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Acceptability and Efficacy of the Zemedy App versus a Relaxation Training and Meditation App for IBS: Protocol for a randomized controlled trial

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Acceptability and Efficacy of the Zemedy App versus a Relaxation Training and Meditation App for IBS: Protocol for a randomized controlled trial

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ABSTRACT

Introduction: Irritable Bowel Syndrome (IBS) is a chronic gastrointestinal (GI) disorder, characterized primarily by abnormal centralized pain processing and altered bowel habits. IBS has high rates of psychiatric comorbidity, and impairs health-related quality of life (HRQL). Cognitive Behavioral Therapy (CBT) is an effective treatment for IBS, but access to this treatment remains low due to high cost and lack of clinicians able to provide GI-specific CBT. Our proposed solution is a CBT-based smartphone app, Zemedy.

Methods and Analysis: The RCT for Version 1.0 of the Zemedy app resulted in reduced IBS symptom severity and improving HRQL. However, users showed only modest engagement. Version 2.0 is designed to address engagement by condensing the modules, improving flow, and adding entertaining animations. The RCT for Version 2.0 utilizes an education and relaxation training active control sham app meant to simulate treatment-as-usual. After completing baseline questionnaires, participants are allocated to either the immediate treatment (Zemedy) or to the active control condition. After 8 weeks, both groups will be surveyed again, and the active control group will be given access to Zemedy. After another 8 weeks, the participants who crossed over to the Zemedy app will be surveyed once more. Follow-up questionnaires will be administered at 3, 6, and 12 months post-treatment. Analysis will include intent-to-treat between-groups comparisons, controlling for baseline symptom severity, as well as moderation and mediation analyses.. We hypothesize that the Zemedy app will outperform the active control app in reducing IBS symptom severity and improving HRQL.

Ethics and Dissemination: This study will provide essential information on the efficacy and acceptability of an app-based CBT treatment for IBS. The data gathered may help establish the Zemedy app as an empirically supported intervention for IBS and will assist funding bodies in deciding whether to invest in its further development and dissemination.

Trial registration number: NCT04665271 (https://clinicaltrials.gov/ct2/show/NCT04665271)

Article Summary:

Strengths and limitations of this study.

- This study will provide essential efficacy and feasibility data regarding the use of a CBT-based self-help app for the treatment of IBS.
- The study design includes an active control condition, which is more robust than the waitlist control used in the RCT for Zemedy 1.0.
- This study does not consider the application of other CBT treatment mechanisms, such as in-person or group-based therapy.

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- Inclusion criteria do not include physician confirmation of diagnosis; however, users of self-help apps are not required to provide proof of diagnosis.

Key Words: digital health; irritable bowel syndrome; cognitive behavioral therapy; CBT; efficacy; mHealth; self-management; IBS; randomized controlled trial; app

BACKGROUND

Irritable Bowel Syndrome (IBS) is a chronic disorder of central-enteric (gut-brain) interaction. It is defined by recurrent abdominal pain that occurs at least one day per week in the past three months, that is associated with two or more of the following: is related to defecation and/or is associated with changes in the frequency and/or form of bowel movements (i.e., characterized by constipation, diarrhea, or an alternating mix of the two). It is highly prevalent (up to 6-7% of the population in the US)[1]. Many studies have demonstrated that IBS has high rates of psychiatric comorbidity (up to 90% in treatment seeking patients)[2,3], and causes social and occupational impairment[4]. Beyond the core symptoms of abdominal pain and altered bowel habits, individuals with IBS suffer from a host of related difficulties that substantially impair health-related quality of life and functioning. Patients with IBS often experience visceral hypersensitivity, a phenomenon in which people feel normal gut sensations that most people would be unaware of, and experience many of those sensations as more painful than healthy controls[5]. Anxiety and visceral hypersensitivity are highly correlated[6]. Anxiety and hypervigilance related to the sensations exacerbates the hypersensitivity[7].

Illness-related anxiety is high among IBS patients, and is a better predictor of impairment in quality of life than actual symptom severity[8]. A major component of this anxiety is "catastrophizing," in which individuals envision the worst possible outcome of their GI symptoms and in turn develop maladaptive coping strategies[4]. Catastrophizing is highly correlated with impairment in health related quality of life in IBS patients[9]. Because of their catastrophizing, many individuals with IBS engage in significant avoidance behavior that can easily meet criteria for agoraphobia[10].

Over the past two decades, cognitive behavioral therapy (CBT) has repeatedly proven to be an efficacious treatment for individuals suffering from IBS[11, 12]. Specifically, there is empirical support that CBT reduces GI symptom severity and impairment in quality of life[13, 14]. CBT treatments typically include components of psychoeducation about the brain-gut axis, mindfulness and relaxation training [15], reducing automatic negative thoughts related to GI catastrophizing[16], exposure therapy to feared and avoided sensations and situations[17] and reducing visceral hypersensitivity[13]. One meta-analysis of twenty psychological treatments for IBS found that GI-cognition change and gastrointestinal specific anxiety were important mediators in improving GI-related quality of life and GI-symptom severity[18].

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While CBT is a promising treatment, access to IBS-specific CBT remains low for patients. There are relatively few clinicians competent in delivering GI-specific CBT[4]. Additionally, the cost of treatment looms high; individuals often lack insurance coverage for psychotherapy and must pay out of pocket, which can be burdensome, especially given the hundreds of dollars their IBS likely already costs them [19]. It is important to develop a less expensive, more broadly available alternative mode of treatment delivery. Many groups have tested variants of CBT for IBS with limited or distant therapist involvement (e.g., via email)[20, 16, 21] and typically obtain robust effect sizes. Studies typically find that web-based and telephone-based CBT improved IBS more than treatment as usual (e.g.[22, 23]). Several treatment manuals and self-help books are available that detail the CBT treatment approach, and one[24] was found to be efficacious as a stand-alone treatment in a randomized controlled trial[25].

In today's digitized world, the mobile health (mHealth) industry is growing. Thousands of mobile applications (apps) exist to improve health across the spectrum. Mobile apps have multiple advantages, including low cost, privacy, accessibility and convenience for the user. The Zemedy app was developed to deliver CBT for IBS directly to users with no direct therapist or clinician interaction required. Version 1.0 of the app was tested in a randomized controlled trial against a wait-list control[26]. Primary outcome measures included both GI symptom severity and HRQL. Secondary outcome measures included GI specific catastrophizing, visceral anxiety, fear of food, and depression. App users showed significant improvement on both primary and secondary outcome measures. Gains were generally maintained at 3 months post-treatment. Moreover, the impact of treatment on HRQL was mediated by reductions in catastrophizing and visceral anxiety.

Despite these promising results, there were several significant limitations to the app itself and to the study. Uptake of the app was modest, with very few users availing themselves of even half of the app's modules. Although users rated the informational content of the app highly, they were less satisfied with the structure and flow of the app and its overall usability. In addition to these concerns, the study design utilized a waitlist control, which is not a particularly robust control, given the high placebo response rate in IBS[27].

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The current study is designed to address all of these concerns. Version 2.0 of the Zemedy App was modified to be significantly more engaging. It has better flow, fewer modules, and more entertaining animations and patient stories. Our hope is that the user uptake and user ratings will be significantly improved compared to Zemedy 1.0. Second, this study utilizes a stronger control group, and will compare Zemedy to a sham app consisting of publicly available educational information (e.g. National Health Service treatment guidelines for IBS, and information from various online sources such as WebMD and the Mayo Clinic website) and links to a number of different relaxation videos. The purpose of this study is to test the acceptability and efficacy of an updated digital health app (Zemedy 2.0) that provides CBT-based treatment for IBS. We hypothesize that Zemedy will prove to be more effective in treating IBS symptom severity and improving quality of life for IBS-sufferers than the active control app.

METHODS

Novel App Description

Zemedy 2.0 is a smartphone application designed by Bold Health (a UK based company) in collaboration with the first author. The app treats irritable bowel syndrome (IBS) through modules guided by the principles of cognitive behavioral therapy specifically for IBS, as well as some gut-based hypnotherapy and psychoeducation on IBS. A chatbot guides users through the six modules of the app.

Module 1, called “Living with IBS and how CBT can help" is devoted to psychoeducation about IBS and why CBT is an effective treatment. It includes engaging animations illustrating the connection between the central and enteric nervous system and why stress can exacerbate GI symptoms, as well as animated “patients” who tell their stories of success with CBT.

Module 2, “Activity and IBS,” focuses on exercise and how physical activity can help manage the symptoms of IBS. It includes motivational interviewing style exercises to help users overcome reluctance to exercise. It also includes links to instructional videos for specific yoga poses, and more animated patient stories to encourage physical activity and model successful management of IBS with exercise.

Module 3, “Managing Thoughts and Worries,” focuses on the basic cognitive model of stress management, including identifying negative automatic thoughts and catastrophic beliefs and using cognitive restructuring to view situations more objectively and realistically. It also applies the cognitive model to specific thoughts and fears about GI symptoms that are common to many patients with IBS.

Module 4, “Managing Avoidance,” focuses on exposure therapy and behavioral experiments to help the user reduce maladaptive avoidance and get back to living their life fully. Patients are encouraged to set up graded exposure exercises for themselves involving any situations (or sensations) that they have been avoiding, including transportation, public venues, and situations involving food and eating.

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Module 5, "Diet & IBS," focuses on the connection between diet and GI symptoms, but strongly encourages users to reduce their fear of food and start eating a more healthful, balanced and less restrictive diet.

Module 6, "Putting it All Together," is the final module of the app, which summarizes the content of the previous 5 modules and explains how to use this information in daily life to manage GI sensations and help prevent relapse.

Users are encouraged to apply these strategies to their daily lives even after they have finished going through the app itself. Participants are meant to complete one module per week, leaving the last two weeks of the protocol to continue working on the skills they learned.

In addition to the six modules that serve as the core of the CBT-guided treatment within the Zemedy app, there are also "tools," which are mainly CBT-based, but also involve mindfulness, attention training and relaxation exercises that users can utilize at any time. Some of these tools are unlocked as users progress through the core modules. Additionally, the app includes a "flare module" which users can access at any point during this intervention to address immediate GI discomfort or anxiety.

Education and Relaxation Training App Description

The education and relaxation training app is a rudimentary app meant to act similarly to treatment as usual. This app consists of 6 modules, of which participants are meant to complete one per week, leaving the last 2 weeks to continue working on the lifestyle changes that some of the modules encourage.

Module 1 includes information from publicly available websites (e.g. Mayo Clinic, Cleveland Clinic, UK NHS and NICE Guidelines) about the presumed etiology of IBS and what symptoms are necessary for a diagnosis. It also discusses the various IBS subtypes (IBS-C, IBS-D, and IBS-M).

Module 2 contains a list of possible over the counter medications and supplements to address IBS symptoms, such as laxatives, anti-diarrheals, peppermint oil, and probiotics.

Module 3 discusses the impact of lifestyle on IBS. For example, it explains that stress can make IBS worse (without elucidating the underlying mechanisms), and contains links to relaxation training videos for participants to use.

Modules 4 and 5 both discuss diet. Module 4 encourages participants to keep a food diary to see which foods potentially trigger flare-ups in their IBS. Module 5 explains some potential dietary changes that participants can make, such as following the low FODMAP diet and restricting caffeine and alcohol intake. The low FODMAP diet is an evidence-based intervention for IBS and is a common recommendation given to patients with IBS by both nutritionists and gastroenterologists[28]. Food diaries and exclusion diets are actually contraindicated in CBT for IBS, but are the most common approaches recommended by gastroenterologists[29].

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Module 6 discusses the importance of exercise (again without actually elucidating the underlying biological mechanisms by which exercise can reduce IBS symptoms), and encourages logging exercise, without any attempt to include motivational interviewing interventions or to help users overcome reluctance to exercise. In sum, the sham app includes standard, treatment-as-usual information and advice that patients with IBS would often be exposed to in other formats, but does not include any of the specific education or treatment strategies that the CBT approach utilizes and that are central to the Zemedy app.

Study Design

This study is a randomized, cross-over trial with an active control group. The study is running from March 1, 2021 to an estimated completion date of May 28, 2023.

Accrual: Participants will be recruited for the trial through IBS specific social media sites, as well as clinical trial listings at clinicaltrials.gov and iffgd.org (the International Foundation for Gastrointestinal Disorders). Most participants came to the original Zemedy study through Facebook, Twitter, and Reddit, so we anticipate that most of our participants for this second study will come from those sites as well. All participants complete informed consent online prior to completing baseline questionnaires. All data are collected online using Qualtrics secure servers and are stored de-identified.

Inclusion and Exclusion Criteria: Inclusion criteria consists of being 18 years of age or older, and participant report of having been previously diagnosed by a physician with IBS or meeting Rome IV criteria[1] by self-report. If participants report having been diagnosed with IBS by a physician, but do not currently meet strict Rome IV diagnostic criteria they are still allowed in the trial. Many refractory IBS patients were diagnosed under the old Rome III criteria and the only criterion they fail to meet currently is frequency of abdominal pain.

Exclusion criteria consists of having another comorbid GI disorder, such as celiac disease or an inflammatory bowel disease. It also includes severe depression and/or suicidal ideation - defined as a positive endorsement at the level of 2 or 3 on the suicide item (item 9) of the Beck Depression Inventory. If a potential participant meets exclusion criteria on the basis of severe depression, the PI (a licensed clinical psychologist) contacts them to conduct a risk assessment and offers referral (if appropriate) to local resources. They are also given immediate access to the Zemedy app, if they are interested, but are not enrolled in the trial.

Power Analysis: Our goal is to recruit 300 participants. Most internet trials have an attrition rate approaching 50%[30], which would leave us with 150 participants in the study total (75 per group). CBT for IBS typically yields large effect sizes, and the effect size of Zemedy 1.0 on the primary outcome

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measure of HRQL was $d = 1.25$. Assuming a modest effect of the control app of approximately $d = .30$, then a final N of 150 will give us 90% power at $p < .05$ to detect a difference between groups.

Randomization: Participants who meet the inclusion criteria will be allocated to one of two conditions using the coin toss feature of random.org. The allocation sequence is concealed to participants until they are enrolled and assigned to the intervention.

Blinding: Because of the nature of the trial (immediate treatment versus active control group), neither participants nor research coordinators are blinded to condition. All outcome data is self-report, thus, blinding of evaluators is neither possible nor necessary.

Intervention and Assessments: Those in the immediate treatment group will be given the link to access the Zemedy app and encouraged to download it and begin working through the modules immediately. The active control group will be given access to the education and relaxation training app, and will be given access to the Zemedy app eight weeks after they are informed of their group assignment. Four weeks after baseline, participants in both groups will be emailed to encourage them to continue using their respective app, and to let them know that they would be receiving the follow-up questionnaires in 4 weeks.

Eight weeks after completing the baseline questionnaires, all participants will be emailed with a second questionnaire battery which includes all the same measures as at baseline. Participants in the immediate treatment group will also complete the Mobile Application Rating Scale (uMars). All participants who complete 8-week questionnaires will be compensated $20 in Amazon credit. Those in the active control condition will then be crossed over to the Zemedy app.

After having access to the Zemedy app for eight weeks, participants in the active-control group will be emailed a third battery of questionnaires which is identical to the battery received by the treatment group after eight weeks of app usage - it includes the same measures as the baseline battery and the Mobile Application Rating Scale (uMars). They will be compensated with a further $20 gift credit upon completion of the post-treatment questionnaires.

See Figure 1 for full Consort diagram.

