure and therapy approach, as IBS and functional dyspepsia are both functional GI disorders and have many similarities and a high degree of overlap (the intervention tested in the prior hypnosis trial by Calvert et al., that showed high success in FD treatment, also utilized modified IBS hypnosis treatment for that purpose).

III. Study Aims

The purpose of this pilot study is to develop and test a hypnotherapy (HYP) treatment program for functional dyspepsia (FD) that can be self-administered using on-line audio recordings. We hypothesize that patients will be receptive to the self-administered treatment design and willing to participate and complete the 12-week treatment program.

Furthermore, we expect that patients will experience a significant reduction in FD symptoms following the intervention. Our specific aims include:

Aim 1: Feasibility and Acceptability of Treatment
The study will assess whether patients with FD will be willing to participate in the on-line treatment program and the majority of patients enrolled in the study will complete the 12 week program, utilize the materials sufficiently, and report average to above average satisfaction with treatment.

Aim 2: Treatment Effectiveness
The primary endpoint for Aim 2 is significant reduction in pre- to post- treatment FD symptom scores. Secondary endpoints include significant improvements in pre- to post-treatment score on psychological indices (e.g., anxiety) and disease-specific quality of life.

IV. Administrative Organization

All administrative activities related to the study will take place within the Division of Gastroenterology and Nutrition at Loyola University Medical Center (LUMC). Administrative offices for the division are located in the Fahey Building on the LUMC campus where office furniture, file cabinets, and use of essential equipment (e.g., copier, fax, phone, computer) will be provided.

V. Study Design

a. Experimental design of the study:
This is a non-randomized observational study designed to provide preliminary data on the feasibility and effectiveness of a self-administered HYP treatment for FD.

b. Study population general description
Eligible patients will be referred by Gastroenterologists within the Digestive Health Program at Loyola University Medical Center and will have received a diagnosis of functional dyspepsia. Additionally, any patients with functional dyspepsia referred by outside providers to Dr. Kinsinger's GI Behavioral Medicine Service at LUMC will be made aware of the study.

c. Sample size determination and power analyses

We will enroll 23 adults with FD from the Loyola University Medical Center outpatient gastroenterology practices, with the aim of assessing feasibility and acceptability of HYP treatment using on-line audio recordings. Sample size was determined for aim 1 of the study. Allowing for up to 20% drop-out and having at least 16 patients complete the study through the end of treatment (where the primary endpoint will be measured) will provide sufficient participant feedback on the web interface as well as the pilot data needed to power a future randomized controlled trial.

d. Study outcomes/endpoints

The primary endpoint for this study will be FD symptom scores. Secondary endpoints will be disease-specific quality of life, psychological indices, and patient satisfaction.

VI. Study Procedures

a. Subject selection procedures:

We will enroll 23 adults with FD.

Inclusion criteria

(1) Diagnosis of functional dyspepsia by a gastroenterologist
(2) Meeting ROME IV diagnostic criteria for functional dyspepsia
(3) At least 18 yrs of age (no upper age limit)
(4) Able to give informed consent
(5) English speaking
(6) Have daily personal access to the Internet via laptop or desktop computer, tablet or a smartphone.

Exclusion criteria

(1) Concomitant organic gastrointestinal disease
(2) Diagnosed or presenting with serious mental illness (e.g., eating disorder, schizophrenia, psychosis, obsessive-compulsive disorder, post-traumatic stress disorder, or a dissociative disorder)
(3) Cognitive or language barriers that make completion of questionnaires difficult or limit understanding of a verbal intervention (hypnosis)

i. Recruitment procedures

1. Where will recruitment occur?
Participants will be recruited from the Loyola University Medical Center outpatient gastroenterology practices. Dr. Mukund Venu, Director of Clinical Operations for the

Division of Gastroenterology will be actively recruiting patients in his clinics and will encourage our gastroenterology colleagues (15 gastroenterologists and 5 mid-level providers) to refer patients to the study. The research coordinator for the study will review patient charts in our division's outpatient gastroenterology practices to pre-screen for eligibility. We will obtain a waiver of consent for this process.
We will also advertise the study on social media (Loyola Medical Center twitter handle and facebook page) and through the Loyola University student listserv. We will obtain IRB approval for all advertisements.

