Zemedy - Evaluation of Zemedy, a Cognitive Behavioral Therapy-based Digital Therapeutic Application for the Treatment of Irritable Bowel Syndrome

Study Protocol and Statistical Analysis Plan

NCT04723056

April 19, 2022

Zemedy Protocol

Protocol VERSION 3, Amendment 2

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Sub-Investigators/ Co-investigators: Sean Spencer, MD

Collaborators: Bold Health

Title: ZEMEDY--Evaluation of Zemedy, a cognitive behavioral therapy-based digital therapeutic application for the treatment of irritable bowel syndrome

Stanford IRB Protocol #: 59029

Objective

Evaluation of Zemedy, a cognitive behavioral therapy-based digital therapeutic application for the treatment of irritable bowel syndrome

Background

Irritable bowel syndrome (IBS) is defined as having recurrent abdominal pain associated with defecation or a change of bowel habits [i] It is a common syndrome affecting 11% (ranging 1.1% to 45%) in prevalence worldwide.[ii] The pathophysiology of IBS is complex and likely due to a combination of factors including altered motility, visceral hypersensitivity, dysbiosis, altered mucosal and immune function and central nervous system processing. The complex interplay between genetic, cultural, environmental and pyschosocial factors, also known as the biopsychosocial model of disease, can lead to the development of functional GI disorders like IBS (Figure 1).[iii]

Treatment of IBS is multifaceted and ranges from exercise, dietary restriction, laxative or anti-diarrheal therapy, antispasmodics, Rifaximin, probiotics, and antidepressants.[1] Psychological treatments to target the gut-brain axis such as cognitive-behavior therapy (CBT) have also been shown to be an effective therapy, and aims to address the psychological and environmental stressors that contribute to symptoms.[iv,v,vi,vii,viii]

This study will investigate the effectiveness of Zemedy, a mobile application that enables the digital delivery of a CBT program to people with IBS. CBT has been shown to reduce the severity of intractable IBS symptoms by as much as 70%, but the provision of the therapy is limited by the availability of qualified therapists to patients in need. Rooted in scientific evidence, Zemedy integrates the 8-week CBT program with other in-app features – such as educational modules and health trackers, to provide an end-to-end IBS management tool. The delivery of the CBT program in itself is guided by a chatbot persona, Elle, that mimics the conversation lead by a healthcare professional in a clinical therapy setting. Educational modules on the Zemedy app range from topics on IBS causes and symptoms, to topics on relevant exercise and diet regimens. Health trackers on the Zemedy app can be used to record flare-ups, mood, and lifestyle information, allowing data to drive the extraction of meaningful patterns in IBS symptom presentation. Therefore, the Zemedy app grants IBS patients the option of and access to invaluable treatment streams.

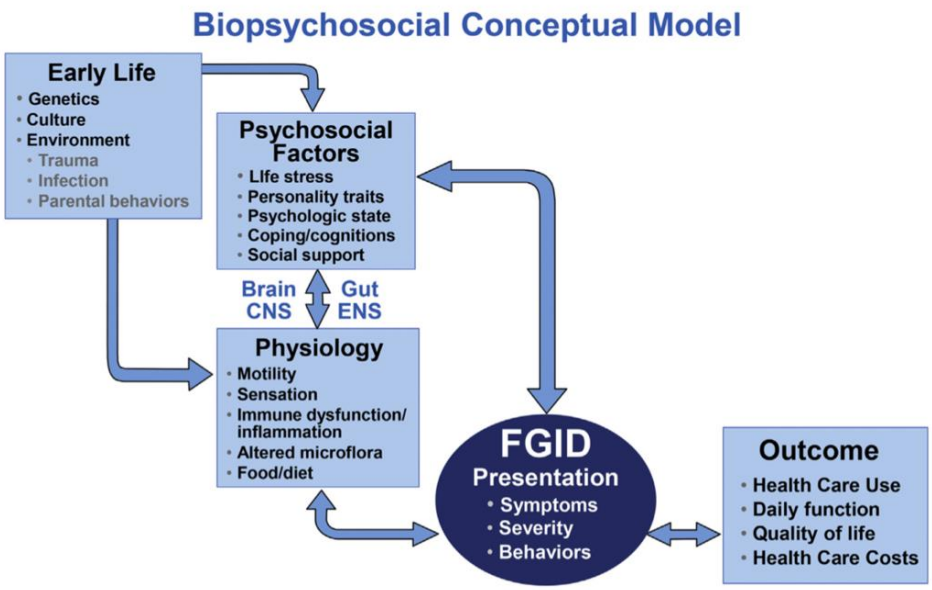

Figure 1. A biopsychosocial conceptualization of the pathogenesis, clinical experience, and effects of functional GI disorders. There is a relationship between early life factors that can influence the psychosocial milieu of the individual, their physiological functioning, as well as their mutual interaction (brain–gut axis). These factors influence the clinical presentation of the disorder and the clinical outcome. Modified from Rome III.[42]

Study Overview

This is an interventional, randomized controlled study with two study arms. The study will utilize Zemedy which provides digital delivery of a CBT program to people with IBS, via a smartphone application.