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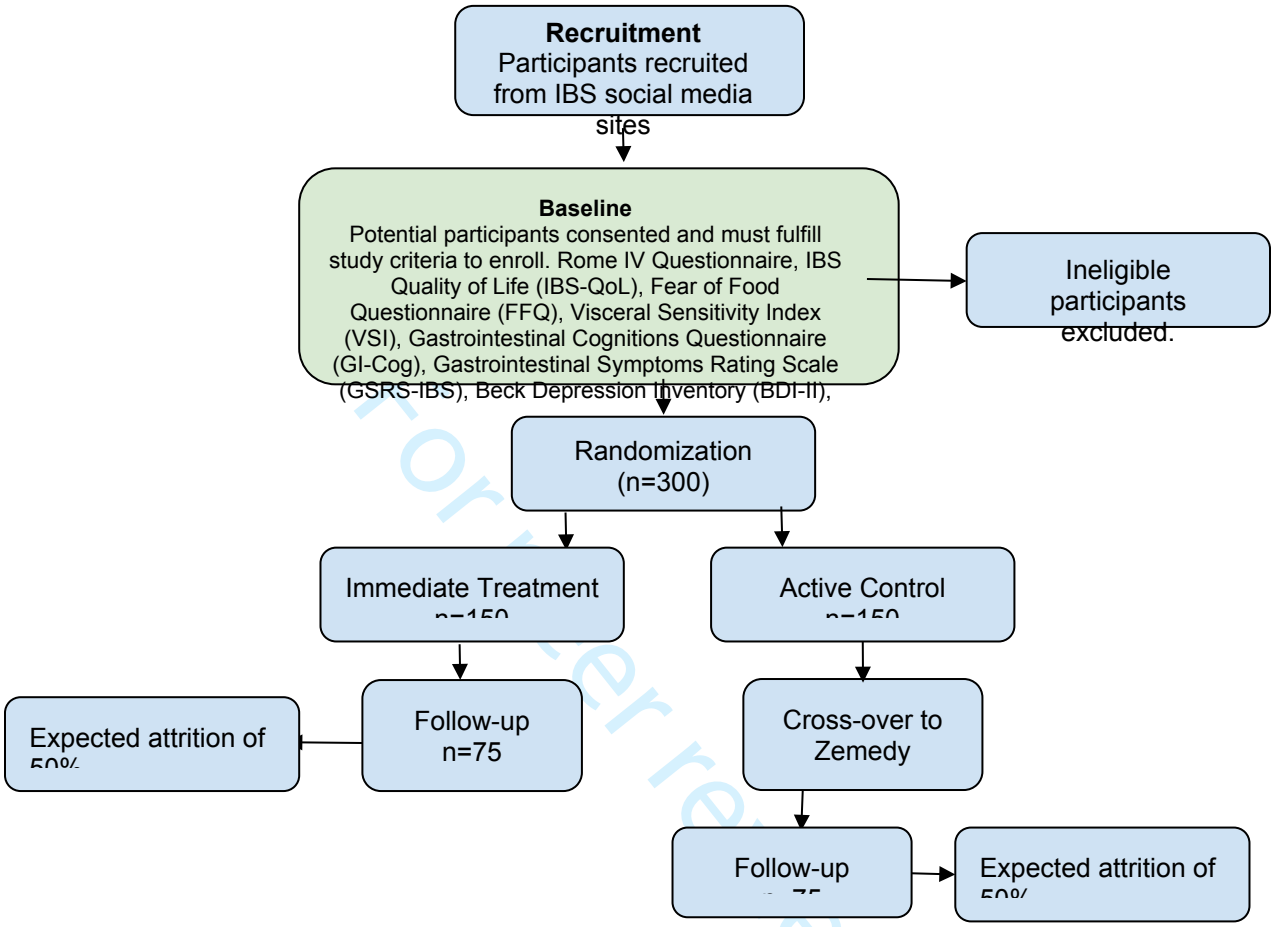

Measures

Primary Outcome Measures.

IBS quality of life (IBS–QoL).

The IBS–QOL[31] is a 34 item, self-report measure specific to IBS designed to assess the impact of IBS on quality of life The IBS–QOL has high internal consistency (Cronbach's α= .95), high reproducibility (ICC = .86) and good construct validity.

Gastrointestinal Symptom Rating Scale–IBS (GSRS–IBS).

The GSRS-IBS contains 13 self-report items rated on a 6-point Likert scale[32] ranging from 1 (no discomfort at all) to 7 (very severe discomfort). Total scores range from 13 to 91. The GSRS-IBS has 5 sub- scales, including abdominal pain, bloating, constipation, diarrhea, and satiety. Each dimension has demonstrated high internal consistency of Cronbach's alpha ranging from .74 (pain) to .85 (satiety). Furthermore, the GSRS- IBS has demonstrated both high test–retest reliability, with intra-class correlations among the factors ranging from .55 (pain) to .70 (bloating), as well as high construct

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validity[32]. The GSRS has been used as a primary outcome measure in a number of recent randomized controlled trials of IBS treatments (e.g.[20]) and the Rome Foundation reports that it is shorter and more user friendly than the IBS Severity Scoring System (IBS-SSS)[33].

Secondary Measures.

Modified Rome IV Questionnaire.

We used a questionnaire to determine whether participants met current Rome IV diagnostic criteria for IBS. Our questionnaire was based on the Rome IV IBS-specific Questionnaire, which is a validated self-report scale that covers the diagnostic criteria for IBS. It has been found to have acceptable sensitivity and high specificity as well as good test–retest reliability[1]. Our measure is shorter (10 items) and uses slightly different numeric scales, but still covers all the primary diagnostic criteria for IBS.

Fear of Food Questionnaire (FFQ).

The FFQ[34]is an 18-item, self-report questionnaire that measures fear, avoidance of food, and life interference and loss of pleasure from eating. Items are rated on a Likert scale ranging from 0 (not at all) to 5 (absolutely). It has excellent internal consistency reliability with Chronbach's $\alpha = 0.96$ and strong two-week test-retest reliability at $r = 0.93$, $p < .001$[34]. It also shows good criterion and known-groups validity.

Visceral sensitivity index (VSI).

The VSI[33, 7] is a unidimensional, 15-item scale that measures gastrointestinal symptom-specific anxiety. Items are rated on a Likert scale ranging from 0 (strongly disagree) to 5 (strongly agree). It has high internal consistency ($\alpha = 0.93$) and a mean inter-item correlation of 0.47[36, 37]. It has good criterion, construct, and predictive validity[7].

Gastrointestinal Cognitions Questionnaire (GI-Cog).

The GI-Cog consists of 16 self-report items that are rated on a 5-point Likert scale, ranging from 0 (Hardly) to 4 (Very much). Individual items are summed, and total scores range from 0 to 64. The questionnaire consists of three subscales, the pain/life interference subscale (e.g. ‘‘When I feel my GI symptoms acting up, I’m afraid the pain will be excruciating and intolerable’’), the social anxiety subscale (e.g. ‘‘If I have to get up and leave an event, meeting, or social gathering to go to the bathroom people will think there’s something wrong with me’’), and the disgust sensitivity subscale (e.g. ‘‘The thought of fecal incontinence is terrifying. If it happened, it would be awful’’). The GI-Cog has been shown to have excellent internal consistency (a = .92) and test-retest reliability (r = .87, p = .001)[35].

Beck Depression Inventory (BDI-II).

The BDI-II consists of 21 self-report items, each on a 4 point scale ranging from 0 to 3 (0 being not at all, and 3 meaning extreme), therefore scores can range from 0 to 63. It is scored by adding the

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severity ratings of each item. A score greater than 20 indicates moderate depression. It has been found to have good internal consistency and test retest reliability[38].

Mobile-Application Rating Scale (uMARS).

The uMARS is an end-user version of the Mobile Application Rating Scale which is a 26-item measure including 4 objective quality subscales (engagement, functionality, aesthetics, and information quality), 1 subjective quality subscale, a 6-item perceived impact subscale, and a space to provide feedback[39]. The uMARS scale is used to obtain user feedback on the quality of mobile apps during the development and testing process. The uMars has been shown to have excellent internal consistency (Cronbach's α = .90), and high internal consistencies of its subscales (engagement α= .80; functionality α= .70; aesthetics α= .71; information α= .78; and satisfaction α= .78)[40]. Test-Retest Reliability of the uMARS scale was found to be good with an average intraclass correlation coefficient (ICC) of 0.68[40].

Data Analysis

Univariate general linear models in SPSS V25 will be used to examine between group effects at post treatment (8 weeks), controlling for baseline levels of the dependent variable. Paired sample t-tests will be used to examine within group change over their treatment phase for each group and maintenance of gains from post treatment to 3 months follow-up. The robustness of these analyses will be examined in an intent-to-treat sensitivity analysis by using multiple imputation. Regression models will then be fitted as in the primary analysis, and pooled estimates of the treatment effect calculated. Three sets of imputed datasets will be created, one for each follow-up data point, baseline measures included in each.

Change in visceral anxiety, catastrophizing and fear of food (calculated as change from baseline to 8 weeks) will be explored as possible mediators of GI symptoms and quality of life at 8 weeks using regression analysis with estimates of indirect effects will be calculated using a percentile bootstrap estimation approach with 5000 samples implemented with the PROCESS macro Version 3.5[41]. Both direct and indirect effects will be reported. The direct effect quantifies the estimated difference in the dependent variable (GI symptoms or quality of life) between two cases that are equal on the mediator but differ by one unit on treatment assignment, i.e., intervention vs waitlist group. The indirect effect quantifies how much two cases, one assigned to immediate treatment, the other to waitlist, are estimated to differ on the dependent variables (GI symptoms or quality of life) as a result of treatments' influence on the mediator, which in turn influences the dependent variable. Two sets of models will be fitted, the first testing the mediator variables separately with simple mediator models, the second fitting a parallel mediator model where the three mediators will be tested simultaneously. The baseline level of the dependent variable will be included as a covariate in all mediation models.

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Patient and public involvement statement

There was no direct patient or public involvement in the design of this research. However, the first author has an active clinical practice in which they work with many IBS patients, and patient feedback and clinical experience informs the development of Zemedy. There was also patient feedback from the RCT of Version 1.0 of Zemedy that guided many of the updates to the app to make it more engaging and user friendly.

ETHICS AND DISSEMINATION

Participants who endorse suicidal ideation will be contacted by the PI who will offer a risk assessment and referrals to local in person providers. The active control app recommends certain approaches (such as restrictive diets) that are contraindicated in CBT, but are widely used management strategies for IBS. After the completion of this study, we hope and expect to find that Zemedy outperforms the educational and relaxation app in improving HRQL and GI symptom severity. We also hope to see that Zemedy 2.0 is rated more highly than Version 1.0 in user engagement, functionality, aesthetics, and information quality. We plan to submit the resulting paper to a high impact peer reviewed journal. De-identified data will be made available in a data repository.

Author Contributions

Melissa Hunt: Conceptualization, Methodology, Designing Intervention, Resources, Writing - Original Draft and Revisions, Supervision. Anika Dalvie: Conceptualization, Methodology, Designing Control Intervention, Writing, Project Administration, Software, Investigation, Participant Recruitment, Data Curation. Simay Ipek: Methodology, Designing Control Intervention, Project Administration, Software, Investigation, Data Curation. Ben Wasman: Designing Control Intervention, Participant Recruitment.

Ethics approval Institutional review board of the University of Pennsylvania.

Funding Statement:

This work was supported by Bold Health. Bold Health also designed and provide tech support to the app itself, and provide some data regarding compliance and utilization of the app.

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Competing Interests Statement:

Melissa Hunt serves as a scientific consultant to Bold Health and accepts a modest (less than $5,000 per annum) consulting fee. She has no ownership interest in the company. None of the other authors have any competing interests to declare.

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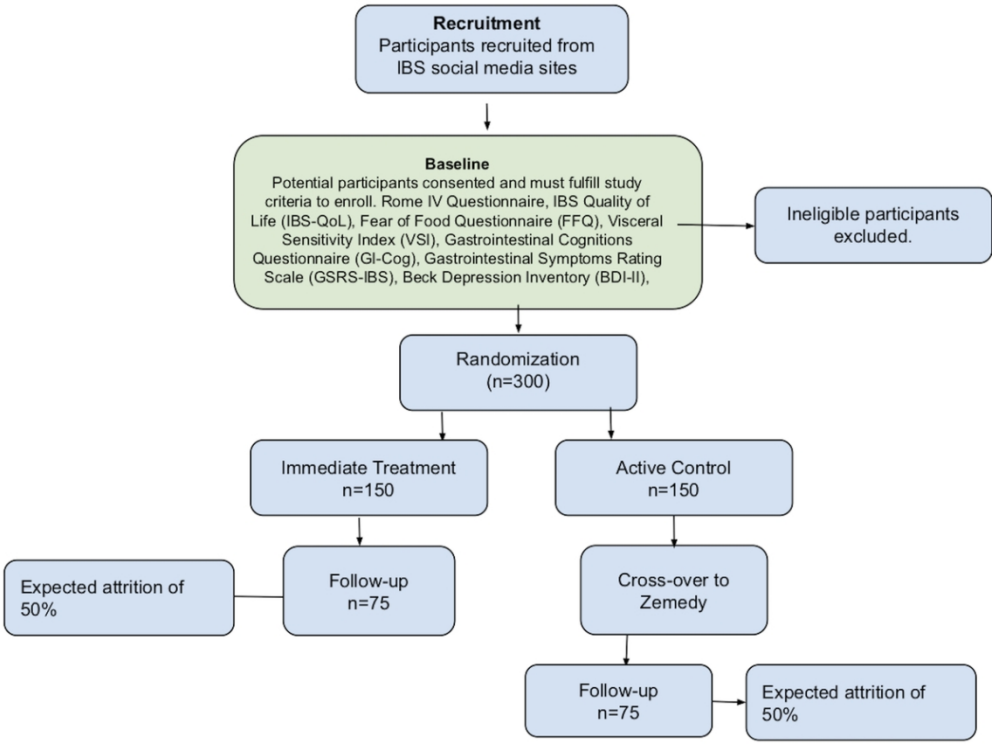

Figure 1 - Consort Diagram

50x38mm (600 x 600 DPI)

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	na
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	na

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	na

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	na
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	na
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	8

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	na
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	na
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	na

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		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	na
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	na

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	na
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	na
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	na
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	na

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Acceptability and Efficacy of the Zemedy App versus a Relaxation Training and Meditation App for IBS: Protocol for a randomized controlled trial

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Mental health
Keywords:	Functional bowel disorders < GASTROENTEROLOGY, MENTAL HEALTH, Adult psychiatry < PSYCHIATRY, Anxiety disorders < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY

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Acceptability and Efficacy of the Zemedy App versus a Relaxation Training and Meditation App for IBS: Protocol for a randomized controlled trial

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ABSTRACT

Introduction: Irritable Bowel Syndrome (IBS) has high rates of psychiatric comorbidity, and impairs health-related quality of life (HRQL). Cognitive Behavioral Therapy (CBT) is an effective treatment for IBS, but access to treatment remains low. Our proposed solution is a CBT-based smartphone app, Zemedy.

Methods and Analysis: This RCT of Version 2.0 of the Zemedy app utilizes an education and relaxation training active control app meant to simulate treatment-as-usual. Participants complete baseline questionnaires and consent at screening, and are then allocated to either the immediate treatment (Zemedy) or the active control. Treatment lasts 8 weeks, after which both groups complete the same battery used at baseline, and the control group is crossed-over to Zemedy. After another 8 weeks, the crossed-over participants will be surveyed once more. Follow-up questionnaires are administered at 3, 6, and 12 months post-treatment. Primary outcomes include GI symptom severity and HRQL. Clinically significant change will be defined as post-treatment scores falling within 2 SD of the healthy mean. Analysis will include intent-to-treat between-groups comparisons, controlling for baseline symptom severity, as well as moderation and mediation analyses. We hypothesize that the Zemedy app will outperform the active control app in reducing IBS symptom severity and improving HRQL.

