The Efficacy of Zemedy, a Mobile Digital Therapeutic for the Self-Management of Irritable Bowel Syndrome: a Cross-Over, Randomized Controlled Trial

Melissa Hunt, Sofia Miguez, Benji Dukas, Obinna Onwude, Sarah White

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Abstract

Background: Patients with irritable bowel syndrome (IBS) experience abdominal pain, altered bowel habits, and defecation-related anxiety which can result in reduced productivity and impaired health related quality of life (HRQL). Cognitive-behavioral therapy (CBT) has been shown to reduce symptoms of IBS and to improve HRQL, but access to qualified therapists is limited. Smartphone-based digital therapeutic interventions have the potential to increase access to guided CBT at scale but require careful study to assess their benefits and risks.

Objective: To test the efficacy of a novel app, Zemedy - a mobile digital therapeutic that delivers a comprehensive CBT program to individuals with IBS.

Methods: This was a cross-over randomized controlled trial (registration number NCT04170686). Participants were recruited online. Patients were randomly allocated to either immediate treatment (N = 62) or waitlist control (N = 59). The Zemedy app consists of 8 modules focusing on psychoeducation, relaxation training, exercise, the cognitive model of stress management, applying CBT to IBS symptoms, reducing avoidance through exposure therapy and behavioral experiments, and information about diet. Users interact with a chatbot that presents the information and encourages specific plans, homework and exercises. The treatment was fully automated, with no therapist involvement or communication. At baseline and after 8 weeks, participants were asked to complete the battery of primary (Irritable Bowel Syndrome Quality of Life (IBS-QoL), Gastrointestinal Symptom Rating Scale (GSRS)) and secondary outcome measures (the Fear of Food Questionnaire (FFQ), the Visceral Sensitivity Index (VSI), the GI Cognition Questionnaire (GI-COG), the Depression, Anxiety Stress Scale (DASS) and the Patient Health Questionnaire (PHQ-9)). Waitlist controls were then offered the opportunity to cross over. All participants were assessed one more time at 3 months post-treatment completion.

Results: Both intent-to-treat and completer analyses at post-treatment revealed significant improvement for the immediate treatment group compared to the waitlist control group on both primary and secondary outcome measures. Gains were generally maintained at 3 months post-treatment. Scores on the GSRS, IBS-QoL, GI-COG, and VSI all improved significantly more in the treatment group [$F(1,79) = 20.49$, $P < .001$, Cohen's $d = 1.01$; $F(1,79) = 20.12$, $P < .001$, $d = 1.25$; $F(1,79) = 34.71$, $P < .001$, $d = 1.47$ and $F(1,79) = 18.7$, $P < .001$, $d = 1.07$]. Fear of food also decreased for the treatment group relative to the control group [$F(1,79) = 12.13$, $P = .001$, $d = .62$]. Depression improved significantly as measured by both the PHQ9 [$F(1,79) = 10.5$, $P = .002$, $d = 1.07$] and the DASS Depression Subscale [$F(1,79) = 6.03$, $P = .016$, $d = .83$], as did the stress subscale of the DASS [$F(1,79) = 4.47$, $P = .04$, $d = .65$] in the completer analysis but not the intent-to-treat analysis. The impact of treatment on HRQL was mediated by reductions in catastrophizing and visceral sensitivity.

Conclusions: Despite its relatively benign physical profile, IBS can be an extraordinarily debilitating condition. Zemedy is an effective modality to deliver CBT for individuals with IBS, and could increase accessibility of this evidence based treatment.

Clinical Trial: This trial was registered at ClinicalTrials.gov as NCT04170686

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Conclusions

Despite its relatively benign physical profile, IBS can be an extraordinarily debilitating condition. Zemedy is an effective modality to deliver CBT for individuals with IBS, and could increase accessibility of this evidence-based treatment.

Trial Registration

This trial was registered at ClinicalTrials.gov as NCT04170686.

Keywords

Digital health; irritable bowel syndrome; cognitive behavioral therapy

Introduction

Background

Irritable Bowel Syndrome (IBS) is a chronic gastrointestinal (GI) disorder of centralized pain processing. It is characterized by recurrent abdominal pain that is relieved by defecation, and is accompanied by abnormalities 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 10% of the population in the US). Many studies have demonstrated that IBS has high rates of psychiatric comorbidity (up to 90% in treatment seeking patients) [1,2], and causes social and occupational impairment [3]. 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. Visceral hypersensitivity, common among IBS patients, is 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 [4]. Anxiety and visceral hypersensitivity are highly correlated [5]. Anxiety and hypervigilance related to the sensations exacerbates the hypersensitivity [6].

Illness-related anxiety is high among IBS patients, and is a better predictor of impairment in quality of life than actual symptom severity [7]. 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 [3]. Catastrophizing is highly correlated with impairment in health related quality of life in IBS patients [8]. Because of their catastrophizing, many individuals with IBS engage in significant avoidance behavior that can easily meet criteria for agoraphobia [9].

Cognitive behavioral therapy for IBS

Over the past two decades, cognitive behavioral therapy (CBT) has repeatedly proven to be an efficacious treatment for individuals suffering from IBS [10, 11]. Specifically, there is empirical support that CBT reduces GI symptom severity and impairment to quality of life [12, 13]. These CBT treatments typically include components of psychoeducation about the brain-gut axis, mindfulness and relaxation training [14], reducing automatic negative thoughts related to GI catastrophizing [15], exposure therapy to feared and avoided sensations and situations [16] and reducing visceral hypersensitivity [12]. 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 [17].

While CBT is a promising treatment, access to IBS-specific CBT remains low for patients. There is a lack of clinicians competent in delivering GI-specific CBT [3]. Additionally, the cost of treatment looms high; individuals often lack insurance coverage for psychotherapy and must pay out of pocket, which can be burdensome given the hundreds of dollars their IBS likely already costs them [18]. It is therefore necessary to develop a cheaper, more easily accessible alternative mode of treatment.
Many groups have tested variants of CBT for IBS with limited or distant therapist involvement (e.g., via email) [19, 15] 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. 20]. Several treatment manuals and self-help books are available that detail the CBT treatment approach, and one [21] was found to be efficacious as a stand-alone treatment in a randomized controlled trial [22].

In today's digitized world, the mobile health (mHealth) industry is growing. The industry is currently valued at close to $50 billion and is expected to multiply by nearly five times over the next decade [23]. 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.

CBT is among the forms of treatment increasingly being delivered via apps. In their review of eight CBT apps, Rathbone, Clarry and Prescott found that CBT self-help apps can be efficacious, most notably in alleviating depressive symptoms [24]. They also cited the willingness of participants to engage in therapy as a key component of the apps' success [24]. A component of many mHealth apps, and specifically those that use CBT, is automated guidance and feedback. Automated guidance has been found to be effective in reducing substance abuse among urban women and emerging adults [25, 26]. Kelders et. al. compared an automated treatment for depression with standard, in-person clinical treatment and found that depressive symptoms were moderately reduced for those in the automated group, though not as strongly as the in-person treatment group [27]. However, Mason and Andrews' internet CBT study found that "specialist assessments and initial face-to-face contact do not influence treatment outcome, and that patients do just as well with an automated assessment" [28]. Hauser-Ulrich et. al. developed a smartphone app to treat chronic pain through CBT [29]. It employs a chatbot that guides users through modules [29]. In their randomized control trial (RCT), the authors found improvements in pain-related impairment, pain intensity, and general well-being for those who used the app for eight weeks [29]. Thus, there is strong evidence to suggest that automated treatment in a CBT app may be highly effective in delivering integrative behavioral health care for patients with disorders at the boundary between physical symptoms and psychological distress.

Aim

As self-help modalities are increasingly available online and through smart phone apps, it is important to test the efficacy of those apps through rigorous, controlled research. The purpose of this study was to test the efficacy of a novel digital app (Zemedy) that applies CBT to IBS.

Methods

Trial Registration

This study was approved by the Institutional Review Board at the University of Pennsylvania. All participants provided electronic consent prior to participation in the study. The de-identified dataset analyzed in the study is available from the corresponding author upon request. This trial was registered at ClinicalTrials.gov as NCT04170686.

