metaMe Health, Inc.
Protocol

Title

A Randomized, Double-Blinded, Comparator-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Self-administered Digital Gut-Directed Hypnotherapy for the Treatment of Adult Subjects with Symptomatic Irritable Bowel Syndrome

Short Title

Efficacy and Safety of IBS Digital GDH Treatment (EASITx)

Sponsor:	metaMe Health, Inc. 222 Merchandise Mart Plaza, Suite 1230 Chicago, IL 60654
metaMe Protocol Number	MM001
Investigational Product:	Gut-directed hypnotherapy (Regulora)
Version Number:	6.0
Version Date	12-June-2020

1 ADMINISTRATIVE INFORMATION

1.1 Contacts

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1.2 Approval by representatives of metaMe Health

REPRESENTATIVES OF METAME SIGNATURE PAGE

This study will be conducted with the highest respect for individual subjects in accordance with the requirements of this study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 21 CFR Part 812)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURE

David Recker, MD
Chief Medical Officer
metaMe Health, Inc.

Date

1.3 Principal Investigator Agreement

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 21 CFR Part 812).
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting adverse events defined in Section 9.3 of this protocol.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

_____

Signature of Principal Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

1.4 Statement of Compliance

The study will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 21 CFR Part 812).

Investigators and clinical study staff who are responsible for the conduct, management, or oversight of this clinical trial have completed Human Subjects Protection and ICH GCP Training as documented in master trial documents maintained by Curebase, Inc.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

1.5 Study Reference Information

Study-Related Responsibilities

The sponsor will perform all study-related activities except for those delegated to Curebase (CRO), Jeff Botbyl (biostatistics) and Nandini Murthy (regulatory). These vendors will perform these activities in full or in partnership with the sponsor.

Coordinating Investigators

metaMe will select two Signatory Coordinating Investigators from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the treatment protocol, expertise in the therapeutic area, and expertise in the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

2 PROTOCOL SUMMARY

2.1 Synopsis

Title:	A Randomized, Double-Blinded, Comparator-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Self-administered Digital Gut-

	Directed Hypnotherapy (GDH) for the Treatment of Adult Subjects with Symptomatic Irritable Bowel Syndrome (IBS).
Study Design:	EASITx is a pivotal study of digital GDH (Regulora), a novel digital therapeutic which delivers the North Carolina GDH treatment protocol to IBS subjects. EASITx tests the hypothesis that the digital version of the North Carolina GDH treatment protocol is safe and, relative to a comparator treatment platform, enables a clinically significant reduction in abdominal pain intensity and other symptoms of IBS. EASITx is a pivotal medical device study, and digital GDH is classified as Software as a Medical Device (SaaMD). The North Carolina GDH treatment protocol consists of 7 unique GDH scripts, each approximately 30 minutes in length and a single practice session, approximately 13 minutes in length. Each script has been converted to a video/audio recording allowing for administration via a mobile device, tablet or personal computer, mimicking the frequency and duration of therapist-administered GDH. The EASITx study will apply state-of-the-art IBS and behavioral research methodology including use of a fully digital treatment platform, a comparator that allows subjects to be blinded to the treatment hypothesis, and a data collection (ePRO) system which creates a double blind, eliminating the potential for investigator bias. The comparator treatment platform will be identical to the GDH treatment platform except that muscle relaxation (MR) video/audio recordings equal in treatment duration and frequency of administration will be substituted for the GDH video/audio recordings. MR was chosen as the control after consultation with the FDA. The EASITx study is 68 weeks in duration and is composed of 4 distinct phases. • Phase 1: A 4-week pre-treatment run-in assessment period (weeks minus 4 through minus 1) • Phase 2: A 12-week treatment period (weeks 1 through 12) • Phase 3: A 4-week post-treatment assessment period (weeks 13 through 16) • Phase 4: A 52-week post-treatment long-term extension (LTE) during which time subjects will be required to complete two 4-week

	assessment periods starting at 5 months post-treatment (weeks 35 through 38) and 11 months post-treatment (weeks 61 through 64). Participation begins with the completion of an online prescreening eligibility survey via Curebase, a clinical research software platform. Subjects who pass prescreening will be consented online and scheduled for a baseline visit with a study physician. At this visit, their IBS diagnosis will be confirmed, inclusion and exclusion criteria will be applied, and subject-facing surveys administered. Subjects will be trained on the use of the electronic patient reported outcomes tool (ePRO) and daily collection of IBS pain and stool symptoms. The Phase 1 period will begin the day after the baseline visit. The Phase 1 4-week run-in period is a baseline symptom assessment period during which time subjects will enter their IBS symptoms daily and record them digitally via the Curebase ePRO on their mobile phone, tablet, or personal computer. This run-in period will provide baseline symptom data for comparison to post-treatment data collected in Phases 3 and 4. The Phase 1 run-in symptom data is also used to determine whether subjects are committed to participation by assessing their ability to consistently and accurately input data into the ePRO, and also establishes that subjects have the minimally required level of IBS symptom severity. Once the run-in is completed, ineligible subjects will be informed, and eligible subjects will receive an "Onboarding Call" from a member of the Curebase study staff. The Onboarding Call will occur as soon as possible after the Phase 1 run-in period (at least 1 day but not more than 14 days). This call will be used to inform subjects of eligibility, confirm participation, create a user account, confirm access to the platform, and provide training on the use of the metaMe treatment platform. During the Onboarding call, subjects will select a treatment day and time that is maintained throughout treatment (Phase 2). Phase 2 will start on the next occurrence of the chosen weekday. Subjects will be randomized 1:1 into the 2 treatment groups by a firewalled Curebase staff member who will enter the treatment group assignment on the metaMe platform. A software switch will directly initiate the assigned treatment allocation. The study is double-blinded, which in the context of EASITx means that subjects will not be aware of which treatment (GDH or the comparator) is

	being evaluated, and at the same time the metaMe staff and investigators will not have knowledge of group assignments (see Section 7.2.1). Subjects will complete treatment, per their group assignment and all subsequent data collection will be done without human intervention via the Curebase platform. The Phase 2 treatment period will initiate within 7 days of the onboarding call. Phase 2 will be initiated with the first treatment session followed by 6 additional treatment sessions occurring every 2 weeks for a total of 7 sessions over 12 weeks. Subjects will receive prompts to complete a short practice sessions on the 5th, 8th, and 11th day between treatments. Practice sessions are recommended but not required. Phase 3 begins immediately after completion of Phase 2 treatment period. Subjects will provide 4 weeks of post-treatment symptom data via the ePRO and the Curebase platform. Symptoms reported in this run-out period will be used to determine the primary outcome and responder definition and secondary outcomes. Phase 4 begins immediately after completion of Phase 3. Subjects will complete two post-treatment assessment periods and provide daily symptom assessments and additional instances of outcomes surveys via the ePRO and the Curebase platform. The LTE 4-week assessment periods are weeks 35 through 38 and weeks 61 through 64. Compliance with treatment and data entry will be facilitated by email and text message reminders and prompts. Each subject will be compensated for participation and data collection based on a pre-defined schedule with a maximal milestone determined compensation of $525 (Section 5.5). ePRO symptom data and outcomes surveys will be collected according to a pre-defined schedule (**Table 1**).
Objectives:	*Primary Objective* The primary objective of this study is to demonstrate that in adults with Irritable Bowel Syndrome (IBS), an all-digital Gut-Directed Hypnotherapy (GDH) treatment program (Regulora) is superior in reducing abdominal pain intensity relative to an all-digital modified Jacobsonian Muscle Relaxation (MR) treatment program.

	Secondary Objectives ● To demonstrate that Regulora has a positive impact on relief of IBS symptoms, quality of life, workplace performance (presenteeism and absenteeism), and psychological distress relative to MR therapy. ● To determine the durability of Regulora in relief of IBS symptoms, quality of life, workplace performance (presenteeism and absenteeism), and psychological distress relative to MR therapy. *Exploratory Objective* The exploratory objective of this study is to investigate predictors of treatment success using the PHQ-4 and Thought Impact Scale (TIS).
Endpoints:	**Primary Endpoint**: The primary endpoint of this study is abdominal pain intensity. The Instrument is a 0-10 numeric rating scale (NRS, 0= no pain, 10= worst pain). The subject is asked to record their "*worst abdominal pain over the past 24-hours"*. An Abdominal Pain Intensity Responder is defined as a subject whose daily abdominal pain intensity averaged over the 4 weeks of Phase 3 (weeks 13 through 16) is 30% reduced compared to the daily abdominal pain intensity averaged over the 4 weeks of Phase 1 (weeks -4 through -1). **Secondary Efficacy Endpoints**: The secondary efficacy endpoints of this study include: ● Overall mean change from Phase 1 to Phase 3 and Phase 1 to Phase 4 (LTE) in: ○ Abdominal pain intensity ○ Abdominal pain frequency ○ Irritable Bowel Syndrome-Quality of Life questionnaire (IBS-QOL) ○ Daily stool consistency (IBS-D and IBS-M) ○ Daily stool frequency (IBS-C) ○ Workplace Productivity and Activity Impairment questionnaire (WPAI) ● 12-week trends during Phase 2 in: ○ Abdominal pain intensity ○ Abdominal pain frequency ○ Daily stool consistency

	○ Daily stool frequency **Secondary Safety Endpoints:** Safety and tolerability will be evaluated by comparing adverse events in the treatment arm versus comparator arm. **Exploratory Endpoints:** ● Prediction of treatment success using the North Carolina Thought Impact Scale (TIS) ● Prediction of treatment success using the PHQ-4 ● Treatment adherence (number of sessions completed) ● Concomitant IBS Medication ● Blinding Assessment ● Satisfaction questions ● IBS-Adequate relief (IBS-AR)
Study Population:	Subjects will include men and women of all ethnic and racial groups between 18 and 70 years of age. They must meet Rome IV Diagnostic Criteria (3) for IBS as established by a licensed physician.
Number of Subjects:	To meet the goal of 380 randomized subjects and 300 evaluable subjects (estimated maximum 20% study dropout rate) we will recruit patients from study physician clinic populations (physicians will be authorized to screen their own subject population for eligibility) and subjects who have been recruited and prescreened via online, digital channels. We estimate needing to pre-screen several thousand subjects to recruit 760 for enrollment in Phase 1 (baseline assessment and eligibility screening). We expect ~50% will fail eligibility screening (see Sec. 6.2 Inclusion Criteria) providing a minimum of 380 subjects for phase 2 (treatment).
Inclusion Criteria:	To be eligible to participate in this study, an individual must meet all of the following criteria, which are assessed at the Baseline Screening event: 1. Provision of signed and dated informed consent form 2. Stated willingness to comply with all study procedures and availability for the duration of the study 3. Male or female, aged 18-70 4. Confirmation of the IBS and IBS subtype diagnosis by a study physician using Rome IV diagnostic criteria (see Appendix A) 5. Possess iOS or Android smartphone or iOS tablet (iPad) released in 2015 or later.

	6. Agreement to input information about their abdominal pain and bowel movements on a daily basis into Curebase software 7. Agreement to have their anonymized data stored in the cloud for up to 2 years after the conclusion of the study, and to have the data used for research purposes. 8. Agreement to maintain stable dosage of IBS medications during the course of treatment and not to add new IBS medication or stop current IBS medications unless directed to do so by the subjects treating physician. Changes in treatment will be captured using a concomitant medication assessment. At the **Day 0 Screening** event, subjects must also meet all of the following criteria: 1. Average "Worst Daily Pain Severity" of ≥3 on a 11-point numeric rating scale (NRS) over the full 28-day symptom tracking period 2. Consistent submission of Pain Severity scores via the Curebase app (data submitted on 70% or more of days in the symptom tracking window)
Exclusion Criteria:	An individual who meets any of the following criteria will be excluded from participation in this study: 1. Evidence of current structural intestinal abnormalities that better explain the subject's IBS symptoms (e.g., celiac disease, inflammatory bowel disease – Crohn's Disease and ulcerative colitis, prior abdominal surgeries such as weight loss surgery or bowel resection) 2. Medication use, other illnesses or conditions that can explain their gastrointestinal symptoms e.g., regular narcotic use or dependency, OTC stimulant laxative dependence (e.g., progressively larger doses of senna or bisacodyl containing compounds are needed to produce a bowel movement), radiation to the abdomen. 3. Diagnosed and/or treated for a malignancy within the past 5 years (other than localized basal or squamous cell carcinomas of the skin) 4. Current psychotherapy, hypnotherapy, or cognitive behavioral therapy (CBT) for IBS 5. Inability to commit to completing all treatment sessions 6. Have an unstable extraintestinal condition whose immediate or foreseeable treatment needs would realistically interfere with study demands, e.g., ability to participate in online treatment sessions or follow daily diary. 7. Active: post-traumatic stress disorder, depression associated with high risk of suicidal behavior, psychotic or delusional disorders,

	dissociative disorders, or gross cognitive impairment. This exclusion does not apply to anxiety or bipolar disorder 8. Subjects that report a current gastrointestinal infection or an infection within the 4 weeks prior to the evaluation that would otherwise obscure IBS symptoms. In cases of gastrointestinal infection baseline evaluation will be delayed a minimum of 4 weeks until after complete recovery. 9. Current or recent use of a gut-targeted antibiotic such as Neomycin or Rifaximin during the 12 weeks prior to baseline assessment. In the case of treatment with rifaximin or neomycin, eligibility will be suspended for 12 weeks from the initial date of use. 10. Any condition that an investigator feels may interfere with the conduct of the study
Description of Facilities Enrolling Subjects:	The EASITx study intends to recruit a highly diverse subject population. To reach these subjects, geographically diverse clinics across no fewer than 10 U.S. states will be enlisted as well as the option for remote virtual study participation. Study physicians will include office-based primary care physicians (PCPs) and community-based gastroenterologists. All study staff will be trained in Good Clinical Practice, the EASITx study protocol and the use of Curebase (clinical research software).
Description of Study Intervention:	The metaMe Health digital GDH treatment (Regulora) is an IBS-specific treatment for use on a smartphone, tablet, or personal computer. The GDH treatment module was adapted from a standardized scripted therapist-administered GDH protocol referred to as the North Carolina Protocol. The North Carolina protocol was developed by Dr. Olafur Palsson at the University of North Carolina and has been used for over 20 years as a therapist administered treatment. metaMe health has licensed the protocol from the inventor for exclusive use through any electronic means.
Duration of Treatment:	12 weeks
Period of Evaluation:	Total of 28 weeks of active evaluation: Phase 1 (4 weeks of run-in assessment), Phase 2 (12 weeks of treatment and assessment), Phase 3 (4 weeks of run-out assessment), Phase 4 (two 4-week follow-up assessments at weeks 35-38 and weeks 61-64).
Subject Duration:	68 weeks