Ethics and Dissemination: This study was approved by the Institutional Review Board at the University of Pennsylvania. Results will provide essential information on the efficacy and acceptability of an app-based CBT treatment for IBS. The data gathered may help establish the Zemedy app as an empirically supported intervention for IBS and will assist funding bodies in deciding whether to invest in its further development and dissemination. The results will be disseminated to patients with IBS via the media and the company website, to healthcare professionals via professional trainings (e.g. webinars and grand rounds talks) and to researchers via conferences and publications. Trial registration number: NCT04665271 (https://clinicaltrials.gov/ct2/show/NCT04665271)

Article Summary:

Strengths and limitations of this study.

- The study is a randomized, controlled trial with high ecological validity.

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- The study design includes an active control condition, which is more robust than the waitlist control used in the RCT for Zemedy 1.0, and is an important strength, since IBS has a relatively high placebo response rate.
- This study does not control for medication use or other therapeutic interventions patients may pursue. .
- Inclusion criteria do not include physician confirmation of diagnosis; however, users of self-help apps are not required to provide proof of diagnosis.

Key Words: digital health; irritable bowel syndrome; cognitive behavioral therapy; CBT; efficacy; mHealth; self-management; IBS; randomized controlled trial; app

BACKGROUND

Irritable Bowel Syndrome (IBS) is a chronic disorder of central-enteric (gut-brain) interaction. It is defined by recurrent abdominal pain that occurs at least one day per week in the past three months, that is associated with two or more of the following: is related to defecation and/or is associated with changes in the frequency and/or form of bowel movements (i.e., characterized by constipation, diarrhea, or an alternating mix of the two). IBS that meets strict Rome IV diagnostic criteria is quite prevalent (up to 6-7% of the population in the US)[1] but self-reported IBS that does not meet strict criteria is highly prevalent (17-18%) and results in equal disability, HRQL impairment, health care utilization and even greater absence from work[2]. Many studies have demonstrated that IBS has high rates of psychiatric comorbidity (up to 90% in treatment seeking patients)[3,4], and causes social and occupational impairment[5]. Beyond the core symptoms of abdominal pain and altered bowel habits, individuals with IBS suffer from a host of related difficulties that substantially impair health-related quality of life and functioning. Patients with IBS often experience visceral hypersensitivity, a phenomenon in which people feel normal gut sensations that most people would be unaware of, and experience many of those sensations as more painful than healthy controls[6]. Anxiety and visceral hypersensitivity are highly correlated[7]. Anxiety and hypervigilance related to the sensations exacerbates the hypersensitivity[8].

Illness-related anxiety is high among IBS patients, and is a better predictor of impairment in quality of life than actual symptom severity[9]. A major component of this anxiety is "catastrophizing," in which individuals envision the worst possible outcome of their GI symptoms and in turn develop maladaptive coping strategies[5]. Catastrophizing is highly correlated with impairment in health related quality of life in IBS patients[10]. Because of their catastrophizing, many individuals with IBS engage in significant avoidance behavior that can easily meet criteria for agoraphobia[11].

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Over the past two decades, cognitive behavioral therapy (CBT) has repeatedly proven to be an efficacious treatment for individuals suffering from IBS[12 , 13]. Specifically, there is empirical support that CBT reduces GI symptom severity and impairment in quality of life[14 , 15]. CBT treatments typically include components of psychoeducation about the brain-gut axis, mindfulness and relaxation training [16], reducing automatic negative thoughts related to GI catastrophizing[17], exposure therapy to feared and avoided sensations and situations[18] and reducing visceral hypersensitivity[14]. One meta-analysis of twenty psychological treatments for IBS found that GI-cognition change and gastrointestinal specific anxiety were important mediators in improving GI-related quality of life and GI-symptom severity[19].

While CBT is a promising treatment, access to IBS-specific CBT remains low for patients. There are relatively few clinicians competent in delivering GI-specific CBT[5]. Additionally, the cost of treatment looms high; individuals often lack insurance coverage for psychotherapy and must pay out of pocket, which can be burdensome, especially given the hundreds of dollars their IBS likely already costs them [20]. It is important to develop a less expensive, more broadly available alternative mode of treatment delivery. Many groups have tested variants of CBT for IBS with limited or distant therapist involvement (e.g., via email)[21 , 17 , 22] and typically obtain robust effect sizes. Studies typically find that web-based and telephone-based CBT improved IBS more than treatment as usual (e.g.[23 , 24]). Several treatment manuals and self-help books are available that detail the CBT treatment approach, and one[25] was found to be efficacious as a stand-alone treatment in a randomized controlled trial[26].

In today's digitized world, the mobile health (mHealth) industry is growing. Thousands of mobile applications (apps) exist to improve health across the spectrum. Mobile apps have multiple advantages, including low cost, privacy, accessibility and convenience for the user. The Zemedy app was developed to deliver CBT for IBS directly to users with no direct therapist or clinician interaction required. Version 1.0 of the app was tested in a randomized controlled trial against a wait-list control[27]. Primary outcome measures included both GI symptom severity and HRQL. Secondary outcome measures included GI specific catastrophizing, visceral anxiety, fear of food, and depression. App users showed both statistically and clinically significant improvement on both primary and secondary outcome measures, yielding a number needed to treat (NNT) of 2. Gains were generally maintained at 3 months post-treatment. Moreover, the impact of treatment on HRQL was mediated by reductions in catastrophizing and visceral anxiety.

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Despite these promising results, there were several significant limitations to the app itself and to the study. Uptake of the app was modest, with very few users availing themselves of even half of the app's modules. Although users rated the informational content of the app highly, they were less satisfied with the structure and flow of the app and its overall usability. In addition to these concerns, the study design utilized a waitlist control, which is not a particularly robust control, given the high placebo response rate in IBS[28].

The current study is designed to address all of these concerns. Version 2.0 of the Zemedy App was modified to be significantly more engaging. It has better flow, fewer modules, and more entertaining animations and patient stories. Our hope is that the user uptake and user ratings will be significantly improved compared to Zemedy 1.0. Second, this study utilizes a stronger control group, and will compare Zemedy to a sham app consisting of publicly available educational information (e.g. National Health Service treatment guidelines for IBS, and information from various online sources such as WebMD and the Mayo Clinic website) and links to a number of different relaxation videos. The purpose of this study is to test the acceptability and efficacy of an updated digital health app (Zemedy 2.0) that provides CBT-based treatment for IBS. We hypothesize that Zemedy will prove to be more effective in treating IBS symptom severity and improving quality of life for IBS-sufferers than the active control app.

METHODS

Novel App Description

Zemedy 2.0 is a smartphone application designed by Bold Health (a UK based company) in collaboration with the first author. The app treats irritable bowel syndrome (IBS) through modules guided by the principles of cognitive behavioral therapy specifically for IBS, as well as some gut-based hypnotherapy and psychoeducation on IBS. A chatbot guides users through the six modules of the app and the app automatically tracks progress, but users work through the modules at their own pace..

Module 1, called "Living with IBS and how CBT can help" is devoted to psychoeducation about IBS and why CBT is an effective treatment. It includes engaging animations illustrating the connection between the central and enteric nervous system and why stress can exacerbate GI symptoms, as well as animated "patients" who tell their stories of success with CBT. Psychoeducation is crucial to get patients to "buy in" to psychosocial approaches to managing IBS.

Module 2, "Activity and IBS," focuses on exercise and how physical activity can help manage the symptoms of IBS. It includes motivational interviewing (MI) style exercises to help users overcome reluctance to exercise. MI reduces resistance to behavior change by validating people's concerns about the challenges of behavior change (e.g. exercise is effortful and uncomfortable), encouraging people to think about their values and goals, and about the costs and benefits of both engaging in a behavior and not

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engaging in a behavior. The module also includes links to instructional videos for specific yoga poses, and more animated patient stories to encourage physical activity and model successful management of IBS with exercise.

Module 3, "Managing Thoughts and Worries," focuses on the basic cognitive model of stress management, including identifying negative automatic thoughts and catastrophic beliefs and using cognitive restructuring to view situations more objectively and realistically. It also applies the cognitive model to specific thoughts and fears about GI symptoms that are common to many patients with IBS. These are basic cognitive therapy skills that are the central component of effective stress management.

Module 4, "Managing Avoidance," focuses on exposure therapy and behavioral experiments to help the user reduce maladaptive avoidance and get back to living their life fully. Patients are encouraged to set up graded exposure exercises for themselves involving any situations (or sensations) that they have been avoiding, including transportation, public venues, and situations involving food and eating. Exposure therapy and reductions in experiential avoidance are crucial components of every effective psychosocial intervention for IBS.

Module 5, "Diet & IBS," focuses on the connection between diet and GI symptoms, but strongly encourages users to reduce their fear of food and start eating a more healthful, balanced and less restrictive diet. Research has shown that fear of food contributes significantly to reductions in HRQL in IBS. The module encourages gradual reintroduction of avoided foods, but no explicit nutritional advice is given.

Module 6, "Putting it All Together," is the final module of the app, which summarizes the content of the previous 5 modules and explains how to use this information in daily life to manage GI sensations and help prevent relapse.

Users are encouraged to apply these strategies to their daily lives even after they have finished going through the app itself. Participants are meant to complete one module per week, leaving the last two weeks of the protocol to continue working on the skills they learned.

In addition to the six modules that serve as the core of the CBT-guided treatment within the Zemedy app, there are also "tools," which are mainly CBT-based, but also involve mindfulness, attention training and relaxation exercises that users can utilize at any time. Some of these tools are unlocked as users progress through the core modules. The ability to unlock new features is a standard approach to "gamifying" apps and is typically expected to enhance engagement. It is possible, however, that users will find this frustrating. We will seek user feedback on this issue at the end of the trial. Additionally, the app includes a "flare module" which users can access at any point during this intervention to address immediate GI discomfort or anxiety.

Education and Relaxation Training App Description

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The education and relaxation training app is a rudimentary app meant to act similarly to treatment as usual. This app consists of 6 modules, of which participants are meant to complete one per week, leaving the last 2 weeks to continue working on the lifestyle changes that some of the modules encourage.

Module 1 includes information from publicly available websites (e.g. Mayo Clinic, Cleveland Clinic, UK NHS and NICE Guidelines) about the presumed etiology of IBS and what symptoms are necessary for a diagnosis. It also discusses the various IBS subtypes (IBS-C, IBS-D, and IBS-M).

Module 2 contains a list of possible over the counter medications and supplements to address IBS symptoms, such as laxatives, anti-diarrheals, peppermint oil, and probiotics.

Module 3 discusses the impact of lifestyle on IBS. For example, it explains that stress can make IBS worse (without elucidating the underlying mechanisms), and contains links to relaxation training videos for participants to use.

Modules 4 and 5 both discuss diet. Module 4 encourages participants to keep a food diary to see which foods potentially trigger flare-ups in their IBS. Module 5 explains some potential dietary changes that participants can make, such as following the low FODMAP diet and restricting caffeine and alcohol intake. The low FODMAP diet is an evidence-based intervention for IBS and is a common recommendation given to patients with IBS by both nutritionists and gastroenterologists[29]. Food diaries and exclusion diets are actually contraindicated in CBT for IBS, but are the most common approaches recommended by gastroenterologists and are quite efficacious at reducing distressing GI symptoms [30]. A recent non-inferiority trial comparing a self-help CBT workbook to a self-help low FODMAP diet book found them to be equally efficacious in the short term at improving HRQL [Hunt, Rio, Dembik, Jileaeva, Wilkins & Reynolds, (unpublished manuscript). CBT versus the Low FODMAP Diet for IBS: A non-inferiority comparison of two self-help books].

Module 6 discusses the importance of exercise (again without actually elucidating the underlying biological mechanisms by which exercise can reduce IBS symptoms), and encourages logging exercise, without any attempt to include motivational interviewing interventions or to help users overcome reluctance to exercise. In sum, the sham app includes standard, treatment-as-usual information and advice that patients with IBS would often be exposed to in other formats, but does not include any of the specific education or treatment strategies that the CBT approach utilizes and that are central to the Zemedy app.

In sum, the control app contains a good deal of informative text and a number of links to engaging relaxation videos. IBS has a relatively high placebo response rate, and we hope the control app will be both credible and somewhat engaging.

Study Design

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This study is a randomized, superiority, non-blinded, cross-over trial with an active control group. The study is running from March 1, 2021 to an estimated completion date of May 28, 2023. Participants are recruited from the United States, and study personnel are based at the University of Pennsylvania's Department of Psychology but because both recruitment, assessment and the treatment itself are all remote, there is no physical location for the study.

Accrual: Participants will be recruited for the trial through IBS specific social media sites, as well as clinical trial listings at clinicaltrials.gov and iffgd.org (the International Foundation for Gastrointestinal Disorders). Most participants came to the original Zemedy study through Facebook, Twitter, and Reddit, so we anticipate that most of our participants for this second study will come from those sites as well. Notices and posts about the study on those sites include a link to a secure Qualtrics survey that contains the consent form and the baseline questionnaires.

Consent: All participants complete informed consent online prior to completing baseline questionnaires. The consent form explains the study, including information about random assignment and the compensation for completing study questionnaires at several follow-up time points.

Inclusion and Exclusion Criteria: Inclusion criteria consists of being 18 years of age or older, and participant self-report of having been previously diagnosed by a physician with IBS or meeting Rome IV criteria[1] by self-report on a standardized questionnaire covering the Rome IV criteria, which will allow for sub-categorization of diarrhea predominant, constipation predominant, mixed or unspecified IBS. If participants report having been diagnosed with IBS by a physician, but do not currently meet strict Rome IV diagnostic criteria on the questionnaire they are still allowed in the trial. Many refractory IBS patients were diagnosed under the old Rome III criteria and the only criterion they fail to meet currently is frequency of abdominal pain. Baseline questionnaire responses are reviewed by the study coordinator to ensure that inclusion criteria are met before participants are enrolled and randomized.

Exclusion criteria consists of having another comorbid GI disorder, such as celiac disease or an inflammatory bowel disease. Current or lifetime eating disorders were not evaluated or excluded. Many patients with IBS will meet criteria for fear based ARFID, but the CBT protocol actually addresses fear and avoidance of food. Exclusion criteria also include severe depression and/or suicidal ideation - defined as a positive endorsement at the level of 2 or 3 on the suicide item (item 9) of the Beck Depression Inventory. If a potential participant meets exclusion criteria on the basis of severe depression, the PI (a licensed clinical psychologist) contacts them to conduct a risk assessment and offers referral (if appropriate) to local resources. They are also given immediate access to the Zemedy app, if they are interested, but are not enrolled in the trial.

Power Analysis: Our goal is to recruit 300 participants. Most internet trials have an attrition rate approaching 50%[31], which would leave us with 150 participants in the study total (75 per group).

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CBT for IBS typically yields large effect sizes, and the effect sizes of Zemedy 1.0 on the primary outcome measures of GI symptom severity and HRQL were quite large (d = 1.02 and *d* = 1.25, respectively). Assuming a modest effect of the control app of approximately *d* = .30, then a final N of 150 will give us 90% power at $p < .05$ to detect a difference between groups.

Randomization: Participants who meet the inclusion criteria will be allocated to one of two conditions using the coin toss feature of random.org. The allocation sequence is concealed to participants until they are enrolled and assigned to the intervention.

Blinding: Because of the nature of the trial (immediate treatment versus active control group), neither participants nor research coordinators are blinded to condition. All outcome data is self-report, thus, blinding of evaluators is neither possible nor necessary. This means that participants are aware of their group allocation upon randomization.

Intervention and Assessments: All potential participants complete the baseline questionnaires as part of the screening process prior to enrollment and randomization. Upon allocation, those in the immediate treatment group will be given the link to access the Zemedy app and encouraged to download it and begin working through the modules immediately. The active control group will be given access to the education and relaxation training app, and will be given access to the Zemedy app eight weeks after they are informed of their group assignment. Four weeks after baseline, participants in both groups will be emailed to encourage them to continue using their respective app, and to let them know that they would be receiving the follow-up questionnaires in 4 weeks.