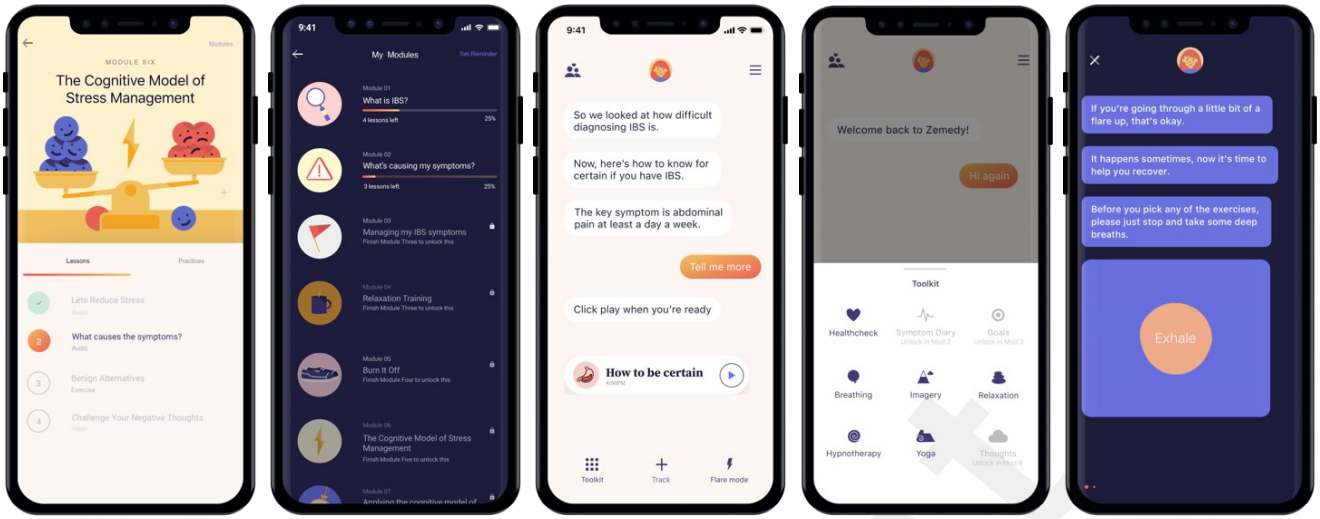
App Description

Zemedy 1.0 is a mobile phone application designed by Bold Health, a UK-based digital health company, in collaboration with Melissa Hunt based on her empirically supported self-help book [21]. The app treats irritable bowel syndrome through cognitive behavioral therapy specifically developed for IBS. Users of either iOS or Android smartphones are guided through the app by a chatbot with whom they "text." The app consists of ten modules. The first two modules are devoted to psychoeducation about the etiology of IBS and CBT's effectiveness in treating it. The remaining eight modules teach users about various CBT strategies to mitigate the impact of IBS on daily life, including relaxation training, exercise, cognitive-restructuring and de-catastrophizing, exposure exercises to reduce avoidance, and behavioral experiments. It also encourages a healthful (but not highly restrictive) diet. See (Figure 1) for screenshots of the Zemedy app. Users are prompted to apply these strategies to their daily lives. Similar to the chronic pain treatment developed by Hauser-Ulrich, et al. (2020), it is designed to be completed in 8 weeks [29]. Participants were encouraged to read through the first 5 modules (education, relaxation training and exercise) in the first week, and to practice relaxation exercises daily. The remaining modules were designed to be worked through approximately one per week, with practice and homework exercises done daily to learn and apply the skills.

The app also includes a "flare module," which users can access at any point to address immediate GI pain and anxiety. Shah et. al. found that mind body interventions, such as relaxation training and hypnosis, have moderate effect sizes in reducing IBS symptoms [14]. The flare module contains a variety of exercises such as deep breathing, progressive muscle relaxation, relaxation imagery, and hypnotherapy scripts that help mitigate distress and discomfort in the moment.

Participants were provided with a link to download the application. They were provided the application at no cost. The entire intervention was delivered within the app with no human involvement (e.g. therapist guidance or feedback). If participants experienced technical difficulties they could reach out to tech support at Bold Health. They received a single email at 4 weeks from a research coordinator in the trial providing general encouragement to continue working through the app (if they were in the immediate treatment group) or to "hang in there" (if they were in the waitlist control group).

Figure 1. Screenshots of Zemedy V1



Design

This was a randomized, wait-list control, cross-over trial with assessments conducted at baseline, post-intervention (8 weeks), post cross over to intervention for the wait-list control group, and at follow-up (3 months post intervention completion). After completing the consent and all the baseline measures, participants were randomly allocated by a research coordinator to either immediate treatment or waitlist control using the coin toss function of random.org. After 8 weeks, all participants were asked to complete the same battery of measures. At that point, participants in the waitlist were crossed over and were given access to the app. After 8 weeks of access, they were asked to complete the battery of questionnaires again. All participants were then assessed one final time 3 months after completing the treatment phase. Unfortunately, the onset of the COVID-19 pandemic coincided with the follow-up portion of the trial, and it is unclear the extent to which the pandemic affected both attrition and long-term results.

Sample Size

The power analysis showed that 30 participants per randomised group, would have 85% statistical power at a two-sided significance level of 0.05 to detect an effect size of 0.76. The effect size was chosen as previous studies of internet delivered CBT for IBS had found effect sizes similar to this for health-related quality of life (HRQL) and GI symptoms outcomes [15, 22]. Assuming 50% attrition, as is common in internet-based intervention studies, we aimed to recruit 120 participants in order to have ample power to both detect main effects and to explore potential mediators and moderators.

Participants

A total of 146 potential participants were screened, of whom 121 met inclusion/exclusion criteria. Participants were recruited for the trial through IBS specific social media sites with a combination of graphic advertisements and posts and comments on threads informing site users about the study. Most participants came to the study through Facebook (N=30), Twitter (N=32), and the IBS subReddit (N=51). There were no face-to-face components to the trial in either recruitment, assessment or intervention. Posts and advertisements included a link to a secure University of Pennsylvania Qualtrics study page. On following the link, potential participants would first see the detailed explanation of the research (Consent Form - See Appendix A) and would consent to completing the baseline questionnaires. Questionnaires were completed via Qualtrics and could be downloaded securely by the research team. Participants were identified by email during data collection. All data was stored de-identified. All recruitment and follow-up occurred between 10/01/2019 and 11/01/2020. The trial ended upon successful completion.

Inclusion and Exclusion Criteria

Inclusion criteria consisted of being 18 years of age or older, and reporting having been previously diagnosed by a physician with IBS. Owning a smartphone and computer/internet literacy were de facto eligibility criteria.

Exclusion criteria consisted of reporting being diagnosed with another comorbid GI disorder, such as celiac disease or an inflammatory bowel disease. Exclusion criteria also included severe depression and/or suicidal ideation - defined as a score of 20 or above on the Patient Health Questionnaire - 9 (PHQ-9) and/or positive endorsement of active suicidal ideation and/or intent on a separate suicide question. Twenty-five individuals met this criterion. They were excluded from the trial, but were given immediate access to the app.

Randomization and Blinding

Participants who met the inclusion and exclusion criteria were allocated to condition using the coin toss feature of random.org. A total of 62 participants were assigned to the immediate treatment condition and 59 were assigned to the waitlist control. The allocation sequence was concealed to participants until they were enrolled, had completed baseline data collection and been assigned to a group. The majority of baseline symptom severity measures were not significantly different between the immediate treatment and waitlist control groups. However, the waitlist control reported statistically significantly more depression and more impaired health related quality of life than the immediate treatment group. While the design should have yielded low risk of bias from randomization, the slight differences in symptom severity at baseline suggest some concerns about randomization, according to the Cochrane risk of bias tool [30].

Because of the nature of the trial (immediate treatment versus waitlist control group), neither participants nor research coordinators were blinded to condition. However, there were no deviations from the intended intervention. Moreover, all outcome data was self-report. Thus, blinding of evaluators was neither possible nor necessary.

Procedure

Those in the immediate treatment group were given the link to access the Zemedy app and encouraged to download it and begin working through the modules immediately. The waitlist-control group was told they would be given access in eight weeks. Four weeks after baseline, participants in the treatment group were emailed to encourage them to continue using the app, and the waitlist-control group was emailed to offer encouragement, remind them they were still enrolled in the study, and let them know that they would be receiving the follow-up questionnaires in 4 weeks.

Eight weeks after completing the baseline questionnaire, all participants were emailed a link to a second Qualtrics page which contained all the same measures as at baseline. Those in the waitlist-control condition were then given access to the app.

After having had access to the app for eight weeks, participants in the waitlist-control group were emailed a link to the third battery of questionnaires which was identical to the battery received by the treatment group after eight weeks of app usage - it included the same measures as the baseline battery.

Finally, all participants were emailed a final link to the last battery of questionnaires (again identical to the battery at baseline and post-treatment) 3 months after they completed the active treatment phase. Upon completion of each round of questionnaires, participants received $20 in Amazon credit.

If at any point a participant had indicated a significant increase in depressive symptoms or the onset of suicidal ideation, the team would have alerted the PI (a licensed clinical psychologist) who would have reached out to that individual to conduct a risk assessment and offer referrals to local resources. No such adverse events occurred.

Primary Outcome Measures

IBS quality of life (IBS–QoL)

The IBS–QOL is a 34 item, self-report measure specific to IBS designed to assess the impact of IBS on quality of life [31, 32]. The IBS–QOL has high internal consistency (Cronbach's α= .95), high reproducibility (ICC = .86) and good construct validity [32]. Qualitative scores ranges are 0-31 (minimal or mild), 32-66 (moderate) and 67-100 severe impairment.