The study will involve a minimum of 44 individuals (randomized 22 in study group and 22 in the control group) with irritable bowel syndrome, who will take part in the intervention for 8 weeks. The study group will receive treatment as usual (TAU) + Zemedy intervention and the control group will receive TAU. TAU for IBS is tailored to the patient and may involve dietary modification, exercise, antispasmodic medication, laxative therapy, anti-diarrheal therapy, and pain medication. Patients will be evaluated in clinic or via telehealth at the beginning of the study, and at weeks 8 and 24. Patients can contact the physician electronically via the MyHealth application in between visits.

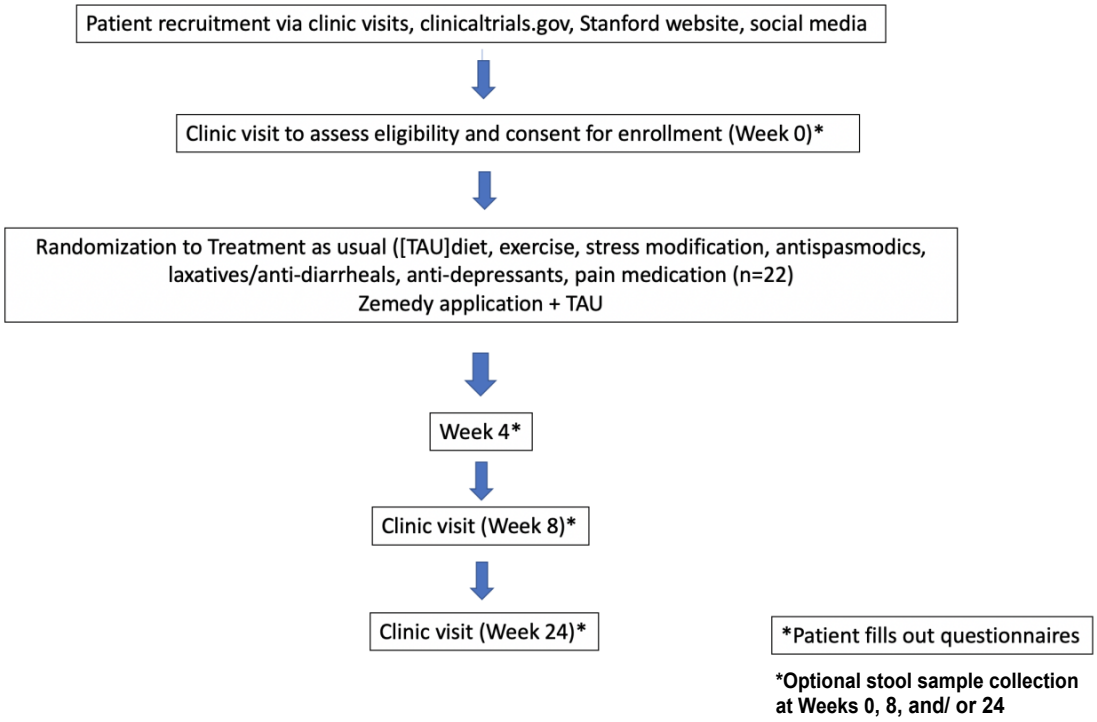

Figure 2: Overview of study design

Study objectives

- Determine the efficacy of the Zemedy application in the reduction of irritable bowel syndrome symptoms

Study design

- Single-blind randomized controlled trial
- Duration: 24 weeks, intervention is 8 weeks long

Primary Endpoint

- Change in IBS symptoms based on the IBS symptom severity score (SSS) score at week 8 compared to baseline

Secondary Endpoints

- Change in IBS symptoms based on the IBS-SSS- at week 24 compared to baseline
- Cohen Perceived Stress Questionnaire (PSQ)
    - Measures degree situation's in one's life are seen as stressful
    - Survey will be distributed at weeks 0 and 24 of the study
- Work and social adjustment scale (WSAS)
    - Measures the effect of IBS on ability to work and manage at home, participate in social and private leisure activities and maintain relationships.
    - Survey will be distributed at weeks 0 and 24 of the study
- Subject's Global Assessment of Relief (SGA)
    - Assesses global symptoms relief asking the question, "Overall, how do you feel?". Scale of -2 to +2 , from completely worse to completely better.1–2 considered responders and 4–5 non-responders.
    - Survey will be distributed at weeks 0 and 24 of the study
- Hospital Anxiety and Depression Scale (HADS).
    - Assesses mood measured by the total distress score (<7 normal, 8-14 borderline, 15 or >15, abnormal)
    - Survey will be distributed at weeks 0, 8 and 24 of the study
- Work Productivity and activity impairment (WPAI) questionnaire
    - Assesses work productivity based on number of days taken off from work due to health
    - Survey will be distributed at weeks 0, 8 and 24 of the study
- Fecal Sampling and Microbiome analysis (optional; opt-in)
    - Assessment of any changes in gut flora (baseline vs after intervention)
    - Stool self collection will occur at weeks 0 and 8 of the study. An additional collection may occur at week 24, contingent on PI judgment.
- Adherence to intervention assessed by use of Zemedy application in the Zemedy arm
- Decreased urgent care/ER/physician appointments due to the patient's IBS
- Application is considered to be safe without adverse events such as worsening irritable bowel syndrome symptoms, hospitalizations, worsened or new mood changes