Eight weeks after completing the baseline questionnaires, all participants will be emailed with a second questionnaire battery which includes all the same measures as at baseline. Participants in the immediate treatment group will also complete the Mobile Application Rating Scale (uMars). All participants who complete 8-week questionnaires will be compensated $20 in Amazon credit. Those in the active control condition will then be crossed over to the Zemedy app.

After having access to the Zemedy app for eight weeks, participants in the active-control group will be emailed a third battery of questionnaires which is identical to the battery received by the treatment group after eight weeks of app usage - it includes the same measures as the baseline battery and the Mobile Application Rating Scale (uMars). They will be compensated with a further $20 gift credit upon completion of the post-treatment questionnaires.

While we hope that compensation will reduce attrition from the study at follow-up assessments, we still anticipate an attrition rate of at least 50%, which is typical for behavioral health studies using online recruitment and low intensity, distance interventions.

See Figure 1 for Consort diagram.

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Figure 1 – Consort Diagram

Measures

Primary Outcome Measures.

IBS quality of life (IBS–QoL).

The IBS–QOL[32] is a 34 item, self-report measure specific to IBS-related HRQL. It is rated on a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely). It is designed to assess the impact of IBS on quality of life. The IBS–QOL has high internal consistency (Cronbach's α= .95), high reproducibility (ICC = .86) and good construct validity. Qualitative score ranges are 0-31 (minimal or mild), 32-66 (moderate), and 67-100 (severe impairment). The mean IBS-QOL score for healthy controls is 5 (SD 11), leading to a cut-off point of 27 to fall within 2 SD of the healthy mean.

Gastrointestinal Symptom Rating Scale–IBS (GSRS–IBS).

The GSRS-IBS contains 13 self-report items rated on a 6-point Likert scale[3 3] ranging from 1 (no discomfort at all) to 7 (very severe discomfort). Total scores range from 13 to 91. The GSRS-IBS has 5 sub- scales, including abdominal pain, bloating, constipation, diarrhea, and satiety. Each dimension has demonstrated high internal consistency of Cronbach's alpha ranging from .74 (pain) to .85 (satiety). Furthermore, the GSRS- IBS has demonstrated both high test–retest reliability, with intra-class correlations among the factors ranging from .55 (pain) to .70 (bloating), as well as high construct validity[33]. The GSRS has been used as a primary outcome measure in a number of recent randomized controlled trials of IBS treatments (e.g.[21]) and the Rome Foundation reports that it is shorter and more user friendly than the IBS Severity Scoring System (IBS-SSS)[34]. Qualitative score ranges are 0-20 (minimal or mild), 21-39 (moderate), and 40-78 (severe). The mean GSRS score for healthy controls is 12 (SD 11), leading to a cut-off point of 34 to fall within 2 SD of the healthy mean.

Secondary Measures.

Modified Rome IV Questionnaire.

We used a questionnaire to determine whether participants met current Rome IV diagnostic criteria for IBS. Additionally, we will use this measure at post-treatment and follow-up timepoints to determine if participants still meet Rome IV criteria for IBS after treatment with the Zemedy app. Our

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questionnaire was based on the Rome IV IBS-specific Questionnaire, which is a validated self-report scale that covers the diagnostic criteria for IBS. It has been found to have acceptable sensitivity and high specificity as well as good test–retest reliability[1]. Our measure is shorter (10 items) and uses slightly different numeric scales, but still covers all the primary diagnostic criteria for IBS.

Fear of Food Questionnaire (FFQ).

The FFQ[35]is an 18-item, self-report questionnaire that measures fear, avoidance of food, and life interference and loss of pleasure from eating. Items are rated on a Likert scale ranging from 0 (not at all) to 5 (absolutely). It has excellent internal consistency reliability with Chronbach's $\alpha = 0.96$ and strong two-week test-retest reliability at $r = 0.93$, $p < .001$[35]. It also shows good criterion and known-groups validity. Qualitative score ranges are 0-15 (minimal), 16-30 (mild), 31-45 (moderate), and 46-90 (severe).

Visceral sensitivity index (VSI).

The VSI[8,363] is a unidimensional, 15-item scale that measures gastrointestinal symptom-specific anxiety. Items are rated on a Likert scale ranging from 0 (strongly disagree) to 5 (strongly agree). It has high internal consistency ($\alpha = 0.93$) and a mean inter-item correlation of 0.47[36]. It has good criterion, construct, and predictive validity[36]. Qualitative score ranges are 0-10 (minimal or mild), 11-30 (moderate), and 31-75 (severe).

Gastrointestinal Cognitions Questionnaire (GI-Cog).

The GI-Cog consists of 16 self-report items that are rated on a 5-point Likert scale, ranging from 0 (Hardly) to 4 (Very much). Individual items are summed, and total scores range from 0 to 64. The questionnaire consists of three subscales, the pain/life interference subscale (e.g. ‘‘When I feel my GI symptoms acting up, I’m afraid the pain will be excruciating and intolerable’’), the social anxiety subscale (e.g. ‘‘If I have to get up and leave an event, meeting, or social gathering to go to the bathroom people will think there’s something wrong with me’’), and the disgust sensitivity subscale (e.g. ‘‘The thought of fecal incontinence is terrifying. If it happened, it would be awful’’). The GI-Cog has been shown to have excellent internal consistency (a = .92) and test-retest reliability ($r = .87$, $p = .001$)[37]. Qualitative score ranges are 0-19 (minimal or mild), 20-39 (moderate), and 40-64 (severe).

Beck Depression Inventory (BDI-II).

The BDI-II consists of 21 self-report items, each on a 4 point scale ranging from 0 to 3 (0 being not at all, and 3 meaning extreme), therefore scores can range from 0 to 63. It is scored by adding the severity ratings of each item. A score greater than 20 indicates moderate depression. It has been found to

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have good internal consistency and test retest reliability[38]. Qualitative score ranges are 0-13 (minimal), 14-20 (mild), 21-30 (moderate), 31-63, (severe).

Mobile-Application Rating Scale (uMARS).

The uMARS is an end-user version of the Mobile Application Rating Scale which is a 26-item measure including 4 objective quality subscales (engagement, functionality, aesthetics, and information quality), 1 subjective quality subscale, a 6-item perceived impact subscale, and a space to provide feedback[41]. The uMARS scale is used to obtain user feedback on the quality of mobile apps during the development and testing process. The uMars has been shown to have excellent internal consistency (Cronbach's α = .90), and high internal consistencies of its subscales (engagement α= .80; functionality α= .70; aesthetics α= .71; information α= .78; and satisfaction α= .78)[39]. Test-Retest Reliability of the uMARS scale was found to be good with an average intraclass correlation coefficient (ICC) of 0.68[40].

Data Analysis

Univariate general linear models in SPSS V25 will be used to examine between group effects at post treatment (8 weeks), controlling for baseline levels of the dependent variable. Paired sample t-tests will be used to examine within group change over their treatment phase for each group and maintenance of gains from post treatment to 3 months follow-up, as well as at 6 and 12 months follow-up. The robustness of these analyses will be examined in an intent-to-treat sensitivity analysis by using multiple imputation. Regression models will then be fitted as in the primary analysis, and pooled estimates of the treatment effect calculated. Three sets of imputed datasets will be created, one for each follow-up data point, baseline measures included in each.

Change in visceral anxiety, catastrophizing (as measured by the GI-cog) and fear of food (calculated as change from baseline to 8 weeks) will be explored as possible mediators of GI symptoms and quality of life at 8 weeks using regression analysis with estimates of indirect effects will be calculated using a percentile bootstrap estimation approach with 5000 samples implemented with the PROCESS macro Version 3.5[41]. Both direct and indirect effects will be reported. The direct effect quantifies the estimated difference in the dependent variable (GI symptoms or quality of life) between two cases that are equal on the mediator but differ by one unit on treatment assignment, i.e., intervention vs waitlist group. The indirect effect quantifies how much two cases, one assigned to immediate treatment, the other to waitlist, are estimated to differ on the dependent variables (GI symptoms or quality of life) as a result of treatments' influence on the mediator, which in turn influences the dependent variable. Two sets of models will be fitted, the first testing the mediator variables separately with simple mediator models, the second fitting a parallel mediator model where the three mediators will be tested simultaneously. The baseline level of the dependent variable will be included as a covariate in all mediation models.

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Finally, baseline symptom severity, depression and IBS subtype will be examined as potential moderators of treatment efficacy.

Patient and public involvement statement

There was no direct patient or public involvement in the design of this research. However, the first author has an active clinical practice in which they work with many IBS patients, and patient feedback and clinical experience informs the development of Zemedy. There was also patient feedback from the RCT of Version 1.0 of Zemedy that guided many of the updates to the app to make it more engaging and user friendly.

ETHICS AND DISSEMINATION

This study was approved by the Institutional Review Board of the University of Pennsylvania. Participants who endorse suicidal ideation will be contacted by the PI who will offer a risk assessment and referrals to local in person providers. The active control app recommends certain approaches (such as restrictive diets) that are contraindicated in CBT, but are widely used management strategies for IBS. After the completion of this study, we hope and expect to find that Zemedy outperforms the educational and relaxation app in improving HRQL and GI symptom severity. We also hope to see that Zemedy 2.0 is rated more highly than Version 1.0 in user engagement, functionality, aesthetics, and information quality. We plan to submit the resulting paper to a high impact peer reviewed journal. De-identified data will be made available in a data repository.

Author Contributions

Melissa Hunt: Conceptualization, Methodology, Designing Intervention, Resources, Writing - Original Draft and Revisions, Supervision. Anika Dalvie: Conceptualization, Methodology, Designing Control Intervention, Writing, Project Administration, Software, Investigation, Participant Recruitment, Data Curation. Simay Ipek: Methodology, Designing Control Intervention, Project Administration, Software, Investigation, Data Curation. Ben Wasman: Designing Control Intervention, Participant Recruitment.

Ethics approval Institutional review board of the University of Pennsylvania.

Funding Statement:

This work was supported by Bold Health. Bold Health also designed and provide tech support to the app itself, and provide some data regarding compliance and utilization of the app.

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Competing Interests Statement:

Melissa Hunt serves as a scientific consultant to Bold Health and accepts a modest (less than $5,000 per annum) consulting fee. She has no ownership interest in the company. None of the other authors have any competing interests to declare.

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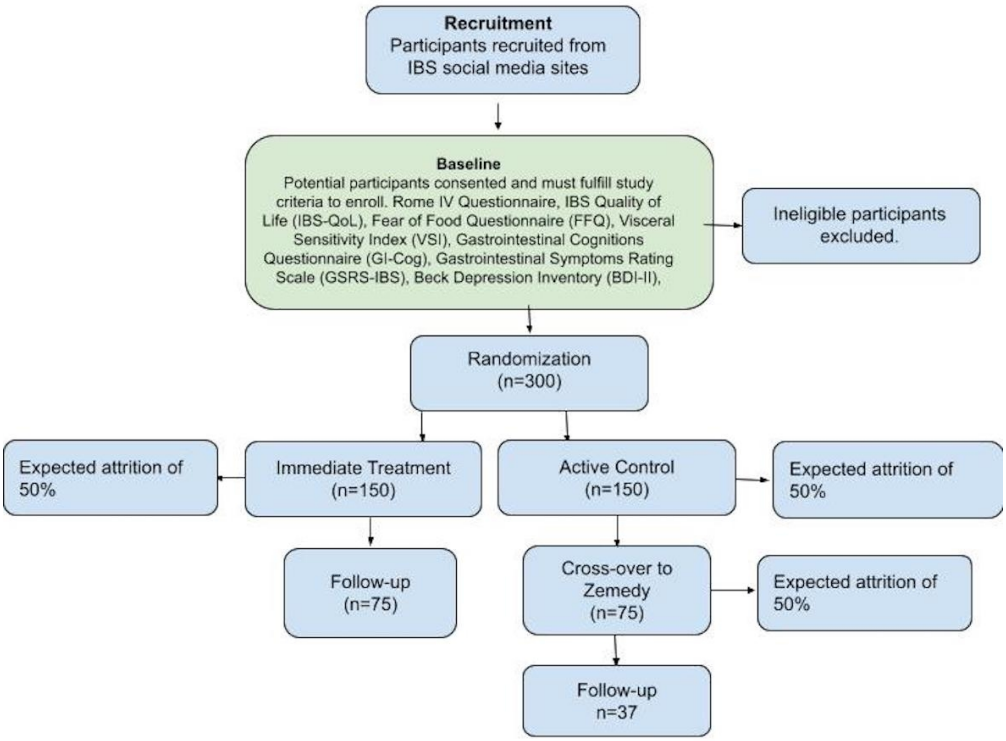

Figure 1 - Consort Diagram

99x75mm (300 x 300 DPI)

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	na
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	na

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	na

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	na
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	na
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	8

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	na
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	na
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	na

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		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	na
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	na

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	na
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	na
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	na
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	na

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Acceptability and Efficacy of the Zemedy App versus a Relaxation Training and Meditation App for IBS: Protocol for a randomized controlled trial

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Word Count: 4609

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ABSTRACT

Introduction: Irritable Bowel Syndrome (IBS) has high rates of psychiatric comorbidity, and impairs health-related quality of life (HRQL). Cognitive Behavioral Therapy (CBT) is an effective treatment for IBS, but access to treatment remains low. Our proposed solution is a CBT-based smartphone app, Zemedy.

Methods and Analysis: This RCT of Version 2.0 of the Zemedy app utilizes an education and relaxation training active control app meant to simulate treatment-as-usual. Participants complete baseline questionnaires and consent at screening, and are then allocated to either the immediate treatment (Zemedy) or the active control. Treatment lasts 8 weeks, after which both groups complete the same battery used at baseline, and the control group is crossed-over to Zemedy. After another 8 weeks, the crossed-over participants will be surveyed once more. Follow-up questionnaires are administered at 3, 6, and 12 months post-treatment. Primary outcomes include GI symptom severity and HRQL. Clinically significant change will be defined as post-treatment scores falling within 2 SD of the healthy mean. Analysis will include intent-to-treat between-groups comparisons, controlling for baseline symptom severity, as well as moderation and mediation analyses. We hypothesize that the Zemedy app will outperform the active control app in reducing IBS symptom severity and improving HRQL.

Ethics and Dissemination: This study was approved by the Institutional Review Board at the University of Pennsylvania. Results will provide essential information on the efficacy and acceptability of an app-based CBT treatment for IBS. The data gathered may help establish the Zemedy app as an empirically supported intervention for IBS and will assist funding bodies in deciding whether to invest in its further development and dissemination. The results will be disseminated to patients with IBS via the media and the company website, to healthcare professionals via professional trainings (e.g. webinars and grand rounds talks) and to researchers via conferences and publications. ~~**Introduction:** Irritable Bowel Syndrome (IBS) is a chronic gastrointestinal (GI) disorder, characterized primarily by abnormal centralized pain processing and altered bowel habits. IBS has high rates of psychiatric comorbidity, and impairs health-related quality of life (HRQL). Cognitive Behavioral Therapy (CBT) is an effective treatment for IBS, but access to this treatment remains low due to high cost and lack of clinicians able to provide GI-specific CBT. Our proposed solution is a CBT-based smartphone app, Zemedy.~~

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Methods and Analysis: The RCT for Version 1.0 of the Zemedy app resulted in reduced IBS symptom severity and improving HRQL. However, users showed only modest engagement. Version 2.0 is designed to address engagement by condensing the modules, improving flow, and adding entertaining animations. The RCT for Version 2.0 utilizes an education and relaxation training active control sham app meant to simulate treatment-as-usual. After completing baseline questionnaires and consent at screening, participants are allocated to either the immediate treatment (Zemedy) or to the active control condition. Treatment lasts After 8 weeks, after which both groups will complete the same battery used at baselinebe surveyed again, and the active control group will be given access to Zemedy. After another 8 weeks, the participants who crossed over to the Zemedy app will be surveyed once more. Follow-up questionnaires will be administered at 3, 6, and 12 months post-treatment. Primary outcomes include GI symptom severity and HRQL. Clinically significant change will be defined as post-treatment scores falling within 2 SD of the healthy mean. Analysis will include intent-to-treat between-groups comparisons, controlling for baseline symptom severity, as well as moderation and mediation analyses.. We hypothesize that the Zemedy app will outperform the active control app in reducing IBS symptom severity and improving HRQL.