Gastrointestinal Symptom Rating Scale–IBS (GSRS–IBS)

The GSRS-IBS contains 13 self-report items rated on a 6-point Likert scale ranging from 1 (no discomfort at all) to 7 (very severe discomfort) [33]. Total scores range from 0 to 78. 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]. Overall internal consistency was good in our sample with Cronbach's a = .81. The GSRS has been used as a primary outcome measure in a number of recent randomized controlled trials of IBS treatments [9] 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)

Secondary Outcome Measures

Rome IV Criteria 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 [35]. We used a modified, shortened version with 10 items that covered all diagnostic criteria.

Fear of Food Questionnaire (FFQ)

The FFQ is an 18-item, self-report questionnaire that measures fear, avoidance of food, as well as life interference and loss of pleasure from eating [36]. Items are rated on a Likert scale ranging from 0 (not at all) to 5 (absolutely). It has excellent internal consistency reliability with Cronbach's $\alpha = 0.96$ and strong two-week test-retest reliability at $r = 0.93$, $p < .001$ [36]. It also shows good criterion and known-groups validity [36]. Qualitative scores ranges are 0-15 (minimal), 16-30 (mild), 31-45 (moderate) and 46-90 (severe).

Visceral sensitivity index (VSI)

The VSI is a unidimensional, 15-item scale that measures gastrointestinal symptom-specific anxiety [6, 37]. 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 [37, 38]. It has good criterion, construct, and predictive validity [6]. Qualitative scores 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) [39]. Qualitative scores ranges are 0-19 (minimal or mild), 20-39 (moderate) and 40-64 (severe).

Depression Anxiety Stress Scale (DASS)

The DASS is a 42-item, self-administered questionnaire which measures the magnitude of depression, anxiety, and stress, independently. Internal consistency for each of the subscales of the questionnaire are high Cronbach’s α of 0.96 to 0.97 for DASS-Depression, 0.84 to 0.92 for DASS-Anxiety, and 0.90 to 0.95 for DASS-Stress [40, 41]. The DASS has been found to be a highly reliable and valid measure of the constructs it is intended to assess [42].

Patient Health Questionnaire - 9 (PHQ-9)

The PHQ-9 is a depression scale that consists of 9 self-report items. The 9 items aim to quantify the 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based. The PHQ-9 can establish depressive disorder diagnosis and depressive symptom severity [43]. Each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day); therefore, scores can range from 0 to 27. The PHQ-9 has been found to demonstrate high internal reliability, with a Cronbach's α of 0.89 when tested in a primary care setting and 0.86 when tested in an Ob-Gyn setting [43].

Dose

Dosage was measured according to the time of mobile app use and frequency of items completed. We calculated both factors based on mobile log data that registered the screens viewed and components used by the participants during each visit, along with the total amount of time spent on the app. Time of app use represents the overall amount of time spent on the Zemedy app. The mobile app sent usage Data to the backend system each time a participant visited the app. Data includes time and date of each session on the app.

Statistical Analysis

Univariate general linear models in SPSS V25 were used to examine between group effects at post treatment (8 weeks), controlling for baseline levels of the dependent variable. Paired sample t-tests were 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 were examined in an intent-to-treat sensitivity analysis by using multiple imputation. As is shown later missing data at follow-up was not entirely missing at random. Therefore baseline outcome measures were included in the imputation model as predictors together with the follow-up set of measures with missing data and imputation using the fully conditional specification [46] conducted to create 15 imputed datasets. Regression models were then fitted as in the primary analysis, and pooled estimates of the treatment effect calculated. Three sets of imputed datasets were created, one for each follow-up data point, baseline measures included in each.

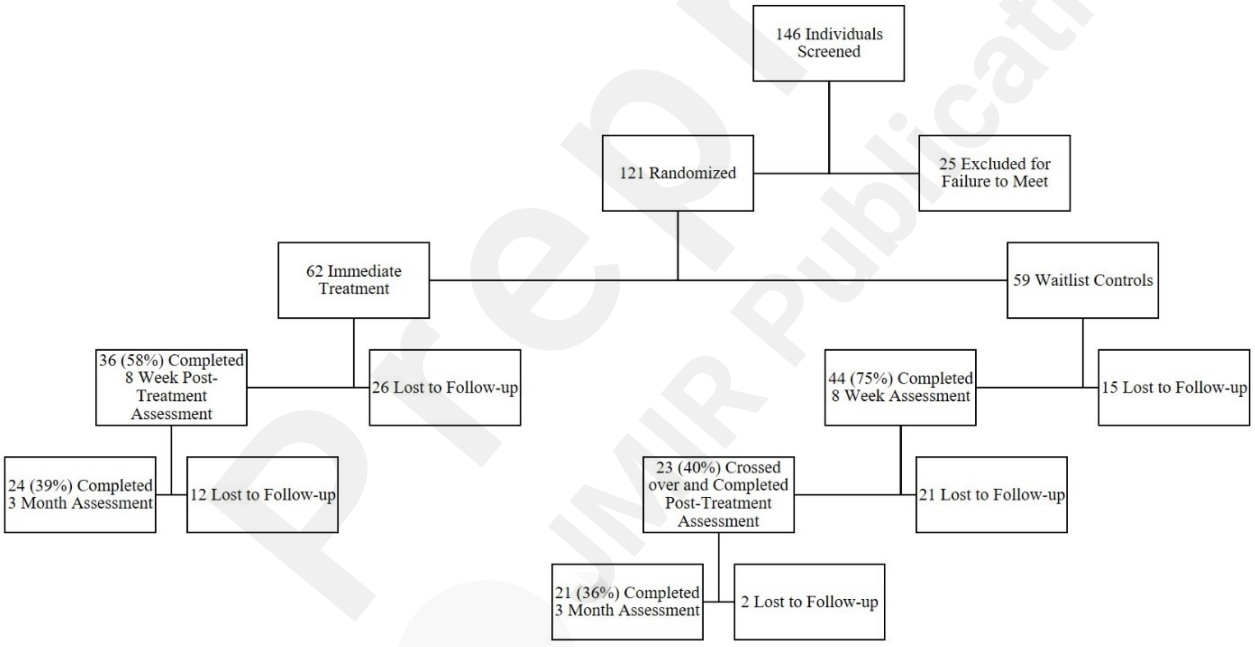
Change in visceral anxiety, catastrophizing and fear of food (calculated as change from baseline to 8 weeks) were explored as possible mediators of GI symptoms and quality of life at 8 weeks using regression analysis with estimates of indirect effects calculated using a percentile bootstrap estimation approach with 5000 samples implemented with the PROCESS macro Version 3.5 [47]. Both direct and indirect effects are 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 were fitted, the first tested the mediator variables separately with simple mediator models, the second fitted a parallel mediator model where the three mediators were tested simultaneously. The baseline level of the dependent variable was included as a covariate in all mediation models.

Results

Participant Characteristics

The mean participant age was 32 (std=10.2, range 18-63). Of the total 121 participants, 76% (92 participants) were white, 6% (7 participants) were Hispanic, 5% (6 participants) were black, 4% (5 participants) were Asian and the remaining 9% (11 participants) identified as mixed race or other. With respect to gender, 75% (91 participants) identified as female and 25% (30 participants) identified as male. With respect to marital status, 43% (52 participants) reported being single at baseline, 32% (39 participants) reported being married at baseline, 19% (23 participants) reported having a partner or cohabiting at baseline, and 6% (7 participants) reported being divorced at baseline. With respect to employment, 22% (27 participants) were students, 16% (19 participants) reported being employed part-time, 48% (58 participants) reported being employed full-time, and 14% (17 participants) reported that they were not working when completing the baseline surveys. See (Figure 2) for the Consort Diagram of participant flow through the study.

Figure 2. Consort Diagram



There were no significant differences between the immediate treatment and waitlist-control groups on any of the demographic variables or in baseline GI symptoms, visceral sensitivity, catastrophizing, or fear of food. However, as noted above, the waitlist-control group was found to be more slightly more distressed than the treatment group at baseline. The waitlist-control group reported statistically significantly more depression [for PHQ, $t(119) = 2.99$, $P = .003$; for DASS Depression $t(119) = 2.11$, $P = .037$] and more impaired health related quality of life than the immediate treatment group [$t(119) = 2.04$, all $P = .044$], although effect sizes were modest [$d = .38$ for the DASS, $d = .54$ for PHQ and $d = .37$ for QoL]. Thus, baseline symptoms were controlled in all analyses.

There were no univariate outliers found at baseline.