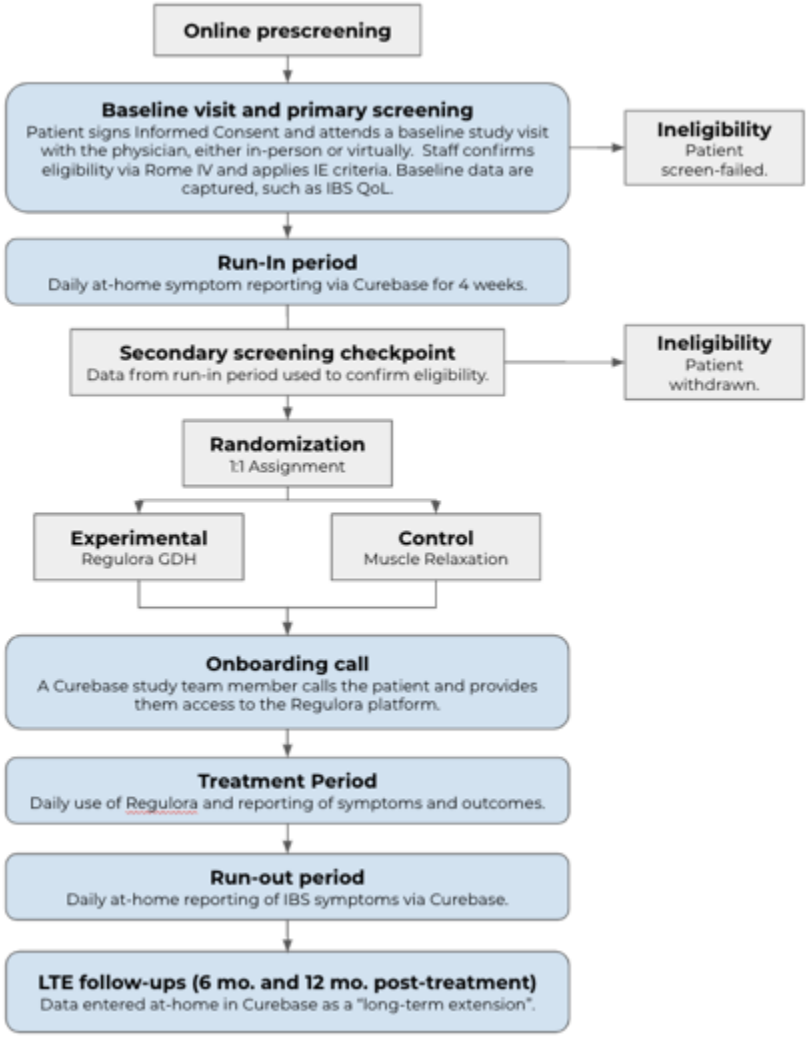
Statistical Analyses:	**<u>Primary Endpoints</u>** The primary endpoint, proportion of overall pain intensity responders, will be compared between the GDH and MR treatment groups using a Cochran-Mantel-Haenszel test adjusted for IBS subtype and gender. Safety will be summarized using descriptive statistics. **<u>Secondary Endpoints</u>** Average abdominal pain frequency and average abdominal pain intensity at Week 13-16 will be statistically compared between GDH and MR using an ANOVA model adjusted for gender and IBS subtype. The least squares (LS) mean estimate of average abdominal pain intensity and LS mean difference and associated 95% CIs will be presented with corresponding p-value. Additionally, change from baseline and at-assessment values of average abdominal pain frequency and average abdominal pain intensity will be analyzed at all 4-week assessment time periods with a mixed effects repeated measures model (MMRM). Average abdominal pain frequency and average abdominal pain intensity will be summarized descriptively by treatment and time period. Stool consistency response will be analyzed with methods similar to those used to assess the primary endpoint, as described in the Statistical Analysis Plan. IBS-QOL, WPAI, PHQ-4 will be analyzed with MMRM and summarized descriptively by treatment and week. See the Statistical Analysis Plan for details regarding all analyses. **<u>Sample Size Justification</u>** In this study, a total of approximately 380 subjects will be randomized in a 1:1 ratio to GDH or comparator to ensure that at least 300 subjects complete their Week 13-16 assessment (Phase 3) for analysis. Three hundred (300) Phase 3 completers will provide at least 90% power to detect an 18 percentage point difference in response rates between the GDH and comparator treatment groups at the 5% significance level. The study was powered assuming that the comparator treatment group is expected to

	demonstrate at most a 26% response rate. To determine the expected response rate in the comparator treatment group, two studies of GDH reporting data that utilized dichotomous outcome measures were examined. The first (9) used an endpoint of % treatment responders (defined as a >50% reduction in IBS-SSS). In this study, 52% of subjects in the GDH group and 26% of subjects in the control group (usual care) were responders. In a more recent study by Flik et al (11) these authors reported an adequate relief response rate of 40% in the GDH group compared to 17% in the education-control group. We therefore have assumed that the response rate in the comparator treatment group in this study is likely to be between 17-26%.

2.2 Schema

The study schema can be found in Figure 1, indicating the flow of actions. The blue flow elements correspond to time points in the Schedule of Activities (SoA) presented in Table 1.

Figure 1 Study Schema



Abbreviations: GDH=gut-directed hypnotherapy; IBS=irritable bowel syndrome; LTE=long-term extension; QOL=quality of life.

2.3 Schedule of Activities

The complete schedule of study activities, often referred to as a "Time and Events" (T+E) table, is presented in Table 1. Please observe the following when interpreting it:

- The **Phase 1 run-in period** will start the day after the **Baseline Visit.**
- The **Onboarding Call** will occur as soon as possible (at least 1 day but not more than 14 days) after the Phase 1 run-in period. The call will take place on the next mutually agreeable non-holiday weekday.
- Randomization occurs on the day of the Onboarding call, which we define as "Day 0" in our framework.
- **Phase 2 (treatment)** will begin no more than 7 days after the Onboarding call.
- As part of ensuring the above schedule of activities are completed in a timely manner and in accordance with the protocol, the study team shall utilize phone call, email, and text-based reminders sent to the study subjects.

Please refer to Section 8 for a detailed description of assessments described in Table 1.

	Online Screening	Baseline Visit	Run-In Period (weeks -4 to -1)	Onboarding Call day 0	Treatment Period (weeks 1-12)	Run-Out Period (weeks 13-16)	LTE 1: (weeks 35-38)	LTE 2: (weeks 61-64)
Informed Consent	X							
Diagnosis (Rome IV)		X						
Inclusion Exclusion Criteria		X						
Abdominal Pain Severity			Daily		Daily	Daily	Daily	Daily
Randomization				X				
Screening & Onboarding				X				
Treatment Adherence Data (Wistia)					Continuous import			
Stool Consistency			Daily		Daily	Daily	Daily	Daily
Stool Frequency			Daily		Daily	Daily	Daily	Daily
Adverse Event Reports			X	X	X	X	X	X
IBS QOL		X				Once at week 16	Once at week 38	Once at week 64
TIS		X						
WPAI		X			Once at week 8	Once at week 16	Once at week 38	Once at week 64
Concomitant medication assessment		X (checked			Once at week 8	Once at week 16	Once at week 38	Once at week 64

		by physician)						
PHQ-4		X				Once at week 16	Once at week 38	Once at week 64
Satisfaction Survey						Once at week 16		
Blinding assessment						Once at week 16		

Table 1 Schedule of Activities

Abbreviations: IBS QOL=Irritable Bowel Syndrome Quality of Life Questionnaire; LTE=long-term extension; PHQ-4=Patient Health Questionnaire-4; TIS=North Carolina Thought Impact Scale; WPAI =Workplace Productivity and Activity Impairment Questionnaire.

Participants are asked to complete their Baseline Surveys within 7 days of enrollment, which include IBS QOL, PHQ4, TIS, and WPAI.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition or Term
AE	adverse event
BSFS	Bristol Stool Form Scale
CBT	cognitive behavioral therapy
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
eCRF	electronic case report form
Enrolled	A participant is **enrolled** when he/she signs the informed consent.
ePRO	electronic patient-reported outcome
FGID	functional gastrointestinal disorder
GCP	Good Clinical Practice
GDH	gut-directed hypnotherapy
GEE	generalized estimating equations
HIPAA	Health Insurance Portability and Accountability Act
IBS	irritable bowel syndrome
IBS-QOL	Irritable Bowel Syndrome Quality of Life questionnaire
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
LS	least squares
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects repeated measures
NRS	numeric rating scale
Participant	Synonymous with “Subject”.
PHQ-4	Patient Health Questionnaire-4
PP	Per Protocol
PRO	patient-reported outcome
Randomized	A participant is **randomized** when he/she is assigned to the Regulora or comparator arm of the study.
Regulora	metaMe Health’s implementation of all-digital GDH for IBS.
SaaMD	Software as a Medical Device
SAE	serious adverse event
SADE	serious adverse device effect
SUADE	serious unanticipated adverse device effect
SAP	statistical analysis plan
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedures
Subject	A person who has interacted with the EASITx study as a potential participant. A subject may or may not be enrolled or randomized.
TIS	North Carolina Thought Impact Scale

WPAI	Workplace Productivity and Activity Impairment questionnaire

3 INTRODUCTION

3.1 Background

Irritable Bowel Syndrome (IBS) is the most common functional gastrointestinal disorder (FGID), affecting approximately 10% of the US adult population (1). IBS is characterized by abdominal pain that is often severe and with an onset that is unpredictable. Episodes of pain are associated with altered bowel habits, which define the three main subtypes: IBS-constipation (IBS-C), IBS-diarrhea (IBS-D), and IBS-mixed (IBS-M). A fourth subtype, IBS-undefined (IBS-U), occurs in <5% of IBS patients and defines a group of subjects who do not fall into the 3 diagnostic subtypes but are still considered to have IBS (2). IBS has significant effects on quality of life, work performance (presenteeism), and work attendance (absenteeism) (3,4,5).

IBS is often referred to as a functional disease because X-ray studies, blood tests, and intestinal endoscopy exams are normal. However, upon careful analysis, IBS patients have an increased likelihood of hypersensitive visceral sensory nerve function, abnormalities in the gut microbiome, and central pain processing. These are important components of the bidirectional brain-gut control pathway referred to as the brain-gut axis, which is dysfunctional in IBS patients (6). IBS is associated with a number of co-morbid psychological disorders (somatization, catastrophization, depression, stress, and anxiety) that place an additional strain on subjects and further affect the function of the brain-gut axis (7).

The treatment of IBS has traditionally included recommendations for dietary changes and over-the-counter medicines, which have modest to no effect on symptoms and do not change the course of the disease. Pharmaceutical drug development has tended to focus on druggable molecular targets that for the most part are not implicated in the pathophysiology of the syndrome but that allow for pharmacologic manipulation of intestinal symptoms. The current class of IBS medicines all work locally within the gut and fail to address the psychological drivers of IBS and the alterations in the brain-gut axis. Moreover, in clinical studies and medical practice these drugs have significant side-effects and are marginally effective at best for the treatment of the full constellation of IBS symptoms, particularly abdominal pain (8). In contrast to the modest efficacy observed with pharmaceuticals, non-pharmacologic behavioral treatments that target the psycho-social co-morbidities and brain-gut axis dysfunction have shown high rates of treatment response (discussed below).

3.2 Study Rationale

Gut-directed hypnotherapy (GDH) is a form of hypnotherapy that is tailored to address the symptoms of IBS. There is a growing body of evidence demonstrating the usefulness of hypnotherapy for a wide range of conditions (9). Recent large randomized controlled trials have demonstrated that therapist-administered GDH is effective for the treatment of IBS with enduring effects on both abdominal pain and gut symptoms (10,11,12). Nevertheless, widespread

use of GDH has been limited despite strong support from gastroenterology professional organizations (13). The reasons for the limited use stem largely from a lack of physician training in hypnotherapy, a limited number of trained hypnotherapists and a limited number of hypnotherapy training programs (14). There is also the issue of therapist fatigue which occurs after repeated administration of the scripted protocol.

The body of scientific evidence supporting the efficacy of GDH in IBS is derived from over 20 studies of therapist-administered GDH, with a reported 50% reduction in gastrointestinal symptom severity and abdominal pain severity (reviewed in 10). The efficacy of GDH in the treatment of IBS has been recently confirmed in a large multicenter randomized controlled trial that examined a standardized GDH protocol, administered either in individual sessions or in group sessions, and compared to an IBS education control (12). At one-year post treatment, 41% of subjects in the individual therapy and 50% of subjects in the group therapy met the primary endpoint of adequate relief of symptoms compared to 23% of subjects in the control group. GDH was statistically superior to control in both the individual and group hypnotherapy groups demonstrating the flexibility of GDH treatment across treatment environments.