Ethics and Dissemination: This study was approved by the Institutional Review Board at the University of Pennsylvania. This study will provide essential information on the efficacy and acceptability of an app-based CBT treatment for IBS. The data gathered may help establish the Zemedy app as an empirically supported intervention for IBS and will assist funding bodies in deciding whether to invest in its further development and dissemination. The results will be disseminated to patients with IBS via the media and the company website, to healthcare professionals via professional trainings (e.g. webinars and grand rounds talks) and to researchers via conferences and publications.

Trial registration number: NCT04665271 (https://clinicaltrials.gov/ct2/show/NCT04665271)

Article Summary:

Strengths and limitations of this study.

- The study is a randomized, controlled trial with high ecological validity.This study will provide essential efficacy and feasibility data regarding the use of a CBT-based self-help app for the treatment of IBS.
- The study design includes an active control condition, which is more robust than the waitlist control used in the RCT for Zemedy 1.0, and is an important strength, since IBS has a relatively high placebo response rate.

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- This study does not control for medication use or other therapeutic interventions patients may pursue. ~~consider the application of other CBT treatment mechanisms, such as in-person or group-based therapy~~.
- Inclusion criteria do not include physician confirmation of diagnosis; however, users of self-help apps are not required to provide proof of diagnosis.

Key Words: digital health; irritable bowel syndrome; cognitive behavioral therapy; CBT; efficacy; mHealth; self-management; IBS; randomized controlled trial; app

BACKGROUND

Irritable Bowel Syndrome (IBS) is a chronic disorder of central-enteric (gut-brain) interaction. It is defined by recurrent abdominal pain that occurs at least one day per week in the past three months, that is associated with two or more of the following: is related to defecation and/or is associated with changes in the frequency and/or form of bowel movements (i.e., characterized by constipation, diarrhea, or an alternating mix of the two). IBS that meets strict Rome IV diagnostic criteria ~~t~~ is ~~highly~~ quite prevalent (up to 6-7% of the population in the US)[1] but self-reported IBS that does not meet strict criteria is highly prevalent (17-18%) and results in equal disability, HRQL impairment, health care utilization and even greater absence from work[2]. Many studies have demonstrated that IBS has high rates of psychiatric comorbidity (up to 90% in treatment seeking patients)[3,4~~2~~,3], and causes social and occupational impairment[5~~4~~]. Beyond the core symptoms of abdominal pain and altered bowel habits, individuals with IBS suffer from a host of related difficulties that substantially impair health-related quality of life and functioning. Patients with IBS often experience visceral hypersensitivity, a phenomenon in which people feel normal gut sensations that most people would be unaware of, and experience many of those sensations as more painful than healthy controls[6~~5~~]. Anxiety and visceral hypersensitivity are highly correlated[7~~6~~]. Anxiety and hypervigilance related to the sensations exacerbates the hypersensitivity[8~~7~~].

Illness-related anxiety is high among IBS patients, and is a better predictor of impairment in quality of life than actual symptom severity[9~~8~~]. A major component of this anxiety is "catastrophizing," in which individuals envision the worst possible outcome of their GI symptoms and in turn develop maladaptive coping strategies[5~~4~~]. Catastrophizing is highly correlated with impairment in health related quality of life in IBS patients[10~~9~~]. Because of their catastrophizing, many individuals with IBS engage in significant avoidance behavior that can easily meet criteria for agoraphobia[11~~0~~].

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Over the past two decades, cognitive behavioral therapy (CBT) has repeatedly proven to be an efficacious treatment for individuals suffering from IBS[12, 13]. Specifically, there is empirical support that CBT reduces GI symptom severity and impairment in quality of life[14, 15]. CBT treatments typically include components of psychoeducation about the brain-gut axis, mindfulness and relaxation training [16], reducing automatic negative thoughts related to GI catastrophizing[17], exposure therapy to feared and avoided sensations and situations[18] and reducing visceral hypersensitivity[14]. One meta-analysis of twenty psychological treatments for IBS found that GI-cognition change and gastrointestinal specific anxiety were important mediators in improving GI-related quality of life and GI-symptom severity[19].

While CBT is a promising treatment, access to IBS-specific CBT remains low for patients. There are relatively few clinicians competent in delivering GI-specific CBT[5]. Additionally, the cost of treatment looms high; individuals often lack insurance coverage for psychotherapy and must pay out of pocket, which can be burdensome, especially given the hundreds of dollars their IBS likely already costs them [20]. It is important to develop a less expensive, more broadly available alternative mode of treatment delivery. Many groups have tested variants of CBT for IBS with limited or distant therapist involvement (e.g., via email)[21, 17, 22] and typically obtain robust effect sizes. Studies typically find that web-based and telephone-based CBT improved IBS more than treatment as usual (e.g.[23, 24]). Several treatment manuals and self-help books are available that detail the CBT treatment approach, and one[25] was found to be efficacious as a stand-alone treatment in a randomized controlled trial[26].

In today's digitized world, the mobile health (mHealth) industry is growing. Thousands of mobile applications (apps) exist to improve health across the spectrum. Mobile apps have multiple advantages, including low cost, privacy, accessibility and convenience for the user. The Zemedy app was developed to deliver CBT for IBS directly to users with no direct therapist or clinician interaction required. Version 1.0 of the app was tested in a randomized controlled trial against a wait-list control[27]. Primary outcome measures included both GI symptom severity and HRQL. Secondary outcome measures included GI specific catastrophizing, visceral anxiety, fear of food, and depression. App users showed both statistically and clinically significant improvement on both primary and secondary outcome measures, yielding a number needed to treat (NNT) of 2. Gains were generally maintained at 3 months post-treatment. Moreover, the impact of treatment on HRQL was mediated by reductions in catastrophizing and visceral anxiety.

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Despite these promising results, there were several significant limitations to the app itself and to the study. Uptake of the app was modest, with very few users availing themselves of even half of the app's modules. Although users rated the informational content of the app highly, they were less satisfied with the structure and flow of the app and its overall usability. In addition to these concerns, the study design utilized a waitlist control, which is not a particularly robust control, given the high placebo response rate in IBS[287].

The current study is designed to address all of these concerns. Version 2.0 of the Zemedy App was modified to be significantly more engaging. It has better flow, fewer modules, and more entertaining animations and patient stories. Our hope is that the user uptake and user ratings will be significantly improved compared to Zemedy 1.0. Second, this study utilizes a stronger control group, and will compare Zemedy to a sham app consisting of publicly available educational information (e.g. National Health Service treatment guidelines for IBS, and information from various online sources such as WebMD and the Mayo Clinic website) and links to a number of different relaxation videos. The purpose of this study is to test the acceptability and efficacy of an updated digital health app (Zemedy 2.0) that provides CBT-based treatment for IBS. We hypothesize that Zemedy will prove to be more effective in treating IBS symptom severity and improving quality of life for IBS-sufferers than the active control app.

METHODS

Novel App Description

Zemedy 2.0 is a smartphone application designed by Bold Health (a UK based company) in collaboration with the first author. The app treats irritable bowel syndrome (IBS) through modules guided by the principles of cognitive behavioral therapy specifically for IBS, as well as some gut-based hypnotherapy and psychoeducation on IBS. A chatbot guides users through the six modules of the app and the app automatically tracks progress, but users work through the modules at their own pace..

Module 1, called "Living with IBS and how CBT can help" is devoted to psychoeducation about IBS and why CBT is an effective treatment. It includes engaging animations illustrating the connection between the central and enteric nervous system and why stress can exacerbate GI symptoms, as well as animated "patients" who tell their stories of success with CBT. Psychoeducation is crucial to get patients to "buy in" to psychosocial approaches to managing IBS.

Module 2, "Activity and IBS," focuses on exercise and how physical activity can help manage the symptoms of IBS. It includes motivational interviewing (MI) style exercises to help users overcome reluctance to exercise. MI reduces resistance to behavior change by validating people's concerns about the challenges of behavior change (e.g. exercise is effortful and uncomfortable), encouraging people to think about their values and goals, and about the costs and benefits of both engaging in a behavior and not

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engaging in a behavior. The module ~~It~~ also includes links to instructional videos for specific yoga poses, and more animated patient stories to encourage physical activity and model successful management of IBS with exercise.

Module 3, "Managing Thoughts and Worries," focuses on the basic cognitive model of stress management, including identifying negative automatic thoughts and catastrophic beliefs and using cognitive restructuring to view situations more objectively and realistically. It also applies the cognitive model to specific thoughts and fears about GI symptoms that are common to many patients with IBS. These are basic cognitive therapy skills that are the central component of effective stress management.

Module 4, "Managing Avoidance," focuses on exposure therapy and behavioral experiments to help the user reduce maladaptive avoidance and get back to living their life fully. Patients are encouraged to set up graded exposure exercises for themselves involving any situations (or sensations) that they have been avoiding, including transportation, public venues, and situations involving food and eating. Exposure therapy and reductions in experiential avoidance are crucial components of every effective psychosocial intervention for IBS.

Module 5, "Diet & IBS," focuses on the connection between diet and GI symptoms, but strongly encourages users to reduce their fear of food and start eating a more healthful, balanced and less restrictive diet. Research has shown that fear of food contributes significantly to reductions in HRQL in IBS. The module encourages gradual reintroduction of avoided foods, but no explicit nutritional advice is given.

Module 6, "Putting it All Together," is the final module of the app, which summarizes the content of the previous 5 modules and explains how to use this information in daily life to manage GI sensations and help prevent relapse.

Users are encouraged to apply these strategies to their daily lives even after they have finished going through the app itself. Participants are meant to complete one module per week, leaving the last two weeks of the protocol to continue working on the skills they learned.

In addition to the six modules that serve as the core of the CBT-guided treatment within the Zemedy app, there are also "tools," which are mainly CBT-based, but also involve mindfulness, attention training and relaxation exercises that users can utilize at any time. Some of these tools are unlocked as users progress through the core modules. The ability to unlock new features is a standard approach to "gamifying" apps and is typically expected to enhance engagement. It is possible, however, that users will find this frustrating. We will seek user feedback on this issue at the end of the trial. Additionally, the app includes a "flare module" which users can access at any point during this intervention to address immediate GI discomfort or anxiety.

Education and Relaxation Training App Description

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The education and relaxation training app is a rudimentary app meant to act similarly to treatment as usual. This app consists of 6 modules, of which participants are meant to complete one per week, leaving the last 2 weeks to continue working on the lifestyle changes that some of the modules encourage.

Module 1 includes information from publicly available websites (e.g. Mayo Clinic, Cleveland Clinic, UK NHS and NICE Guidelines) about the presumed etiology of IBS and what symptoms are necessary for a diagnosis. It also discusses the various IBS subtypes (IBS-C, IBS-D, and IBS-M).

Module 2 contains a list of possible over the counter medications and supplements to address IBS symptoms, such as laxatives, anti-diarrheals, peppermint oil, and probiotics.

Module 3 discusses the impact of lifestyle on IBS. For example, it explains that stress can make IBS worse (without elucidating the underlying mechanisms), and contains links to relaxation training videos for participants to use.

Modules 4 and 5 both discuss diet. Module 4 encourages participants to keep a food diary to see which foods potentially trigger flare-ups in their IBS. Module 5 explains some potential dietary changes that participants can make, such as following the low FODMAP diet and restricting caffeine and alcohol intake. The low FODMAP diet is an evidence-based intervention for IBS and is a common recommendation given to patients with IBS by both nutritionists and gastroenterologists[298]. Food diaries and exclusion diets are actually contraindicated in CBT for IBS, but are the most common approaches recommended by gastroenterologists and are quite efficacious at reducing distressing GI symptoms [3029]. A recent non-inferiority trial comparing a self-help CBT workbook to a self-help low FODMAP diet book found them to be equally efficacious in the short term at improving HRQL [Hunt, Rio, Dembik, Jileaeva, Wilkins & Reynolds, (unpublished manuscript). CBT versus the Low FODMAP Diet for IBS: A non-inferiority comparison of two self-help books].

Module 6 discusses the importance of exercise (again without actually elucidating the underlying biological mechanisms by which exercise can reduce IBS symptoms), and encourages logging exercise, without any attempt to include motivational interviewing interventions or to help users overcome reluctance to exercise. In sum, the sham app includes standard, treatment-as-usual information and advice that patients with IBS would often be exposed to in other formats, but does not include any of the specific education or treatment strategies that the CBT approach utilizes and that are central to the Zemedy app.

In sum, the control app contains a good deal of informative text and a number of links to engaging relaxation videos. IBS has a relatively high placebo response rate, and we hope the control app will be both credible and somewhat engaging.

Study Design

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This study is a randomized, superiority, non-blinded, cross-over trial with an active control group. The study is running from March 1, 2021 to an estimated completion date of May 28, 2023. Participants are recruited from the United States, and study personnel are based at the University of Pennsylvania's Department of Psychology but because both recruitment, assessment and the treatment itself are all remote, there is no physical location for the study.

Accrual: Participants will be recruited for the trial through IBS specific social media sites, as well as clinical trial listings at clinicaltrials.gov and iffgd.org (the International Foundation for Gastrointestinal Disorders). Most participants came to the original Zemedy study through Facebook, Twitter, and Reddit, so we anticipate that most of our participants for this second study will come from those sites as well. Notices and posts about the study on those sites include a link to a secure Qualtrics survey that contains the consent form and the baseline questionnaires.

Consent: All participants complete informed consent online prior to completing baseline questionnaires. The consent form explains the study, including information about random assignment and the compensation for completing study questionnaires at several follow-up time points. ~~All data are collected online using Qualtrics secure servers and are stored de-identified.~~

Inclusion and Exclusion Criteria: Inclusion criteria consists of being 18 years of age or older, and participant self-report of having been previously diagnosed by a physician with IBS or meeting Rome IV criteria[1] by self-report on a standardized questionnaire covering the Rome IV criteria, which will allow for sub-categorization of diarrhea predominant, constipation predominant, mixed or unspecified IBS. ~~-~~ If participants report having been diagnosed with IBS by a physician, but do not currently meet strict Rome IV diagnostic criteria on the questionnaire they are still allowed in the trial. Many refractory IBS patients were diagnosed under the old Rome III criteria and the only criterion they fail to meet currently is frequency of abdominal pain. Baseline questionnaire responses are reviewed by the study coordinator to ensure~~insure~~ that inclusion criteria are met before participants are enrolled and randomized.

Exclusion criteria consists of having another comorbid GI disorder, such as celiac disease or an inflammatory bowel disease. Current or lifetime eating disorders were not evaluated or excluded. Many patients with IBS will meet criteria for fear based ARFID, but the CBT protocol actually addresses fear and avoidance of food. Exclusion criteria ~~It~~ also include~~s~~ severe depression and/or suicidal ideation - defined as a positive endorsement at the level of 2 or 3 on the suicide item (item 9) of the Beck Depression Inventory. If a potential participant meets exclusion criteria on the basis of severe depression, the PI (a licensed clinical psychologist) contacts them to conduct a risk assessment and offers referral (if appropriate) to local resources. They are also given immediate access to the Zemedy app, if they are interested, but are not enrolled in the trial.