Outcomes

Completer analyses assessing the impact of treatment on outcome at 8 weeks revealed significant improvement for the immediate treatment group, relative to the waitlist control group, for both primary outcomes of GI symptom severity and HRQL [$F(1,79) = 20.12$, $P < .001$, Cohen's $d = 1.02$ and $F(1,79) = 20.49$, $P < .001$, $d = 1.25$, respectively]. With respect to the secondary outcome measures. GI specific catastrophizing, visceral anxiety and fear of food all improved significantly more in the treatment group [$F(1,79) = 34.71$, $P < .001$, $d = 1.47$, $F(1,79) = 18.7$, $P < .001$, $d = 1.07$, and $F(1,79) = 12.13$, $P = .001$, $d = .62$, respectively]. Finally, depression improved significantly more in the immediate treatment group as measured by both the PHQ9 [$F(1,79) = 10.5$, $P = .002$, $d = 1.07$] and the DASS Depression Subscale [$F(1,79) = 6.03$, $P = .016$, $d = .83$], as did the stress subscale of the DASS [$F(1,79) = 4.47$, $P = .038$, $d = .65$]. Only the DASS Anxiety subscale failed to show a significant advantage for the treatment group [$F(1,79) = 1.84$, $P = .18$, $d = .41$]. See (Table 1) for all means and standard deviations across all assessment timepoints. These results were replicated in the intent-to-treat analyses using multiple imputation, with the exception of the PHQ and DASS which were non-significant. See (Table 2).

Table 1. Means and Standard Deviations for all Outcome Measures Across Trial

	Baseline			**8-Weeks**			**Waitlist Post-Treatment**			**3 Months**
	N	M	SD	N	M	SD	N	M	SD	N
IBS-QoL										
Immediate Tx	62	53.63	18.67	36	34.25	19.78				24
Waitlist Control	59	60.48	18.29	44	58.19	18.53	23	47.6	20.07	21
GSRS										
Immediate Tx	62	36.76	12.77	36	27.56	10.12				24
Waitlist Control	59	37.75	12.02	44	38.18	10.79	23	34.26	14.98	21
GICog										
Immediate Tx	62	36.92	13.35	36	22.44	13.72				24
Waitlist Control	59	40.07	12.04	44	40.84	11.23	23	33.3	12.34	21
VSI										
Immediate Tx	62	51.74	12.29	36	38.14	16.21				24
Waitlist Control	59	53.54	11.44	44	53.57	12.37	23	46.43	12.78	21
FFQ										
Immediate Tx	62	52.87	19.14	36	41.22	22.23				24
Waitlist Control	59	55.46	18.21	44	53.75	18.08	23	46.1	19.87	21
PHQ										
Immediate Tx	62	8.32	5.29	36	5.78	4.2				24
Waitlist Control	59	11.03	4.66	44	10.32	4.29	23	10.30	5.80	21
DASS Depression										
Immediate Tx	62	11.65	9.88	36	7.83	7.88				24
Waitlist Control	59	15.59	10.69	44	15.45	10.39	23	14.43	10.89	21
DASS Stress										

Immediate Tx	62	17.84	9.56	36	12.72	8.65				24
Waitlist Control	59	18.71	8.97	44	18.82	9.99	23	18.78	10.03	21
DASS Anxiety										
Immediate Tx	62	12.03	7.35	36	8.67	6.38				24
Waitlist Control	59	12.19	9.14	44	12.05	9.72	23	11.83	9.72	21

Table 2. Significance of TX allocation at 8 weeks using multiple imputation

Measure	t	Sig. (2-tailed)
IBS-QoL	-2.8	.005
GSRS	-2.8	.005
GI-COG	-3.4	.001
VSI	-2.8	.006
FFQ	-2.4	.017
PHQ	-1.7	.083
DASS Depression	-1.3	.207
DASS Stress	-1.2	.247
DASS Anxiety	-0.6	.553

For the immediate treatment group, all of the outcome variables changed significantly from pre to post treatment with the exception of the DASS depression scale, which showed only marginally significant improvement. See (Table 3). Sensitivity analysis using multiple imputation found the same pattern of significance.

Table 3. Improvement from Baseline to Post-Treatment for the Immediate Treatment Group

Measure	t	df	Sig. (2-tailed)
IBS-QoL	4.368	35	<.001
GSRS	3.312	35	.002
GI-COG	5.603	35	<.001
VSI	3.454	35	.001
FFQ	3.523	35	.001
PHQ	2.327	35	.026
DASS Depression	1.707	35	.097
DASS Stress	2.273	35	.029

DASS Anxiety	2.164	35	.037

Clinically Significant Change

In terms of *clinically* significant change we used Criterion B (falling within 2 SD of the healthy mean) which is more conservative than Criterion A (falling 2 SD below the pathological mean) [48]. For GI symptoms, the mean GSRS score for healthy controls is 12 with a standard deviation of 11, leading to a cutpoint of 34. In the immediate treatment group, 24 out of 36 participants (66%) met this criterion at post-treatment. For HRQL, the mean IBSQoL score for healthy controls is 5 with a standard deviation of 11, leading to a cutpoint of 27. In the immediate treatment group 16 out of 36 participants (44%) met this criterion at post-treatment. Looked at another way, the qualitative range for minimal to mild impairment on the IBSQoL is 0-31. An additional 2 participants would meet this slightly less stringent criterion, leading to a total of 50% of participants in the immediate treatment group showing an excellent response. This yields a number-needed-to-treat (NNT) of 2.

After completing the 8 week follow-up questionnaires, the waitlist group was crossed over to active treatment and was given access to the app for eight weeks. Paired samples T-tests comparing their scores at the initial 8 week follow-up to their scores post-treatment revealed significant improvement in health related quality of life, catastrophizing, visceral anxiety and fear of food, but not on GI symptoms, depression or anxiety. See (Table 4). Sensitivity analysis using multiple imputation showed a similar pattern of significance at the 5% level but with lower p-values closer to the significance level.

Table 4. Improvement in Wait-List Control Group After Cross-Over to Active Treatment

Measure	t	df	Sig. (2-tailed)
IBS-QoL	-3.124	22	.005
GSRS	-1.308	22	.204
GI-COG	-2.748	22	.012
VSI	-2.618	22	.016
FFQ	-3.509	22	.002
PHQ	.103	22	.919
DASS Depression	-1.537	22	.139
DASS Stress	-.361	22	.722
DASS Anxiety	.360	22	.723

Three month follow-up data were collected for all subjects (both the immediate treatment group and the wait list group, who had been crossed over to treatment) between March and October of 2020. Unfortunately, this meant that all follow-up data were collected after the onset of the COVID-19 pandemic. Nevertheless, participants (all of whom had had access to the active treatment at this point) continued to show significant improvement over baseline on all outcome variables except depression. See (Table 5).

Table 5. Difference between Baseline and Three Month Follow-Up Data All Subjects

Measure	***t***	***df***	***Sig. (2-tailed)***
IBS-QoL	5.136	44	.000
GSRS	4.064	44	.000
GI-COG	6.090	44	.000
VSI	4.261	44	.000
FFQ	4.000	44	.000
PHQ	1.489	44	.144
DASS Depression	.499	44	.620
DASS Stress	2.264	44	.029
DASS Anxiety	3.012	44	.004

Finally, we assessed maintenance of treatment gains from post-treatment to 3 month follow-up. Without exception, gains were maintained, and there were no significant changes or relapse in symptoms, except for a slight rise in depression. Thus, even in the face of an incredibly stressful global pandemic, by and large our participants showed remarkable resilience and their HRQL, GI symptoms, GI specific catastrophizing, anxiety and fear of food remained much improved. See (Figure 3). See (Figure 4). See (Table 6). This analysis was confirmed in a sensitivity analysis using multiple imputation. See (Table 7).

Figure 3. Reduction in IBS-QoL scores from baseline to follow-up

Figure 4. Reduction in GSRS scores from baseline to follow-up

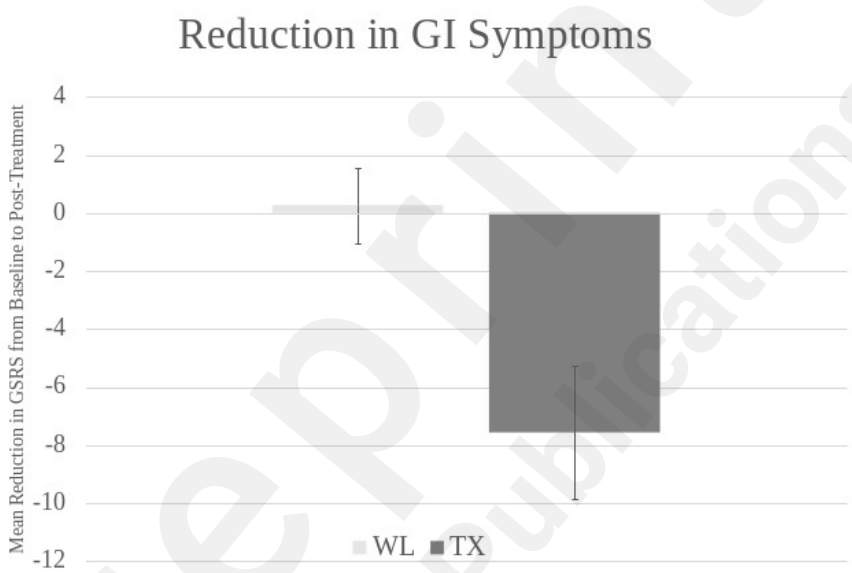


Table 6. Maintenance of Gains from Post-Treatment to 3 Months

Measure	**t**	**df**	**Sig. (2-tailed)**
IBS-QoL	.289	43	.774
GSRS	.636	43	.528
GI-COG	.841	43	.405
VSI	.056	43	.955
FFQ	.240	43	.812
PHQ	-.530	43	.599
DASS	-1.614	43	.114