2. Where and when will consent be obtained?
Consent will be obtained either at the patient's outpatient visit with their gastroenterologist or at the time of the screening evaluation visit with Dr. Kinsinger. The research coordinator will recruit patients from designated gastroenterology clinics and consent patients at those visits. If patients are referred for the study from other gastroenterology clinics that are not staffed by the research coordinator, Dr. Kinsinger will obtain consent at the time of the screening visit. The consent process will occur prior to beginning the screening evaluation. During the COVID-19 health crisis, all screening visits will be conducted electronically via telemedicine and consent will be obtained orally. The study coordinator will email participants a PDF copy of the consent form prior to their telehealth screening visit to review. The study investigator (Dr. Kinsinger) will then review the consent form at the start of the video screening visit and ask the participant to state their consent verbally on the video in response to the following question: "Have you read the consent form and do you understand the procedure, risks, and benefits of the research study and agree to participate?". The study investigator will document the patient's verbal consent.

3. Who will obtain consent? Dr. Kinsinger or the research coordinator will obtain consent.
4. What is the advertising plan, if applicable?
    a. Social media (Loyola Medical Center twitter handle and facebook page; Dr. Kinsinger's LUMC webpage)
    b. Loyola University student listservs
    c. Display brochures in gastroenterology outpatient clinics

5. What recruitment materials will be provided to the potential participant (brochures/information sheets/video presentation)?
    a. Website describing the study
    b. Brochures with study information
    c. Brief video conducted by Dr. Kinsinger describing the study (see Appendix A for a script of this video; filming will be done after IRB approval is obtained)
    d. We are in the process of developing these marketing materials and will submit all advertisements to the IRB to obtain approval prior to use.

ii. Screening procedures

1. What procedures are required for screening?

    Eligible participants referred by a Loyola Gastroenterologist will meet with Dr. Kinsinger for a screening evaluation. The purpose of this appointment is to determine appropriateness for behavioral treatment and provide education on FD, inform potential participants about the study and complete written or oral consent if they choose to participate and are eligible. Patients that learn about the study from outside of Loyola will need to meet with a Gastroenterologist (Dr. Venu, Co-I) to confirm diagnosis of functional dyspepsia prior to being enrolled in the study.

    Dr. Kinsinger has dedicated space within the Loyola Outpatient Center for patient care that can be utilized for the screening evaluation where patient privacy and confidentiality can be maintained.

    During the COVID-19 health crisis, the screening visit will be conducted electronically via one of the telehealth video platforms approved by Loyola Medicine for use with patients during the pandemic (doxy.me, Doximity, Skype, FaceTime, or Zoom).

    Following this screening appointment, enrolled patients will receive an email with information for accessing the on-line platform where they will complete pre-treatment assessment forms and access treatment materials.

2. What is the screening schedule (number of visits, length of visits)? Screening will involve a single, 1 hr appointment.

3. Which screening tests/procedures are part of standard care and which are for research purposes only? The screening will be for the purpose of the research study.

4. What happens with screen failures (including any data gathered during screening)? Data will not be collected on patients that are screened as ineligible for the study. However, these patients will be provided with recommendations for alternative treatment options by their gastroenterologist (medications, diet changes), alternative psychological treatments within the Loyola GI behavioral medicine program, or a referral to an outside provider depending on patients' needs.

b. Randomization procedures (if applicable): N/A
c. Study Intervention

Patients will be given access to a password protected website containing HYP treatment materials. They will be instructed by the study coordinator to log on to the website within 1 week to complete baseline assessment questionnaires and watch an instructional video. This video will be pre-recorded by Dr. Kinsinger (study PI). The content of the video will include educational information about the patient's diagnosis, provide rationale for hypnotherapy treatment, set expectations for treatment, and dispel myths about hypnotherapy. The video will also provide instructions on implementing the treatment protocol, including guidance on selecting a time and place to practice hypnotherapy and recommendations for weekly practice with audio recordings (5x per week). See Appendix B for a full script of this introductory video (video will be filmed after we receive IRB approval).

We have developed a 7- session, hypnosis protocol for functional dyspepsia that is similar to an evidence-based protocol for irritable bowel syndrome developed by co-investigator Dr. Palsson, which has been found to be efficacious in 7 published studies[24]. This protocol was jointly scripted by Drs. Kinsinger and Palsson, and is based on the successful scripted therapy approach for IBS, with appropriate adaptations. See Appendix C for the full scripted protocol of the 7 hypnotherapy sessions as well as the shorter practice session that will be audio recorded. This will be the full content of the audio recordings, subject to final minor edits and polishing, prior to recording which will be scheduled after we receive IRB approval.