Patient recruitment

- Patients recruited via advertisements online (clinicaltrials.gov) and in the clinics in the Digestive Health Center at Stanford Healthcare as well as social media (eg. Twitter, Facebook)
- Individuals screened by research assistant to assess eligibility
- Individuals invited for an assessment conducted by a study physician
- Those wishing to proceed sign a consent form to demonstrate their informed consent.
- Inclusion criteria
    - Male and female patients >=18 years old
    - Meet Rome IV criteria for IBS for at least 6 months
        - No restrictions on type of IBS
    - English proficiency (in order to understand use of the application)
    - Patient must be on a stable regimen for IBS for at least 30 days
    - Patients must own a smartphone (iOS or Android) in order to participate in the CBT application
- Exclusion criteria
    - Laboratory or imaging evidence of an alternative explanation of patient's symptoms
    - Active gastrointestinal disease such as Crohn's disease, ulcerative colitis, history of complete colon resection, acute infection, or any disease that precludes participation in CBT application
    - Patient already undergoing cognitive behavioral therapy
    - Psychiatric hospitalization within 10 years
    - Current or past diagnosis of a major mental illness such as schizophrenia, bipolar disorder, personality disorder or substance abuse
    - Active (within the past 3 months) suicidal ideation
    - Prisoners or other detained individuals.
    - Adults unable to consent
    - Pregnant people.

Randomization

- Random assigned to CBT vs TAU group using randomization software

Patient visits

- Patients will be seen in clinic at weeks 0, 8 and 24. Patients will be seen either in person or via telehealth. Consent will be obtained at the initial clinic visit either online via Recap or by paper. Optional microbiome analysis samples will be self-collected by patients at weeks 0 and 8 (and possibly 24) and returned by mail or in person. Stool collection kits will be given or mailed after consent, and CBT patients instructed to begin use of the app only after the first stool collection. The physician assessment will include a safety assessment for suicidal ideation.

Compensation

- Patients enrolled in the trial will receive a total of [redacted] each upon completion of the study. A [redacted] will be given at week 8 and week 24.

Interventions

1. Zemedy application

a. A mobile application that enables the digital delivery of a CBT program to people with IBS. Zemedy integrates the 8-week CBT program with other in-app features – such as educational modules and health trackers, to provide an end-to-end IBS management tool. The delivery of the CBT program in itself is guided by a chatbot persona, Elle, that mimics the conversation lead by a healthcare professional in a clinical therapy setting. Educational modules on the Zemedy app range from topics on IBS causes and symptoms, to topics on relevant exercise and diet regimens. Health trackers on the Zemedy app can be used to record flare-ups, mood, and lifestyle information, allowing data to drive the extraction of meaningful patterns in IBS symptom presentation. Therefore, the Zemedy app grants IBS patients the option of and access to invaluable treatment streams.

   Patients will be guided on how to onboard the app after randomization.

Outcome assessment

- Assess outcomes at weeks 8 and 24, after randomization by randomization software

Table 1: Collection of Questionnaire Data

Questionnaire	**Week 0** (Day 0)	**Week 4** (Day 28)	**Week 8** (Day 56)	**Week 24** (Day 168)
Demographic information	x			
Prior IBS Medication Usage	x			
Current medication usage	x	x	x	
IBS-SSS	x	x	x	x
PSQ	x			x
WSAS	x			x
SGA	x			x
HADS	x		x	x
WPAI	x		x	x

Power

We estimate that with an initial sample size of 22 participants per intervention group and 22 per control group, we will have 80% power (alpha 0.05) to detect the minimal clinically important difference on the IBS-SSS. We expect a minimum reduction in score

of 50 points, which is considered to be a considerable improvement.[ix] In order to account for patient withdrawal from the trial we aim to enroll 30 patients in each study group.

Statistical evaluation

The statistical analyses will be done in cooperation with a statistician. The analyses will compare scores in each evaluation point between evaluation points between the intervention and the control group. Outcomes will be assessed at weeks 8 and 24 of the study. Analyses will be conducted on the full sample (intent to treat analysis).