Depression			
DASS Stress	.335	43	.739
DASS Anxiety	.935	43	.355

Table 7. Intent-to-Treat Sensitivity Analysis of Within Group Change Using Multiple Imputation

	0 - 8 weeks TX only n=62		**8 weeks – Post TX WL only n=59**		**Post TX – 3 months All n=121**	
Measure	**t**	**Sig. (2-tailed)**	**t**	**Sig. (2-tailed)**	**t**	**Sig. (2-tailed)**
IBS-QoL	4.7	<0.001	3.5	.001	-.47	.645
GSRS	3.3	.001	2.0	.055	.19	.849
GI-COG	5.2	<.001	2.9	.008	.10	.925
VSI	3.7	<0.001	2.4	.024	-.26	.798
FFQ	3.2	.002	2.0	.047	-.15	.880
PHQ	2.1	.041	2.0	.053	-.32	.751
DASS Depression	1.2	.234	1.8	.084	-.87	.390
DASS Stress	2.4	.016	1.5	.153	.47	.643
DASS Anxiety	2.3	.024	1.9	.069	-.14	.888

Attrition

There was significant attrition from the study in the immediate treatment and waitlist-control groups. See (Figure 2) for a flow chart of study enrollment. An independent samples-T-test demonstrated that the only predictors of attrition at the 8-week follow-up were more severe visceral sensitivity [t(119) = 2.18, *P* = .03] and fear of food [t(119) = 1.79, *P* = .075] for participants in both the immediate treatment and waitlist group. About half of the participants (21 out of 44) in the wait-list control group who were offered cross-over to active treatment were lost to follow-up at their post-treatment assessment. None of the measures at 8 weeks predicted attrition in this group. Of the 58 participants across both groups who completed the active treatment and the post-treatment questionnaires, 14 were lost to follow-up prior to the 3 month assessment. Subjects who were lost to follow-up at that point were more likely to be *less* stressed [t(56) = 2.19, *P* = .03], catastrophized *less* [t(56) = 2.21, *P* = .03] and were somewhat *less* depressed [t(56) = 1.72, *P* = .091] at post-treatment.

Mediation

Another aim of the study was to test whether changes in catastrophic thinking, visceral sensitivity, and fear of food would at least partially mediate reductions in GI symptom severity and improvement in quality of life.

The simple mediator models for GI symptom severity show that change in visceral anxiety, catastrophizing and fear of food were all significant mediators of the relationship between treatment and GI symptom severity. Participants assigned to immediate treatment had a greater decrease in visceral anxiety, catastrophizing and fear of food and participants who had a greater decrease in visceral anxiety (indirect effect = -4.3, BCCI 95% -7.0 to -1.8, *P* = .002), catastrophizing (indirect effect = -3.7, BCCI 95% -7.1 to -1.2, *P* = .007) and fear of food (indirect effect = -9.8, BCCI 95% -7.2 to -1.5, *P* = .003) had lower GI symptom severity at 8 weeks while controlling for baseline GI symptom severity. The statistically significant direct effect for each of the simple models indicates that treatment directly influenced GI symptom severity independent of the indirect effect of the mediating variables. The parallel multiple mediator model indicates that the indirect effects of visceral anxiety and fear of food were independent mediators but the effect of catastrophizing is not significant (95% BCCI encompass zero) and its effect is taken up by the other mediators. Once again there was a significant direct effect of treatment independent of mediators on GI symptom severity, *P* < .001

Participants assigned to immediate treatment had a greater decrease in visceral anxiety, catastrophizing and fear of food and participants who had a greater decrease in visceral anxiety (indirect effect = -12.2, BCCI 95% -18.2 to -6.4, *P* < .001), catastrophizing (indirect effect = -15.4, BCCI 95% -21.6 to -9.6, *P* < .001) and fear of food (indirect effect = -4.0, BCCI 95% -16.3 to -3.8, *P* = .008) had lower scores on IBS QoL at 8 weeks while controlling for baseline IBS QoL. The statistically significant direct effect for the model including fear of food indicates that treatment directly influenced quality of life independent of the indirect effect of fear of food. However, having accounted for the effect of change in visceral anxiety and catastrophizing no statistically significant direct effect of treatment remained. The parallel multiple mediator model indicates statistically significant indirect effects of the three mediators with no direct effect of treatment. See (Table 8).

Table 8. Direct and Indirect Mediation Results

		GI symptom severity			**IBS Quality of Life**		
		Effect	**95% BCI**	***P***	**Effect**	**95% BCI**	***P***
Visceral anxiety	**Indirect**	-4.3	-7.0, -1.8	.0022	-12.2	-18.2, -6.4	<.001
	Direct	-5.1	-8.8, -1.4	.0070	-4.6	-9.8, .56	.0796
GI specific catastrophizing	**Indirect**	-3.7	-7.1, -1.2	.0066	-15.4	-21.6, -9.6	<.001
	Direct	-5.6	-10.2, -1.1	.0152	-1.4	-7.9, 5.1	.6669
Fear of food	**Indirect**	-4.0	-7.2, -1.5	.0031	-9.8	-16.3, -3.8	.0008
	Direct	-5.4	-9.1, -1.6	.0053	-7.0	-12.7, -1.4	.0153
Parallel multiple mediator model	**Direct**	-9.4	-13.5, -5.3	<.001	-.5	-5.2, 4.2	.8284
	ViS	-3.4	-6.2, -1.0		-7.0	-11.3, -3.4	
	COG	1.8	-1.0, 4.4		-5.1	-9.0, -1.8	

	FoF	-2.7	-5.5, -0.8		-4.3	-8.3, -1.2	

Moderation

Univariate Analysis of data revealed that Rome IV criteria moderated the effectiveness of the treatment. That is, there was a significant interaction between condition and Rome IV status such that the app was more helpful to the participants who reported meeting stringent Rome IV criteria for IBS at baseline than those who did not for both GI symptoms [F(3,76) = 2.919, $P < .05$] and HRQL [F(3,76) = 6.652, $P = 0.001$]. The only difference at baseline between those who met criteria and those who did not was severity of GI symptoms [t(144) = 3.75, $P < .001$]. No other baseline variables were significantly different. When the sample is restricted to *only* those individuals who met strict Rome IV criteria, the advantage of the treatment group over the waitlist group is even more marked for improvement in GI symptoms [F(1,56) = 30.2, $P < .001$]; HRQL [F(1,56) = 47.42, $P < .001$], catastrophizing [F(1,56) = 51.10, $P < .001$], visceral anxiety [F(1,56) = 28.84, $P < .001$] and fear of food [F(1,56) = 22.11, P < .001].

Dose Dependent Response

Because the app itself tracks objective progress through the modules, we were able to examine the effect of "dose" (measured as components of the app accessed) on outcome. For the immediate treatment group, dosage was marginally correlated improvement in HRQL ($r = .33$, $P = .072$) and depression ($r = .33$, $P = .075$). This suggests that the more participants used the app, the more their quality of life and depressive symptoms improved.

Discussion

The purpose of this study was two-fold. First, we tested the efficacy of a cognitive-behavioral intervention for IBS delivered via a digital self-help app, with no therapist feedback or involvement. Completer analyses yielded statistically and clinically significant improvement, with treatment having a positive impact on both GI symptom severity and quality of life. Intent-to-treat sensitivity analysis using multiple imputation replicated those findings. After treatment, individuals reported significantly lower levels of IBS symptoms and less impairment to their quality of life. Effects size for the primary outcomes and most of the secondary outcomes were all in the very large range. This eight-week intervention appears to have substantially reduced the burden of illness compared to wait-list controls.

Secondly, we tested whether reductions in IBS specific catastrophic thinking, visceral sensitivity, and fear of food might mediate the efficacy of treatment. Reductions in these three variables did appear to mediate the impact of treatment on health related quality of life, though not on GI symptoms themselves. The app worked by reducing catastrophic thinking, visceral sensitivity to GI symptoms, and fear of food, which in turn improved individuals' quality of life. This is consistent with prior findings about the impact of CBT on IBS.

Overall, we are strongly encouraged by the results of this study, which appear to suggest that effective CBT for IBS can be successfully delivered via an app. The Zemedy app seems to be an effective means to improve the lives of individuals with IBS. Zemedy, which is already in the App Store and Google Play Store for download, could dramatically increase the accessibility of effective treatment for this debilitating disorder.