Participants will have access to audio recordings of the protocol (pre-recorded by Dr. Kinsinger, study PI) via secure streaming online that will work on any computer or mobile device with internet access. Patients will be assigned a new hypnotherapy session to listen to every 2 weeks and these will become automatically available in the correct sequence. Each hypnotherapy session

will be approximately 30 mins in length. The hypnotherapy sessions are verbally guided exercises, similar to guided meditation. The hypnotherapy sessions encourage patients to enter a state of focused mental attention and deep physical relaxation during which images and verbal suggestions are used to positively influence emotional and physical symptoms. The session developed for this intervention will specifically focus on mechanisms that contribute to functional dyspepsia symptoms, such as impaired relaxation of the stomach and pain sensitivity. For example, after facilitating a deeply relaxed state patients will be asked to visualize drinking a cool liquid that has a therapeutic effect on the stomach (i.e., decreases pain, allows the stomach to stretch and make room for food). Each of the 7 sessions will utilize different imagery.

Patients will be instructed to practice a shorter 10-12 minute audio recording 5 times per week in between the longer sessions. After the 12-week treatment course is completed, patients will be able to continue to listen to the shorter home hypnosis recordings as often as they choose for up to one year.

The web page will give patients pop-up notices to encourage them to increase their frequency of practice if their weekly frequency drops below the recommended 5 days of home practice. Patients who do not log into the online system to complete a hypnosis exercise for 7 consecutive days will be contacted by the study coordinator to discuss whether the patient is interested in continuing with the trial.

Additionally, patients will receive phone or MyLoyola messaging (patient preference) from a study coordinator every 2 weeks to encourage adherence and troubleshoot any difficulty using the recordings and assess any adverse effects. If they have any difficulties or discomforts associated with the self-administered hypnosis intervention during the trial, they will have an opportunity to talk with Dr. Kinsinger on the phone to resolve these.

<u>The Study Website</u>

The patient portal where study participants will access the hypnosis audio recordings and study questionnaires is www.FDHypnosis.com. It is a secured web page where the patients log in with their unique study ID and password. Once patients log-in, they are presented with an online audio player that enables them to either play one of seven main hypnosis sessions, which are to be completed in a fixed sequence -- one every two weeks during the intervention period, or they will be presented instead with the shorter hypnosis exercise to be completed five times a week in between the main hypnosis session. Which type of session is presented at a given time is automatically determined by the web page software. This ensures that the participants complete the main intervention sessions approximately on schedule. When it is time for participants to complete study questionnaires, a study questionnaire button will also become visible within this patient portal, with instructions to click it to complete the study questions. In this way, the patient portal ensures that patients complete their study tasks at the right times. The web system will record patient completion of hypnosis practice sessions. Patients are asked to

press a button after listening to each audio session to indicate that they have completed that session successfully. The web audio player is a streaming internet player, but it completes background download of the whole hypnosis session file in use soon after playing of the session starts, so the audio recording will continue playing to completion of the session even if Internet connection is interrupted during the listening.

To safeguard the privacy of study participants online, they will complete all study tasks in the online patient portal in a de-identified manner. No information that can reveal their personal identity is collected by the portal web page or the online study questionnaires: No IP addresses, names, e-mail addresses, dates of birth or any such identifying information is collected online. Patients are only identified in the online study system by their randomly assigned study ID number.

In a separate study management web page, study staff will be able to log in to see which main hypnosis sessions each patient has completed and whether they are significantly overdue for completing the next session, and also whether they have completed the study questionnaire at the expected time points, and the frequency of practice of the shorter exercises for each individual. This information will alert the study staff to contact patients who are not keeping up with study tasks with reminders.

d. Study Assessments and Activities

Study Assessments:

At baseline (week 0), week 6 (mid-treatment), week 12 (post-treatment), and at 12 weeks following end of treatment (i.e., 3 month follow up) participants will be asked to complete a set of questionnaires listed below. See Appendix D for a complete list of survey items and questionnaires. Study assessments will be administered electronically through the password-protected online platform via highly secure Qualtrics Research Suite Software, and all questionnaire data will be collected in a fully de-identified manner that neither obtains nor stores online any information that can reveal the personal identify of participants. Participants will be assigned a unique subject code that will be associated with his/her questionnaire data.