In long-term follow-up studies, GDH has shown sustained effectiveness for up to 5 years after a single course of treatment (15). Recent advances in neuroscience and neuroimaging have provided tools needed to unravel the complex central nervous system effects of hypnosis (9). It has been suggested that the mechanisms responsible for hypnotherapy-induced improvements in chronic pain, anxiety and mood arise from hypnotic induction and a re-focusing of attention away from the immediate environment towards an imaginative involvement. The use of metaphor, parable and story is used to communicate imagery, direct messages, and indirect messages that facilitate the reprograming of the subliminal function of the unconscious mind. In other words, since most people with IBS are vigilant and focused on their symptoms, communicating with the unconscious brain entails getting the conscious brain to allow direct dialogue with the subconscious brain, the critical manager of automatic functions such as pain perception. Hypnotherapy provides a hypothetical mechanism for linking the conscious with the unconscious, which in turn facilitates cognitive restructuring, changes in automatic functions involved in gut function and amelioration of associated psychosocial disorders. Data from a controlled study measuring fMRI signals in IBS patients pre and post-GDH supports this theory and demonstrates that GDH results in normalization of brain activation and fMRI signals, supporting a role for GDH above and beyond improvements in mood (16).

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

Hypnotherapy is generally considered to be safe and low risk. Safety concerns have been proposed based on the observation that subjects with dissociative disorders (i.e., multiple

personality disorder) have an enhanced hypnotizability and under hypnosis may adopt an alternate identity or personality state (17-19). Elicitation of an alternate personality state and/or repressed memories, which are often past traumatic events, can be a painful experience for subjects. At the same time, it is important to note that hypnosis is used to treat dissociative disorder and the closely related syndrome of post-traumatic stress disorder (20). Therefore, the standard approach to minimizing the risk in hypnotherapy studies requires exclusion of subjects with these psychiatric conditions. In a review examining data from 7 hypnotherapy trials on ClinicalTrials.gov, it was found that studies that use these exclusion criteria had low rates of treatment-related adverse events (AEs) (<1% non-serious AEs) and no serious adverse events (SAEs) (20). Of the treatment-related AEs, there were 2 cases of disturbing images and thoughts and 2 cases of nightmares. A recent large European study confirmed these results: in 300 subjects allocated to therapist-administered GDH there were no SAEs or AEs that were deemed related to treatment (12).

It is also believed that the hypnotizability of subjects with active co-morbid psychiatric/mood disorders may be diminished and available literature indicates that subjects with these conditions should generally be excluded from clinical trials.

Finally, there are anecdotal therapist reports of mild headache, lightheadedness and disorientation that tend to spontaneously resolve within a short period after post-hypnotherapy arousal. As a precaution, subjects will be told to find a quiet place to view the treatment sessions and not to undergo treatment while driving or performing other tasks.

3.3.2 Known Potential Benefits

Digital GDH and MR have not been studied and the potential benefits can only be derived from studies and subject reports after therapist-administration.

3.3.3 Assessment of Potential Risks and Benefits

The risks of this study are minimal. The primary risks include:

- Possible temporary discomfort from answering personal questions regarding subject health.
- The possibility that subjects may not experience substantial reduction of symptoms or those symptoms may worsen.
- The possibility that subjects may feel sleepy or drowsy for a short while after treatment
- The possibility that subject muscles may feel tight or ache for a short while after treatment.

If subject IBS symptoms were to change or worsen, subjects may call Curebase or seek advice from the study physician. The staff of Curebase and study physicians will be closely supervised by the Principal Investigator, Dr. Lucy Pun.

The secondary risks include answering symptom survey questions on a daily basis for 7 total months, which may seem burdensome. On the other hand, some volunteers find recording daily symptoms useful and informative.

Potential benefits include:

- Free evaluation of IBS from health care professionals.
- Free treatment for IBS.
- Possibility of reduction in the frequency, duration, and severity of IBS and related problems.
- Relaxation and a sense of well-being

4 OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

4.1.1 Primary Objective

The primary objective of this study is to demonstrate that in adults with Irritable Bowel Syndrome (IBS), an all-digital Gut-Directed Hypnotherapy (GDH) treatment program (Regulora) is superior in reducing abdominal pain intensity relative to an all-digital modified Jacobsonian Muscle Relaxation (MR) treatment program.

4.1.2 Secondary Objective

The secondary objectives of this study are:

- To demonstrate that Regulora has a positive impact on relief of IBS symptoms, quality of life, workplace performance (presenteeism and absenteeism), and psychological distress relative to MR therapy.
- To determine the durability of Regulora in relief of IBS symptoms, quality of life, workplace performance (presenteeism and absenteeism), and psychological distress relative to MR therapy.

4.1.3 Exploratory Objective

The exploratory objective of this study is to investigate predictors of treatment success using the PHQ-4 and Thought Impact Scale (TIS).

4.2 Study Endpoints

For details on assessments and analyses, refer to Section 9 and Section 10, respectively.

4.2.1 Primary Endpoint

The primary endpoint of this study is abdominal pain intensity. The Instrument is a 11-point numeric rating scale (0= no pain, 10= worst pain). The subject is asked to record their "*worst abdominal pain over the past 24-hours"*. An Abdominal Pain Intensity Responder is defined as a subject whose daily abdominal pain intensity averaged over the 4 weeks of Phase 3 (weeks 13 through 16) is 30% reduced compared to the daily abdominal pain intensity averaged over the 4 weeks of the Phase 1 (weeks -4 through -1).

4.2.2 Secondary Endpoints

The secondary efficacy endpoints of this study include:

- Overall mean change from Phase 1 to Phase 3 and Phase 1 to Phase 4 (LTE) in:

- Abdominal pain intensity
- Abdominal pain frequency
- Irritable Bowel Syndrome-Quality of Life questionnaire (IBS-QOL)
- Daily stool consistency (IBS-D and IBS-M)
- Daily stool frequency (IBS-C)
- Workplace Productivity and Activity Impairment questionnaire (WPAI)

- 12-week trends during Phase 2 in:
  - Abdominal pain intensity
  - Abdominal pain frequency
  - Daily stool consistency
  - Daily stool frequency

Safety and tolerability will be evaluated by comparing adverse events in the treatment arm versus comparator arm.

4.2.3 Exploratory Endpoints

The exploratory Endpoints of this study are:

- Prediction of treatment success using the North Carolina Thought Impact Scale (TIS) (23)
- Prediction of treatment success using the PHQ-4 (24)
- Treatment adherence (number of sessions completed)
- Concomitant IBS Medication
- Blinding Assessment (25)
- Satisfaction questions
- IBS-Adequate relief (IBS-AR)

5 STUDY DESIGN

5.1 Overall Design

EASITx is a pivotal study of digital GDH (Regulora), a novel digital therapeutic that delivers the North Carolina GDH treatment protocol to IBS subjects. EASITx tests the hypothesis that the digital version of the North Carolina GDH treatment protocol is safe and, relative to a comparator treatment platform, enables a clinically significant reduction in abdominal pain intensity and other symptoms of IBS. EASITx is a pivotal medical device study, and digital GDH is classified as Software as a Medical Device (SaaMD).

The North Carolina GDH treatment protocol consists of 7 unique GDH scripts, each approximately 30 minutes in length and a single practice session, approximately 13 minutes in length. Each script has been converted to a video/audio recording allowing for administration via a mobile device, tablet, or personal computer, mimicking the frequency and duration of administration of therapist-administered GDH.

The EASITx study will apply state-of-the-art IBS and behavioral research methodology including use of a fully digital treatment platform, a comparator allowing for subject-blinding to treatment hypothesis, and a data collection (ePRO) system that allows for a double blind, eliminating the potential for investigator bias. The comparator-treatment platform will be identical to the GDH treatment platform, except that muscle relaxation (MR) audio recordings equal in treatment duration and frequency of administration will be substituted for the GDH video/audio recordings. MR was chosen as the control after consultation with the FDA.

Participation in the EASITx study will last 68 weeks and is divided into 4 phases:

- Phase 1: A 4-week pre-treatment run-in assessment period (weeks -4 through -1)
- Phase 2: A 12-week treatment period (weeks 1 through 12)
- Phase 3: A 4-week post-treatment assessment period (weeks 13 through 16)
- Phase 4: A 52-week post-treatment long term extension (LTE) during which time subjects will be required to complete two 4-week assessment periods starting 5 months post-treatment (weeks 35 through 38) and 11 months post-treatment (weeks 61 through 64).

Participation begins with the completion of an online prescreening eligibility survey via Curebase, a clinical research software platform, followed by an online informed consent. Subjects who pass prescreening and sign the informed consent will attend a baseline visit with a study physician. At this visit, their IBS diagnosis will be confirmed, inclusion and exclusion criteria will be applied, and experimental baseline endpoints will be collected in the form of subject-facing surveys.

After the baseline visit, subjects will enter Phase 1 a 4-week run-in period. During Phase 1, subjects will assess their IBS symptoms daily and record them digitally via the Curebase ePRO from their mobile phone, tablet device, or personal computer. This run-in period will establish that subjects are committed to participation (by assessing their ability to consistently and accurately input data into Curebase), and also establish that they have the minimally required level of IBS symptom severity.

Once the run-in is completed, ineligible subjects will be informed. Eligible subjects will receive an "Onboarding Call" from a member of the Curebase study staff. This call will be used to inform subjects of eligibility, create a user account on the EASITx treatment website. Subjects will be randomized 1:1 into 2 groups in a double-blind scheme, in which only the Curebase Staff member is aware of the group assignment. This staff member will enter the treatment group assignment on the metaMe platform and ensures that the correct treatment allocation is initiated.

In the EASITx randomization scheme, subjects will either receive the digital GDH intervention or the muscle relaxation therapy delivered through the same digital delivery platform (comparator treatment arm). As described in Section 7.2, the study is double-blinded such that subjects, metaMe staff, and investigators will have no knowledge of group assignments (see designated firewalled exceptions in Section 7.2). Participants will complete treatment per their group assignment over the course of 12 weeks and track their symptoms daily via Curebase. All study activities may be fully remote and can be completed from home. The baseline visit may be conducted in-person per the participant's preference.

The Phase 2 treatment period will include 7 unique sessions (GDH or MR) of ~30 minutes each, every other week over the 12-week treatment period. During treatment, a practice session (GDH or MR) will be made available to the subjects, with an email encouraging completion of practice on the 5th, 8th, and 11th day between treatment sessions. Subjects will be required to complete assessments according to the schedule in Table 1.

Data collected in the Phase 3 post-treatment assessment period (run-out period) and the Phase 4 LTE will be compared to data collected in the Phase 1 pre-treatment assessment period (run-in period). Subjects will complete daily symptom assessments and additional instances of the concomitant medication check list, PHQ-4, IBS-QOL and WPAI outcomes surveys according to the schedule in Table 1.

The EASITx study seeks to enroll subjects from no fewer than 10 medical clinics across several U.S. states to capture a geographically diverse IBS population. Subjects will be recruited from existing practices and via online recruitment.

5.2 Scientific Rationale for Study Design

5.2.1 Rationale for Treatment Frequency

The 7 digital GDH treatments that compose the North Carolina GDH protocol are administered every other week. The frequency of treatment administration in this study was chosen to mirror the protocol used in studies of the North Carolina protocol when administered by therapists in face-to-face treatment sessions (9, 27). The practice sessions are designed to be administered as needed to support engagement, however, there is no evidence that practice sessions modulate treatment outcome. The treatment frequency of the comparator control will exactly mirror the frequency of GDH treatments and practice sessions.

5.2.2 Rationale for Comparator Control

The Jacobsonian Muscle Relaxation (JMR) (9) protocol leverages a fully digital platform, which allows delivery in a video or audio format. This configuration allows for the blinding of subjects to the randomized treatment since muscle relaxation is a credible behavioral treatment. Currently in the US, there are no approved digital behavioral therapeutics for the treatment of IBS.

5.2.3 Rationale for Endpoints

The primary and key secondary endpoints were derived from the FDA guidance on the development of pharmaceuticals for the treatment of IBS (28). The WPAI and IBS-QOL are validated measures for IBS. The PHQ-4 is a validated four-item questionnaire for anxiety and depression (24).

5.3 Premature Termination or Suspension of Study

5.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless either of the following criteria are satisfied that require temporary suspension or early termination of the study.

a) Evidence of a serious clinical problem that would put subjects exposed to treatment (either GDH or MR) at risk
b) Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives

6 STUDY POPULATION

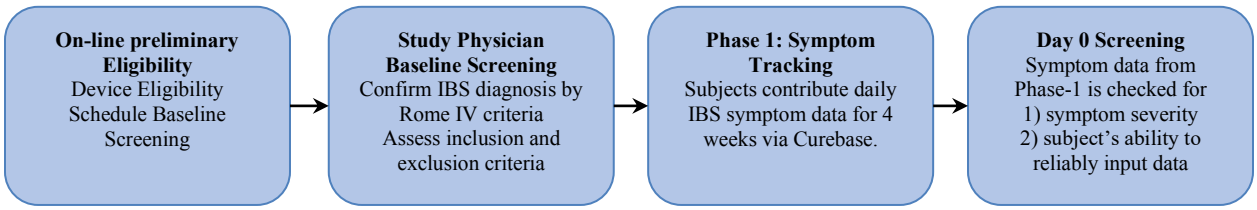
6.1 Screening Events

Study eligibility is determined at 3 distinct events for the study. These events are:

1. **Online pre-screening assessment** includes a brief inclusion and exclusion criteria and technology assessment (subjects are eligible if they use an iOS or Android smartphone or iOS (iPad) tablet released in 2015 or later).
2. **Baseline Screening/Study Physician Visit.** The subject's IBS diagnosis and general medical history is confirmed, and complete inclusion/exclusion criteria are applied to assess preliminary eligibility.
3. **Day 0 Screening.** After the 4 week symptom tracking (Phase 1) the subject's full eligibility for the study is confirmed using data from symptom tracking completed over those 4 weeks. Subjects that fail to screen-in will be notified that they are ineligible. Subjects that screen-in will be scheduled for a Day 0 phone call and informed of their eligibility.