Limitations

This study had a number of limitations. The first was the lack of rigorous diagnostic interviewing and/or physician confirmation of the IBS diagnosis. While we did include a check on the Rome IV criteria in the baseline survey, meeting the criteria for IBS was not a requirement of the study. Twenty-six participants meet our inclusion criteria but did not meet strict diagnostic criteria for IBS. Eleven participants (7.5% of the total sample) indicated that their abdominal pain was only associated with bowel movements a quarter of the time or less. Seven participants (4.8% of sample) felt abdominal pain less than four days a month. Four had not had pain for six months and three only had pain during their menstrual period. Importantly, the Rome IV criteria are stricter than the previous ROME III [1] and many of these individuals would have met the threshold for IBS according to earlier criteria.

The choice to include participants who did not meet Rome IV criteria was made because the aim of the study was to determine the efficacy of the app for individuals *who believe they have IBS and are searching for self-help materials*. The app will be accessible to all, and even those who perceive they have IBS without a clinical diagnosis or meeting criteria will use it. Thus, it is important to test the app among anyone who believes it to be relevant to his/her life. Interestingly, individuals who *did* meet criteria for IBS actually showed significantly better response to the app. The app includes educational material about the importance of a thorough differential diagnostic evaluation, and especially the importance of ruling out other potential causes of GI symptoms (such as celiac disease and inflammatory bowel diseases). Moving forward, it may be important for the app to encourage people who do *not* meet Rome IV criteria to consult with their physicians about other possible causes of their symptoms.

The second limitation was the rate of attrition, with 36% not completing follow-up measures. Of those who completed 8-week follow up measures, most had not made it through a substantial portion of the app's content. On the other hand, the attrition rate from treatment of 36% is actually lower than the rate of 47% on average typically found in studies of online behavioral health interventions [49].

In addition, people did not drop out entirely at random. Participants who dropped out during the initial treatment phase had significantly higher rates of visceral anxiety and fear of food at baseline (although there were no other significant differences). Since CBT for IBS typically encourages acceptance of visceral sensations, and reduction of behavioral avoidance (especially avoidance of food and food related social situations), the treatment may have seemed particularly challenging for those individuals. Those might be the folks who need more personal guidance, encouragement and support from in person therapy.

A third limitation of the study was the inability to statistically establish the temporal precedence of the proposed mediators of change. In the study design, there was no mid-point survey to show that visceral anxiety, catastrophizing, and fear of food changed *before* quality of life improved. We did not include this intermediate survey during the treatment phase because we were concerned that it would increase attrition of participants, though a future study of the app would benefit from data obtained at this point.

Additionally, the PHQ is a poor measure of depression severity because it only measures symptom frequency and does not take intensity of symptoms into account. For example, at baseline, someone might endorse feeling tired or having little energy nearly every day (scoring a 3), because they are so anergic they can barely get out of bed. By the end of a trial, they might still endorse feeling tired or having little energy nearly every day (scoring a 3) because they still feel chronically fatigued, but they are getting up and going to work every day. The *severity* of their anergia would have declined significantly, but the PHQ would reflect no change. Furthermore, the item that assesses suicidality makes no distinctions at all with respect to passive versus active ideation, nor does it capture intent. An individual who has passive suicidal ideation daily, but no intent, would actually score *higher* than an individual who experiences less frequent, but intense active suicidal ideation with wavering intent. Although the PHQ has been used in many other clinical trials of behavioral health interventions, and it *did* show significant improvement over the course of this trial in the completer sample (but not the intent-to-treat analyses), we were dissatisfied with its sensitivity to treatment effects. Future studies of the app will employ more sensitive measures.

Finally, the last phase of the trial occurred during the COVID-19 global pandemic. Since all waitlist participants had already been crossed over to the active treatment phase, the 3 month follow-up data may reflect less the enduring effects of the treatment and more the massive social, economic and personal upheaval the pandemic has caused. Indeed, the end of the treatment phase for all subjects coincided with the COVID-19 pandemic's arrival in the United States. With massive shutdowns and quarantines, it is highly likely that distress increased for all participants. The fact that treatment gains were generally maintained and that participants remained much improved over baseline (except for some recurrence of depression) even in the face of an unprecedented global health crisis, is encouraging.

Conclusion

Despite the limitations, we believe that this study is of significant value. It successfully demonstrated the efficacy of an app which provided CBT for IBS patients. The intervention was not restricted by geography or scheduling constraints, and required no face-to-face contact with a clinician, aspects which dramatically increase the accessibility and portability of treatment. Despite its relatively benign physical profile, IBS can be an extraordinarily debilitating condition. Finding novel ways to disseminate evidence based, effective treatments remains an important challenge, and Zemedy is a promising and effective way to help those suffering from IBS.

Acknowledgements

Melissa Hunt substantively designed the content of the intervention, designed and ran the trial, conducted most statistical analyses and wrote the most of the paper. Sofia Miguez and Benjamin Dukas were the research coordinators who oversaw much of the day to day administration of the trial, including recruitment, randomization, scheduling assessments and scoring and cleaning the data. In addition, Sofia Miguez assisted with statistical analyses and drafting the manuscript. Obinna J Onwude oversaw the conversion of the CBT protocol into the digital format, coordinating the team of programmers and designers who created the app itself. Sarah White conducted the intent-to-treat and mediation analyses and drafted those sections of the manuscript. Bold Health provided some funding to pay for recruitment advertisements and participant incentives. All authors reviewed and approved the manuscript.

Conflicts of Interest

Dr. Onwude has a financial ownership stake in Bold Health which developed and markets the Zemedy App. Dr. Hunt, Ms. Miguez, Mr. Dukas and Dr. White have no FCOI to declare.

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Abbreviations

IBS = Irritable Bowel Syndrome; GI = Gastrointestinal CBT = Cognitive Behavioral Therapy; IBS–QoL = IBS Quality of Life Impairment; GSRS = Gastrointestinal Symptom Rating Scale; GI-CoG = Gastrointestinal Cognitions Questionnaire; VSI = Visceral Sensitivity Index; FFQ = Fear of Food Questionnaire; PHQ = Patient Health Questionnaire; DASS = Depression Anxiety Stress Scale.

Appendix A - Consent Form

Consent Form
Acceptability and Efficacy of Zemedy App for IBS

Principal Investigator:
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Invitation: You are being invited to participate in a research study of a self-help treatment (the Zemedy phone app) for irritable bowel syndrome (IBS) because you have been diagnosed with IBS by a medical professional, and don't have another serious GI disorder (like Crohn's disease or ulcerative colitis). You must be at least 18 years of age or older to participate, and you must own a smart phone and be willing to download the Zemedy App at no cost.

Purpose: The purpose of this research is to determine whether a self-help app, based on a number of empirically supported treatments for IBS including cognitive-behavioral therapy, gut directed hypnotherapy, exercise, relaxation, stress management and dietary management can be an effective treatment for IBS.

Procedures: First, we will ask you to complete a number of baseline demographic, mood and symptom questionnaires so that we can get a good sense of how severe your IBS is, how much it is impacting your life, and how it affects your mood. At any time, you may skip any questions that make you uncomfortable. Once the investigators receive this data, they will contact you directly via e-mail within 24 business hours, informing you whether or not you are eligible to be in the study. Everyone who meets the study criteria will be assigned to one of two groups at random (like flipping a coin) - the immediate treatment group or the wait-list group. The e-mail will tell you which group you have been assigned to.

If you are assigned to the **wait-list**, we will ask you to continue with whatever you've been doing to manage your IBS without changing anything dramatically (like starting a new medication or going on a restrictive diet). After 8 weeks, we will ask you to complete the symptom measures

again. When we get those measures, you will be offered the chance to get the app and start working through it. Once you get the app, the study will proceed as outlined in the next paragraph on immediate treatment.

If you are in the **immediate treatment** group, your first email from the investigators will contain instructions for downloading the app to your phone. During the treatment phase, you will be asked to complete a number of tasks, including:
1. Reading educational materials about IBS.
2. Tracking your IBS symptoms.
3. Practicing relaxation exercises.
4. Keeping records of your thoughts and feelings in situations in which you experienced IBS symptoms.
5. Learning new ways of thinking about social and work situations, especially about how they are impacted by your IBS symptoms.
6. Practicing new skills (e.g. relaxation, new ways of thinking) in situations you might usually prefer to avoid.
7. Learning about diet and exercise management strategies.
8. Using imagery to think about IBS symptoms differently

Your IBS symptom severity will be measured again after you have spent 8 weeks using the app. We will also ask for your feedback on the app – how user friendly it felt, how much you liked it, and so on, including any suggestions you have to make it better. Three months later, you will be contacted one last time via e-mail and will be asked to complete the symptom severity measures one last time.

Risks:

There are some risks to taking part in this study. You may find yourself more aware of your physical sensations and IBS symptoms for a period of time after using the app. You will also be asked to think in new ways about problems and situations that might come up in your life, including your IBS itself. Sometimes it can be uncomfortable or even scary to think about things differently, or to practice new skills. One of the questionnaires in the study will ask about symptoms of depression. If you indicate that you are severely depressed or actively thinking about suicide, the study PI (who is a licensed clinical psychologist) will reach out to you via email to check on your safety and offer you referrals to local mental health services if desired.