Patients will be paid for completing each of the assessments: They will receive Amazon gift certificates in the amount of $25 each time, except the amount will be $50 at the end-of-treatment point (as this is the most important assessment time point). Thus, patients will receive a total compensation of $125 for completing all 4 assessments in the study.

Additionally, participants will be invited to participate in a phone interview to provide qualitative feedback about their experience with the intervention and using the web interface. This will be a semi-structured

interview with the research coordinator to assess patient experience and satisfaction. The interview will take place within one month following the final hypnotherapy session.

Patients will complete the following questionnaires:

- **Demographics** and psychosocial history (administered at week 0 only): basic demographic data (e.g., age, gender, education) as well as disease related information (symptom severity, medication use).
- **The Rome IV Dyspepsia Module** will be administered at baseline to confirm diagnosis of functional dyspepsia**.** This self-report questionnaire is used to diagnosis functional GI disorders based on Rome IV criteria.[2]
- **The Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM)** will be administered to assess symptom severity. The PAGI-SYM measures 20 dyspeptic symptoms on a 6-point Likert scale, 0 (no complaints) – 5 (severe complaints), subdivided into six subscales: heartburn/regurgitation, nausea/vomiting, postprandial fullness/early satiets, bloating, upper abdominal pain, and lower abdominal pain. The measure has demonstrated good reliability and validity for measuring symptom severity in patients with functional dyspepsia.[25]
- **The Short Form Napean Dyspepsia Index** (NDI-SF) is a 10-item disease specific quality of life questionnaire developed for clinical trials in functional dyspepsia. The NDI has been established to have excellent psychometric properties[26] and responsiveness to treatment change has been confirmed[27] and the 10-item short form is recommended for use in clinical trials.[28]
- **Visceral Anxiety (VSI):** The VSI is a 15-item questionnaire that will be used to assess gastrointestinal specific anxiety[29] . This measure assesses fears of GI symptoms and is a predictor of symptom severity in patients with functional GI disorders. The VSI uses a 6 point likert scale response format with total scores ranging from 0 to 75; higher scores indicate more severe symptom-related anxiety.
- **The Brief Symptom Inventory (BSI)** will be used to assess depression, anxiety, and somatization.[30] The BSI is an 18-item questionnaire using a 5-point likert scale with scores ranging from 0 to 68; higher scores indicate higher levels of distress.
- **Thought Impact Scale- Short Form (TIS-SF).** This 17-item questionnaire is a short-form version of the Thought Impact Scale, a newly validated measure designed to predict clinical response to hypnosis treatment. The TIS-SF will be administered at baseline only to assess whether the traits that it measures (i.e., subconscious

connectedness) correlates with the degree of FD symptom improvement in the study.[31]

- **Adherence to Hypnosis Practice**: Use of hypnosis sessions will be recorded automatically by the audio player page on the treatment web page, to track frequency of home practice of hypnotherapy by the HYP intervention participants.
- **Health care utilization**: Patients will be asked at baseline, end of treatment and at 3-month follow-up to report the number of outpatient visits and procedures they have had within the last 3 months related to their functional dyspepsia symptoms. They will also be asked to report any changes in medications they have taken related to their functional dyspepsia symptoms.
- **Satisfaction with the treatment and global outcome**: At the end of treatment only (12 weeks), patients will be asked additional two questions to assess how satisfied they were overall with their assigned treatment (on a 7-point scale from "Extremely dissatisfied" to "Extremely satisfied") and how they feel their FD symptoms have changed overall since before the start of treatment (from "very much worse" to "very much improved").
- **Satisfaction with web-based platform**. At the end of treatment only (12 weeks)**,** patients will be asked an open-ended question to obtain feedback on their experience using the web-based platform for treatment ("Please describe any difficulties you had using the web interface and/or suggestions on ways we could improve the website.").

VII. Safety Monitoring Plan

a. Definition of adverse events, serious adverse events

- Participant risks in this study are minimal. We will screen individuals prior to enrolling them in the study and any patients with psychological comorbidities that increase risk of adverse events associated with hypnotherapy (e.g., post-traumatic stress disorder) will be ineligible to participate. However, even with careful screening, it is possible that participants may experience emotional discomfort or increased anxiety as a result of participating in the hypnotherapy treatment or completing study questionnaires. We will encourage participants to contact us should they experience discomfort or emotional distress during course of treatment. Dr. Kinsinger, study PI and licensed clinical psychologist, will be available to discuss these concerns and further assess the patients psychological functioning and

discontinue treatment if necessary. We will also provide referrals for counseling outside of the study if needed.