The relationship between the 3 screening events and Phase 1 symptom tracking is shown in Figure 2.

Figure 2 Study Screening



Abbreviations: IBS=irritable bowel syndrome.

Only subjects who meet the screening criteria for both screening events will be permitted to initiate treatment in the study.

6.2 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria, which are assessed at the Baseline Screening event (see previous section):

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18-70
4. Confirmation of the IBS and IBS subtype diagnosis by a study physician using Rome IV diagnostic criteria (see Appendix A)
5. Possess an iOS or Android smartphone or an iOS tablet (iPad) released in 2015 or later.
6. Agreement to input information about their abdominal pain and bowel movements on a daily basis into Curebase software
7. Agreement to have their anonymized data stored in the cloud for up to 2 years after the conclusion of the study, and to have the data used for research purposes.

8. Agreement to maintain stable dosage of IBS medications during the course of treatment and not to add new IBS medication or stop current IBS medications unless directed to do so by the subjects treating physician. Changes in treatment will be captured using a concomitant medication assessment.

At the **Day 0 Screening** event, subjects must also meet the following criteria:

1. Average "Worst Daily Pain Severity" of ≥3 on an 11-point NRS over the full 28-day symptom tracking period
2. Consistent submission of Pain Severity scores via the Curebase app (data submitted on 70% or more of days in the symptom tracking window)

This study attempts to achieve excellent representation of women and minorities in the enrolled population, and there are no restrictions on eligibility based on the subject's sex, gender, or race. Please see Section 5.5 for information about how women and minorities will be recruited into the study.

6.3 Exclusion Criteria

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

1. Evidence of current structural intestinal abnormalities that better explain the subject's IBS symptoms (e.g., celiac disease, inflammatory bowel disease – Crohn's Disease and ulcerative colitis, prior abdominal surgeries such as weight loss surgery or bowel resection).
2. Medication use, other illnesses or conditions that can explain their gastrointestinal symptoms e.g., regular narcotic use or dependency, OTC stimulant laxative dependence (e.g., progressively larger doses of senna or bisacodyl containing compounds are needed to produce a bowel movement), radiation to the abdomen.
3. Diagnosed and/or treated for a malignancy within the past 5 years (other than localized basal or squamous cell carcinomas of the skin).
4. Current psychotherapy, hypnotherapy, or cognitive behavioral therapy (CBT) for IBS
5. Inability to commit to completing all treatment sessions.
6. Have an unstable extraintestinal condition whose immediate or foreseeable treatment needs would realistically interfere with study demands, e.g., ability to participate in online treatment sessions or follow daily diary.
7. Active: post-traumatic stress disorder, depression associated with high risk of suicidal behavior, psychotic or delusional disorders, dissociative disorders, or gross cognitive impairment. This exclusion does not apply to anxiety or bipolar disorder.
8. Subjects that report a current gastrointestinal infection or an infection within the 4 weeks prior to the evaluation that would otherwise obscure IBS symptoms. In cases of gastrointestinal infection baseline evaluation will be delayed a minimum of 4 weeks until after complete recovery.

9. Current or recent use of a gut-targeted antibiotic such as Neomycin or Rifaximin during the 12 weeks prior to baseline assessment. In the case of treatment with rifaximin or neomycin, eligibility will be suspended for 12 weeks from the initial date of use.
10. Any condition that an investigator feels may interfere with the conduct of the study

These exclusion criteria do not present meaningful exclusion of minority populations and do not present a threat to population diversity with respect to race, gender, or age.

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. The primary reason for screen failure, demographics and other minimal information is recorded in the eCRF using the following categories:

- AE
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason)
- Significant protocol deviation
- Lost to follow-up during baseline screening
- Voluntary withdrawal (specify reason)
- Study termination

Subject ID numbers assigned to subjects who fail screening will not be reused for a different subject. Individuals who do not meet the criteria for participation in this study (screen failure) because of a conflicting psychological treatment for IBS, either for IBS or another condition referenced in the exclusion criteria (e.g. gastrointestinal infection) may be rescreened after the period of time indicated in the exclusion criteria (See Section 5.3). Rescreened subjects should be assigned the same subject number as for the initial screening.

6.5 Strategies for Recruitment and Retention

The study seeks to enroll adult subjects, ages 18 to 70 years of age, who have a confirmed diagnosis of IBS via the Rome IV diagnostic criteria. To meet the enrollment goal of approximately 380 randomized subjects and 300 evaluable subjects (estimated maximum 20% study dropout rate) patients will be recruited from participating clinic populations (study physicians will be authorized to screen their own subject population for eligibility) and subjects who have been recruited and prescreened via online, digital channels.

Planned traditional recruitment channels include:

- Distribution of flyers to our clinics
- Distribution of flyers to university health centers
- Informational outbound phone calls to subjects from study staff
- Referrals by family members of subjects to the study

Planned digital recruitment channels include:

- Social media community groups
- Facebook
- Craigslist
- Instagram

It is desirable to enroll many minorities and women and create a diverse population. 60-65% of IBS subjects are female. No special action will be employed to ensure adequate female enrollment.

Subjects will be compensated for participation in the study.

Participants will receive their compensation payments via Curebase so long as they continue to contribute data consistently. Payments will be withheld for subjects that fail to complete ≥5 out of 7 of the weekly abdominal pain score surveys. Participants will be provided a warning after they miss 1 of the weekly data collection points.

7 STUDY INTERVENTION

7.1 Study Intervention Administration

7.1.1 Study Intervention Description

The metaMe Health digital GDH product for IBS is named Regulora. Regulora is an IBS-specific treatment platform delivered via a smartphone, tablet, or personal computer. The delivery platform for EASITx is a mobile app available in the Apple and Android app stores under the name of EAGLEFISH. The GDH treatment module was adapted from a standardized scripted therapist-administered GDH protocol referred to as the North Carolina Protocol (10,27). The North Carolina protocol has been licensed by metaMe Health from the inventor (Dr. Olafur Palsson) for exclusive use through any electronic means.

The North Carolina protocol differs from standard hypnotherapy through the use of intensive relaxation methodology, IBS-specific use of metaphor, symptom imagery, and direct and indirect suggestion (27). The North Carolina protocol consists of 7 unique treatment sessions each lasting ~30 minutes provided every-other week over 12 weeks. The first half of the 30-minute treatment session is spent producing deep physical and autonomic relaxation, along with a mental state of narrowed focus of attention and heightened receptivity to suggestions, commonly referred to as the trance state. This is followed by the use of metaphorical storytelling, and a combination of direct and indirect suggestions targeted at somatic control and perception mechanisms that influence IBS symptoms. The treatment sessions are iterative and progressively build relaxation skills, which are required to maximally incorporate the disease-specific aspects of treatment. Subjects become familiar with the use of hypnotherapy tools such as counting and the use of imagery focused on the senses, i.e., touch, smell, sight and hearing (see Appendix B for scripts of the 7 sessions). As treatment sessions progress, direct suggestion and metaphor are used to overcome the exaggerated response to pain signals imparted by the anticipatory response to IBS symptoms.

The comparator control group will listen to digital video/audio recordings of 7 guided muscle relaxation (MR) sessions of approximately equivalent length to the GDH sessions (see Appendix D for session scripts), as well as a daily practice session approximately equivalent in length to the GDH practice sessions (see Appendix E for script) (9). Guided MR was chosen as the comparator control treatment after consultation with the FDA because of (a) the ease with which it can be adapted to a digital format and support the creation of a comparator treatment and (b) credibility as a treatment for IBS albeit with limited demonstrated efficacy (9).

The GDH and MR treatment modules consist of seven ~30-minute digital video and audio recordings of a female therapist. The video component of the treatment sessions occurs at the beginning of the treatment session and is used to simulate the face-to-face interaction of the therapist encounter. The video component is short and typically lasts less than 5 minutes before the screen goes black and subjects are taken through the audio component of treatment. The digital production of the GDH and MR scripts was a verbatim reading. In the case of the GDH scripts the therapist reader provided hypnotherapy-appropriate speech patterns (inflection, pause, and tone). Once therapy is initiated, subjects receive all 7 treatment sessions, every other week for a total treatment period of 12 weeks. During the 13 days between treatment sessions, a short audio session referred to as a “practice session” is made available to subjects. There is a single practice session script for each of the two treatment arms lasting 15 minutes. Subjects receive text message and email reminders with a recommendation to complete a minimum of three practice sessions during the 13 days between treatments. Practice sessions are recommended but not required (see Appendix C and Appendix E: Daily Practice Sessions).

The metaMe treatment platform also tracks subject use and progress with treatment modules. For example, the exact time that a subject starts and stops a treatment or practice module is captured by the treatment platform. The software also tracks treatment sessions and only allows subjects to access treatments in sequence. The metaMe treatment platform on the EAGLEFISH app contains these major functional elements:

1. Treatment videos/audios
2. A secure cloud-based data repository.
3. A simple user interface (UI) with an arrow play button that starts the treatment session. (see Figure 3)

In addition to the EAGLEFISH app, subjects enrolled in the EASITx study will be required to enter study data in a second platform. The Curebase platform is for data collection and administers the daily ePRO and provides access to periodic surveys. Subjects will be introduced to the Curebase platform at the baseline screening clinic visit by the research study staff. Study staff will explain the use of the app and the process by which subjects will enter data in the ePRO.

After completion of the 4-week run-in period (Phase 1), subjects will be informed of eligibility, and eligible subjects will be scheduled for a day 0 phone call (scheduled as soon as possible but no more than 14 days from completion of the run-in period). On the day 0 phone call, after a subject is randomized, the Curebase staff will confirm the subject's preferred day of the week, time of day and start date for treatment. Curebase staff will enter the treatment schedule and randomization code (blinded treatment allocation) into a secure metaMe portal that automatically triggers the assigned treatment and the subject-specific treatment reminder and scheduling system. Curebase staff will assist subjects in accessing the metaMe digital platform by guiding them through the process of creating a metaMe login username and password and reviewing the process for accessing the treatment app. Subjects will be guided through the login process and directed to the navigation menu. The navigation menu contains the following items:

1. The home button
2. Account information
3. Treatment schedule
4. Logout
5. Help section. Contains a link to watch or read a transcript to the intro video (see below), FAQ and contact information for technical support and problems with treatment.

The treatment process will commence within 7 days of the day 0 call and will be initiated by system-generated text and email reminders of upcoming treatment sessions. Subjects will be sent an email reminder 24 hours and 1 hour before each session, and a text message reminder 5 minutes before each session. Subjects will be able to access the treatment app via a hyperlink in these messages or directly by opening the app on their device. Once in the app, subjects will

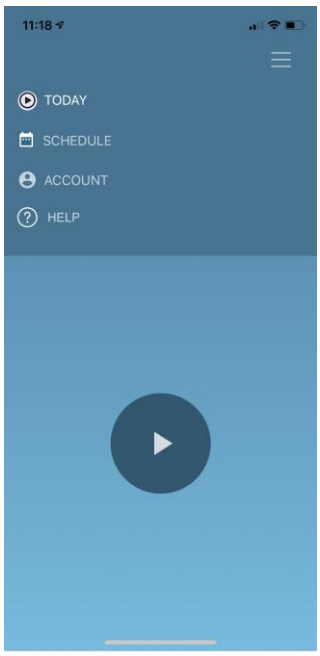
initiate treatment by pressing the large arrow start button on the home screen (see User Guide and Figure 3). The first thing subjects will see is a short 3-minute intro video that explains the following details of treatment:

1. Treatment session length
2. The treatment reminder system, which uses emails and text messages to alert subjects of upcoming treatment sessions and to remind subjects to complete treatment.
3. The process for rescheduling and managing missed treatment sessions (subjects have 3 additional days to complete the treatment before they are considered a missed treatment)
4. Rules on interrupted treatment sessions (subjects must start over from the beginning and have 3 opportunities to finish the treatment before they are considered a missed treatment)
5. The recommended minimum number of practice sessions is 3 over the 13 days between treatments.

There are two intro videos customized to each of the two treatments. They differ in the treatment-specific instructions; in the case of the GDH treatment, the video has specific instructions on how to manage re-alerting after hypnotherapy (see Appendix F). In the case of the MR treatment, subjects are given guidance on how to manage muscle-specific complaints (see Appendix G) After the completion of the treatment session, subjects will be instructed to click a button indicating they have completed the session. This button appears upon completion of 100% of the length of the treatment session. A session is also considered completed if greater than 95% of the video is played and no button is pressed by midnight of that day local time. Subjects who miss their scheduled treatment will have 3 additional days in which to complete the treatment. They will receive daily text and email reminders to complete treatment. If after 3 days the subject has not completed the treatment session they will be locked out of that treatment and it will be scored as a missed treatment session. Similarly, subjects will receive a one-time reminder about Practice sessions on the 5^{th}, 8^{th}, and 11^{th} day after each treatment. Subjects will be allowed to access one practice session per day for as many non-treatment days as they like but they will only receive 3 reminders at the indicated days.

The subject experience with the EAGLEFISH app is illustrated in the User Guide and briefly in Figure 3.