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Power Analysis: Our goal is to recruit 300 participants. Most internet trials have an attrition rate approaching 50%[31], which would leave us with 150 participants in the study total (75 per group). CBT for IBS typically yields large effect sizes, and the effect sizes of Zemedy 1.0 on the primary outcome measures of GI symptom severity and HRQL ~~w~~were quite large ~~as~~ (d = 1.02 and *d* = 1.25, respectively). Assuming a modest effect of the control app of approximately *d* = .30, then a final N of 150 will give us 90% power at $p < .05$ to detect a difference between groups.

Randomization: Participants who meet the inclusion criteria will be allocated to one of two conditions using the coin toss feature of random.org. The allocation sequence is concealed to participants until they are enrolled and assigned to the intervention.

Blinding: Because of the nature of the trial (immediate treatment versus active control group), neither participants nor research coordinators are blinded to condition. All outcome data is self-report, thus, blinding of evaluators is neither possible nor necessary. This means that participants are aware of their group allocation upon randomization.

*Intervention and Assessments: All potential participants complete the baseline questionnaires as part of the screening process prior to enrollment and randomization. Upon allocation, ~~T~~*those in the immediate treatment group will be given the link to access the Zemedy app and encouraged to download it and begin working through the modules immediately. The active control group will be given access to the education and relaxation training app, and will be given access to the Zemedy app eight weeks after they are informed of their group assignment. Four weeks after baseline, participants in both groups will be emailed to encourage them to continue using their respective app, and to let them know that they would be receiving the follow-up questionnaires in 4 weeks.

Eight weeks after completing the baseline questionnaires, all participants will be emailed with a second questionnaire battery which includes all the same measures as at baseline. Participants in the immediate treatment group will also complete the Mobile Application Rating Scale (uMars). All participants who complete 8-week questionnaires will be compensated $20 in Amazon credit. Those in the active control condition will then be crossed over to the Zemedy app.

After having access to the Zemedy app for eight weeks, participants in the active-control group will be emailed a third battery of questionnaires which is identical to the battery received by the treatment group after eight weeks of app usage - it includes the same measures as the baseline battery and the Mobile Application Rating Scale (uMars). They will be compensated with a further $20 gift credit upon completion of the post-treatment questionnaires.

While we hope that compensation will reduce attrition from the study at follow-up assessments, we still anticipate an attrition rate of at least 50%, which is typical for behavioral health studies using online recruitment and low intensity, distance interventions.

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See Figure 1 for ~~full~~ Consort diagram.

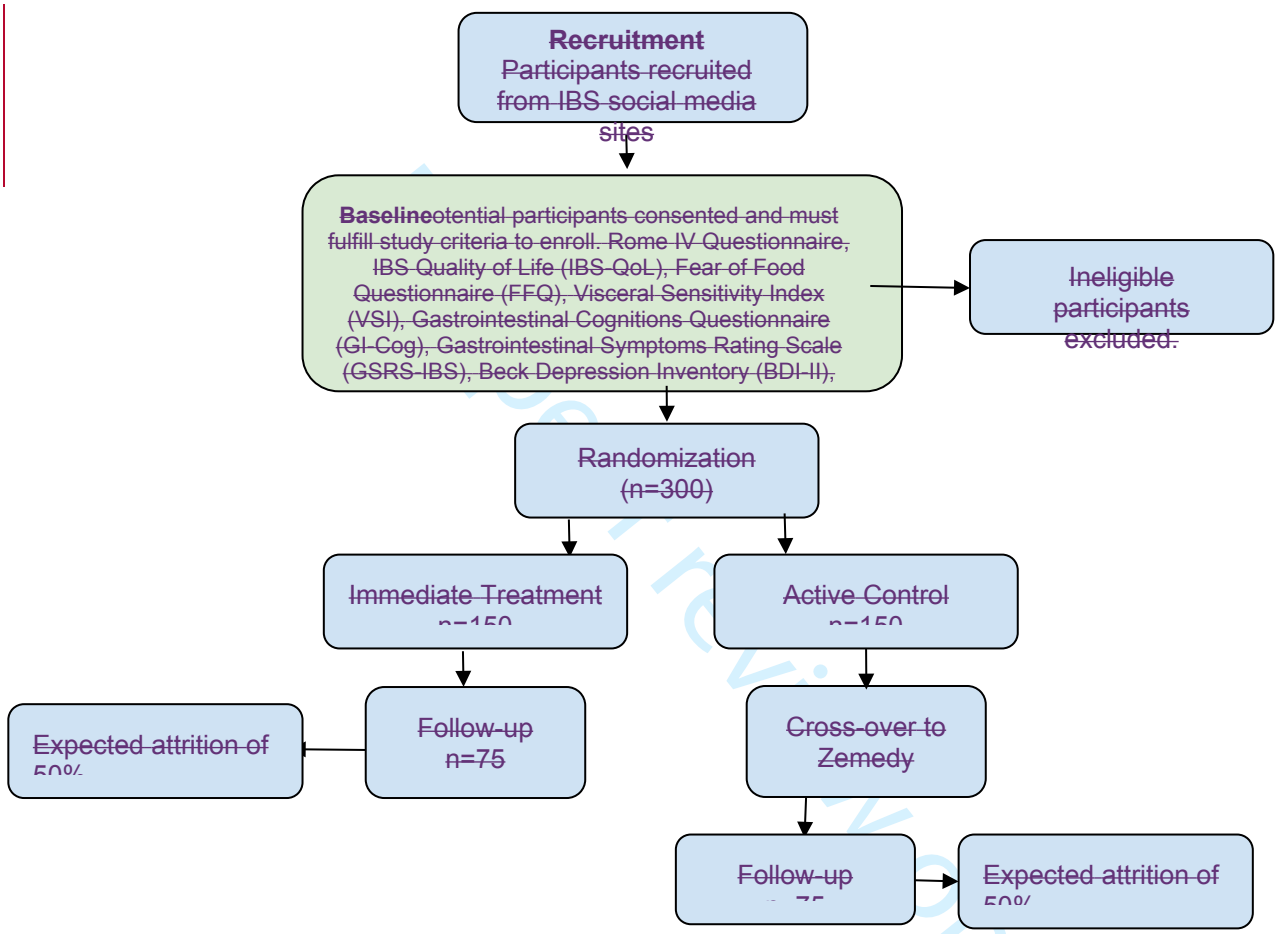

Figure 1 – Consort Diagram

Measures

Primary Outcome Measures.

IBS quality of life (IBS–QoL).

The IBS–QOL[32] is a 34 item, self-report measure specific to IBS-related HRQL. It is rated on a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely). It is ~~umeasure specific to IBS~~ designed to assess the impact of IBS on quality of life. The IBS–QOL has high internal consistency (Cronbach's α= .95), high reproducibility (ICC = .86) and good construct validity. Qualitative score ranges are 0-31 (minimal or mild), 32-66 (moderate), and 67-100 (severe impairment). The mean IBS-QOL score for healthy controls is 5 (SD 11), leading to a cut-off point of 27 to fall within 2 SD of the healthy mean.

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Gastrointestinal Symptom Rating Scale–IBS (GSRS–IBS).

The GSRS-IBS contains 13 self-report items rated on a 6-point Likert scale[3 3] ranging from 1 (no discomfort at all) to 7 (very severe discomfort). Total scores range from 13 to 91. The GSRS-IBS has 5 sub--scales, including abdominal pain, bloating, constipation, diarrhea, and satiety. Each dimension has demonstrated high internal consistency of Cronbach's alpha ranging from .74 (pain) to .85 (satiety). Furthermore, the GSRS- IBS has demonstrated both high test–retest reliability, with intra-class correlations among the factors ranging from .55 (pain) to .70 (bloating), as well as high construct validity[3~~2~~3]. The GSRS has been used as a primary outcome measure in a number of recent randomized controlled trials of IBS treatments (e.g.[2~~1~~0]) and the Rome Foundation reports that it is shorter and more user friendly than the IBS Severity Scoring System (IBS-SSS)[3~~4~~5~~3~~]. Qualitative score ranges are 0-20 (minimal or mild), 21-39 (moderate), and 40-78 (severe). The mean GSRS score for healthy controls is 12 (SD 11), leading to a cut-off point of 34 to fall within 2 SD of the healthy mean.

Secondary Measures.

Modified Rome IV Questionnaire.

We used a questionnaire to determine whether participants met current Rome IV diagnostic criteria for IBS. Additionally, we will use this measure at post-treatment and follow-up timepoints to determine if participants still meet Rome IV criteria for IBS after treatment with the Zemedy app.- Our questionnaire was based on the Rome IV IBS-specific Questionnaire, which is a validated self-report scale that covers the diagnostic criteria for IBS. It has been found to have acceptable sensitivity and high specificity as well as good test–retest reliability[1]. Our measure is shorter (10 items) and uses slightly different numeric scales, but still covers all the primary diagnostic criteria for IBS.

Fear of Food Questionnaire (FFQ).

The FFQ[3~~5~~4]is an 18-item, self-report questionnaire that measures fear, avoidance of food, and life interference and loss of pleasure from eating. Items are rated on a Likert scale ranging from 0 (not at all) to 5 (absolutely). It has excellent internal consistency reliability with Chronbach's $\alpha = 0.96$ and strong two-week test-retest reliability at $r = 0.93$, $p < .001$[3~~5~~6~~4~~]. It also shows good criterion and known-groups validity. Qualitative score ranges are 0-15 (minimal), 16-30 (mild), 31-45 (moderate), and 46-90 (severe).

Visceral sensitivity index (VSI).

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The VSI[8,3635] is a unidimensional, 15-item scale that measures gastrointestinal symptom-specific anxiety. Items are rated on a Likert scale ranging from 0 (strongly disagree) to 5 (strongly agree). It has high internal consistency (α = 0.93) and a mean inter-item correlation of 0.47[36, 37]. It has good criterion, construct, and predictive validity[367]. Qualitative score ranges are 0-10 (minimal or mild), 11-30 (moderate), and 31-75 (severe).

Gastrointestinal Cognitions Questionnaire (GI-Cog).

The GI-Cog consists of 16 self-report items that are rated on a 5-point Likert scale, ranging from 0 (Hardly) to 4 (Very much). Individual items are summed, and total scores range from 0 to 64. The questionnaire consists of three subscales, the pain/life interference subscale (e.g. ‘‘When I feel my GI symptoms acting up, I’m afraid the pain will be excruciating and intolerable’’), the social anxiety subscale (e.g. ‘‘If I have to get up and leave an event, meeting, or social gathering to go to the bathroom people will think there’s something wrong with me’’), and the disgust sensitivity subscale (e.g. ‘‘The thought of fecal incontinence is terrifying. If it happened, it would be awful’’). The GI-Cog has been shown to have excellent internal consistency (a = .92) and test-retest reliability (r = .87, p = .001)[375]. Qualitative score ranges are 0-19 (minimal or mild), 20-39 (moderate), and 40-64 (severe).

Beck Depression Inventory (BDI-II).

The BDI-II consists of 21 self-report items, each on a 4 point scale ranging from 0 to 3 (0 being not at all, and 3 meaning extreme), therefore scores can range from 0 to 63. It is scored by adding the severity ratings of each item. A score greater than 20 indicates moderate depression. It has been found to have good internal consistency and test retest reliability[38]. Qualitative score ranges are 0-13 (minimal), 14-20 (mild), 21-30 (moderate), 31-63, (severe).

Mobile-Application Rating Scale (uMARS).

The uMARS is an end-user version of the Mobile Application Rating Scale which is a 26-item measure including 4 objective quality subscales (engagement, functionality, aesthetics, and information quality), 1 subjective quality subscale, a 6-item perceived impact subscale, and a space to provide feedback[4139]. The uMARS scale is used to obtain user feedback on the quality of mobile apps during the development and testing process. The uMars has been shown to have excellent internal consistency (Cronbach's α = .90), and high internal consistencies of its subscales (engagement α= .80; functionality α= .70; aesthetics α= .71; information α= .78; and satisfaction α= .78)[42039]. Test-Retest Reliability of the uMARS scale was found to be good with an average intraclass correlation coefficient (ICC) of 0.68[41040].

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Data Analysis

Univariate general linear models in SPSS V25 will be used to examine between group effects at post treatment (8 weeks), controlling for baseline levels of the dependent variable. Paired sample t-tests will be used to examine within group change over their treatment phase for each group and maintenance of gains from post treatment to 3 months follow-up, as well as at 6 and 12 months follow-up. The robustness of these analyses will be examined in an intent-to-treat sensitivity analysis by using multiple imputation. Regression models will then be fitted as in the primary analysis, and pooled estimates of the treatment effect calculated. Three sets of imputed datasets will be created, one for each follow-up data point, baseline measures included in each.

Change in visceral anxiety, catastrophizing (as measured by the GI-cog) and fear of food (calculated as change from baseline to 8 weeks) will be explored as possible mediators of GI symptoms and quality of life at 8 weeks using regression analysis with estimates of indirect effects will be calculated using a percentile bootstrap estimation approach with 5000 samples implemented with the PROCESS macro Version 3.5[~~43~~41]. Both direct and indirect effects will be reported. The direct effect quantifies the estimated difference in the dependent variable (GI symptoms or quality of life) between two cases that are equal on the mediator but differ by one unit on treatment assignment, i.e., intervention vs waitlist group. The indirect effect quantifies how much two cases, one assigned to immediate treatment, the other to waitlist, are estimated to differ on the dependent variables (GI symptoms or quality of life) as a result of treatments' influence on the mediator, which in turn influences the dependent variable. Two sets of models will be fitted, the first testing the mediator variables separately with simple mediator models, the second fitting a parallel mediator model where the three mediators will be tested simultaneously. The baseline level of the dependent variable will be included as a covariate in all mediation models.

Finally, baseline symptom severity, depression and IBS subtype will be examined as potential moderators of treatment efficacy.

Patient and public involvement statement

There was no direct patient or public involvement in the design of this research. However, the first author has an active clinical practice in which they work with many IBS patients, and patient feedback and clinical experience informs the development of Zemedy. There was also patient feedback from the RCT of Version 1.0 of Zemedy that guided many of the updates to the app to make it more engaging and user friendly.

ETHICS AND DISSEMINATION

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This study was approved by the Institutional Review Board of the University of Pennsylvania. Participants who endorse suicidal ideation will be contacted by the PI who will offer a risk assessment and referrals to local in person providers. The active control app recommends certain approaches (such as restrictive diets) that are contraindicated in CBT, but are widely used management strategies for IBS. After the completion of this study, we hope and expect to find that Zemedy outperforms the educational and relaxation app in improving HRQL and GI symptom severity. We also hope to see that Zemedy 2.0 is rated more highly than Version 1.0 in user engagement, functionality, aesthetics, and information quality. We plan to submit the resulting paper to a high impact peer reviewed journal. De-identified data will be made available in a data repository.

Author Contributions

Melissa Hunt: Conceptualization, Methodology, Designing Intervention, Resources, Writing - Original Draft and Revisions, Supervision. Anika Dalvie: Conceptualization, Methodology, Designing Control Intervention, Writing, Project Administration, Software, Investigation, Participant Recruitment, Data Curation. Simay Ipek: Methodology, Designing Control Intervention, Project Administration, Software, Investigation, Data Curation. Ben Wasman: Designing Control Intervention, Participant Recruitment.

Ethics approval Institutional review board of the University of Pennsylvania.

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This work was supported by Bold Health. Bold Health also designed and provide tech support to the app itself, and provide some data regarding compliance and utilization of the app.

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Competing Interests Statement:

Melissa Hunt serves as a scientific consultant to Bold Health and accepts a modest (less than $5,000 per annum) consulting fee. She has no ownership interest in the company. None of the other authors have any competing interests to declare.