- We will take steps to reduce the risk of discomfort associated with answering questions on assessment measures related to psychological functioning by allowing participants to leave blank any questions that may make them uncomfortable. The participant will be reminded that s/he has the option of stopping treatment and can refuse to answer any questions s/he is asked that s/he finds distressing. However, the study team shall determine if the extent of refusal may warrant removal of the participant from the research study to ensure complete and accurate data collection.

b. What procedures will be used to monitor subject safety?
   - Participants will be given contact information for study personnel and encouraged to reach out if they experience an increase in psychological distress related to the treatment. Participants will be told that they are welcome to withdraw from the study at any time.
   - We plan to use an electronic platform for this study to deliver the hypnotherapy sessions as well as to conduct all patient evaluations online. It is same technology as Dr. Palsson has used successfully for online data collection in multiple NIH-funded RCT clinical trials. All study questionnaires will be administered electronically in the password-protected online portal via highly secure Qualtrics Research Suite software, and all questionnaire data will moreover be collected in a fully de-identified manner that neither obtains nor stores online any information that can reveal the personal identity of participants. This is accomplished by associating patient responses only with their randomly assigned study ID numbers.
   - The online hypnotherapy program is considered an investigational device under the Food and Drug Administration (FDA) regulations and is categorized as a nonsignificant risk device.
   - Patient names will be keyed into unique subject code and the keyed file will be kept separate from the data file to ensure patient confidentiality. Data downloads will be stored in a secure study folder in HIPAA-compliant LUMC file server space, with study folder access restricted to IRB-approved study personnel. Any non-electronic study data will be stored in locked filing cabinets, accessible only by IRB-approved study personnel. Data will be stored for 7 years after study completion per IRB policy.

c. Who (list names) will identify, document, and report adverse events?
   Dr. Sarah Kinsinger, study PI

d. What is the frequency for review of summarized safety information and who will perform the review (e.g., safety monitoring board)?

e. What are the stopping rules with regard to efficacy and safety?
Patients are free to withdraw from treatment at any time.

VIII. Analysis Plan

Aim 1: Feasibility and Acceptability of Treatment. Methods: Eligible and enrolled patients will be followed to assess the percentage who log-in to the web interface, utilize the materials sufficiently, complete the 12 week program, and report at least average satisfaction with treatment. We will present descriptive statistics to report treatment satisfaction and patient-reported global ratings of outcome, both of which will only be assessed at 12 weeks. Feasibility will be calculated as the proportion of participants who complete the FD HYP treatment program in comparison to those who drop out before treatment is completed. We expect that the proportion of participants who are retained will be 80%, demonstrating feasibility of recruitment and retention. Treatment satisfaction will be calculated as the proportion of patients who started treatment (dropouts included) who report that they are satisfied with the treatment (i.e., endorse the response either options "Somewhat satisfied", "Very satisfied" or "Extremely satisfied" on the 7-point treatment satisfaction measure). We expect that the majority of patients will report satisfaction with the treatment. Sample size justification: For the aim of retention, a sample size of n=23 achieves 92.8% power for a one-sided exact test for a proportion retained of 80%. This test assumes the null hypothesis proportion retained is 50%, and we will reject the null hypothesis and conclude retention is acceptable should at least n=16 (69.6%) be retained. Similarly, for the aim of satisfaction, a sample size of 21 achieves 90.5% power for a one-sided exact test for a proportion satisfied of 50%. This assumes 20% satisfaction under the null hypothesis, and we will reject the null hypothesis if at least 39% of the sample report they are satisfied with treatment. Both tests were targeted at an α=0.05 significance level.

Aim 2: Treatment Effectiveness. Methods: The primary analyses to estimate treatment effects in this study will be linear mixed effects regression analysis. Mixed effects regression is flexible for modeling linear and nonlinear trends over time and robust to data missing at random. A separate mixed effects model will be specified for each of our primary outcome variables (DSSI and NDI-SF). Residual analysis will be performed and transformations of outcome measures will be applied as necessary. These models will estimate treatment effects at each follow-up time point controlling for baseline score. Secondary endpoints include significant improvements in pre- to post- treatment score on psychological indices (e.g., anxiety) and disease-specific quality of life. We will apply a similar approach using mixed effects regression analyses for these outcomes. Analyses will be performed using SAS 9.4 (SAS Institute, Cary, NC).

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