Benefits:

There is no promise of direct benefit to you for participating in this study. It is possible that this self-help intervention will help reduce your Irritable Bowel Syndrome symptoms and improve your quality of life.

Compensation:

If you are in the immediate treatment group, you will be compensated $20 for completing the post-treatment follow-up questionnaires in the week or so after you complete the program. You will be compensated a further $20 for completing the follow-up questionnaires 3 months after completing the program. Thus, your total compensation could be as much as $40.

If you are in the waitlist control group, you will be compensated $20 for completing the follow-

up questionnaires 8 weeks after the initial questionnaires. You will be compensated a further $20 for completing another set of follow-up questionnaires in the week or so after you complete the program. Finally, you will be compensated a further $20 for completing the follow-up questionnaires 3 months after completing the program. Thus, your total compensation could be as much as $60. People who are randomly assigned to the waitlist control group can be compensated a bit more money to help make up for the fact that they had to wait for two months to access the app, and have to fill out the questionnaires one extra time.

All compensation will be in the form of Amazon.com gift vouchers that can be spent on anything you like within the Amazon system.

Conflict of Interest:

The originators of the Zemedy App could make money from sales of the app in the future. However, the Principal Investigator, Dr. Hunt, has no financial interest in this product, and does not stand to profit from it.

Confidentiality:

Use of the Zemedy application is covered by the Bold Health Privacy Policy and Terms of Use. All information collected in this study (e.g. questionnaires about your symptoms) will be kept strictly confidential, except as may be required by law.

Your information will be de-identified. De-identified means that all identifiers (like name and email address) have been removed. The information could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law.

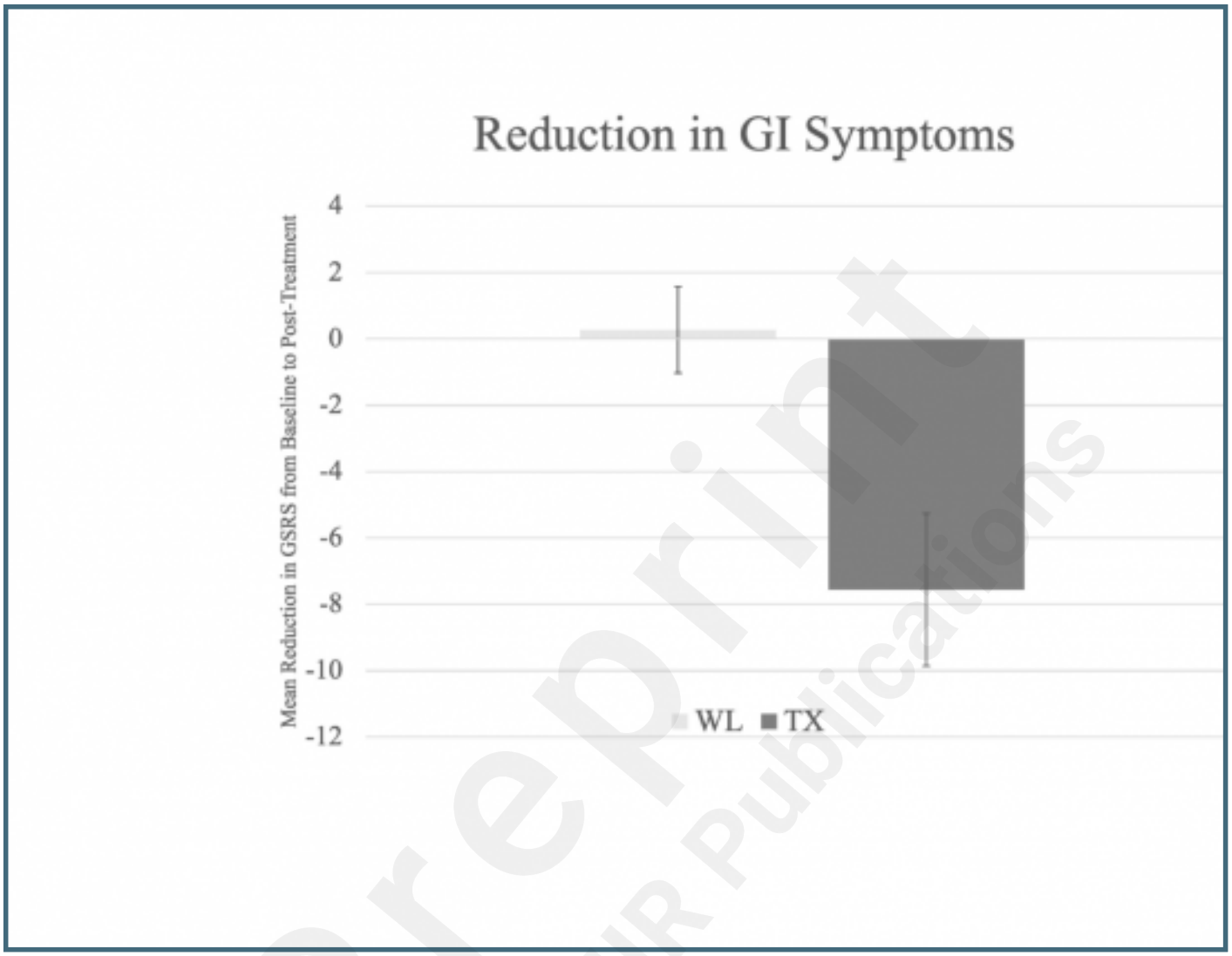
Your participation in this study is voluntary, and you may withdraw at any time, or skip questions you do not wish to answer. The alternative to participating in this research study is not to participate. If you wish further information regarding your rights as a research subject, you may contact the Director of Regulatory Affairs at the University of Pennsylvania by telephoning 215-898-2614. Upon clicking the “I consent” button below, you acknowledge that you have read and understood this consent form and that you agree to participate in this research study.

By clicking on the “I consent” button below you are agreeing to take part in this research study. If you have any questions or there is something you do not understand, feel free to contact us by phone or e-mail as listed above.