Figure 3 metaMe Treatment Visual Narrative



EAGLEFISH User Interface (UI)

When subjects open the EAGLEFISH app, the main screen appears. The large arrow button, when clicked, is used to access treatment and practice sessions. The first time the button is pressed, the patient will view the introduction video, which is required viewing before the first treatment session and optional thereafter. The app is programmed so that the appropriate content (a treatment or practice session) is displayed each day. Subjects are prevented from re-taking treatment sessions, and subjects cannot access practice sessions on days they have a treatment available (the assigned treatment day plus 3 days in the case that subjects miss treatment on their assigned treatment day). Subjects will be required to complete the treatment/practice session in a single sitting. If the subject is interrupted during treatment, the subject may press the "begin again" button, which starts the session over from the beginning. In this case, subjects will be required to re-start the treatment/practice session from the beginning. Subjects will have 3 days after the initial treatment day to complete treatment sessions. After the treatment/practice session video has played to 100% of its length, subjects may indicate that they have completed the session by clicking on the "Complete Session" button. A session is also considered completed if greater than 95% of the video is played and no button is pressed by midnight of that day local time.

7.2 Measures to Minimize Bias: Blinding and Randomization

7.2.1 Blinding

Blinding of participants to treatment in a psychological or behavioral intervention is generally not possible. By the nature of the intervention, subjects are aware of the type of intervention they are receiving. Instead, in studies involving a psychological or behavioral intervention, blinding the participants to the hypothesis being evaluated in the study is considered the best and most practical strategy for preventing study bias. The EASITx study incorporates this blinding strategy coupled with state-of-the-art IBS and behavioral research methodology.

The comparator-treatment platform will be identical to the GDH treatment platform, except that muscle relaxation (MR) audio recordings equal in treatment duration and frequency of

administration will be substituted for the GDH video/audio recordings. The comparator control group will listen to digital audio recordings of 7 guided muscle relaxation (MR) sessions of approximately equivalent length to the GDH sessions (see Appendix D for session scripts), as well as a daily practice session approximately equivalent in length to the GDH practice sessions (see Appendix E for script) (9). Guided MR was chosen as the comparator control treatment after consultation with the FDA because of (a) the ease with which it can be adapted to a digital format and support the creation of a comparator treatment and (b) credibility as a treatment for IBS albeit with limited demonstrated efficacy (9). The goal of this blinding strategy is to present two treatments that are credible to the study participants, who are themselves unaware of what the other study arm is, whether their assigned treatment (GDH or MR) is the one under study being compared to the other arm, or indeed whether both are active treatments being compared to each other.

The data collection (ePRO) system creates a double blind and eliminates the potential for investigator bias. metaMe staff and investigators will not have knowledge of group assignments, with the following exceptions:

- An independent statistician who will formulate the randomization tables.
- A firewalled Curebase staff member who will enter the treatment group assignment on the metaMe platform.
- A firewalled metaMe staff member (the CTO) who will monitor technical aspects of the study to ensure technical compliance to the protocol and in this capacity may have access to participant randomization assignments.

7.2.2 Randomization Code Creation and Procedure

Following successful completion of the run-in period, subjects will be randomized 1:1 to either GDH or comparator MR treatment. Randomization will be stratified by gender and IBS subtype. Eight separate randomization schedules will be generated to account for the stratification (Male/IBS IBS-C, Male/IBS-D, Male/IBS-M, Male/IBS-U, Female/IBS-C, Female/IBS-D, Female/IBS-M, Female/IBS-U). Additionally, continuous monitoring of enrollment will occur to ensure that at least approximately 20% of the randomized population is male and at least approximately 25% of the randomized population includes each of the three major IBS subtypes (IBS-C, IBS-D, and IBS-M). Screening of female subjects will be discontinued if approximately 270 female subjects are randomized. If randomization into a particular IBS subtype reaches approximately 144 subjects, then screening of subjects with that particular IBS subtype will be temporarily discontinued until the IBS subtypes lacking enrollment have randomized approximately 90 subjects. Finally, if randomization into the rare IBS-U subtype reaches 20 total subjects, enrollment will be discontinued for that subtype.

The randomization schedule will be prepared by an unblinded statistician before the start of the study. As this is a double-blind study, only unblinded personnel (unblinded statistician, Curebase randomization staff) will have access to the randomization schedule before official unblinding of treatment assignment post database lock.

Randomization will occur during the "Onboarding Call" when a member of the Curebase randomization staff will enter the treatment group allocation on the metaMe platform. No subject will be randomized into this study more than once. All randomization information will be stored in a secured area, accessible only by authorized personnel.

7.2.3 Unblinding and Decoding Procedure

The study treatment blind shall not be broken unless information concerning the study treatment is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study treatment blind is broken to discuss the need for unblinding.

The sponsor must be notified as soon as possible if the study treatment blind is broken and record the date and time. The study treatment can be unblinded by the designated unblinded Curebase staff member. The reason, time and date the blind is broken must be recorded in the eCRF.

7.3 Participant compliance to Study Intervention

Curebase will store all study subject-reported data generated through the Curebase web application on a secure and HIPAA-compliant database. However, subject adherence data, defined as completion of required treatment sessions and numbers of practice sessions will be generated by our video server, Wistia. Wistia is a video hosting service that is able to securely keep and record detailed information about when and how long videos are accessed by a given user. Wistia-generated usage data is anonymously generated and stored and is transferred to metaMe through an API and matched to a subject ID (email address) on metaMe servers. Linking usage data to email address is a necessary part of the metaMe notification and treatment tracking system. Usage data is used to generate adherence information that is in turn used to send reminders and prompts for a missed treatment session. Note that most other subject notifications like appointment reminders are generated based on the treatment schedule, not real-time adherence data. The adherence data is also used to ensure that the proper treatment content is available at the correct time and in the correct sequence. For example, the app may use the data from Wistia to determine if a session has been completed on the scheduled day; if it is not, the session remains available to the subject throughout the treatment window. If the session is completed, a practice session is made available the following day. Each day, all adherence data is transferred to the Curebase platform and stored. Curebase will provide long-term, HIPAA

compliant storage of adherence data for use in later analysis. Intervention compliance will be calculated by determining the number of completed treatment sessions and the number of completed practice sessions for each subject. We also will collect related contextual data, such as how much of the video was watched per attempt, whether the session was restarted at any point, whether the session was rescheduled, and whether the session was viewed late (after the scheduled day).

7.4 Concomitant Therapy

Requirements and proscriptions on concomitant therapy are outlined in the Inclusion/Exclusion Criteria (Section 5.2 and Section 5.3).

Concomitant medication is any drug given in addition to the study treatment. These may be prescribed by a physician or obtained by the subject over the counter and are not provided by the sponsor. Subjects will be allowed to continue use of any concomitant IBS medications including probiotic supplements as permitted by the study inclusion and exclusion criteria. Subjects are required to maintain a stable dose during the treatment period unless otherwise advised by a physician. Changes to concomitant medications shall be evaluated at the predetermined timepoints. Dosage and frequency of treatment will be collected at the beginning of the study and again at week 8, 16, 38 and 64. Concomitant medication therapy will be coded using the WHO-DDE Medical Coding Dictionary.

8 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 Criteria for Discontinuation or Withdrawal of a Subject

GDH is a non-significant risk behavioral intervention. Given this, there are no foreseeable safety-related reasons to discontinue the study. Subjects may freely withdraw their individual participation in the study at any time. However, in case there is a reason for discontinuation or withdrawal of the subject from the study this should be recorded in the eCRF using the following categories (for screen failure subjects, refer to Section 5.4):

1. Treatment discontinuation due to an AE. The subject has experienced an AE that in the opinion of the investigator may expose them to undue risk or could interfere with his/her continued participation in the study.
2. Important protocol deviation. The discovery post randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health, following consultation with the sponsor or designee.
3. Lost to follow-up. The subject stops responding to requests and reminders for data collection or treatment and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's electronic source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, must be recorded in the eCRF. Note: All attempts should be made to determine the underlying reason for the withdrawal and where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Subject is found to have a life-threatening medical illness or serious mental health disorder
7. Any other clinical event or finding that, in the opinion of the study team, jeopardizes subject safety, privacy, or the scientific validity of the study.

8.2 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 8.1. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. Subjects withdrawn by the sponsor due to investigator error in applying protocol inclusion/exclusion criteria or technical issues in the Curebase software that

prevent appropriate execution of the trial will be replaced. Otherwise, subjects will not be replaced.

8.3 Lost to Follow-Up

When a subject misses a required treatment session, there is a 3-day grace period during which subjects can access treatment from the app. During this time, subject will receive email and text message reminders to complete treatment. Similarly, subjects that miss a data collection point will be contacted by Curebase via email and phone and in the case of surveys, Curebase will attempt to contact the subject and reschedule the missed data collection as soon as possible. The study physician staff and Curebase will counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. Subjects that do not respond to contact attempts and do not complete the minimum number of surveys in phase 3 will be classified as described in the Statistical Analysis Plan.

Study Assessments and Procedures

8.4 Efficacy Assessments

The efficacy of GDH will be established using a set of patient-reported outcomes (PROs). These include PROs to capture:

- Abdominal Pain
- Stool Consistency

The primary endpoint of EASITx is abdominal pain, and as such the most important PRO instrument in the study is the **Abdominal Pain Daily Survey.**

Stool frequency and consistency are secondary endpoints of EASITx, so the second-most important PRO instrument in the study is the **Daily Stool Consistency Diary, which uses the Bristol Stool Scale Form.**

Other PROs are assessed at baseline (Week -4), the final week of Phase 3 (week 16), and via the LTE questionnaires at 6-months post-treatment (week 38) and 12-months post-treatment (week 64). These include:

- IBS Quality of Life
- TIS (measured at baseline only)
- WPAI (also at week 8)
- PHQ-4
- Adequate Relief

The Satisfaction Questions will be asked only during the last week of Phase 3 (week 16).

Certain endpoints will be calculated based on the data input via the PROs. These include:

- Stool frequency
- Pain frequency

During the baseline visit, physicians will obtain questions regarding the subject's medical history; for example, physicians will inquire about prior treatments for IBS and history of taking medications that may conflict with the eligibility criteria for the study. However, no medical records or EMR-originating source documentation will be collected. The IBS diagnosis is established at the baseline visit via Rome IV criteria. There is no imaging or laboratory testing required in the study and all endpoints are obtained via PROs via the Curebase software.
All subjects who enroll in EASITx will electronically sign a HIPAA Authorization Form, which permits the use of a pseudonymized form of their data to be used for research purposes.

8.4.1 Daily Abdominal Pain Intensity

The daily pain intensity measurement is recorded at approximately the same time each day and is the worst abdominal pain score for the previous 24-hour period using the 11-point NRS of pain intensity.

8.4.2 Daily Abdominal Pain Frequency

The daily pain frequency measurement is derived from the daily pain intensity measurement. Days where severity is >0 are considered a day with pain and are recorded as positive. Days with a score of 0 are days without pain.

8.4.3 Daily Stool Consistency

The daily stool consistency measurement is based on the Bristol Stool Form Scale (BSFS). The BSFS is a scale with pictures and associated descriptions of stools with different consistency. The stool consistency is designated on the scale as 1 (separate hard lumps) to 7 (watery, no solid pieces) and is recorded at approximately the same time each day by referring to pictures and verbal descriptors in the Curebase ePRO (29).

Subjects will be asked for the number of bowel movements in the previous 24 hours. For days where subjects report ≥1 bowel movement they will use the BSFS to score the worst stool in the preceding 24 h period.

8.4.4 Daily Stool Frequency

All subjects will record the daily number of bowel movements for the previous 24-hour period.

8.4.5 IBS-QOL

The IBS-QOL is a 34-item questionnaire (21). The items are summed and transformed to a 0-100-point scale. Higher scores indicate better IBS quality of life. The mean IBS-QOL score measured at weeks 16, 38, and 64 will be used for comparison.

8.4.6 WPAI

The WPAI is a 6-question survey of presenteeism and absenteeism (22). Because it has a recall period of 7 days, it will be measured at the baseline screening visit, week 8, week 16, and again during the LTE at weeks 38 and 64.

8.4.7 TIS

The TIS is a 17-item questionnaire of personal characteristics thought to be related to therapeutic response to clinical hypnosis (23). TIS will be measured at baseline in the pre-treatment run-in period and used to model outcomes at treatment completion.

8.4.8 PHQ-4

The PHQ-4 is a simple 4 item measure of anxiety (2 items) and depression (2 items) (24). Each item is scored on a 4-point (0-3) NRS and the items are summed to give a total score ranging from 0-12. The total score provides an assessment of psychological distress. The 2-item anxiety and depression scales can also be scored and scores of 3 or greater are considered positive for screening purposes. The PHQ-4 will be measured at baseline in the Phase 1 pre-treatment run-in period, week 16 (Phase 3), week 38, and at week 64 in the LTE.

8.4.9 Adequate Relief Question

The following question will be asked during week 16, 38, and 64 via the Curebase data collection (ePRO) system:

- On average, over the past 2 weeks have you had adequate relief of your IBS symptoms? (Y/N)

8.4.10 Satisfaction Questions

The following questions will be asked during the last week of Phase 3 (week 16) via the Curebase data collection (ePRO) system:

- Overall, how satisfied were you with the therapy you received? (1-5 scale)
- Would you recommend the therapy you received to someone with IBS? (Y/N)
- Would you recommend using the therapy you received before trying a prescription drug? (Y/N)

8.5 Safety and Other Assessments

Safety will be assessed using AE reporting (see Section 9.3).