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Acceptability and Efficacy of the Zemedy App versus a Relaxation Training and Meditation App for IBS: Protocol for a randomized controlled trial

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ABSTRACT

Introduction: Irritable Bowel Syndrome (IBS) has high rates of psychiatric comorbidity, and impairs health-related quality of life (HRQL). Cognitive Behavioral Therapy (CBT) is an effective treatment for IBS, but access to treatment remains low. Our proposed solution is a CBT-based smartphone app, Zemedy.

Methods and Analysis: This RCT of Zemedy(2.0) utilizes an education and relaxation training active control app meant to simulate treatment-as-usual. A target N of 300 participants complete baseline questionnaires and consent at screening, and are then allocated to either the immediate treatment (Zemedy) or the active control. Treatment lasts 8 weeks, after which both groups complete the same battery used at baseline, and the control group is crossed-over to Zemedy. After another 8 weeks, the crossed-over participants will be surveyed once more. Follow-up questionnaires are administered at 3, 6, and 12 months post-treatment. Primary outcomes include GI symptom severity and HRQL. Clinically significant change will be defined as post-treatment scores falling within 2 SD of the healthy mean. Analysis will include intent-to-treat between-groups comparisons, controlling for baseline symptom severity, as well as moderation and mediation analyses. We hypothesize that the Zemedy app will outperform the active control app in reducing IBS symptom severity and improving HRQL.

Ethics and Dissemination: This study was approved by the Institutional Review Board at the University of Pennsylvania. Results will provide essential information on the efficacy and acceptability of an app-based CBT treatment for IBS. The data gathered may help establish the Zemedy app as an empirically supported intervention for IBS and will assist funding bodies in deciding whether to invest in its further development and dissemination. The results will be disseminated to patients with IBS via the media and the company website, to healthcare professionals via professional trainings (e.g. webinars and grand rounds talks) and to researchers via conferences and publications. **Trial registration number:** NCT04665271 (https://clinicaltrials.gov/ct2/show/NCT04665271)

Article Summary:

Strengths and limitations of this study.

- The study is a randomized, controlled trial with high ecological validity.

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- The study design includes an active control condition, which is more robust than the waitlist control used in the RCT for Zemedy 1.0, and is an important strength, since IBS has a relatively high placebo response rate.
- This study does not control for medication use or other therapeutic interventions patients may pursue. .
- Inclusion criteria do not include physician confirmation of diagnosis; however, users of self-help apps are not required to provide proof of diagnosis.

Key Words: digital health; irritable bowel syndrome; cognitive behavioral therapy; CBT; efficacy; mHealth; self-management; IBS; randomized controlled trial; app

BACKGROUND

Irritable Bowel Syndrome (IBS) is a chronic disorder of central-enteric (gut-brain) interaction. According to the non-profit Rome Foundation diagnostic criteria [1], it is characterized by recurrent abdominal pain that occurs at least four times per month (or about one day per week) over at least three months. The pain must be associated with two or more of the following: it must be related to defecation and/or be associated with changes in the frequency and/or form of bowel movements. There are several subtypes, including constipation predominant, diarrhea predominant, mixed bowel habits and unclassified. IBS that meets strict Rome IV diagnostic criteria is quite prevalent (up to 6-7% of the population in the US)[1] but self-reported IBS that does not meet strict criteria is highly prevalent (17-18%) and results in equal disability, health related quality of life (HRQL) impairment, health care utilization and even greater absence from work[2]. Thus, IBS is a serious public health challenge.

Patients with IBS who are actively seeking treatment show extremely high rates of psychiatric comorbidity, with up to 90% meeting criteria for a disorder such as major depression, an anxiety disorder, post-traumatic stress disorder and/or a health anxiety related disorder such obsessive compulsive disorder. [3,4]. IBS also causes significant social and occupational impairment, and can lead to substantial reductions in HRQL [5]. Patients with IBS typically develop visceral hypersensitivity, which maintains a cycle of awareness of and hypervigilance towards GI sensations and exacerbates the experience of pain [6]. Visceral hypersensitivity is highly correlated with anxiety about GI sensations [7], and the anxiety and hypervigilance about GI sensations in turn exacerbate the hypersensitivity[8].

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Patients with IBS often exhibit significant anxiety about GI symptoms, and that anxiety is a better predictor impaired HRQL than symptom severity per se[9]. Many patients with IBS start catastrophizing about their symptoms, and about the social and occupational implications of their symptoms. Catastrophizing is associated with impaired HRQL in and of itself [10], but can also lead to the development of maladaptive coping strategies [5]. Maladaptive coping can include significant avoidance that can easily meet criteria for agoraphobia [11], especially in patients who are terrified of the possibility of fecal incontinence. Given the significant conceptual and comorbidity overlap with panic, agoraphobia, social anxiety, illness anxiety, depression and trauma, it is not surprising that IBS responds quite well to cognitive behavioral therapy (CBT). Indeed, CBT has been shown to be an efficacious treatment for IBS in multiple clinical trials [12 , 13], and should be considered an empirically supported treatment for IBS. Specifically, CBT reduces GI symptom severity and improves HRQL [14 , 15]. CBT typically includes psychoeducation about the brain-gut axis, relaxation training [16], cognitive therapy to target and reframe GI catastrophizing[17], exposure therapy to reduce avoidance of GI sensations, food and situations in which the person fears experiencing GI sensations or being too far away from a convenient, available restroom [18] and reducing visceral hypersensitivity[14]. Changes in GI specific cognitions and reductions in GI specific anxiety have been shown to mediate the impact of CBT on both HRQL and GI symptom severity. [19].

While CBT is an effective treatment for IBS, it is unfortunately difficult for many patients to get access to it. There are relatively few clinicians trained in GI-specific CBT[5], and the cost of treatment, which typically must be paid for out of pocket, can be prohibitive. This is especially problematic given the economic burdens living with IBS often imposes [20]. Thus, in order to disseminate CBT for IBS more broadly, we must develop a less expensive, more accessible mode of treatment delivery. Several low intensity versions of CBT for IBS (e.g. with limited or distant therapist involvement such as via email) have been tested [21 , 17 , 22] and typically obtain robust effect sizes. Patients treated with web-based and telephone-based CBT improve more than those given treatment as usual (e.g.[23 , 24]). Several treatment manuals and self-help books are available that outline or deliver IBS specific CBT , and one in particular [25] was found to be efficacious as a stand-alone self-help treatment in a randomized controlled trial[26].

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In today's digitized world, many consumers readily turn to mobile health apps. Mobile apps have multiple advantages, including low cost, accessibility and convenience for the user. The Zemedy app was developed to deliver CBT for IBS directly to users with no direct therapist or clinician interaction required. Version 1.0 of the app was tested in a randomized controlled trial against a wait-list control[27]. Primary outcome measures included both GI symptom severity and HRQL. Secondary outcome measures included GI specific catastrophizing, visceral anxiety, fear of food, and depression. App users showed both statistically and clinically significant improvement on both primary and secondary outcome measures, yielding a number needed to treat (NNT) of 2. Gains were generally maintained at 3 months post-treatment. Moreover, the impact of treatment on HRQL was mediated by reductions in catastrophizing and visceral anxiety.

Despite these promising results, there were several significant limitations to the app itself and to the study. Uptake of the app was modest, with very few users availing themselves of even half of the app's modules. Although users rated the informational content of the app highly, they were less satisfied with the structure and flow of the app and its overall usability. In addition to these concerns, the study design utilized a waitlist control, which is not a particularly robust control, given the high placebo response rate in IBS[28].

The current study is designed to address all of these concerns. Version 2.0 of the Zemedy App was modified to be significantly more engaging. It has better flow, fewer modules, and more entertaining animations, videos and patient stories. Our hope is that the user uptake and user ratings will be significantly improved compared to Zemedy 1.0. Second, this study utilizes a stronger control group, and will compare Zemedy to a sham app consisting of publicly available educational information (e.g. National Health Service treatment guidelines for IBS, and information from various online sources such as WebMD and the Mayo Clinic website) and links to a number of different relaxation videos. The purpose of this study is to test the acceptability and efficacy of an updated digital health app (Zemedy 2.0) that provides CBT-based treatment for IBS. We hypothesize that Zemedy will prove to be more effective in treating IBS symptom severity and improving quality of life for IBS-sufferers than the active control app.

METHODS

Novel App Description

Zemedy 2.0 is a smartphone application designed by Bold Health (a UK based company) in collaboration with the first author. The app treats irritable bowel syndrome (IBS) through modules guided by the principles of cognitive behavioral therapy specifically for IBS, as well as some gut-based

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hypnotherapy and psychoeducation on IBS. A chatbot guides users through the six modules of the app and the app automatically tracks progress, but users work through the modules at their own pace..

Module 1, called “Living with IBS and how CBT can help" is devoted to psychoeducation about IBS and why CBT is an effective treatment. It includes engaging animations illustrating the connection between the central and enteric nervous system and why stress can exacerbate GI symptoms, as well as animated “patients” who tell their stories of success with CBT. Psychoeducation is crucial to get patients to “buy in” to psychosocial approaches to managing IBS.

Module 2, “Activity and IBS,” focuses on exercise and how physical activity can help manage the symptoms of IBS. It includes motivational interviewing (MI) style exercises to help users overcome reluctance to exercise. MI reduces resistance to behavior change by validating people’s concerns about the challenges of behavior change (e.g. exercise is effortful and uncomfortable), encouraging people to think about their values and goals, and about the costs and benefits of both engaging in a behavior and not engaging in a behavior. The module also includes links to instructional videos for specific yoga poses, and more animated patient stories to encourage physical activity and model successful management of IBS with exercise.

Module 3, “Managing Thoughts and Worries,” focuses on the basic cognitive model of stress management, including identifying negative automatic thoughts and catastrophic beliefs and using cognitive restructuring to view situations more objectively and realistically. It also applies the cognitive model to specific thoughts and fears about GI symptoms that are common to many patients with IBS. These are basic cognitive therapy skills that are the central component of effective stress management.

Module 4, “Managing Avoidance,” focuses on exposure therapy and behavioral experiments to help the user reduce maladaptive avoidance and get back to living their life fully. Patients are encouraged to set up graded exposure exercises for themselves involving any situations (or sensations) that they have been avoiding, including transportation, public venues, and situations involving food and eating. Exposure therapy and reductions in experiential avoidance are crucial components of every effective psychosocial intervention for IBS.

Module 5, “Diet & IBS,” focuses on the connection between diet and GI symptoms, but strongly encourages users to reduce their fear of food and start eating a more healthful, balanced and less restrictive diet. Research has shown that fear of food contributes significantly to reductions in HRQL in IBS. The module encourages gradual reintroduction of avoided foods, but no explicit nutritional advice is given.

Module 6, “Putting it All Together,” is the final module of the app, which summarizes the content of the previous 5 modules and explains how to use this information in daily life to manage GI sensations and help prevent relapse.

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Users are encouraged to apply these strategies to their daily lives even after they have finished going through the app itself. Participants are meant to complete one module per week, leaving the last two weeks of the protocol to continue working on the skills they learned.

In addition to the six modules that serve as the core of the CBT-guided treatment within the Zemedy app, there are also "tools," which are mainly CBT-based, but also involve mindfulness, attention training and relaxation exercises that users can utilize at any time. Some of these tools are unlocked as users progress through the core modules. The ability to unlock new features is a standard approach to "gamifying" apps and is typically expected to enhance engagement. It is possible, however, that users will find this frustrating. We will seek user feedback on this issue at the end of the trial. Additionally, the app includes a "flare module" which users can access at any point during this intervention to address immediate GI discomfort or anxiety.

Education and Relaxation Training App Description

The education and relaxation training app is a rudimentary app meant to act similarly to treatment as usual. This app consists of 6 modules, of which participants are meant to complete one per week, leaving the last 2 weeks to continue working on the lifestyle changes that some of the modules encourage.

Module 1 includes information from publicly available websites (e.g. Mayo Clinic, Cleveland Clinic, UK NHS and NICE Guidelines) about the presumed etiology of IBS and what symptoms are necessary for a diagnosis. It also discusses the various IBS subtypes (IBS-C, IBS-D, and IBS-M).

Module 2 contains a list of possible over the counter medications and supplements to address IBS symptoms, such as laxatives, anti-diarrheals, peppermint oil, and probiotics.

Module 3 discusses the impact of lifestyle on IBS. For example, it explains that stress can make IBS worse (without elucidating the underlying mechanisms), and contains links to relaxation training videos for participants to use.

Modules 4 and 5 both discuss diet. Module 4 encourages participants to keep a food diary to see which foods potentially trigger flare-ups in their IBS. Module 5 explains some potential dietary changes that participants can make, such as following the low FODMAP diet and restricting caffeine and alcohol intake. The low FODMAP diet is an evidence-based intervention for IBS and is a common recommendation given to patients with IBS by both nutritionists and gastroenterologists[29]. Food diaries and exclusion diets are actually contraindicated in CBT for IBS, because they work via opposing mechanisms. Nevertheless, restrictive diets are empirically supported, are the most common approach recommended by gastroenterologists and are quite efficacious at reducing distressing GI symptoms [30]. Module 6 discusses the importance of exercise (again without actually elucidating the underlying biological mechanisms by which exercise can reduce IBS symptoms), and encourages logging exercise, without any attempt to include motivational interviewing interventions or to help users overcome

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reluctance to exercise. In sum, the sham app includes standard, treatment-as-usual information and advice that patients with IBS would often be exposed to in other formats, but does not include any of the specific education or treatment strategies that the CBT approach utilizes and that are central to the Zemedy app.

In sum, the control app contains a good deal of informative text and a number of links to engaging relaxation videos. IBS has a relatively high placebo response rate, and we hope the control app will be both credible and somewhat engaging.

Study Design

Because there is considerable overlap between the basic design and materials of this study and the published study of Zemedy 1.0 [27] there is also considerable overlap between the two papers in the description of the basic methods, materials and data analysis plan. Rather than referring readers to the prior paper, some of that text is reproduced here.

This study is a randomized, superiority, non-blinded, cross-over trial with an active control group. The study is running from March 1, 2021 to an estimated completion date of May 28, 2023. Participants are recruited from the United States, and study personnel are based at the University of Pennsylvania's Department of Psychology but because both recruitment, assessment and the treatment itself are all remote, there is no physical location for the study.

Accrual: Participants will be recruited for the trial through IBS specific social media sites, as well as clinical trial listings at clinicaltrials.gov and iffgd.org (the International Foundation for Gastrointestinal Disorders). Most participants came to the original Zemedy study through Facebook, Twitter, and Reddit, so we anticipate that most of our participants for this second study will come from those sites as well. Notices and posts about the study on those sites include a link to a secure Qualtrics survey that contains the consent form and the baseline questionnaires.

Consent: All participants complete informed consent online prior to completing baseline questionnaires. The consent form explains the study, including information about random assignment and the compensation for completing study questionnaires at several follow-up time points. The consent form includes the information that participants will be compensated with $20 in Amazon credit after each round of follow-up questionnaire completion.

Inclusion and Exclusion Criteria: Inclusion criteria consists of being 18 years of age or older, and participant self-report of having been previously diagnosed by a physician with IBS and/or meeting Rome IV criteria[1] by self-report on a standardized questionnaire covering the Rome IV criteria, which will allow for sub-categorization of diarrhea predominant, constipation predominant, mixed or unspecified IBS. If participants report having been diagnosed with IBS by a physician, but do not currently meet

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strict Rome IV diagnostic criteria on the questionnaire they are still allowed in the trial. Many refractory IBS patients were diagnosed under the old Rome III criteria and the only criterion they fail to meet currently is frequency of abdominal pain. In addition, many patients who fail to meet strict diagnostic criteria still self-report experiencing IBS symptoms that result in equal distress and disability, and even great work impairment [2]. Thus, our inclusion criteria ensure that our sample will reflect the population of interest – people who believe they have IBS, having been told so by a physician and/or who meet strict Rome IV criteria, who are unhappy with their health status and are interested in trying a self-help app. Baseline questionnaire responses are reviewed by the study coordinator to ensure that inclusion criteria are met before participants are enrolled and randomized.