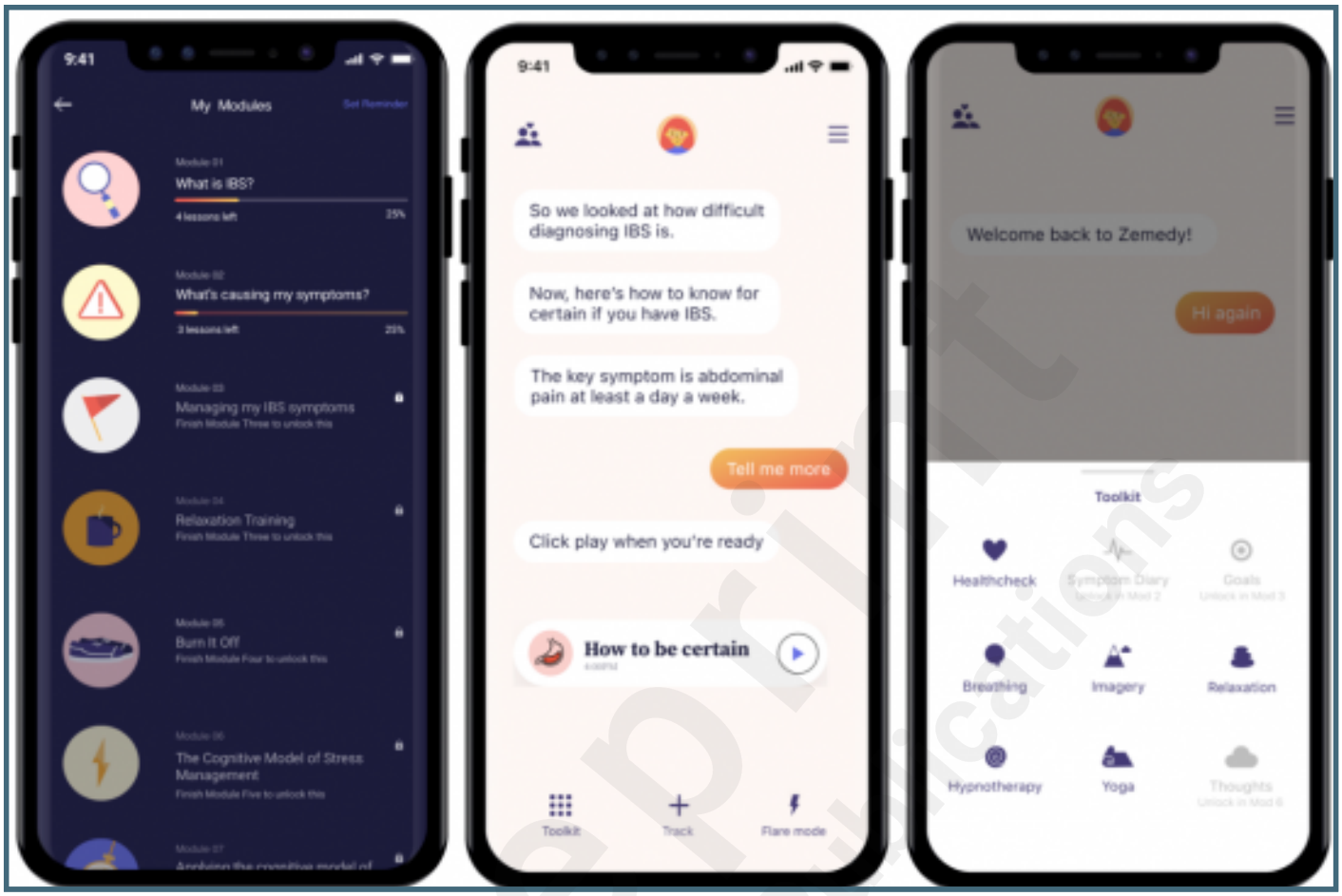
Supplementary Files

Figures

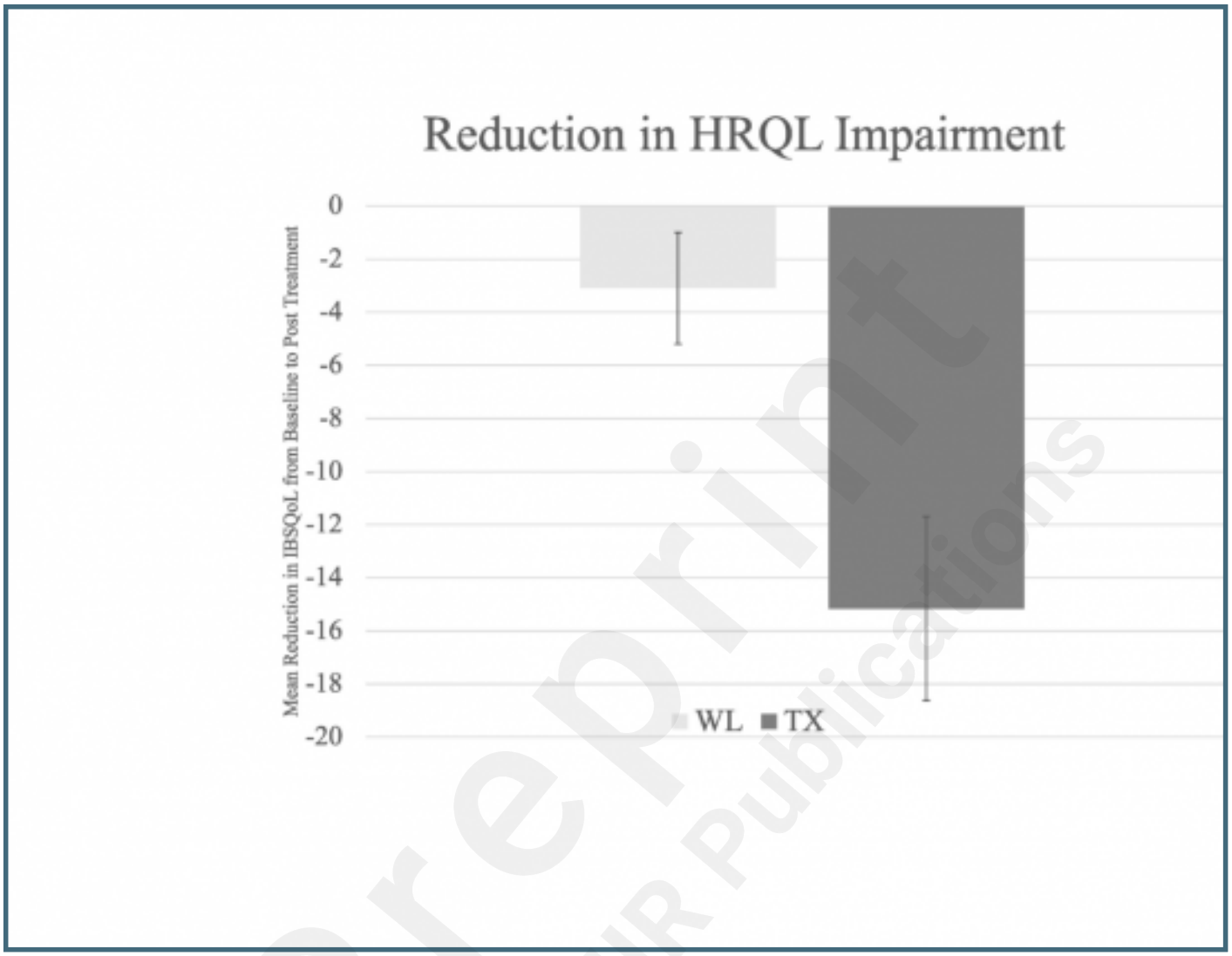
Improvement in GI Symptoms.



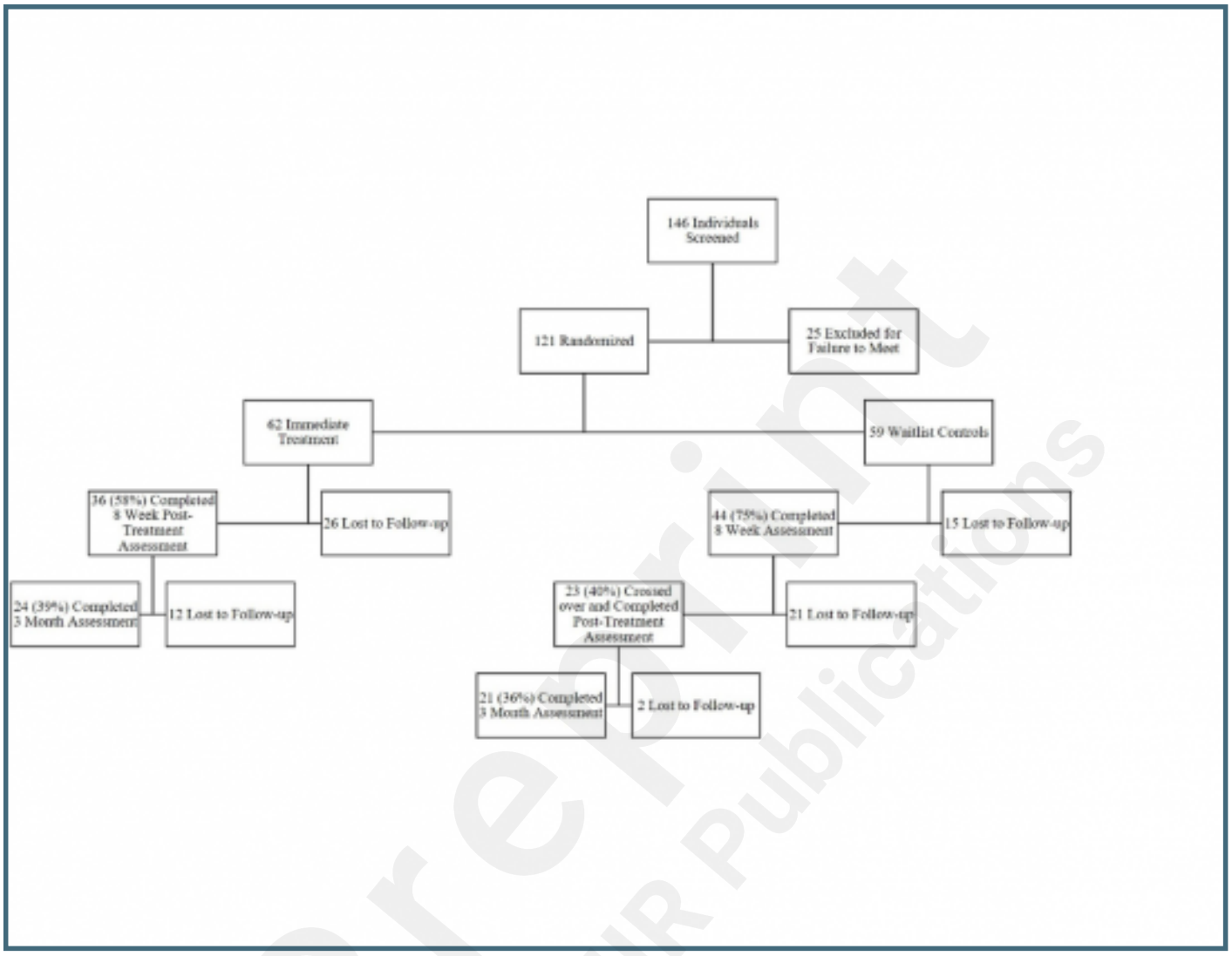
Screenshots of Zemedy.



Improvement in HRQL.



Consort Diagram.



CONSORT (or other) checklists

Submission Checklist.
URL: https://asset.jmir.pub/assets/7ef4b76670981ed2ce6e450af96feddd.pdf