8.5.1 Concomitant Medication/Therapy

Concomitant medications and treatment will be collected at the baseline screening visit, week 8 and week 16. Concomitant medications and treatment use will also be collected at week at 38 and 64 in the LTE. The following information will be collected:

1. Concomitant Medications
    a. Medication name
    b. Indication
    c. Medication form (e.g., tablet, capsule, etc.)
    d. Medication dose units (e.g., gram, IU, etc.)
    e. Medication schedule (e.g., QD, BID, etc.)
    f. Start date
    g. End date
2. Non-medication Therapy

a. Indication
b. Schedule/Frequency (daily, weekly, monthly, other)
c. Type of therapy
    i. Physical therapy
    ii. Occupational therapy
    iii. Psychotherapy (talk therapy)
    iv. Cognitive Behavioral therapy (CBT)
    v. Counselling
    vi. Guided self-help
    vii. Behavioral activation
    viii. Mindfulness therapy
    ix. Other
d. Start date
e. End date

8.5.2 Blinding Assessment

Subject blinding will be assessed in the last week of Phase 3 using the following question:

Even if you do not feel you received benefit from your treatment program, do you believe the program you received could be beneficial to others with IBS?

Answers will be on a 7-point NRS, with the following guidelines:
1 – Definitely could not help others with IBS
4 – May or may not help others with IBS
7 – Definitely could help others with IBS

Given that this study is hypothesis blinded, the blinding assessment is designed to assess the credibility of the treatment and the credibility of the comparator as a treatment for IBS.

8.6 Adverse Events and Serious Adverse Events

8.6.1 Definition of Adverse Events

Adverse event[1] means any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, whether or not related to the investigational medical device (21 CFR 312.32 (a)).

In the context of the investigational device, an AE constitutes:

- any unintentional, unfavorable clinical sign or symptom, including complications of IBS (but not IBS itself).
- any new illness or disease or the deterioration of existing IBS

[1] ISO14155 and 21 CFR 812

- any clinically significant deterioration in any clinical assessment or outcome measure
- Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device

Pre-existing conditions (unless worsened significantly during treatment) or routine diagnostic and therapeutic procedures normally administered in the treatment of IBS do not constitute AEs. AEs will be collected from the time a subject signs the informed consent until study withdrawal, screen failure, or study completion.

If the subject experiences a worsening or complication of an AE after ongoing treatment, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

In this study, it is possible that some subjects may experience a worsening of IBS symptoms. As the primary endpoint of this study, worsening of IBS symptoms is captured as part of the efficacy parameter. Worsening of IBS symptoms should not be considered an AE unless the worsening of the symptoms is associated with a cause other than the subject's IBS.

All AEs that occur in study subjects during the AE reporting period specified in the protocol must be reported, WHETHER OR NOT THE EVENT IS CONSIDERED RELATED TO THE STUDY TREATMENT.

NONSERIOUS AEs are to be documented on the AE CRFs.

8.6.2 Definition of Serious Adverse Events

An AE that meets one or more of the following criteria/outcomes is classified as serious (term definitions follow):

- Death
- Is deemed life-threatening
- Results in inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in a congenital anomaly/birth defect
- Important medical event

Term definitions:

Life-threatening – Any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have

caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred.

Hospitalization – Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (e.g. elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the course of the study).

Disability – Defined as a substantial disruption in a person's ability to conduct normal life functions.

Congenital Anomaly/birth defect: Congenital anomaly/birth defect in offspring, or led to fetal distress, or fetal death

Important Medical Event – is an event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment of the study physicians, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include suicidality, psychosis, behavioral upset, or emergent medical condition requiring emergency hospitalization or intervention.

8.6.3 Classification of an Adverse Event

8.6.3.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities or safety.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning or safety.
- **Severe** – Events interrupt a subject's usual daily activity and may require active medical treatment or intervention to ameliorate. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.6.3.2 Device related AEs

Device-related adverse events are events directly attributable to the device itself.

- Adverse Device Effect (ADE): Non-serious adverse event related to the use of an investigational medical device

- Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.6.3.3 Serious Unanticipated Adverse Device Effect

Serious Unanticipated Adverse Device Effects (SUADEs) are any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan.

8.6.3.4 Relationship to Study Intervention

All AEs must have their relationship to study intervention assessed by a clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the study treatment must always be suspect.

- **Reasonable Possibility** – A clinical event, including an abnormal clinical test result, whose temporal relationship to study treatment makes a causal relationship possible. (There is reasonable evidence to suggest a partial or direct causal relationship e.g., the event occurred within a reasonable time after administration of the study treatment). Other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **No Reasonable Possibility** – A clinical event, including an abnormal clinical test result, whose temporal relationship to study treatment makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study treatment) and in which other therapies or underlying disease provides more plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

8.6.3.5 Anticipated AEs:

The following are anticipated AEs that one or more scientific publications have previously identified as possibly related to GDH or MR therapies:

- Headache
- Drowsiness
- Fatigue
- GI discomfort
- Muscle tightness
- Muscle soreness

The Sponsor will be responsible for determining whether an AE is device-related or not.

8.6.3.6 Device malfunction

Device malfunction denotes a failure of one or more of the components of digital app that could potentially result in lack of patient access to the digital app, inconvenience. The manufacturer must confirm device failure.

8.6.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study team will record all events with start dates occurring any time after informed consent is obtained through the end of Phase 4 (LTE) or until the end of study participation.
Events will be followed for outcome information until resolution or stabilization.

8.6.5 Adverse Event and Serious Adverse Event Reporting

The occurrence of AEs, SAEs, and Protocol Deviations (PDs) shall be reported through a unidirectional, HIPAA-compliant, web-based communication channel. Event reports may be initiated at any time by the subject or the investigator. All logging of event reports shall be retained for the duration of the study to provide proper documentation in accordance with FDA and ICH GCP requirements. The adverse event will be triaged based on subject content and urgency.

In the event of an AE, SAE, or PD, the message will be immediately sent to the Curebase team for determination of severity and relatedness to the investigational treatment. The study team will

collect information from the subject as necessary and create a final event report for logging within a specified timeframe. Reports containing AEs will be processed and documented.

Reports containing SAEs shall be completed and filed per regulatory requirements. The information in a SAE report should be completed as fully as possible and contain at a minimum:

- Subject ID number
- Start date of the event
- Description of the event
- Study physician's name
- Investigator causality assessment
- Investigator seriousness assessment

If safety information not available at the time of the first report becomes available at a later date, the study team member should submit follow-up safety information to Curebase. All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report. Detailed study reporting procedures shall be standardized as documented in a formal Safety Monitoring Plan.

9 Statistical Considerations

A Statistical Analysis Plan (SAP) will be prepared and finalized before unblinding of subjects' treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. A blinded data review will be conducted before unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

9.1 Statistical Hypotheses

The primary endpoint for this study will be the proportion of overall pain intensity responders to GDH and comparator following 12 weeks of treatment. An abdominal pain intensity responder is defined as a subject whose daily abdominal pain intensity averaged over the 4 weeks of Phase 3 (weeks 13 through 16) is 30% reduced compared to the daily abdominal pain intensity averaged over the 4 weeks of the Phase 1 run-in (weeks -4 through -1).

The proportion of responders in each treatment group in the Intent-to-Treat (ITT) population will be estimated along with corresponding two-sided 95% confidence intervals (CIs). For this study the null and alternative hypotheses that will be tested are:

- H0: $P1 = P2$
- H1: $P1 \neq P2$

Where P1 and P2 are the proportion of responders in GDH and Comparator treatment groups, respectively.

9.2 Sample Size Determination

In this study, 380 subjects will be randomized in a 1:1 ratio to GDH or comparator to ensure that at least 300 subjects complete their Week 13-16 assessment for analysis. Three hundred (300) subjects completing Phase 3 will provide at least 90% power to detect an 18 percentage point difference in response rates between the GDH and comparator treatment groups at the 5% significance level. The study was powered assuming that the comparator treatment group is expected to demonstrate a 26% response rate. To determine the expected response rate in the comparator treatment group, two studies of GDH reporting data that utilized dichotomous outcome measures were examined. The first (9) used an endpoint of % treatment responders (defined as a >50% reduction in IBS-SSS). In this study, 52% of subjects in the GDH group and 26% of subjects in the control group (usual care) were responders. A more recent study by Flik et al (12) reported an "adequate relief" response rate of 40% in the GDH group compared to 17% in the Edu control group. It is believed the response rate in the comparator treatment group in this study is likely to be ~26%.

9.3 Populations for Analyses

Enrolled Population: The enrolled population will include all subjects who sign informed consent and meet the inclusion/exclusion criteria. This population will be used for evaluation of demographics and baseline characteristics.

Intent-to-Treat (ITT) Population: The ITT population will include all subjects who are randomized to treatment. Subjects that are replaced due to failed inclusion/exclusion criteria or technical issues in the Curebase software will be excluded. This population will be used for the evaluation of efficacy and all safety analyses.

Per Protocol (PP) Population: The PP population will consist of all subjects in the ITT population with no major protocol deviations that may affect efficacy. This population will be used as a supportive analysis of the primary endpoint.

9.4 Statistical Analyses

9.4.1 General Approach

The SAS System, Version 9.4 (or higher), will be used for all analyses, unless otherwise specified. Continuous variables (e.g., age) will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables (e.g., sex, race) will be summarized using the number of observations (n) and percentage in each category.

All data used in analyses and/or collected during the study will be provided in listings. Subjects withdrawn prior to end of Phase 3 (Weeks 13-16) assessment period will be considered as prematurely withdrawn. All available data for subjects who prematurely withdraw from the study will be included in all analyses. All 4-week assessment periods in MMRM and GEE models will include: Phase 1 (weeks minus 4 through minus 1), Phase 2 weeks 1-4, Phase 2 weeks 5-8, Phase 2 weeks 9-12, Phase 3 (weeks 13-16), LTE Period 1 (weeks 35 through 38), and LTE period 2 (weeks 61 through 64). At timepoints during the study that require 4 weeks of daily IBS symptom and pain assessment, at least 50% of the required assessments must be collected to be able to derive the average daily abdominal pain intensity and like endpoints. Study withdrawals, reasons for withdrawal, and missing assessment collections will be summarized.

Analyses of treatment will be performed using two different approaches to account for missing data during the treatment phase:

1. At-assessment Analysis: Missing values at post-baseline assessments will not be replaced and will be regarded as missing in analyses.
2. Multiple Imputation: Missing values at post-baseline assessments will be imputed using the multiple imputation method.

Additional details of the statistical methods are provided in the SAP.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint, proportion of overall pain intensity responders is defined as a subject whose daily abdominal pain intensity averaged over the 4 weeks of Phase 3 (weeks 13 through 16) is 30% reduced compared to the daily abdominal pain intensity averaged over the 4 weeks of Phase 1 (weeks -4 through -1) (27). Responders will be compared between the GDH and comparator treatment groups using a Cochran-Mantel-Haenszel test adjusted for IBS subtype and gender. If the resulting p-value is less than 0.05 and the magnitude of the difference in pooled proportions is at least 10 percentage points, then it will be concluded that the primary endpoint has been met.

9.4.3 Analysis of the Secondary Efficacy Endpoint(s)

9.4.3.1 Abdominal Pain Intensity

Average abdominal pain intensity will be calculated as the average of the daily abdominal pain intensity scores recorded by each participant. Averages will be calculated for each week and for each 4-week assessment period (i.e., Phase 1 [Week -4 to -1,], Phase 3 [Week 13 – 16], etc.).

Average abdominal pain intensity at Week 13-16 will be statistically compared between GDH and MR using an ANOVA model adjusted for gender and IBS subtype. The least squares (LS) mean estimate of average abdominal pain intensity and LS mean difference and associated 95% CIs will be presented with corresponding p-value.

Additionally, change from baseline and at-assessment values of average abdominal pain intensity will be analyzed at all 4-week assessment time periods with a mixed effects repeated measures model (MMRM). The model will include treatment, time period, IBS subtype, gender, and treatment by time period interaction as fixed effects and participant as a random effect. The unstructured covariance matrix will be used to model the within-participant correlation. Using the ESTIMATE and LSMEANS statements within PROC MIXED, the model-based LS means and LS mean differences (GDH minus comparator) and associated 95% CIs for each time period and overall will be estimated.

Average abdominal pain intensity will be summarized descriptively by treatment and time period.

Additionally, overall pain intensity response at all 4-week assessment time periods will be analyzed with a random effects generalized estimating equations (GEE) with a logit link. The model will include treatment, time period, IBS subtype, gender, and treatment by time period interaction as fixed effects and subject as a random effect. The unstructured covariance matrix will be used to model the within-subject correlation. Using the ESTIMATE and LSMEANS statements within PROC GLIMMIX, the model-based responder rates and odds ratio (GDH relative to comparator) and associated 95% CIs for each time period and overall will be estimated.

9.4.3.2 Average Abdominal Pain Frequency

Average abdominal pain frequency is defined as the average number of days during the 4-week assessment period in which the subjects recorded a 1 or greater on the daily pain severity measurement. Only days during which an assessment is recorded will be included in the calculation of average abdominal pain frequency.

Average abdominal pain frequency at Week 13-16 will be statistically compared between GDH and comparator using an ANOVA model adjusted for gender and IBS subtype. The least squares (LS) mean estimate of average abdominal pain frequency and LS mean difference and associated 95% CIs will be presented with corresponding p-value.

Additionally, change from baseline and at-assessment values of average abdominal pain frequency will be analyzed at all 4-week assessment time periods with a mixed effects repeated measures model (MMRM). The model will include treatment, time period, IBS subtype, gender, and treatment by time period interaction as fixed effects and subject as a random effect. The unstructured covariance matrix will be used to model the within-subject correlation. Using the ESTIMATE and LSMEANS statements within PROC MIXED, the model-based LS means and LS mean differences (GDH minus comparator) and associated 95% CIs for each time period and overall will be estimated.

Average abdominal pain frequency will be summarized descriptively by treatment and time period.