Roles and resourcing of the study

Principal Investigators (PI) Irene Sonu, MD and Linda Nguyen, MD will be responsible for the oversight of the study, and are responsible for approving all candidates to become study participants. Both PIs are responsible for making sure that the study is conducted in an ethically sound manner as well as is safe for the participating patients.

Ethical considerations

Completing the questionnaires, taking part in the digital program, being in the control group, and all other time spent related to the study are additional efforts to the treatment the subjects would otherwise receive. In our view, the burden of taking part in the study is moderate for the participant. They are advised to contact the study PIs at any point if any questions or adverse effects arise. An interim safety analysis will be performed under consultation with the team gastroenterology psychologist.

All participating individuals will sign an informed consent to take part in the study and they will have an appropriate amount of time to familiarize themselves with the study before making the decision to participate. The study and all related activities such as extra phone consultation are completely free of charge for the participants. The results are confidential and will be kept in a safe and encrypted storage within the Redcap system (more information in the Data collection chapter). The statistical analyses will be performed without any personal identification information by assigning anonymous identification codes to all subjects.

Data collection

All captured study data and personal information (such as the participant's name, phone number, address and any free-text entered by the participants) will be stored in the Redcap system. It will be blinded from any analysis or data extraction. Patient identifiers and contact information will only be available to the study investigator, study therapist or any support staff working directly with patients that need this information for logistical or patient support purposes. All data used for reporting or publications will be anonymized.

All Zemedy related data (such as exercises related data or patient nick name) will be stored in the Zemedy application system. The Zemedy application system is not collecting or maintaining personal identifiable information and is thus not a patient registry.

Data to be collected include age, gender, comorbidities, medications (prescription and over the counter) and diagnostic testing performed (bloodwork, procedures)

Quality assurance

All data captured in the study will be in electronic format and stored in the Redcap system and/or in the Zemedy Program system. All patient identifiable information and data will be stored in the Redcap system which is a safe server-system with appropriate data protection, privacy and information security features.

Adverse experience reporting

Any adverse experiences with the Zemedy Program will be monitored during the study by the study investigators. PIs will consult with the team's Gastroentrology psychologist.

Human subjects

Ethical committee review and informed consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB committee responsible for oversight of the study. A consent form will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, or legal guardian, and this fact will be documented in the subject's record.

Confidentiality

All captured data will be identified only by the Study Identification Number to maintain subject confidentiality. All captured data will be encrypted in the database. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the sponsor, or the sponsor's designee.

Study modification/discontinuation

The study may be modified or discontinued at any time by the IRB, the sponsor, as part of their duties to ensure that research subjects are protected.

Study completion

Patients who have completed all of the IBS-SSS at weeks 0, 4, 8, and 24 will be considered completers of the study.

SCHEDULE OF ASSESSMENTS				
Protocol Activity	**Week 0 Day 0***	**Week 4 Day 28***	**Week 8 Day 56***	**Week 24 Day 168***
Informed consent	X			
Inclusion/Exclusion Screening	X			
Randomization	X			
Zemedy onboarding (if CBT)	X			
Physician Visit	X		X	X
Demographic Information	X			
Current Medications	X	X	X	
Fecal Sampling/Microbiome (opt-in)	X		X	X**
IBS-SSS	X	X	X	X
PSQ	X			X
WSAS	X			X
SGA	X			X
HADS	X		X	X
WPAI	X		X	X
Compensation			X	X

**The study window is six days, + / - 3 days from the noted day.*

***Sample collection contingent on PI judgment.*

Amendment Summary

Amendment 1 (Protocol Version 2)

- Addition of Sean Spencer, MD as sub-investigator
- Addition of fecal sampling (weeks 0, 8, and possibly 24) and microbiome analysis
    - Optional; patient must be willing and able to provide stool sample
    - Stool kits will be given or mailed after consent
- Adjustment to exclusion criteria
    - Current or past diagnosis of a major mental illness such as schizophrenia, bipolar disorder, personality disorder or substance abuse
    - Prisoners or other detained individuals.
    - Adults unable to consent
    - [Pregnant] "people"

Amendment 2 (Protocol Version 3)

- Correction of scheduling typos in secondary endpoint section
- Addition of HADS assessment to Week 8 visit in the schedule of assessments
- Adjustment to HADS abnormal threshold (>15 instead of >11)
- Adjustment to exclusion criteria
    - Removal of
        - Severe anxiety or depression assessed by the HADS scale
    - Addition of
        - Psychiatric hospitalization within 10 years
        - Active (within the past 3 months) suicidal ideation
- Addition of safety assessment for suicidal ideation to Physician's Visit
- Addition of gastroenterology psychologist consult
    - for adverse events
    - for interim safety analysis

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