Exclusion criteria consists of having another comorbid GI disorder, such as celiac disease or an inflammatory bowel disease. Current or lifetime eating disorders were not evaluated or excluded. Many patients with IBS will meet criteria for fear based ARFID, but the CBT protocol actually addresses fear and avoidance of food. Exclusion criteria also include severe depression and/or suicidal ideation - defined as a positive endorsement at the level of 2 or 3 on the suicide item (item 9) of the Beck Depression Inventory. If a potential participant meets exclusion criteria on the basis of severe depression, the PI (a licensed clinical psychologist) contacts them to conduct a risk assessment and offers referral (if appropriate) to local resources. They are also given immediate access to the Zemedy app, if they are interested, but are not enrolled in the trial. Finally current pregnancy is also an exclusion criterion.

Power Analysis: Our goal is to recruit 300 participants. Most internet trials have an attrition rate approaching 50%[31], which would leave us with 150 participants in the study total (75 per group). CBT for IBS typically yields large effect sizes, and the effect sizes of Zemedy 1.0 on the primary outcome measures of GI symptom severity and HRQL were quite large (d = 1.02 and d = 1.25, respectively). Assuming a modest effect of the control app of approximately d = .30, then a final N of 150 will give us 90% power at $p < .05$ to detect a difference between groups.

Randomization: Participants who meet the inclusion criteria will be allocated to one of two conditions using the coin toss feature of random.org. The allocation sequence is concealed to participants until they are enrolled and assigned to the intervention.

Blinding: Because of the nature of the trial (immediate treatment versus active control group), neither participants nor research coordinators are blinded to condition. All outcome data is self-report, thus, blinding of evaluators is neither possible nor necessary. This means that participants are aware of their group allocation upon randomization.

Intervention and Assessments: All potential participants complete the baseline questionnaires as part of the screening process prior to enrollment and randomization. Upon allocation, those in the immediate treatment group will be given the link to access the Zemedy app and encouraged to download

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it and begin working through the modules immediately. The active control group will be given access to the education and relaxation training app upon allocation. Both groups work through their respective apps at their own pace during the following 8 weeks. , Four weeks after baseline, participants in both groups will be emailed to encourage them to continue using their respective app, and to let them know that they will be receiving the follow-up questionnaires in 4 weeks.

Eight weeks after allocation, all participants will be emailed with a second questionnaire battery which includes all the same measures as at baseline. Participants in the immediate treatment group will also complete the Mobile Application Rating Scale (uMars) for the purposes of quality improvement and product development. All participants who complete 8-week questionnaires will be compensated $20 in Amazon credit. The compensation is intended to incentivize participants to complete the questionnaires, and has no bearing on their actual use of the app. Upon completion of the follow-up questionnaires, participants in the active control condition will then be crossed over to the Zemedy app.

After having access to the Zemedy app for eight weeks, participants in the active-control group will be emailed a third battery of questionnaires which is identical to the battery received by the treatment group after eight weeks of app usage - it includes the same measures as the baseline battery and the Mobile Application Rating Scale (uMars). They will be compensated with a further $20 gift credit upon completion of the post-treatment questionnaires.

While we hope that compensation will reduce attrition from the study at follow-up assessments, we still anticipate an attrition rate of at least 50%, which is typical for behavioral health studies using online recruitment and low intensity, distance interventions.

See Figure 1 for Consort diagram.

Figure 1 – Consort Diagram

Measures

Baseline Screening Measure

Modified Rome IV Questionnaire.

We used a questionnaire to determine whether participants met current Rome IV diagnostic criteria for IBS. Our questionnaire was based on the Rome IV IBS-specific Questionnaire, which is a validated self-report scale that covers the diagnostic criteria for IBS. It has been found to have acceptable sensitivity and high specificity as well as good test–retest reliability[1]. Our measure is shorter (10 items) and uses slightly different numeric scales, but still covers all the primary diagnostic criteria for IBS.

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Primary Outcome Measures.

IBS quality of life (IBS–QoL).

The IBS–QOL[32] is a 34 item, self-report measure specific to IBS-related HRQL. It is rated on a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely). It is designed to assess the impact of IBS on quality of life. The IBS–QOL has high internal consistency (Cronbach's α= .95), high reproducibility (ICC = .86) and good construct validity. Qualitative score ranges are 0-31 (minimal or mild), 32-66 (moderate), and 67-100 (severe impairment). The mean IBS-QOL score for healthy controls is 5 (SD 11), leading to a cut-off point of 27 to fall within 2 SD of the healthy mean.

Gastrointestinal Symptom Rating Scale–IBS (GSRS–IBS).

The GSRS-IBS contains 13 self-report items rated on a 6-point Likert scale[33] ranging from 1 (no discomfort at all) to 7 (very severe discomfort). Total scores range from 13 to 91. The GSRS-IBS has 5 sub-scales, including abdominal pain, bloating, constipation, diarrhea, and satiety. Each dimension has demonstrated high internal consistency of Cronbach's alpha ranging from .74 (pain) to .85 (satiety). Furthermore, the GSRS- IBS has demonstrated both high test–retest reliability, with intra-class correlations among the factors ranging from .55 (pain) to .70 (bloating), as well as high construct validity[33]. The GSRS has been used as a primary outcome measure in a number of recent randomized controlled trials of IBS treatments (e.g.[21]) and the Rome Foundation reports that it is shorter and more user friendly than the IBS Severity Scoring System (IBS-SSS)[34]. Qualitative score ranges are 0-20 (minimal or mild), 21-39 (moderate), and 40-78 (severe). The mean GSRS score for healthy controls is 12 (SD 11), leading to a cut-off point of 34 to fall within 2 SD of the healthy mean.

Secondary Measures.

Fear of Food Questionnaire (FFQ).

The FFQ[35]is an 18-item, self-report questionnaire that measures fear, avoidance of food, and life interference and loss of pleasure from eating. Items are rated on a Likert scale ranging from 0 (not at all) to 5 (absolutely). It has excellent internal consistency reliability with Chronbach's $\alpha = 0.96$ and strong two-week test-retest reliability at $r = 0.93$, $p < .001$[35]. It also shows good criterion and known-groups validity. Qualitative score ranges are 0-15 (minimal), 16-30 (mild), 31-45 (moderate), and 46-90 (severe).

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Visceral sensitivity index (VSI).

The VSI[8,36] is a unidimensional, 15-item scale that measures gastrointestinal symptom-specific anxiety. Items are rated on a Likert scale ranging from 0 (strongly disagree) to 5 (strongly agree). It has high internal consistency ($\alpha = 0.93$) and a mean inter-item correlation of 0.47[36]. It has good criterion, construct, and predictive validity[36]. Qualitative score ranges are 0-10 (minimal or mild), 11-30 (moderate), and 31-75 (severe).

Gastrointestinal Cognitions Questionnaire (GI-Cog).

The GI-Cog consists of 16 self-report items that are rated on a 5-point Likert scale, ranging from 0 (Hardly) to 4 (Very much). Individual items are summed, and total scores range from 0 to 64. The questionnaire consists of three subscales, the pain/life interference subscale (e.g. ‘‘When I feel my GI symptoms acting up, I’m afraid the pain will be excruciating and intolerable’’), the social anxiety subscale (e.g. ‘‘If I have to get up and leave an event, meeting, or social gathering to go to the bathroom people will think there’s something wrong with me’’), and the disgust sensitivity subscale (e.g. ‘‘The thought of fecal incontinence is terrifying. If it happened, it would be awful’’). The GI-Cog has been shown to have excellent internal consistency (a = .92) and test-retest reliability (r = .87, p = .001)[37]. Qualitative score ranges are 0-19 (minimal or mild), 20-39 (moderate), and 40-64 (severe).

Beck Depression Inventory (BDI-II).

The BDI-II consists of 21 self-report items, each on a 4 point scale ranging from 0 to 3 (0 being not at all, and 3 meaning extreme), therefore scores can range from 0 to 63. It is scored by adding the severity ratings of each item. A score greater than 20 indicates moderate depression. It has been found to have good internal consistency and test retest reliability[38]. Qualitative score ranges are 0-13 (minimal), 14-20 (mild), 21-30 (moderate), 31-63, (severe).

Work Productivity and Activity Impairment: plus Classroom Impairment Questionnaire, Irritable Bowel Syndrome (WPAI+CI:IBS)

The WPAI is a standard measure of the economic, occupational and/or educational impact of a disease or disability [39]. It has been adapted for a number of specific conditions, including IBS. Questions cover missed hours of work or school due to IBS, and participant rated impact on productivity (at work or in school) and daily activities. The measure has good construct validity and adequate reproducibility. [39]

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Quality Improvement and Product Development Measure

Mobile-Application Rating Scale (uMARS).

The uMARS is an end-user version of the Mobile Application Rating Scale which is a 26-item measure including 4 objective quality subscales (engagement, functionality, aesthetics, and information quality), 1 subjective quality subscale, a 6-item perceived impact subscale, and a space to provide feedback[40]. The uMARS scale is used to obtain user feedback on the quality of mobile apps during the development and testing process. The uMars has been shown to have excellent internal consistency (Cronbach's α = .90), and high internal consistencies of its subscales (engagement α= .80; functionality α= .70; aesthetics α= .71; information α= .78; and satisfaction α= .78)[39]. Test-Retest Reliability of the uMARS scale was found to be good with an average intraclass correlation coefficient (ICC) of 0.68[41]. It is not a clinical outcome measure, but will be used to inform future product development.

Data Analysis

Univariate general linear models in SPSS V25 will be used to examine between group effects at post treatment (8 weeks), controlling for baseline levels of the dependent variable. Paired sample t-tests will be used to examine within group change over their treatment phase for each group and maintenance of gains from post treatment to 3 months follow-up, as well as at 6 and 12 months follow-up. The robustness of these analyses will be examined in an intent-to-treat sensitivity analysis by using multiple imputation. Regression models will then be fitted as in the primary analysis, and pooled estimates of the treatment effect calculated. Three sets of imputed datasets will be created, one for each follow-up data point, baseline measures included in each.

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Change in visceral anxiety, catastrophizing (as measured by the GI-cog) and fear of food (calculated as change from baseline to 8 weeks) will be explored as possible mediators of GI symptoms and quality of life at 8 weeks using regression analysis with estimates of indirect effects will be calculated using a percentile bootstrap estimation approach with 5000 samples implemented with the PROCESS macro Version 3.5[42]. Both direct and indirect effects will be reported. The direct effect quantifies the estimated difference in the dependent variable (GI symptoms or quality of life) between two cases that are equal on the mediator but differ by one unit on treatment assignment, i.e., intervention vs waitlist group. The indirect effect quantifies how much two cases, one assigned to immediate treatment, the other to waitlist, are estimated to differ on the dependent variables (GI symptoms or quality of life) as a result of treatments' influence on the mediator, which in turn influences the dependent variable. Two sets of models will be fitted, the first testing the mediator variables separately with simple mediator models, the second fitting a parallel mediator model where the three mediators will be tested simultaneously. The baseline level of the dependent variable will be included as a covariate in all mediation models.

Finally, baseline symptom severity, depression and IBS subtype will be examined as potential moderators of treatment efficacy.

Patient and public involvement statement

There was no direct patient or public involvement in the design of this research. However, the first author has an active clinical practice in which they work with many IBS patients, and patient feedback and clinical experience informs the development of Zemedy. There was also patient feedback from the RCT of Version 1.0 of Zemedy that guided many of the updates to the app to make it more engaging and user friendly.

ETHICS AND DISSEMINATION

This study was approved by the Institutional Review Board of the University of Pennsylvania. Participants who endorse suicidal ideation will be contacted by the PI who will offer a risk assessment and referrals to local in person providers. The active control app recommends certain approaches (such as restrictive diets) that are contraindicated in CBT, but are widely used management strategies for IBS. After the completion of this study, we hope and expect to find that Zemedy outperforms the educational and relaxation app in improving HRQL and GI symptom severity. We also hope to see that Zemedy 2.0 is rated more highly than Version 1.0 in user engagement, functionality, aesthetics, and information quality. We plan to submit the resulting paper to a high impact peer reviewed journal. De-identified data will be made available in a data repository.

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Author Contributions

Melissa Hunt: Conceptualization, Methodology, Designing Intervention, Resources, Writing - Original Draft and Revisions, Supervision. Anika Dalvie: Conceptualization, Methodology, Designing Control Intervention, Writing, Project Administration, Software, Investigation, Participant Recruitment, Data Curation. Simay Ipek: Methodology, Designing Control Intervention, Project Administration, Software, Investigation, Data Curation. Ben Wasman: Designing Control Intervention, Participant Recruitment.

Ethics approval Institutional review board of the University of Pennsylvania.

Funding Statement:

This work was supported by Bold Health. Bold Health also designed and provide tech support to the app itself, and provide some data regarding compliance and utilization of the app.

Competing Interests Statement:

Melissa Hunt serves as a scientific consultant to Bold Health and accepts a modest (less than $5,000 per annum) consulting fee. She has no ownership interest in the company. None of the other authors have any competing interests to declare.

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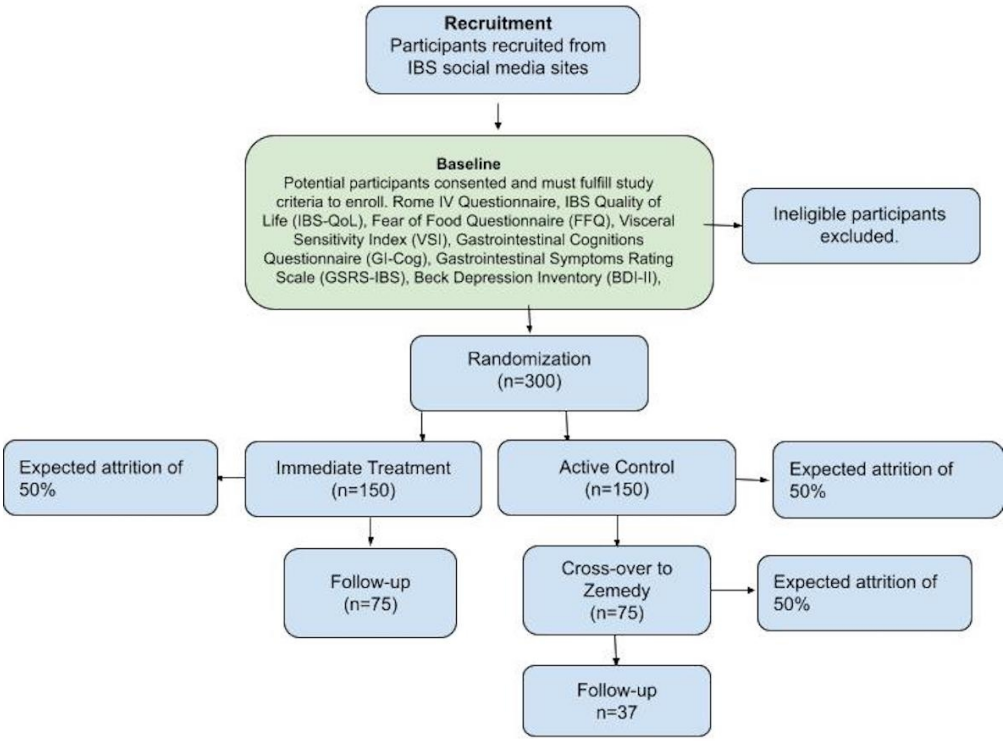

Figure 1 - Consort Diagram

99x75mm (300 x 300 DPI)

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

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Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	na
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	na

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	na

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	na
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	na
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	8

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	na
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	na
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	na

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		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	na
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	na

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	na
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	na
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	na
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	na

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