9.4.3.3 Stool Consistency

Stool Consistency will be calculated using the BSFS. The BSFS is recorded at approximately the same time each day. Subjects will be asked for the number of bowel movements in the previous

24 hours. Subjects will use the BSFS to score the worst stool in the preceding 24 hour period. Extreme stool consistency is defined as 1, 2, 6, or 7 on the BSFS, while BSFS scores of 3,4 and 5 are considered within the normal range. The BSFS scores will be grouped as 1,2 (Group 1), 3,4,5 (Group 2) and 6,7 (Group 3). For participants in the IBS-D and IBS-M subtypes, a stool consistency response is defined as having a greater than or equal to 50% reduction from baseline (Phase 1) in the number of days with a BSFS score of 6 or 7. Stool consistency response for the IBS-D and IBS-M subtypes will be analyzed with methods similar to those used to assess the primary endpoint described in Section 10.4.2.

Additionally, change from baseline in the percentage of days with a BSFS score in Group 2 will will be analyzed at all 4-week assessment time periods with a mixed effects repeated measures model (MMRM). The model will include treatment, time period, IBS subtype, gender, and treatment by time period interaction as fixed effects and subject as a random effect. The unstructured covariance matrix will be used to model the within-subject correlation. Using the ESTIMATE and LSMEANS statements within PROC MIXED, the model-based LS means and LS mean differences (GDH minus comparator) and associated 95% CIs for each time period and overall will be estimated.

The percentage of the number of days with a BSFS score in each BSFS group will be summarized descriptively by treatment, IBS subtype and time period.

9.4.3.4 Stool Frequency

Analyses of daily stool frequency will only include participants with IBS-C.

Daily stool frequency will be calculated as the average number of stools per day during each 4-week assessment period. Only days during which an assessment is recorded will be included in the calculation of average stool frequency.

For participants in IBS-C subtype, a stool frequency response is defined as an increase from baseline (Phase 1) of ≥1 bowel movement per day. Stool frequency response for IBS-C participants will be analyzed with methods similar to those used to assess the primary endpoint described in Section 10.4.2.

Change from baseline and at-assessment values of daily stool frequency will be analyzed at all 4-week assessment time periods with a mixed effects repeated measures model (MMRM). Separate models will performed for each IBS subtype. The model will include treatment, time period, gender, and treatment by time period interaction as fixed effects and participant as a random effect. The unstructured covariance matrix will be used to model the within-participant

correlation. Using the ESTIMATE and LSMEANS statements within PROC MIXED, the model-based LS means and LS mean differences (GDH minus comparator) and associated 95% CIs for each time period and overall will be estimated.

Daily stool frequency will be summarized descriptively by treatment and time period.

9.4.3.5 IBS-QOL

The IBS-QOL is a 34-item questionnaire. The items are summed and transformed to a 0-100-point scale. Higher scores indicate better IBS quality of life.

Change from baseline and at-assessment values of IBS-QOL score measured at the Baseline visit, week 16, week 38, and week 64 will be analyzed with a MMRM. The model will include treatment, week, IBS subtype, gender, and treatment by week interaction as fixed effects and subject as a random effect. The unstructured covariance matrix will be used to model the within-subject correlation. Using the ESTIMATE and LSMEANS statements within PROC MIXED, the model-based LS means and LS mean differences (GDH minus comparator) and associated 95% CIs for each week and overall will be estimated.

IBS-QOL score will be summarized descriptively by treatment and week.

9.4.3.6 Workplace Presenteeism and Absenteeism

The Workplace Productivity and Activity Impairment Questionnaire (WPAI) is a 6-question survey of presenteeism and absenteeism and it will be measured at the Baseline visit, week 8, 16, 38, and 64.

Percent overall work impairment due to problem and percent activity impairment due to problem will be analyzed similarly to IBS-QOL.

Percent work time missed due to problem, percent impairment while working due to problem, percent overall work impairment due to problem and percent activity impairment due to problem will be summarized descriptively by treatment and week.

9.4.4 Exploratory Analyses

The following exploratory endpoints will be detailed out in the statistical analysis plan.

- PHQ-4
- TIS
- IBS-AR
- Blinding question
- Satisfaction questionnaire

- Treatment adherence
- Concomitant medication usage

9.4.5 Safety Analyses

All AEs will be coded to System Organ Class (SOC) and Preferred Term using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects that experience at least one AE, grade 3-5 AEs, related AEs, SAEs, and related SAEs will be summarized by treatment group. Additionally, AEs will be summarized by severity and relatedness.

9.4.6 Baseline Descriptive Statistics

Demographic and baseline characteristics will be listed and summarized descriptively by treatment group.

9.4.7 Planned Interim Analyses

There are no planned interim analyses.

9.4.8 Sub-Group Analyses

The primary and secondary endpoint analyses will be conducted in the following subgroups:

- Gender
- IBS subtype
- Age group (<=median, > median)
- Concomitant medication
    - On IBS drug therapy vs not on IBS drug therapy
    - IBS-C on IBS drug therapy vs IBS-C not on IBS drug therapy
    - IBS-D on IBS drug therapy vs IBS-D not on IBS drug therapy

Further details will be provided in the statistical analysis plan.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent

Written informed consent must be obtained from all subjects prior to entry into the study. Written consent documents will embody the elements of informed consent described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The informed consent form will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The PI/Sponsor is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by the IRB. The informed consent must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or delegated staff to explain the detailed elements of the informed consent form to the subject.

Curebase will use an electronic consent platform (eConsent) to facilitate the consent process. The eConsent will be introduced to subjects as part of an on-line pre-screening interview. The pre-screening process requires subjects to create an account and login that allows ongoing access to their secure Curebase platform account. Once subjects pass their pre-screening they will be able to review the eConsent, HIPAA Authorization, and the Experimental Subjects' Bill of Rights using their own personal electronic devices, like a phone, tablet, or computer. During the subject's review they will be provided an opportunity to discuss the content of the eConsent with study personnel via email or telephone.

Subjects will have the option to delay document signing and proceed to the study visit where they can further discuss the consent with the study physician prior to signing. Each subject will be required to electronically sign the study informed consent, HIPAA Authorization, and the Experimental Subjects' Bill of Rights before they are allowed to participate in the study. After signing each document, subjects will be sent digital PDFs of their documents for their personal records. The original informed consent form will be stored in the eCRF. In the case of revisions to the informed consent form, subjects will be contacted and revised eConsent forms must be reviewed and signed by subjects. The date the revised consent was obtained will be recorded with the eConsent.

10.1.2 Study Discontinuation and Closure

metaMe reserves the right to terminate or suspend the study at any time for any reason. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, and/or Food and Drug Administration (FDA).

10.1.3 Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. All research activities will be conducted in as private a setting as possible.

Curebase, Inc. will prepare and maintain adequate and accurate electronic source documents designed to record all observations and other pertinent data for each subject screened or enrolled in the study. All data from subjects will be collected, managed, and securely stored by Curebase. Curebase stores all data in a secure cloud server (AWS) and complies with HIPAA and GDPR standards, including but not limited to: password protection, platform encryption, and 2-factor verification. Curebase takes as much action as possible to maximize the protection and security of subject's sensitive information. In order to maintain subject confidentiality, subjects will not be identified by name in any reports or study documents to be collected by the Sponsor (or designee), but will be identified by a clinic number and subject number.

metaMe Health, Inc. will collect and store PHI. This information is needed to correctly target treatment notification, treatment reminders, and to administer the treatment. There will be no data link between PHI and treatment allocation or data used to determine treatment compliance (see Section 6.3). metaMe Health stores all data in a secure cloud server (AWS) and complies with HIPAA and GDPR standards, including but not limited to password protection and platform encryption. To maintain subject confidentiality, subjects will not be identified by name in any reports or study documents to be collected by the Sponsor (or designee), but will be identified by a clinic number and subject number.

Refer to Section 10.1.6 for additional information on how data will be collected and secured.

10.1.4 Clinical Monitoring

Curebase will provide clinical monitoring during the study to ensure that:

1. The rights and well-being of human subjects are protected
2. The reported study data are accurate and complete
3. The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements.

Refer also to Sections 11.1.5 and 11.1.6 for additional details.

10.1.5 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system. Data QC checks will be remotely run on the database and shall be generated on an ongoing basis to verify the accuracy and integrity of data being collected. Any missing data or data anomalies will be communicated to the investigators for clarification and resolution.

Following written standard operating procedures (SOPs), the monitor will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

The investigators will provide direct access to all study related records, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by the relevant regulatory authorities.

10.1.6 Data Collection, Retention, and Monitoring

Investigators and their representatives will be required to complete a training on using the Curebase platform prior to working with subjects. Training material will include instructions on how to enter data correctly, how to enter protocol deviations and AEs, and how to modify and update the eCRF. Training of investigators and research personnel will be tracked by Curebase using study-specific activation logs. Following written SOPs, the study monitors will verify that the clinical study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Study personnel will enter data collected during the baseline visit into the Curebase eCRF. If a correction is required for a subject's eCRF, the time and date stamp tracks the person entering or updating eCRF data and creates an electronic audit trail. The Investigators and Curebase are responsible for all information collected on subjects enrolled in this study.

Curebase will provide clinical monitoring during the study to ensure that:

1. The rights and well-being of human subjects are protected
2. The reported study data are accurate and complete
3. The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements.

4. Correct coding of AEs, medical history, and concurrent medical conditions using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHO).

10.1.6.1 Data Collection Instruments

Curebase will provide eCRFs to each subject who signs an informed consent and completes the clinic visit screening. These forms are used to transmit the information collected in the performance of this study to sponsor and regulatory authorities. After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the PI or designees and will be addressed by the clinic research staff. The PI must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in form to third parties, except for authorized representatives of appropriate governmental regulatory authorities.

Investigators and their representatives will be required to complete a training on using the Curebase platform prior to working with subjects, including how to enter data correctly, how to enter protocol deviations and AEs, and how to correct mistakes. Trainings will be tracked by Curebase on study-specific activation logs. Following written SOPs, the study monitors will verify that the clinical study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Study personnel at each research clinic will enter data corresponding to a subject's visit into the protocol-specific eCRF. If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

10.1.6.2 Data Management Procedures

All data will be entered into Curebase, which is a validated database. The Curebase team or delegate will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

10.1.6.3 Data Quality Control and Reporting

Quality control (QC) procedures will be implemented beginning with the data entry system. After the data has been entered into the Curebase database, a system of computerized data validation checks will be implemented and applied to the database every 2 weeks. Query reports pertaining to missing data or data discrepancies will be forwarded to the Investigators, clinical team and study monitors for clarification/resolution. A Curebase representative will follow up to ensure that the corrections are completed and documented appropriately. The study database will be updated in accordance with the resolved queries. Following completion of the study data collection, Curebase will provide a thorough quality control review of all records. Finalized data will then be designated for database lock prior to statistical analysis. In addition, following written standard operating procedures (SOPs), the monitor will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

The investigators will provide direct access to all study related records, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by the relevant regulatory authorities.

10.1.6.4 Archival of Data and Record Retention

The database is safeguarded against unauthorized access by established security procedures. Appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the Curebase database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis are locked and cleaned per established procedures.

All data pertaining to a clinical study, including protected health information (PHI), will be retained for the duration of the study, and for 2 years thereafter, in compliance with International Conference on Harmonisation (ICH) E6 Section 4.9.5 and specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified treatment being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the agreement between the investigator and sponsor. At this point, the identifiable PHI obtained during the study will be deleted. Curebase will share pseudonymized data collected from subjects with metaMe Health Inc.
After 2 years have elapsed since the completion of a clinical investigation, Curebase will retain a de-identified version of the data obtained during that study. Curebase may retain these data indefinitely and may use them for a variety of purposes that will include, but are not be limited

to, making improvements to the Curebase product. MetaMe Health will be permitted to retain the pseudonymized Curebase data set, even after the 2-year post-study period has elapsed.

Curebase will not delete clinical data, even upon request, during the clinical study and for 2 years thereafter. Although Curebase respects the rights of its users to be forgotten, Curebase is also bound by an obligation to deliver study data to the Sponsor for scientific analysis, and to fulfill monitoring obligations.

MetaMe Health reserves the right to keep the pseudonymized data retrieved from Curebase for the entire duration the company is functioning and active. MetaMe Health will keep this information in a private and secure internal database.

10.1.6.5 Monitoring

Electronic monitoring visits will be conducted by representatives of Curebase, Inc according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). Study investigators will provide direct access to all clinical records, study source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. By signing this protocol, the Investigator grants permission to Curebase and appropriate regulatory authorities to conduct monitoring and/or auditing of all appropriate study documentation.

10.1.6.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol and ICH GCP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study research staff. As a result of deviations, corrective actions are to be developed by the study physicians and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the study physicians and study monitors to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be categorized as either significant or minor. Significant deviations are those events that cause or could cause harm to subjects or others or that affect the fidelity of the research. Curebase will maintain a database of protocol deviations for the duration of the study and shall be responsible for triaging report writing and internal documentation. Significant protocol deviations will be

sent to the reviewing Institutional Review Board (IRB) per their policies. The study physicians and study monitors are responsible for knowing and adhering to the reviewing IRB requirements.

10.1.6.7 Clinical Trial Results Disclosure

metaMe will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by metaMe policy/standard, applicable laws, and/or regulations.

10.1.6.8 Publication and Data Sharing Policy

Curebase will provide metaMe with all data collected during the study. After study completion, only metaMe may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinic research agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor. metaMe reserves the right to publish any data from the study without the consent of investigators. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document.

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APPENDIX A ROME IV CRITERIA

Question	Answer
1. In the last 3 months, how often did you have pain anywhere in your abdomen?	0. Never (Skip to end of questionnaire) 1. Less than one day a month 2. One day a month 3. Two to three days a month 4. Once a week 5. Two to three days a week 6. Most days 7. Every day 8. Multiple times per day or all the time
2. How often did this pain in your abdomen happen close in time to a bowel movement -- just before, during, or soon after? (Percent of times with pain)	0. %0 or Never 1. 10% 2. 20% 3. 30% 4. 40% 5. 50% 6. 60% 7. 70% 8. 80% 9. 90% 10. 100%
3. How often did your stools become either softer than usual or harder than usual when you had this pain? (Percent of times with pain)	0. %0 or Never 1. 10% 2. 20% 3. 30% 4. 40% 5. 50% 6. 60% 7. 70% 8. 80% 9. 90% 10. 100%
4. How often did your stools become either more frequent than usual or less frequent than usual when you had this	0. %0 or Never 1. 10% 2. 20% 3. 30% 4. 40% 5. 50%

pain? (Percent of times with pain)	6. 60% 7. 70% 8. 80% 9. 90% 10. 100%
5. Has it been 6 months or longer since you started having this pain?	0. No 1. Yes

Rome IV Scoring
Irritable Bowel Syndrome
Must fulfill the following criteria for the past 3 months:
1. Recurrent abdominal pain
Q1 = at least weekly
2. Pain is associated with two or more of the following criteria:
    a. Related to defecation
    Q2 = at least 30% of occasions
    b. Associated with a change in frequency of stool
    Q3 = at least 30% of occasions
    c. Associated with a change in form (appearance) of stool
    Q4 = at least 30% of occasions
1. Symptom onset at least 6 months prior to diagnosis
Q5 = yes

APPENDIX B GUT-DIRECTED HYPNOTHERAPY SESSION SCRIPTS

IBS Session One

[redacted]

[redacted]

[redacted]

[redacted]

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IBS Session Two

[redacted]

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IBS Session Three

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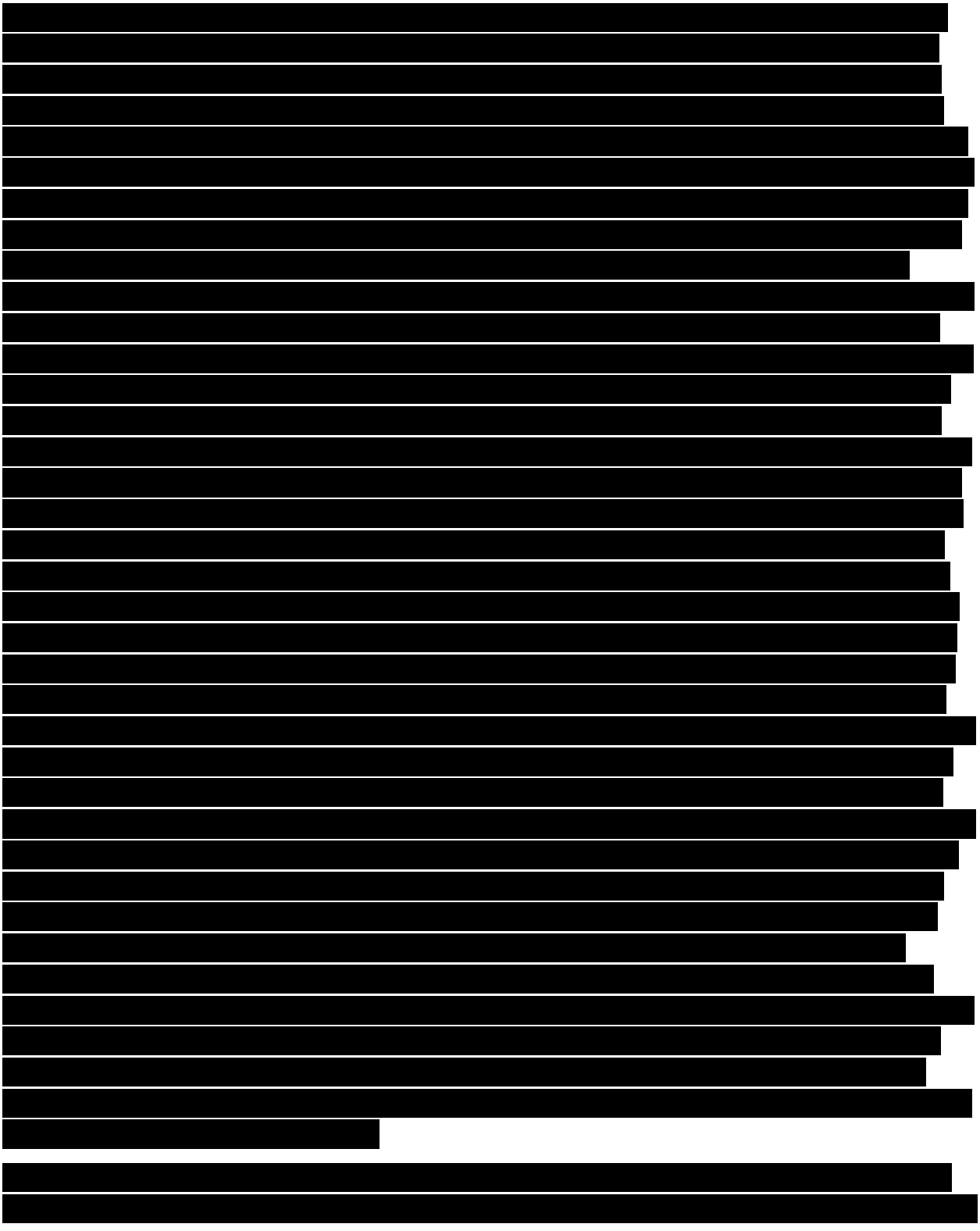

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IBS Session Four

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IBS Session Five

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IBS Session Six

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IBS Session Seven

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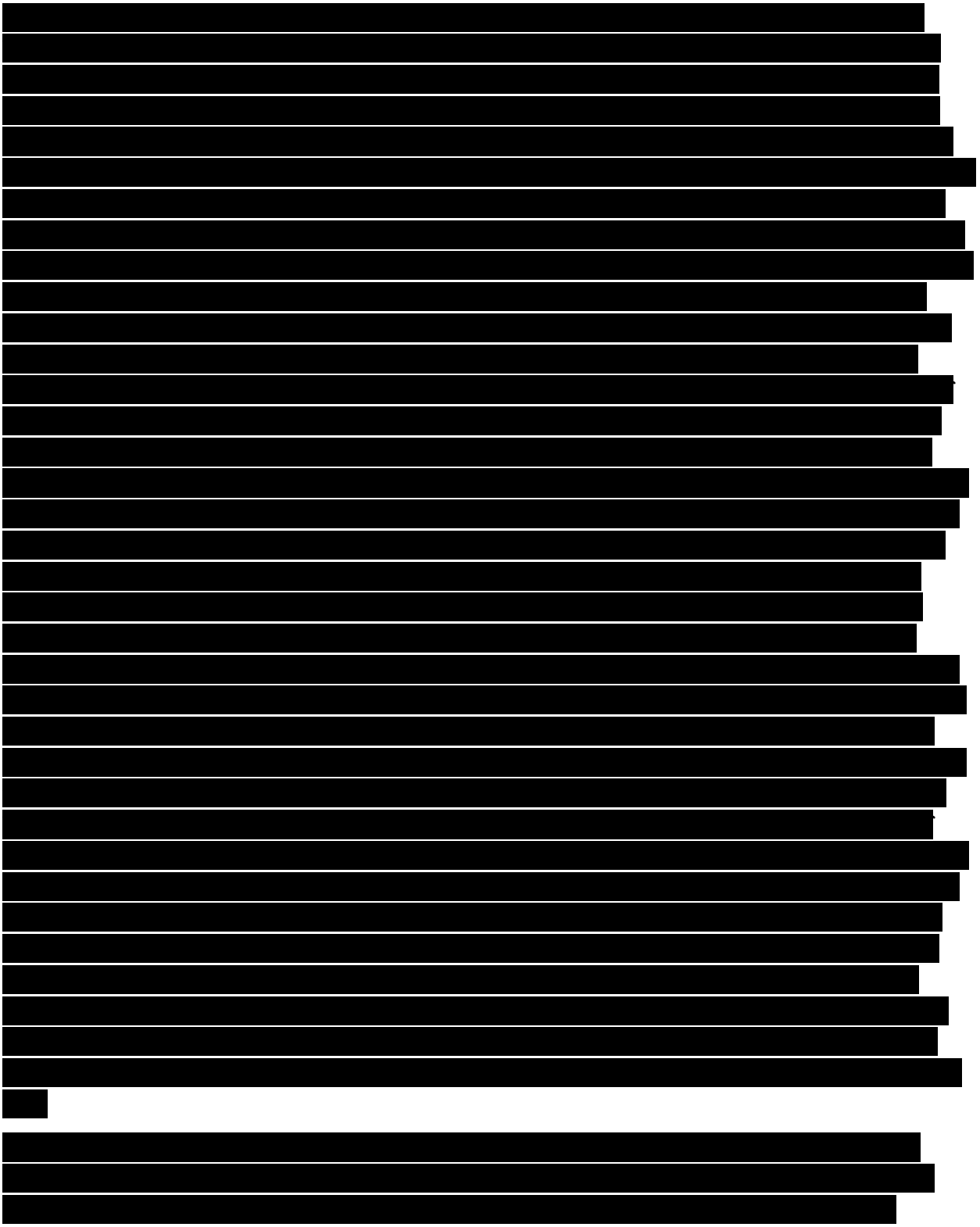

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APPENDIX C. GUT-DIRECTED HYPNOTHERAPY DAILY PRACTICE SESSION SCRIPT

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APPENDIX D MUSCLE RELAXATION SCRIPTS

Session One

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Session Two

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Session Three

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Session Four

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Session Five

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Session Six

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Session Seven

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APPENDIX E. MUSCLE RELAXATION DAILY PRACTICE SESSION SCRIPT

[redacted]

APPENDIX F GDH INTRO SCRIPT

Implementation notes:

1. The intro video will be played before the first treatment (no option to opt out).
2. Starting with Session 2, intro video will be accessible from a button/link near the large video play button (opt-in to watch).
3. The intro video will also be accessible from the help section of the app.

Intro Script (sentences in italics indicate GDH-specific text):

Welcome and thank you for participating in this important clinical study. Your treatment session will begin after this two-minute introductory video. Your treatment program will consist of seven 30-minute sessions, with two weeks between each session. You will be sent an email reminder 24 hours and 1 hour before each of your sessions, and a text message reminder 5 minutes before each of your sessions. It is important to do your treatment session on the day that it is scheduled. If you do miss a session, you will be notified by email. If you know in advance that you can't make your scheduled session time, you may re-schedule it in your app. All treatment sessions must be completed within 3 days of the originally scheduled date.

On days you don't have a treatment session, a "practice" session will be available to you. A minimum of three practice sessions per week is recommended, but you may complete a practice session every day you don't have a treatment session. You can always access your treatment or practice sessions by logging into this app. To play your treatment or practice session, press the large arrow-button on your app. The button is designed to always play the correct treatment or practice session.

If you are interrupted for any reason during your session, it's best to start over from the beginning. To do this, you may press the "begin again" button at any time. You may restart each of your sessions up to three times. When you successfully complete a session, press the "complete session" button.

Relaxation can improve gut symptoms. That's why during your sessions, *it is important to be in a quiet place where you can sit comfortably and will not be disturbed*. Be sure to place your phone in "Do Not Disturb" mode. Choose a place you can adjust the lights so that they are not too bright, and a place with a good wifi or cellular network connection. If possible, loosen any restrictive clothing. We recommend using headphones, earbuds, or quality speakers. Never view or listen to your sessions in a car, even if it is not moving.

If after completing your session you still feel like you are not fully alert, it is ok to sit for another few minutes before getting up. Thank you again for participating in this study.

APPENDIX G MUSCLE RELAXATION INTRO SCRIPT

Implementation notes:

1. The intro video will be played before the first treatment (no option to opt out).
2. Starting with Session 2, intro video will be accessible from a button/link near the large video play button (opt-in to watch).
3. The intro video will also be accessible from the help section of the app.

Welcome and thank you for participating in this important clinical trial. Your treatment session will begin after this 2-minute introductory video.

Your treatment program will consist of seven 30-minute sessions, with 2 weeks between each session. An email reminder will be sent to you 24 hours and 1 hour before each of your sessions. And a text message reminder will be sent to you 5 minutes before each of your sessions.

It's important to do your treatment session on the day that it's scheduled. If you miss a session, you'll be notified by email. If you know in advance that you cannot make a scheduled session, you may re-schedule it in this app. But all treatment sessions must be completed within 3 days of the originally scheduled date.

On days when you **don't** have a treatment session, a "practice" session will be available. A minimum of 3 practice sessions between treatment sessions is recommended. You may complete a practice session on any day that you don't have a treatment session.

You can always access your treatment or practice sessions by logging into this app. To play your treatment or practice session, press the large arrow button in the app. It will always play the correct treatment or practice session.

If you're interrupted during a session, it's best to start over from the beginning. To do this, press the "Begin Again" button at any time. You may restart each session up to 3 times.

When you successfully complete a session, press the "complete session" button.

Relaxation can improve gut symptoms. That's why it is important to find a comfortable position for your sessions, preferably lying in a recliner or on a bed. Be sure you're in a quiet place where you won't be disturbed. And put your phone in "Do Not Disturb" mode. If possible, loosen any tight or restrictive clothing. Choose a place where you can adjust the lights so they're not too bright, and someplace with a good Wi-Fi or cellular network connection. Place your smartphone

or mobile device close enough so you can hear it. Or better yet, use headphones, earbuds, or quality speakers. Never listen to your sessions in a car, even if it's not moving.

If you ever have any muscle discomfort during your session, immediately release and relax the muscle. If you have discomfort with a muscle group, you may choose not to try that muscle group again and wait until the session takes you to the next muscle group. Thank you again for participating in this trial.